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Interventions for the Treatment of Obstructive Sleep Apnea in Adults: A Health Technology Assessment

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Abbreviations

A1C	glycated hemoglobin
AE	adverse event
AF	atrial fibrillation
AHI	Apnea–Hypopnea Index
AHRQ	Agency for Healthcare Research and Quality
AI	arousal index
AMSTAR	Assessment of Multiple Systematic Reviews
APAP	autotitrating positive airway pressure
BDI	Beck Depression Inventory
BiPAP	bilevel positive airway pressure
BMI	body mass index
BP	blood pressure
BSI	Brief Symptom Inventory
BSI-A	Brief Symptom Inventory–Anxiety Subscale
BSI-D	Brief Symptom Inventory–Depression Subscale
CBD	cerebrovascular disease
CDSR	Cochrane Database of Systematic Reviews
CEAC	cost-effectiveness acceptability curve
CENTRAL	Cochrane Central Register of Controlled Trials
CES-D	Center for Epidemiological Studies Depression Scale
CI	confidence interval
CONSORT	Consolidated Standards of Reporting Trials
CPAP	continuous positive airway pressure
CV	cardiovascular
CVD	cardiovascular disease
CVE	cardiovascular event
DARE	Database of Abstracts of Reviews of Effects
DBP	diastolic blood pressure
DI	desaturation index
EDS	excessive daytime sleepiness
EPAP	expiratory positive airway pressure
EPHPP	Effective Public Health Practice Project
EQ-5D-3L	EuroQol-5 dimensions–3 levels
ESS	Epworth Sleepiness Scale
FOSQ	Functional Outcomes of Sleep Questionnaire

GHQ	General Health Questionnaire
GP	genioplasty
GQL	glaucoma quality of life
GRADE	Grading of Recommendations Assessment, Development and Evaluation
GTA	genial tubercle advancement
HADS-A	Hospital Anxiety and Depression Scale–Anxiety Subscale
HADS-D	Hospital Anxiety and Depression Scale–Depression Subscale
HAM-D	Hamilton Rating Scale for Depression
HDL	high-density lipoprotein
HF	heart failure
HTA	health technology assessment
ICUR	incremental cost-utility ratio
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LOCF	last observation carried forward
MA	meta-analysis
MAD	mandibular advancement device
MADRS	Montgomery–Åsberg Depression Rating Scale
MAS	mandibular advancement splint
MD	mean difference
MI	myocardial infarction
MeSH	Medical Subject Heading
MMA	maxillomandibular advancement
MMPI	Minnesota Multiphasic Personality Inventory
MMPI-Pt	Minnesota Multiphasic Personality Inventory–Psychasthenia Subscale
MR	meta-regression
MVA	motor vehicle accident
NA	not available
NHP	Nottingham Health Profile
NMA	network meta-analysis
NICE	National Institute for Health and Care Excellence
NR	not reported
OA	oral appliance
ODI	oxygen desaturation index
OR	odds ratio
OSA	obstructive sleep apnea
PAP	positive airway pressure
POMS-D	Profile of Mood States–Depression Subscale

POMS-T	Profile of Mood States–Tension and Anxiety Subscale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PSG	polysomnography
PTCA	percutaneous transluminal coronary angiography
QA	quality assessment
QALY	quality-adjusted life-year
QoL	quality of life
QSQ	Quebec Sleep Questionnaire
RCT	randomized controlled trial
RDI	respiratory disturbance index
RoB	risk of bias
RoBANS	Risk of Bias Assessment Tool for Nonrandomized Studies
ROBIS	Risk of Bias in Systematic Reviews
RR	relative risk
SAHS	sleep apnea/hypopnea syndrome
SAQLI	Calgary Sleep Apnea Quality of Life Index
SBP	systolic blood pressure
SD	standard deviation
SDS	Zung Self-Rating Depression Scale
SF	Short Form Health Survey
SHHS	Sleep Heart Health Study
SPT	sleep position trainer
SR	systematic review
SSS	Stanford Sleepiness Scale
STAI	State-Trait Anxiety Inventory
TAS	Tension Anxiety Scale
Tot-C	total cholesterol
TRD	tongue-retaining device
TSD	tongue-stabilizing device
UMACL	University of Wales Mood Adjective Checklist
UPPP	uvulopalatopharyngoplasty
UWIST	University of Wales Institute of Science and Technology
WHO-5	World Health Organization–Five Well-Being Index
WHOQOL	World Health Organization Quality of Life questionnaire
WSCS	Wisconsin Sleep Cohort Study

Protocol Amendments

Section	Amendment	Page
Clinical Review	For selection criteria, success or cure rate was added to the list of outcomes.	18, 21
	For quality assessment, a fourth item from the AMSTAR checklist was added to the list of additional criteria.	23
	For quality assessment, the network meta-analyses were assessed, using the ISPOR questionnaire, in addition to the ROBIS tool.	23
	For analysis and synthesis, quality assessment of primary studies included in the systematic reviews was presented in the quality assessment section of this report, instead of the summary of study characteristics.	24
All sections	Throughout the report, EPAP was separated from PAP devices.	All

Executive Summary

Issue

Obstructive sleep apnea (OSA) affects as many as one in four adults in Canada. Untreated OSA is associated with increased risk of motor vehicle crashes, various chronic diseases, and death. A wide range of treatment options exist, but selecting the most appropriate therapy remains a challenge across Canadian jurisdictions.

Objectives

The aim of this health technology assessment (HTA) was to assess the clinical effectiveness, cost-effectiveness, patient perspectives and experiences, ethical issues, implementation issues, and environmental impacts of positive airway pressure (PAP) devices, expiratory positive airway pressure (EPAP) valves, oral appliances (OAs), surgery, and lifestyle modifications for the treatment of OSA in adults.

Clinical Evidence

Methods: A systematic review of the literature was conducted, using MEDLINE, Embase, the Cochrane Database of Systematic Reviews, DARE, Cochrane Central, and PubMed, for an overview of systematic reviews (SRs), meta-analyses (MAs), and HTAs, supplemented by a review of primary studies for areas with gaps, where data were lacking. In total, 33 SRs and 41 primary studies were included in the overview and review, respectively, on adults with OSA who were treated with PAP devices, EPAP valves, OAs, surgery, and lifestyle interventions and assessed on various outcomes, with excessive daytime sleepiness (EDS) as the primary outcome.

Results: The majority of relevant studies identified in the published literature pertained to continuous PAP (CPAP) and mandibular adjustment devices (MADs). The results indicated that CPAP, MADS, EPAP, tongue-retaining devices (TRDs), maxillomandibular advancement (MMA), genial tubercle advancement (GTA), weight-loss programs, and positional therapy were all effective at reducing EDS, commonly measured by Epworth Sleepiness Scale, compared with inactive controls or pre-treatment. Effect sizes were similar across the interventions, except for patients with severe cases of OSA, who may benefit more from CPAP than from MADs, but this may not be clinically significant. Based on the analysis using OSA severity as the outcome, commonly measured by the Apnea–Hypopnea Index (AHI), effect sizes varied across the interventions, with CPAP showing the largest effect. Among a select subgroup of OSA patients for whom surgery may be appropriate, MMA with or without GTA may substantially improve EDS and OSA severity. The majority of studies on MMA and GTA, however, were in highly selected patients in uncontrolled pre-and-post studies with sample sizes of fewer than 10 patients. The results, therefore, must be interpreted with great caution, especially given the invasiveness of the procedures and potential adverse events. Limited evidence was found on non-PAP or non-OA interventions and other outcomes, such as blood pressure, cardiovascular events (CVEs), quality of life, and mortality. The 33 SRs and 41 primary studies were assessed to generally be of high quality, using accepted quality assessment tools, but concerns were identified regarding the study eligibility criteria for the SRs and small samples and uncontrolled pre-and-post study designs for the primary studies. The primary studies included in the 33 SRs ranged widely in their quality.

Economic Evidence

Methods: A Markov cohort model was constructed in order to evaluate the cost-effectiveness of various treatment strategies in adult patients diagnosed with OSA (i.e., 76.5% males, 55 years of age) over a patient's lifetime from a Canadian health care payer perspective. The effect of treatment in terms of change in AHI and blood pressure was determined from the clinical review and was translated to changes in the risk of CVEs and motor vehicle accidents (MVAs) in the economic model. The primary outcome was cost per quality-adjusted life-years (QALYs) gained, in 2016 Canadian dollars. The base-case analysis compared a "no-treatment" strategy against PAP therapy, MADs, and

surgery (i.e., MMA with or without GTA). A separate scenario analysis was conducted on obese or overweight patients, in which weight loss would be a suitable treatment strategy.

Results: Cost-effectiveness of treatment strategies for OSA was found to be dependent on a patient's baseline disease severity, as measured by AHI (i.e., lower AHI equates to less severe OSA). In patients presenting with mild baseline severity (AHI < 15), no treatment would be cost-effective if the willingness-to-pay was less than $175,000/QALY. In patients with a baseline AHI of 15, PAP therapy would be cost-effective if the willingness-to-pay was between $8,058/QALY and $9,276/QALY, and thereafter, at a willingness-to-pay greater than $9,276/QALY, MAD would be the most likely cost-effective intervention. In patients with severe AHI (AHI ≥ 30), both PAP therapy and surgery are potentially cost-effective strategies. Specifically, PAP therapy was cost-effective in the lower range of severe OSA (e.g., incremental cost-utility ratio [ICUR] at a baseline AHI of 30 = $7,420) while surgery was cost-effective in the higher range of severe OSA (e.g., ICUR at a baseline AHI of 60 = $17,125). Absolute gains in QALYs from treatment were found to follow a unimodal distribution and were a function of disease severity. Those with mild or more severe OSA had lower gains in QALYs, whereas the largest gains were observed in patients whose baseline severity reduced from severe (AHI ≥ 30) or moderate (15 < AHI < 30) to mild-to-moderate OSA (AHI < 30) or mild OSA (AHI < 15), respectively, due to its impact on subsequent morbidity and mortality risks. Incremental costs were largely driven by the costs of treatment and long-term maintenance costs, given the longer life expectancies of patients on treatment. It is important to note that the estimates on the clinical effectiveness of surgery were taken from the clinical review and, thus, caution is required when interpreting the cost-effectiveness results of surgery. Not all patients will be suitable for surgery and, in such instance, the economic analysis suggests that MAD would be cost-effective for moderate OSA if willingness-to-pay was $7,984/QALY while PAP therapy would be cost-effective for severe OSA if willingness-to-pay was $7,470. The model was found to be most sensitive to changes in treatment adherence.

Patient Perspectives and Experience Evidence

Methods: An SR and thematic synthesis of the literature relevant to the research question on patient experience and perspectives was conducted. Patient experience information was identified by searching the following databases: MEDLINE (1946–), Embase (1974–), and PsycINFO (1967–) via Ovid; CINAHL (1981–) via EBSCO; and PubMed. Studies were eligible if they presented the patient or non-clinical caregiver experience. Qualitative studies, surveys, studies with mixed methodology, or systematic reviews of descriptive studies were eligible. A maximum variation approach was used to identify articles for inclusion in the thematic synthesis from a list of eligible articles. A thematic synthesis was conducted, comprising three stages: coding, developing descriptive themes, and developing analytic themes.

Results: Thirty-two studies, of moderate to good quality, were included in the thematic synthesis, the coding and analysis of which led to two analytic themes. The first theme states that a range of characteristics and factors influence whether people seek and initiate OSA treatment. The second analytic theme states that interventions for OSA require adaptation to daily routines and relationships; some patients are able to integrate these interventions into their lives and experience benefits, while others are unable to do so.

Ethical Issues

Methods: A review of the normative bioethics literature was conducted to identify literature relevant to the identification and analysis of the potential ethical issues on interventions for OSA (i.e., articles that explicitly and specifically raise ethical issues). A CADTH Information Specialist performed targeted literature searches in MEDLINE, PubMed, and CINAHL from database inception to March 2016. Key terms for ethics concepts and related terms were used and combined with search terms for OSA. The search was limited to English- or French-language literature. The selection of relevant literature occurred in two stages. In the first stage, the title and abstracts of citations were independently screened for relevance by two reviewers. Articles were categorized as "potentially relevant" or "not relevant" based on whether ethical issues were explicitly mentioned. In the second stage, full-text reports that pertained to OSA treatments in adults and suggested implicit ethical issues were identified.

Results: The literature search yielded 1,268 unique citations, none of which passed the first stage of screening because no articles on OSA treatment were found that explicitly mentioned ethical issues. However, in the second stage the reviewers selected 142 potentially relevant articles that raised implicit ethical issues. Ethical issues relating to OSA were explored according to six key values that emerged from the literature review. This includes the duties to respect individual autonomy, maximize benefits and minimize harm for patients, maximize benefits and minimize harms for others affected by OSA, maximize benefits and minimize harms for populations, distribute benefits and burdens of health care resources fairly, and steward scarce resources.

Implementation Issues

Methods: A narrative literature review was conducted to identify some of the implementation issues associated with the different interventions for the treatment of OSA in adults. Citations arising from the literature searches conducted to address the clinical, economic, patient perspectives and experience, and ethical issues were screened independently in duplicate for information related to implementation issues. Issues identified from relevant studies are organized by OSA intervention (i.e., PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications) and further categorized by the level where the issue arises: individual, team, organization, or system or policy. This information was summarized narratively.

Results: From the 29 included studies, one of the biggest implementation issues identified for OSA treatment is the difficulty in accessing sleep specialists and specialized sleep labs. Home-based portable diagnostic devices and treatment titration options with telehealth-based support are suggested solutions. Most of the implementation evidence focuses on CPAP devices. Barriers to CPAP use include cost and lack of funding as well as patient discomfort or use problems. Suggested CPAP supports include patient education, training, and support as well as providers and centres that are accredited for the treatment of OSA. Barriers to treatment with OAs include lack of physician knowledge and awareness, anatomical and dental health requirements, and the need for regular re-evaluations. Multidisciplinary sleep clinics that include medical and dental professionals are suggested supports. Little evidence on implementation issues for OSA surgery or lifestyle interventions was found.

Environmental Impact

Methods: Citations arising from the clinical literature search were screened for information relating to environmental considerations associated with OSA.

Results: One narrative review article was identified regarding the environmental implications associated with OSA. The review article briefly examined the environmental considerations of the CPAP unit, including manufacturers adopting green shipping and production methods and creating products that are more energy efficient and more recyclable.

Conclusions

Clinical data show that across all OSA severities, various treatment interventions for OSA were found to significantly improve sleepiness, but CPAP had the largest effect on improving OSA severity. Treatment of patients with moderate-to-severe OSA appears to be a cost-effective use of resources under a willingness-to-pay threshold of $50,000/QALY.

Nevertheless, for any non-surgical therapy, patient adherence was considered key in achieving treatment success and cost-effectiveness. Relevant patient factors were highly individualized and contextual and the factors that influence whether patients seek treatment and how they experience treatment will differ for each individual. It may be that patients who are symptomatic, have a supportive partner, experience resolution of their symptoms when using CPAP or an OA, and experience few or mild side effects may be more likely to be adherent with these interventions. Patients appear to make a trade-off between the discomfort of CPAP and OAs, and the perceived benefits of using these devices. If patients find these interventions acceptable, they experience a period of problem-solving and

adaptation to integrate these interventions into their lives. Information needs were expressed during the patient experience, from diagnosis and throughout treatment. Support from peers, health care professionals, and bed partners was also important, although some patients did not feel supported in using interventions for OSA.

From an ethics perspective, interventions for OSA have been shown to offer benefit to OSA patients and to reduce overall costs, and so appear to live up to the values of conferring benefit at a population level and stewarding scarce resources. In light of the significant personal and public harms that undiagnosed OSA can cause, further consideration of screening protocols and public education is warranted. In addition, our duties to distribute benefits and burdens fairly require that we are attentive to the accessibility of testing and diagnostic services, recognizing any sociocultural factors (e.g., gender, ethnicity, socioeconomic class) that may unjustly affect this access. Optimizing interventions for OSA that reflect individuals' individual contexts and abilities appear most likely to maximize adherence, thus leading to benefits at the individual and the population level. OSA treatment should be provided through an ongoing partnership between health care provider and patient, rather than through discrete events of diagnosis, decision, and intervention.

The review of implementation issues further highlighted the difficulties in accessing sleep specialists and laboratories as being critical to initiating treatment of OSA, as well as the benefits of multidisciplinary sleep clinics. A single review was found to recommend environmental considerations for CPAP, such as energy-efficient and recyclable products and green shipping and production methods. Therefore, for the treatment of OSA, in addition to clinical and cost-effectiveness evidence, patient, provider, supplier, and system readiness for the various interventions will need to be considered.

Introduction

Background

Obstructive sleep apnea (OSA) is a common disorder that is characterized by narrowing and collapse of the upper airway during sleep and is associated with arousals and awakenings. A 2009 Canadian survey reported that 3% of Canadian adults were diagnosed with sleep apnea, making it as common as hypertension or diabetes.[1,2] Cross-sectional and longitudinal data would suggest that the prevalence of OSA is 15% in males and 5% in females.[3,4] The prevalence may be even higher, with more than one in four adults presenting symptoms and factors associated with having or developing OSA.[1,5] Its major symptoms include snoring, unrefreshing sleep, excessive daytime sleepiness (EDS), lack of concentration, impaired memory and lower quality of life (QoL).[5,6] Aging, the male sex, and obesity are its main risk factors.[7,8] Untreated OSA is associated with motor vehicle accidents (MVAs), cardiovascular disease (CVD), stroke, hypertension, diabetes, cognitive dysfunction, and all-cause mortality.[1,5,9-11] Untreated OSA is also a known surgical risk and can give rise to cardiovascular (CV) and pulmonary complications.[12]

Treatment of OSA includes a wide range of options.[13] Positive airway pressure (PAP) devices and various oral appliances (OAs) splint the airways open to facilitate airflow. Continuous positive airway pressure (CPAP) forces air into the upper airways to prevent soft tissues from collapsing and is considered the gold standard for the treatment of OSA.[13-15] Other PAP technologies, such as autotitrating PAP (APAP) and bilevel PAP (BiPAP), may be offered to patients with specific needs.[13,14] An alternative treatment for OSA is nasal expiratory positive airway pressure (EPAP) valves, which are disposable devices that use a patient's own breathing to create positive end-expiratory pressure that prevents obstructive breathing.[16] OAs, including mandibular advancement devices (MADs), also known as mandibular advancement splints (MASs) or dental devices, and tongue-retaining devices (TRDs), can be offered as an alternative to CPAP.[14,17,18] For patients with mild or asymptomatic OSA, lifestyle interventions, such as exercise programs, diet changes, and positional therapies, may be proposed before proceeding to other interventions.[19] Surgeries may be indicated for patients with a defined anatomical obstruction or morbid obesity, or as alternatives in cases where other interventions cannot be considered or have failed.[20,21] Upper airway surgeries such as uvulopalatopharyngoplasty (UPPP) aim to facilitate air flow by remodelling soft tissue structure. In contrast, surgical maxillomandibular advancement (MMA) permanently pulls the lower jaw forward to create more space and prevent airway collapse.[22,23] Genial tubercle advancement (GTA) is a surgical intervention that removes bone tissue from the chin and pulls the base of the tongue forward to create more airway space, and can be performed in conjunction with MMA or other surgeries to potentially improve therapeutic success.[24,25]

Therapy selection is based on an assessment of the patient by lab-based polysomnography (PSG) or home-based portable monitors.[26] The goal is to determine the presence and severity of OSA by measuring the number of apnea or hypopnea events per hour, which constitutes the Apnea–Hypopnea Index (AHI), as well as the blood oxygen levels and other cardiorespiratory indicators.[14] The AHI correlates with the risk of various CV outcomes, including hypertension, as well as all-cause mortality,[5,8,10,26,27] and can also be used to determine the effectiveness of interventions intended to treat OSA. As a general rule, the therapeutic effect size is proportional to the severity of OSA.[9,10] Other diagnostic measurements include the respiratory disturbance index (RDI) and time spent at oxygen saturation (SpO_2) < 90%,[7] as well as the Epworth Sleepiness Scale (ESS)[14] and the oxygen desaturation index.[28] Despite the positive outlook for CPAP, positioning it as the gold standard for treating OSA, between 29% and 83% of patients ultimately fail to comply with regular device use,[29-31] which limits its impact. In fact, low CPAP adherence is associated with significantly higher mortality.[2] Because of technical challenges, adherence with MADs is not as well documented but is regarded as being superior to CPAP.[28,32] Therefore, patient adherence may be a factor in therapy selection and effectiveness. In that respect, surgical interventions may be attractive solutions for circumventing the issue of nightly adherence. However, they are invasive procedures for which evidence of effectiveness and safety is less convincing.[14] Overall, while OSA interventions have shown effectiveness at reducing AHI, sleepiness, and some CV measures, such as blood pressure, no large randomized controlled trial (RCT) has yet demonstrated benefits on cardiovascular events (CVEs) or mortality.[33]

Across jurisdictions, OSA is associated with a substantial economic and societal burden.[7,8,34] A cross-sectional study[35] in the United States (US) found that, in the year prior to the diagnosis of OSA, the mean annual medical cost per patient was $2,720 for OSA cases, versus $1,384 for age- and sex-matched controls. In the US, OSA was established as the cause of 800,000 MVAs in 2000, for a total of 1,400 deaths and a cost of $15.9 billion to society.[8,36] In Australia, the total impact of managing sleep disorders — including direct hospital and non-hospital costs, as well as the costs of associated conditions, such as stroke, heart disease, depression, and accidents — was estimated at $818 million in 2010.[37] In Canada, the Assistive Devices Program within Ontario's Ministry of Health and Long-Term Care received approximately 28,000 applications for CPAP in 2008.[38] Although no trend information is available, assuming new devices are required each year, extrapolating these figures to the entire Canadian OSA population would result in roughly 72,400 new devices each year. At a cost of approximately $2,000 for CPAP or MADs,[38,39] a total of $145 million per year would be incurred as direct expenses.

Currently, public coverage for treatment of OSA varies widely across Canadian jurisdictions, which translates into differences in access. Ontario, Saskatchewan, Newfoundland and Labrador, Manitoba, Yukon, and some federal programs for special populations, including military personnel, support CPAP therapy for OSA patients, by either leasing equipment or reimbursing part of the acquisition cost.[2] Further, criteria for patient selection and monitoring using CPAP, as well as supply agreements for lease or reimbursement, vary across these jurisdictions.[2] With regard to dental devices, no provincial programs reimburse their cost, while some federal programs will do so for eligible patients.

Given the broad range of therapeutic approaches and the diversity of clinical presentations influenced by OSA severity, symptoms, and comorbidities, the major common issue in Canadian jurisdictions is the challenge of selecting the most appropriate therapy for OSA patients with different clinical profiles and treatment histories.

Policy Question

What is the optimal use of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?

Objectives

The aim of this health technology assessment (HTA) was to inform the policy question through an assessment of the clinical effectiveness, cost-effectiveness, patient perspectives and experiences, ethical issues, implementation issues and environmental impacts of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults.

Research Questions

This HTA addressed the following research questions:

1. What are the clinical effectiveness, comparative clinical effectiveness, and safety of PAP devices, EPAP valves, oral appliances, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?

    1a. What are the clinical effectiveness, comparative clinical effectiveness, and safety of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of adult patients with different OSA severity (i.e., mild, moderate, severe)?

    1b. What are the clinical effectiveness, comparative clinical effectiveness, and safety of interventions for the treatment of adult OSA patients with or without comorbidities (e.g., obesity, hypertension, diabetes)?

2. What is the cost-effectiveness of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?
3. What are the experiences and perspectives of adult patients, their family members, and their caregivers regarding PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?
4. What ethical issues are raised by providing PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults? How should these issues be addressed?
5. What are some of the implementation issues associated with PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?
6. What are some potential environmental impacts associated with PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?

Clinical Review

This section addressed Research Question 1: What are the clinical effectiveness, comparative clinical effectiveness, and safety of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults? This section also addressed the following two sub-questions: 1a. What are the clinical effectiveness, comparative clinical effectiveness, and safety of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of adult patients with different OSA severity (i.e., mild, moderate, severe)? 1b. What are the clinical effectiveness, comparative clinical effectiveness, and safety of interventions for the treatment of adult OSA patients with or without comorbidities (e.g., obesity, hypertension, diabetes)?

Methods

Study Design

An overview of SRs, meta-analyses (MAs), and HTAs available in the literature on the clinical effectiveness, comparative clinical effectiveness, and safety of interventions for the treatment of OSA in adults was conducted, considering the large volume of literature currently available. Where no published SRs, MAs, or HTAs on any given intervention-comparator combination or certain intervention-comparator-outcome combinations of interest were identified, an SR of primary studies was conducted.

A protocol for the overview of reviews (CRD42016036348)[40] was written a priori and followed throughout the review process. A protocol for the review of primary studies was written a priori, as an addendum to the protocol for the overview[40] to address gaps within the published SR, MA, and HTA literature, and followed throughout the review process. Any changes to the protocol were identified, and reasons for the changes were provided, throughout this report and in the Protocol Amendments table (see Protocol Amendments).

Literature Search Strategy

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[41]

Published literature for the original search for SRs, MAs, and HTAs was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; the Cochrane Database of Systematic Reviews (CDSR) and the Database of Abstracts of Reviews of Effects (DARE) via Ovid; and PubMed. Published literature for the supplemental search for primary studies was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via Ovid; The Cochrane Central Register of Controlled Trials (CENTRAL) via Ovid; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's Medical Subject Heading (MeSH) terms, and keywords. The main search concepts for the original search for SRs, MAs, and HTAs were sleep apnea and sleep-disordered breathing. The main search concepts for the supplemental search for primary studies were sleep apnea, sleep-disordered breathing, PAP devices, EPAP, MADs, TRDs, MMA, GTA, and lifestyle modifications.

For the original search, methodological filters were applied to limit retrieval to SRs, MAs, HTAs, network meta-analyses (NMAs), overviews of reviews, and guidelines. Retrieval was limited to documents published since January 1, 2011, considering the large volume of literature currently available on clinical effectiveness. For the supplemental search, no methodological filters were applied to limit retrieval. For this search, retrieval was limited to documents published since January 1, 2006. Both searches were limited to English- or French-language publications. Conference abstracts were excluded from the search results. Detailed strategies for all searches can be found in **Appendix 1**.

The original search was completed on February 26. The supplemental search was completed on May 13, 2016. Regular alerts were established to update the searches until the publication of the final report. Regular search

updates were performed on databases that do not provide alert services. Studies identified in the alerts and that met the selection criteria of the review were incorporated into the analysis if they were identified prior to the completion of the stakeholder feedback. Any studies that were identified from the external peer-reviewer phase until the publication of the report were described briefly in the discussion, with a focus on comparing the results of these new studies to the results of the analysis conducted for this report.

Grey literature (literature that is not commercially published) was identified by searching the *Grey Matters* checklist[42] (https://www.cadth.ca/grey-matters), which includes the websites of HTA agencies, clinical guideline repositories, SR repositories, economics-related resources, patient-related groups, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry. For the supplemental search, an additional search of clinical trial registries was undertaken to retrieve study data from completed trials. More information on the grey literature search strategy can be found in **Appendix 1**.

Selection Criteria

Overview of Reviews

Inclusion Criteria

The inclusion criteria for the overview of reviews can be found in Table 1. For the overview, the selection criteria apply to the criteria used by the potentially relevant SRs, MAs, and HTAs in identifying primary studies to include. In addition to the list of outcomes pre-specified in the protocol,[40] success or cure rate was identified during the review process as a relevant outcome. An amendment was made to the protocol[40] to add it to the list of outcomes.

Table 1: Inclusion Criteria for the Overview of Reviews

Population	• Adults (i.e., aged ≥ 18 years[a]), diagnosed with any severity of OSA (either treatment-naive or previously treated), as measured objectively by PSG or portable monitoring (Type I to Type IV sleep monitors)[b] Subgroups: ○ With or without comorbidities, except heart failure or stroke[c] ○ OSA severity (i.e., mild, moderate, or severe, assessed by baseline AHI, ODI, or RDI) ○ EDS (i.e., mild, moderate, or severe, assessed by ESS) ○ Sex (i.e., male or female) ○ Age (e.g., < 50 years or ≥ 50 years) ○ BMI (e.g., < 30 kg/m^2 or ≥ 30 kg/m^2) ○ Adherence (e.g., < 4 hours/night or ≥ 4 hours/night for CPAP or OAs) ○ Treatment duration (e.g., ≤ 12 weeks or > 12 weeks)
Intervention	• PAP devices as follows: ○ A/Bi/CPAP • EPAP • OAs as follows: ○ MAD[d] ○ TRD • Surgical interventions as follows: ○ MMA ○ GTA • Lifestyle modifications[e] as follows: ○ Exercise program ○ Diet or weight-loss program ○ Positional therapy[f]

	• Combination therapy (i.e., combinations of two or more interventions in scope)
Comparator	• Inactive controls (e.g., pre-treatment,[g] oral placebo, sham therapy, or supportive care) • Active controls (i.e., other interventions in scope)
Outcome	**Primary outcome** • EDS (assessed by ESS)[h] **Secondary outcomes** • OSA severity (assessed by AHI,[i] ODI, or RDI) • Success or cure rate (assessed by AHI[i] and defined to depict large reductions in AHI or low post-treatment levels of AHI) • BP (e.g., daytime, morning, or 24-hour, measured in office or home) • Type 2 diabetes mellitus (i.e., incidence or markers of diabetes in diabetic populations [e.g., A1C, insulin resistance]) • CVEs (i.e., hypertension, AF, or MI) • CBEs (i.e., stroke) • Accidents (i.e., occupational or motor vehicle) • Cognitive function (e.g., memory or concentration, assessed using standardized scales) • Psychological function (i.e., depression or anxiety, assessed using standardized scales) • Health-related QoL (assessed using standardized scales) • Mortality • AEs (i.e., any types, including surgical complications, harms, and treatment withdrawal due to AEs) • Adherence (e.g., proportions of patients adhering to treatment) • Snoring (assessed using standardized scales) • Fatigue (assessed using standardized scales) • Change in facial aesthetics (for MMA only)
Study Design	• SRs, MAs, and HTAs
Time Frame	• Publications within the last 5 years (i.e., between January 2011 and March 2016)

A1C = glycated hemoglobin; AE = adverse event; AF = atrial fibrillation; AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; BMI = body mass index; BP = blood pressure; CBE = cerebrovascular event; CPAP = continuous positive airway pressure; CVE = cardiovascular event; EDS = excessive daytime sleepiness; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; GTA = genial tubercle advancement; HF = heart failure; HTA = health technology assessment; MA = meta-analysis; MAD = mandibular advancement device; MI = myocardial infarction; MMA = maxillomandibular advancement; OA = oral appliance; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; QoL = quality of life; RDI = respiratory disturbance index; SR = systematic review; TRD = tongue-retaining device.

[a] Studies that included participants aged < 18 years old would be included if ≥ 80% were adults aged ≥ 18 years.

[b] Studies that did not identify criteria for diagnosing OSA would still be included. Studies that included non-OSA would be included if ≥ 80% were diagnosed with any severity of OSA or if data for participants with OSA were presented separately.

[c] Studies of patients with HF or stroke would be excluded because central sleep apnea might occur with those conditions.

[d] Only personalized MADs, and not over-the-counter, non-personalized devices, were included. If it was unclear from the study report whether in cases where the device was personalized, the study was included.

[e] Lifestyle interventions, including clinician-directed or -prescribed programs, were considered as interventions, while advice was considered as inactive control.

[f] Positional therapy prevents patients from sleeping in the supine position (e.g., by attaching a tennis ball onto the back of patients' pyjamas).

[g] Pre-treatment refers to baseline in a pre-and-post study design, where patients serve as their own controls.

[h] EDS severity, based on ESS scores, was defined as follows: normal or mild from 0 to 9; moderate from 10 to 15; and severe from 16 to 24.

[i] OSA severity, based on AHI, was defined as follows: normal < 5; mild from 5 to < 15; moderate from 15 to < 30; and severe from and > 30.

There was no restriction regarding the therapy duration or length of follow-up. To be included, SRs and MAs had to have the term “systematic review” or “meta-analysis” in the title or elsewhere in the text; include a detailed description of comprehensive selection criteria and search methods (i.e., as described in the Assessment of Multiple Systematic Reviews [AMSTAR] checklist item #3, with at least two electronic sources having been searched, with adequate reporting of years searched, databases used, and keywords or MeSH terms used and, where feasible, the search strategy provided); assess the quality, or risk of bias, of included studies; and synthesize the findings quantitatively or qualitatively.[43] For SRs that did not conduct quality assessment of included studies, they were included only if they had relevant outcomes or subgroups that were not present in any of the other SRs included in this report. In this case, quality assessment of primary studies was conducted de novo in duplicate. To be included, HTAs had to comprise all of the aforementioned elements of SRs, with or without an economic analysis. Only the clinical portion of HTAs was used in the clinical review.

Exclusion Criteria

Studies were excluded if they did not meet the inclusion criteria outlined in Table 1 or if they were duplicate publications. Multiple publications of the same study were excluded, unless they provided additional outcomes of interest. Older SRs (based on publication year) identified in the literature search results were excluded if all the included studies were included in newer SRs included in this report. However, two or more SRs with overlapping primary studies were included if they reported different outcomes or identical outcomes but in different subgroups of interest. The degree of overlap was judged by building a matrix of included studies in the SRs and reported within the Results section of this report.

Review of Primary Studies

Inclusion Criteria

The inclusion criteria for the review of primary studies can be found in Table 2. For the review, which was designed to focus on identified gaps within the published SR, MA, and HTA literature, only certain combinations of interventions, comparators, and outcomes were of interest, as identified in Table 2. In addition to the list of outcomes pre-specified in the protocol,[40] success or cure rate was identified during the review process as a relevant outcome. An amendment was made to the protocol[40] to add it to the list of outcomes.

Table 2: Inclusion Criteria for the Review of Primary Studies

Population	• Adults (i.e., aged ≥ 18 years[a]), diagnosed with any severity of OSA (either treatment-naive or previously treated), as measured objectively by PSG or portable monitoring (Type I to Type IV sleep monitors)[b] Subgroups: ○ With or without comorbidities, except heart failure or stroke[c] ○ OSA severity (i.e., mild, moderate, or severe, assessed by baseline AHI, ODI, or RDI) ○ EDS (i.e., mild, moderate, or severe, assessed by ESS) ○ Sex (i.e., male or female) ○ Age (e.g., < 50 years or ≥ 50 years) ○ BMI (e.g., < 30 kg/m^2 or ≥ 30 kg/m^2) ○ Adherence (e.g., < 4 hours/night or ≥ 4 hours/night for CPAP or OAs) ○ Treatment duration (e.g., ≤ 12 weeks or > 12 weeks)
Intervention, Comparator, and Outcome Combinations	**Intervention and comparator combinations:** • EPAP versus active comparators, including: ○ PAP devices (i.e., APAP, BiPAP, or CPAP) ○ OAs (i.e., MAD[d] or TRD) ○ Surgery (i.e., MMA or GTA)

- Lifestyle modifications[e] (i.e., exercise, diet, or weight-loss program or positional therapy[f])
- MAD[d] versus active comparators, including:
  - Other OAs (i.e., TRD)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight-loss program or positional therapy[f])
- TRD versus inactive and active comparators, including:
  - Inactive controls (e.g., pre-treatment,[g] oral placebo, sham therapy, or supportive care)
  - PAP devices (i.e., APAP, BiPAP, or CPAP)
  - Surgery (i.e., MMA or GTA)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight-loss program or positional therapy[f])
- MMA versus active comparators, including:
  - PAP devices (i.e., APAP, BiPAP, or CPAP)
  - OAs (i.e., MAD[d] or TRD)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight-loss program or positional therapy[f])
- GTA versus inactive and active comparators, including:
  - Inactive controls (e.g., pre-treatment,[g] oral placebo, sham therapy, or supportive care)
  - PAP devices (i.e., APAP, BiPAP, or CPAP)
  - OAs (i.e., MAD[d] or TRD)
  - Other surgery (i.e., MMA)
  - Lifestyle modifications[e] (i.e., exercise, diet, or weight-loss program or positional therapy[f])
- Positional therapy versus inactive comparators, including:
  - Inactive controls (e.g., pre-treatment,[g] oral placebo, sham therapy, or supportive care)
- Combination therapy (i.e., combinations of two or more PAP devices, EPAP, OAs, surgery, or lifestyle modifications[e] interventions) versus:
  - Inactive controls (e.g., pre-treatment, oral placebo, sham therapy, or supportive care)
  - Active comparators (i.e., PAP devices, EPAP, OAs, surgery, and lifestyle modifications[e])

For the following outcomes:

Primary outcome

- EDS (assessed by ESS)[h]

Secondary outcomes

- OSA severity (assessed by AHI,[i] ODI, or RDI)
- Success or cure rate (assessed by AHI[i] and defined to depict large reductions in AHI or low post-treatment levels of AHI)
- BP (e.g., daytime, morning, or 24-hour, measured in office or home)
- Type 2 diabetes mellitus (i.e., incidence or markers of diabetes in diabetic populations [e.g., A1C, insulin resistance])
- CVEs (i.e., hypertension, AF, or MI)
- CBEs (i.e., stroke)
- Accidents (i.e., occupational or motor vehicle)

	• Cognitive function (e.g., memory or concentration, assessed using standardized scales) • Psychological function (i.e., depression or anxiety, assessed using standardized scales) • Health-related QoL (assessed using standardized scales) • Mortality • AEs (i.e., any types, including surgical complications, harms, and treatment withdrawal due to AEs) • Adherence (e.g., proportions of patients adhering to treatment) • Snoring (assessed using standardized scales) • Fatigue (assessed using standardized scales) • Change in facial aesthetics (for MMA only)
	Intervention and comparator combinations: • MMA versus inactive comparators, including: ○ Inactive controls (e.g., pre-treatment,[g] oral placebo, sham therapy, or supportive care) **For the following outcomes:** • Mortality • Change in facial aesthetics
Study Design	For intervention and comparator combinations that involve an active comparator, studies of the following designs were considered for inclusion: • RCTs • Non-randomized controlled studies (i.e., controlled clinical trials, cohort studies, case-control studies, and controlled before-and-after studies) In addition, for intervention and comparator combinations that include an inactive comparator, studies of the following design were additionally considered for inclusion: • Uncontrolled pre-and-post studies
Time Frame	• Publications within the last 10 years (i.e., between January 2006 and May 2016)[j]

A1C = glycated hemoglobin; AE = adverse event; AF = atrial fibrillation; AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; BMI = body mass index; BP = blood pressure; CBE = cerebrovascular event; CPAP = continuous positive airway pressure; CVE = cardiovascular event; EDS = excessive daytime sleepiness; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; GTA = genial tubercle advancement; HF = heart failure; MAD = mandibular advancement device; MI = myocardial infarction; MMA = maxillomandibular advancement; OA = oral appliance; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; QoL = quality of life; RCT = randomized controlled trial; RDI = respiratory disturbance index; TRD = tongue-retaining device.

[a] Studies that included participants aged < 18 years old would be included if ≥ 80% were adults aged ≥ 18 years or if data for participants aged ≥18 years were presented separately.

[b] Studies that did not identify criteria for diagnosing OSA would still be included. Studies that included non-OSA would be included if ≥ 80% were diagnosed with any severity of OSA or if data for participants with OSA were presented separately.

[c] Studies of patients with HF or stroke would be excluded because central sleep apnea might occur with those conditions.

[d] Only personalized MADs, and not over-the-counter, non-personalized devices, would be included. If it was unclear from the study report whether in cases the device was personalized, the study would be included.

[e] Lifestyle interventions, including clinician-directed or -prescribed programs, would be considered as interventions, while advice would be considered as inactive control.

[f] Positional therapy prevents patients from sleeping in the supine position (e.g., by attaching a tennis ball onto the back of patients' pyjamas).

[g] Pre-treatment refers to baseline in a pre-and-post study design, where patients serve as their own controls.

[h] EDS severity, based on ESS scores, was defined as follows: normal or mild from 0 to 9; moderate from 10 to 15; and severe from 16 to 24.

[i] OSA severity, based on AHI, was defined as follows: normal < 5; mild from 5 to < 15; moderate from 15 to < 30; and severe from and > 30.

[j] The date limit of 10 years was established in consultation with clinical experts, based on their understanding that this limit would capture studies relevant to current clinical practice.

Exclusion Criteria

Studies were excluded if they did not meet the selection criteria outlined in Table 2, if they were case series or case reports, or if they were duplicate publications. Multiple publications of the same study were excluded, unless they provided additional information on the outcomes of interest. There was no restriction regarding the therapy duration or length of follow-up. Studies were excluded if they were not published in English or French.

Screening and Selection of Studies

Two reviewers independently screened the titles and abstracts of all citations retrieved from the literature search, followed by an independent review of the full-text articles, based on the pre-determined selection criteria outlined in Table 1 for the overview of reviews or Table 2 for the review of primary studies. The two reviewers then compared their included and excluded studies from their full-text review and resolved any disagreements through discussion until consensus was reached, involving a third reviewer when necessary.

The study selection process was presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart[43] and can be found in **Appendix 2**. A list of included studies can be found in **Appendix 3**. A list of excluded studies, with reasons for exclusion after full-text review, can be found in **Appendix 4**.

Data Extraction Strategy

Standardized data extraction forms were designed a priori to document and tabulate all relevant information from included studies.

For the overview of reviews, relevant information included both descriptive data and results reported in all included SRs, such as the numbers and types of primary studies included in the SRs; sample size, age, OSA severity, and comorbidities of the study populations included in the SRs; types of interventions and controls, as well as the therapy durations and lengths of follow-up, included in the SRs; types of outcomes included in the SRs; types of subgroup analyses, meta-regression, and MAs, if conducted in the SRs; results (i.e., either narrative description or pooled effect sizes for outcomes meta-analyzed) and conclusions regarding the outcomes of interest (Table 1) and comorbidities reported in the SRs; and types of tools used and results reported regarding quality assessment, if conducted in the SRs.

For the review of primary studies, relevant information included both descriptive data and results reported in all included studies; for example, participant characteristics, types of interventions and controls, therapy duration, length of follow-up, outcomes, results, and subgroup analyses.

Data were extracted by one reviewer and checked for accuracy by a second reviewer. Disagreements were resolved through discussion until consensus was reached, involving a third reviewer when necessary.

Quality Assessment Strategy

Overview of Reviews

The Risk of Bias in Systematic Reviews (ROBIS) tool,[44] designed to assess the risk of bias in SRs of RCTs and non-randomized studies, with its 21 questions across four domains, was used as the primary instrument for evaluating the included SRs. Each question was answered as “yes,” “probably yes,” “probably no,” “no,” or “no information,” with “yes” indicating very low concerns and “no” indicating very high concerns about potential bias.

Four additional criteria (i.e., inclusion of grey literature, provision of a list of included studies and a list of excluded studies, and declaration of conflicts of interest) from the AMSTAR checklist,[45] designed to assess the quality of SRs of RCTs, were used to supplement the methodological assessment of the included SRs on items that are not included in the ROBIS tool. While the protocol[40] had listed three, and not four, additional criteria, during the review process, an additional item from the AMSTAR checklist[45] that was not included in the ROBIS tool was identified (i.e.,

provision of a list of included studies), and an amendment was made to the protocol[40] to include the fourth item. Each question was answered as “yes,” “no,” “unclear,” or “not applicable”, with “yes” indicating high quality and “no” indicating low quality.

Because some of the included SRs conducted NMAs, an amendment was made to the protocol[40] to also assess the relevance and credibility of the NMAs, using a questionnaire developed by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR),[46] with its 26 questions across six domains. Each question was answered “yes,” “no,” or “cannot answer” to evaluate the level of confidence in the results.

For the one included SR[47] that did not conduct quality assessment of included studies but was included in this report as the only report on accidents for outcomes, the Risk of Bias Assessment Tool for Nonrandomized Studies (RoBANS) tool,[48] designed to assess the risk of bias in all study designs, including pre-and-post, with its eight domains, was used to evaluate the included primary studies. Each domain was rated as “low,” “high,” or “unclear,” with “low” indicating low concerns and “high” indicating high concerns about potential risk.

A list of the questions from the ROBIS tool, AMSTAR checklist, ISPOR questionnaire, and RoBANS tool can be found in **Appendix 5**. One reviewer independently assessed the included studies, and another reviewer checked the assessments for accuracy. Disagreements were resolved through discussion, involving a third reviewer when necessary. Although the results of the methodological assessments were not used to exclude the included SRs, the conclusions and discussion of this report focused on the findings of the SRs of higher quality.

Review of Primary Studies

RCTs were assessed using the Cochrane Risk of Bias tool,[49] with its seven questions. Each question was answered “yes,” “no,” or “unclear,” with “yes” indicating low concerns and “high” indicating high concerns about potential bias. Non-randomized studies were assessed using the RoBANS tool,[48] with its eight domains. Each domain was rated “low,” “high,” or “unclear,” with “low” indicating low concerns and “high” indicating high concerns about potential risk.

A list of the questions from the Cochrane and RoBANS tools can be found in **Appendix 5**. One reviewer independently assessed the included studies, and another reviewer checked the assessments for accuracy. Disagreements were resolved through discussion, involving a third reviewer when necessary. Although the results of the methodological assessments were not used to exclude the included primary studies, the conclusions and discussion of this report focused on the findings of the primary studies of higher quality.

Data Analysis and Synthesis Strategy

Description of Study Characteristics and Findings

For the overview of reviews, a summary of SR characteristics, including the total number of SRs, as well as the number of primary studies and patients included in each SR, by population, intervention, comparator, outcomes, and study design (PICOS) elements; years of publication, and countries of development and findings was provided in the form of tables and a narrative summary. While the protocol[40] had also listed quality assessment of primary studies included in the SRs as part of this summary, an amendment was made to the protocol[40] to present it in the quality assessment section of this report, together with the quality assessment of the included SRs. In cases where more than one SR was included for a given intervention, comparator, and outcome of interest, any overlap of included studies among the included SRs was described and presented, by preparing a matrix of included studies in the SRs. A narrative synthesis of the results of included SRs was conducted.

For the review of primary studies, a summary of study characteristics, including the total number of studies by PICOS elements, years of publication, and countries of development, was provided in the form of tables and a narrative summary. The feasibility of conducting MAs of the included primary studies was explored but deemed inappropriate, because of clinical heterogeneity related to the study design and length of follow-up of the included studies. Instead, a narrative synthesis of the results of included primary studies was conducted.

The findings were grouped based on interventions and comparators, and an overview of the outcomes was synthesized narratively, highlighting any trends across studies, subgroup-specific findings, and short-term versus long-term effects. Active and direct comparisons between interventions were reported as such, and no formal testing was conducted to indirectly compare interventions that were not assessed in a head-to-head study. The three PAP devices (i.e., APAP, BiPAP, and CPAP) were considered as one group, because evidence has shown that these devices were similar in adherence and effectiveness.[5] For OAs, MADs and TRDs were considered separately. For lifestyle modifications, the interventions were considered separately, unless they had been combined in included SRs, in which case the interventions were considered in combination. No re-synthesis of the findings from primary studies was conducted. Results were presented as reported in the studies, including a summary estimate and confidence intervals, measures of heterogeneity, and numbers of studies and participants contributing to each estimate, as available. Tables were developed to present results by outcome and to accompany the narrative summary, to ensure consistency of presented information across all included studies and to facilitate comparisons by the reader. For each outcome of interest, analysis was conducted for the overall study population and also for each subgroup listed in Tables 1 and 2.

Description of Quality Assessments

For the overview of reviews, a narrative summary of the quality assessment of primary studies included in the SRs was provided. Specifically, a table was developed to summarize the descriptions and overall ratings presented in each included SR, accompanied by a narrative summary of the quality assessment of each included SR. Specifically, a table was developed to present the answers to the questions of the ROBIS tool, using colour codes, where green and light green indicated “yes” and “probably yes,” respectively; red and light red indicated “no” and “probably no,” respectively; and yellow indicated “no information” for each question. The table also presented the answers to the select questions of the AMSTAR checklist, with colour codes, where green, red, and yellow indicated “yes,” “no,” and “unclear,” respectively, for each question. The answers to the questions of the ISPOR questionnaire were not colour coded, as “yes” and “no” did not always correspond to high and low confidence, respectively. Instead, a table was developed to summarize the assessments.

For the review of primary studies, a narrative summary of the results of the risk of bias assessment for each included study was provided. Specifically, a table was developed to present the answers to the questions of the Cochrane Risk of Bias tool, using colour codes, where green, red, and yellow indicated “yes,” “no,” and “unclear,” respectively, for each question. Another table was developed to present the answers to the questions of the RoBANS tool, using colour codes, where green, red, and yellow indicated “low,” “high,” and “unclear” risk, respectively, for each domain.

A narrative description of the strengths and limitations of the included studies was also presented in the main text of the report to provide the reader with a holistic, qualitative overview of the literature.

Results

Quantity of Research Available

The literature search for the overview of reviews yielded 1,087 citations. Upon screening titles and abstracts, 125 potentially relevant articles were retrieved for full-text review. Twenty-three reports were retrieved from other sources (i.e., grey literature, handsearch, and search alerts). Of the 148 potentially relevant articles, 33 SRs[5,10,19,24,47,50-77] were included in the overview.

The literature search for the review of primary studies yielded 2,207 citations. Upon screening titles and abstracts, 109 potentially relevant articles were retrieved for full-text review. Six reports were retrieved from other sources (i.e., grey literature, handsearch, and search alerts). Of the 115 potentially relevant articles, 41 primary studies[78-118] were included in the review.

The study selection process is outlined in a PRISMA flowchart (**Appendix 2**). The lists of included and excluded studies are provided in **Appendix 3** and **Appendix 4**, respectively.

Study Characteristics

Overview of Reviews

The characteristics of the included SRs, with respect to the review methods used; numbers, types, and publication years of primary studies included; populations, interventions, comparators, and outcomes studied, and subgroup or meta-regression analyses conducted are summarized in **Appendix 6**.

Study Dates, Locations, Funding, and Design

The 33 included SRs were published between 2011 and 2016. Twelve SRs were published in 2016,[24,50-60] 11 in 2015,[61-71] five in 2014,[10,72-75] three in 2013,[19,76,77] and two in 2011.[5,47]

Based on the location of the corresponding authors, 11 SRs were conducted in China,[52,53,57,64-66,69-72,77] seven in the US,[5,24,50,55,60,67,68] four in the United Kingdom (UK),[19,59,61,76] two in Canada,[54,75] two in Italy,[10,51] two in Switzerland,[62,63] one in Australia,[73] one in Greece,[47] one in Japan,[74] one in South Korea,[56] and one in Spain.[58]

Seven SRs[51,60,61,67,70,73,77] did not report their sources of funding. Ten SRs[10,24,53-55,57,58,64,72,75] reported that they did not receive any funding. The remaining 16 SRs[5,19,47,50,52,56,59,62,63,65,66,68,69,71,74,76] reported that they received funding from non-industry sources.

All SRs, except one,[58] conducted MAs for at least one outcome of interest. Two SRs[62,63] conducted both pairwise MAs and NMAs for two outcomes of interest (i.e., EDS and blood pressure). One SR[55] conducted NMAs for two outcomes of interest (i.e., EDS and OSA severity).

The number of databases and time frames searched to identify primary studies varied across the SRs. Although one SR[47] did not perform any quality assessment of its included primary studies, it was included in the overview because its outcome (i.e., road traffic accidents) was of interest to this report and had not been included in any of the other SRs. The quality assessment of the primary studies included in that SR[47] was performed by two reviewers (KT and JK), engaging a third reviewer (KS) to resolve any disagreements.

Eighteen SRs[5,10,19,51,53,55,57,59,62,63,65,66,70,72-75,77] included RCTs only, with numbers of RCTs ranging from three[72] to 80.[55] One SR[52] included 11 cohort studies. The remaining 14 SRs[24,47,50,54,56,58,60,61,64,67-69,71,76] included both RCTs and observational studies, with numbers of included studies ranging from six[64] to 45.[60]

Populations

The total number of patients in the SRs that included RCTs only varied from 22[5] from one RCT to 7,882[55] from 80 RCTs. The total number of patients in the SR[52] that included cohort studies only was 3,112,644 from 11 studies. The total number of patients in the SRs that included both RCTs and observational studies varied from 128 from six studies[64] to 60,186 from eight studies.[56] All but six SRs[58,60,61,66,69,70] reported mean age ranges of patients across the included primary studies, with the lowest mean age at 32 years[50] and the highest at 78 years.[52,62,75] All but 10 SRs[19,24,51,55,58,61,69-71,76] reported that the patients across the included primary studies were predominantly male, with mean proportions varying from 61%[57] to 99%.[50]

All but three SRs[52,64,67] reported including primary studies on patients with mixed levels of OSA severity. One SR[72] included studies on patients with mild-to-moderate OSA, with the mean AHI ranging from 13 to 23 events/hour. Seventeen SRs[5,10,19,50,54-56,58,59,61-63,66,68,75-77] included studies on patients with mild-to-severe OSA, with the lowest mean AHI at 3.5 events/hour[50] and the highest at 90 events/hour[61]). Eleven SRs[24,47,51,53,57,65,69-71,73,74] included studies on patients with moderate-to-severe OSA, with the lowest mean AHI at 13 events/hour[24] and the highest at 88 events/hour.[24] One SR[60] included studies on patients with severe OSA, with the mean AHI at 57 events/hour. Three SRs[52,64,67] did not specify OSA severity.

All but nine SRs[24,52,55,56,69-71,74,77] included patients who were overweight or obese, as classified by the body mass index (BMI). One SR[75] included studies on normal-to-obese patients, with the mean BMI ranging from 24.7 kg/m^2 to 43 kg/m^2. Nineteen SRs[5,10,19,47,50,51,53,54,57-59,61-63,66-68,73,76] included studies on overweight-to-obese patients, with the mean BMI ranging from 25 kg/m^2 [62,67] to 55 kg/m^2.[76] Four SRs[60,64,65,72] included studies on obese patients, with the

mean BMI ranging from 30 kg/m^2 [72] to 43 kg/m^2.[64] Seven SRs[24,52,55,56,69-71,74,77] did not report BMI from their included studies. Other comorbidities reported by the SRs included hypertension[65] or resistant hypertension,[57,65] type 2 diabetes,[64] and nocturia.[70]

Comparisons, Outcomes, and Subgroups

Twelve major groups of comparisons between the interventions and comparators of interest were identified from the included SRs. Table 3 presents the breakdown of the included SRs into different types of comparisons, highlighting any gaps, where no SRs were found. Table 4 summarizes the outcomes and subgroup or meta-regression analyses reported by the SRs and presents them by comparison. Detailed information can be found in Appendix 7 and Appendix 8.

Table 3: Number of Included Systematic Reviews for Each Comparison

Interventions	Comparators											
	Inactive Control	A/Bi/CPAP	EPAP	OA (Mixed)	MAD	TRD	Surgery (Mixed)	MMA	GTA	Lifestyle (Mixed)	Weight Loss	Positional Therapy
A/Bi/CPAP	19[5,10,47,52-57,59,62-67,69,70,75] (3 NMAs[55,62,63])	-	x	3[54,74,77]	5[5,55,59,62,63] (3 NMAs[55,62,63])	x	x	x	x	NA[a]	3[19,54,55] (1 NMA[55])	2[5,72]
EPAP	1[68]	-	-	x	x	x	x	x	x	x	x	x
OA (mixed)	2[71,74]	-	-	-	x	x	x	x	x	x	x	x
MAD	8[5,51,55,58,59,62,63,75] (3 NMAs[55,62,63])	-	-	-	-	1[5b]	x	x	x	x	1[55c] (1 NMA[55])	x
TRD	x	-	-	-	-	-	x	x	x	x	x	x
Surgery (mixed)	x	-	-	-	-	-	-	x	x	x	x	x
MMA	1[60]	-	-	-	-	-	-	-	x	x	x	x
GTA	1[24]	-	-	-	-	-	-	-	-	x	x	x
Lifestyle (mixed)	x	-	-	-	-	-	-	-	-	-	x	x
Weight loss	7[5,19,50,55,61,73,76] (1 NMA[55])	-	-	-	-	-	-	-	-	-	1[55d] (1 NMA[55])	x
Positional therapy	x	-	-	-	-	-	-	-	-	-	-	-
Combination therapy	1[5e]										1[19f]	x

APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; NA = not applicable; NMA = network meta-analysis; OA = oral appliance; SR = systematic review; TRD = tongue-retaining device.
Note: Dark grey cells, marked with -, identify duplicate combinations. Light grey cells, marked with x, identify gaps, where no systematic reviews were found.
[a] Because literature on individual interventions was found, there was no need for literature on mixed interventions.
[b] This SR was from 2011 and was therefore updated by the review of primary studies.
[c] This SR was identified after the literature search for the review of primary studies to address gaps within the published SR literature had been conducted.
[d] This SR was on diet programs versus exercise programs.
[e] This SR was on TRDs plus positional therapy versus inactive controls.
[f] The SR was on CPAP plus diet programs versus diet programs.

Table 4: Summary of Outcomes and Subgroup or Meta-Regression Analyses in Included Systematic Reviews by Comparison

Comparisons (Number of Reviews [Number of NMAs])	Outcomes	Subgroup or Meta-Regression Analyses (Outcomes)
1. A/B/CPAP versus inactive controls (19 SRs [3 NMAs])	ESS, AHI, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence Missing: success rate, snoring, fatigue	• Baseline ESS (ESS, AHI, BP) • Baseline AHI (ESS, AHI, BP, psychological functions, mortality) • Baseline BP (BP) • Hypertension (BP, CVEs) • Diabetes (CVEs) • Baseline depression (psychological functions) • Age (ESS, BP, CVEs) • Sex (BP, CVEs) • Baseline BMI (BP, CVEs) • Adherence level (ESS, BP, CVEs, diabetes, psychological functions) • Study duration (ESS, AHI, BP, CVEs, stroke, psychological functions, mortality)
2. EPAP versus inactive controls (1 SR)	ESS, AHI, snoring Missing: success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, fatigue	None
3. OA versus inactive controls (10 SRs [3 NMAs])	ESS, AHI, success rate, BP, cognitive functions, psychological functions, QoL, AEs, adherence, snoring Missing: diabetes, CVEs, stroke, accidents, mortality, fatigue	• Baseline ESS (ESS, AHI) • Baseline AHI (ESS, AHI) • Study duration (ESS, AHI)
4. Surgery versus inactive controls (2 SRs)	ESS, AHI, success rate Missing: BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue, facial aesthetics	• Baseline AHI (AHI, success rate)
5. Lifestyle interventions versus inactive controls (7 SRs [1 NMA])	ESS, AHI, success rate, BP, diabetes, AEs Missing: CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, adherence, snoring, fatigue	• Baseline AHI (AHI) • Change in BMI (AHI) • Study duration (AHI)
6. CPAP versus OAs (8 SRs [3 NMAs])	ESS, AHI, success rate, BP, cognitive functions, psychological functions, QoL, AEs, adherence Missing: diabetes, CVEs, stroke, accidents, mortality, snoring, fatigue	• Baseline ESS (ESS, AHI) • Baseline AHI (ESS, AHI, success rate) • Study duration (ESS, AHI)

Table 4: Summary of Outcomes and Subgroup or Meta-Regression Analyses in Included Systematic Reviews by Comparison

Comparisons (Number of Reviews [Number of NMAs])	Outcomes	Subgroup or Meta-Regression Analyses (Outcomes)
7. CPAP versus lifestyle interventions (5 SRs [1 NMA])	ESS, AHI, cognitive functions, psychological functions, QoL Missing: success rate, BP, diabetes, CVEs, stroke, accidents, mortality, AEs, adherence, snoring, fatigue	None
8. MADs versus TRDs (1 SR)	AHI Missing: ESS, success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
9. MADs versus lifestyle interventions (1 SR [1 NMA])	ESS, AHI Missing: success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
10. Diet versus exercise (1 SR [1 NMA])	ESS, AHI Missing: success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
11. TRDs plus positional therapy versus inactive controls (1 SR)	AHI Missing: ESS, success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
12. CPAP plus diet versus diet (1 SR)	ESS, QoL Missing: AHI, success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, mortality, AEs, adherence, snoring, fatigue	None

AE = adverse event; AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; CVE = cardiovascular event; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; MAD = mandibular advancement device; NMA = network meta-analysis; OA = oral appliance; QoL = quality of life; SR = systematic review; TRD = tongue-retaining device.

1) Positive airway pressure devices versus inactive controls

Nineteen SRs[5,10,47,52-57,59,62-67,69,70,75] included studies that compared PAP devices with inactive controls. All 19 SRs included CPAP as the intervention, and no other PAP devices, except for one SR,[5] which also included APAP in its reporting of adverse events. Control groups varied across the SRs from pre-treatment to no treatment, sham devices, placebo, usual care, or conservative therapy (e.g., advice on sleep hygiene or weight loss). All but three SRs[52,64,67] reported that patients had mild-to-severe[5,10,54-56,59,62,63,66,75] or moderate-to-severe[47,53,57,65,69,70] OSA. Patients' comorbidities were poorly reported, although most patients were overweight to obese, as classified by BMI. Two SRs[57,65] included studies of patients with hypertension or resistant hypertension, one SR[64] included studies of patients with diabetes, and one SR[70] included studies of patients with nocturia. Study duration of the included primary studies, reported by all but two SRs,[67,69] ranged from one week[5,62,63,66,75] to 132 months.[56] Loss to follow-up in the included primary studies, reported by two SRs,[5,53] ranged from 0%[5] to 47%.[5] Detailed information can be found in **Appendix 6** and **Appendix 7**.

Outcomes reported by the SRs included ESS,[5,53-55,59,62,70] AHI/ODI/RDI,[5,54,55,59,70] blood pressure,[5,10,53,57,63,65] diabetic outcomes,[5,64] CVEs,[53,56,67,69] stroke,[53,56] road traffic accidents,[47] cognitive functions,[5,66] psychological functions,[54,75] QoL,[5,54] mortality,[52,53,56,69] adverse events,[5] and adherence.[5] Detailed information can be found in Table 4.

For ESS, one SR[59] conducted subgroup analyses on baseline AHI, baseline ESS, and study duration, and one SR[62] conducted meta-regression analyses on baseline AHI, baseline ESS, age, adherence level, and study duration. For AHI, one SR[59] conducted subgroup analyses on baseline AHI, baseline ESS, and study duration. For blood pressure, four SRs[10,57,63,65] conducted subgroup or meta-regression analyses on baseline AHI,[10,57,63,65] baseline ESS,[10,57,65] baseline blood pressure,[57,63,65] hypertension,[10,65] age,[10,65] sex,[65] baseline BMI,[57,65] adherence level,[10,57,63,65] and study duration.[10,57,63,65] For diabetic outcomes, one SR[64] conducted subgroup analyses on adherence levels. For CVEs, one SR[56] conducted subgroup analyses on adherence level, one SR[53] conducted subgroup analyses on study duration, and one SR[67] conducted meta-regression analyses on hypertension, diabetes, age, sex, and baseline BMI. For stroke, one SR[53] conducted subgroup analyses on study duration. For psychological function, one SR[75] conducted subgroup or meta-regression analyses on baseline AHI, depression, adherence level, and study duration. For mortality, one SR[69] conducted subgroup analyses on baseline AHI, and one SR[53] conducted subgroup analyses on study duration. No subgroup or meta-regression analyses were conducted for road traffic accidents, cognitive functions, QoL, adverse events, or adherence. Detailed information can be found in Appendix 8.

2) Expiratory positive airway pressure versus inactive controls

One SR[68] included studies that compared outcomes before and after EPAP. A total of 920 patients had mild-to-severe OSA and were overweight to obese. Study duration of the included primary studies ranged from one night to 12 months. Loss to follow-up in the included primary studies was not reported. Outcomes reported included ESS, AHI, and snoring. No subgroup or meta-regression analyses were conducted for any outcome. Detailed information can be found in Table 4, **Appendix 6**, **Appendix 7**, and **Appendix 8**.

3) Oral appliances versus inactive controls

Ten SRs[5,51,55,58,59,62,63,71,74,75] included studies that compared OAs with inactive controls. Control groups varied across the SRs from pre-treatment to no treatment, sham devices, placebo, or usual care. Patients had mild-to-severe[55,58,59,62,63] or moderate-to-severe[5,51,71,74,75] OSA. Patients' comorbidities were poorly reported, although most patients were overweight to obese, as classified by BMI. Study duration of the included primary studies, reported by all but one SR,[55] ranged from one week[5,62,63,71,75] to 84 months.[58] Loss to follow-up in the included primary studies, reported by three SRs,[5,58,74] ranged from 0%[5] to 29%.[5] Detailed information can be found in **Appendix 6** and **Appendix 7**.

Outcomes reported by the SRs included ESS,[5,55,58,59,62,71,74] AHI/ODI,[5,55,58,59,71,74] success rate,[51] blood pressure,[5,63] cognitive functions,[5] psychological functions,[75] QoL,[5,74] adverse events,[5,58] adherence,[75] and snoring.[58] Detailed information can be found in Table 4.

For ESS and AHI, two SRs[59,71] conducted subgroup analyses on baseline ESS,[59] baseline AHI,[59,71] and study duration.[59] No subgroup or meta-regression analyses were conducted for any other outcome. Detailed information can be found in **Appendix 8**.

4) Surgery versus inactive controls

Two SRs[24,60] included studies that compared outcomes before and after genioplasty (GP) or GTA[24] or MMA with (i.e., 33.6%) or without (i.e., 66.4%) GTA.[60] One SR[24] included patients who had moderate-to-severe OSA.[24] The other SR[60] included patients with severe OSA, as measured by mean AHI, who were obese, as measured by mean BMI. Study duration of the included primary studies, reported by one SR,[60] ranged from two months to six months. Loss to follow-up in the included primary studies was not reported. Outcomes reported included ESS,[24,60] AHI,[24,60] RDI,[60] and success and cure rates.[60] For AHI and success and cure rates, one SR[60] conducted subgroup analyses on baseline AHI. No subgroup or meta-regression analyses were conducted for any other outcome. Detailed information can be found in Table 4, **Appendix 6**, **Appendix 7**, and **Appendix 8**.

5) Lifestyle interventions versus inactive controls

Seven SRs[5,19,50,55,61,73,76] included studies that compared lifestyle interventions with inactive controls. Lifestyle interventions included exercise or diet programs. Control groups varied across the SRs from pre-treatment to no treatment, general counselling, placebo, usual diet, or usual care. Patients had mild-to-severe[5,19,50,55,73,76] or moderate-to-severe[61] OSA. Six SRs[5,19,50,61,73,76] reported that patients were overweight to obese, while one SR[55] did not report on comorbidities. Study duration of the included primary studies, reported by all but one SR,[55] ranged from four weeks[76] to 94 months.[61] Loss to follow-up in the included primary studies, reported by one SR,[5] ranged from 3% to 17%. Detailed information can be found in **Appendix 6** and **Appendix 7**.

Outcomes reported by the SRs included ESS,[5,19,50,55,73,76] AHI/ODI[5,19,50,50,55,61,73,76] treatment response,[5] blood pressure,[5] diabetes,[5] and adverse events.[5] Detailed information can be found in Table 4.

For AHI, one SR[76] conducted subgroup or meta-regression analyses on baseline AHI, change in BMI, and study duration. No subgroup or meta-regression analysis was conducted for any other outcome. Detailed information can be found in **Appendix 8**.

6) Continuous positive airway pressure versus oral appliances

Eight SRs[5,54,55,59,62,63,74,77] included studies that compared CPAP with MADs[5,55,59,62,63] or undefined OAs.[54,74,77] Patients had mild-to-severe,[55,62,63,77] moderate,[54] or moderate-to-severe[5,59,74] OSA. Five SRs[5,54,59,62,63] reported that patients were overweight to obese, while three SRs[55,74,77] did not report on comorbidities. Study duration of the included primary studies, reported by all but one SR,[55] ranged from one week[62,63] to 157 weeks.[62,63] Loss to follow-up in the included primary studies, reported by two SRs,[5,74] ranged from 0%[5] to 24%.[5] Detailed information can be found in **Appendix 6** and **Appendix 7**.

Outcomes reported by the SRs included ESS,[5,54,55,59,62,74,77] AHI/ODI,[5,54,55,59,74,77] treatment response,[5] blood pressure,[63,77] cognitive functions,[5,77] psychological functions,[54,77] QoL,[5,54,74,77] adverse events,[77] and adherence.[5,77] Detailed information can be found in Table 4.

For ESS and AHI, one SR[59] conducted subgroup analyses on baseline AHI, baseline ESS, and study duration. For treatment response, one SR[5] conducted subgroup analyses on baseline AHI. No subgroup or meta-regression analyses were conducted for any other outcome. Detailed information can be found in **Appendix 8**.

7) Continuous positive airway pressure versus lifestyle interventions

Five SRs[5,19,54,55,72] included studies that compared CPAP with lifestyle interventions. Lifestyle interventions included diet programs,[19,55] exercise programs,[54,55] and positional therapy.[5,72] Patients had mild-to-moderate,[72] mild-to-severe,[55] moderate,[5,54] or moderate-to-severe[19] OSA. Four SRs[5,19,54,72] reported that patients were overweight,[54] overweight to obese,[19] or obese,[5,72] while one SR[55] did not report on comorbidities. Study duration of the included primary studies, reported by all but one SR,[55] ranged from three nights[72] to 24 months.[19] Loss to follow-up in the

included primary studies, reported by one SR,[5] ranged from 0% to 7%. Detailed information can be found in **Appendix 6** and **Appendix 7**.

Outcomes reported by SRs included ESS,[5,19,54,55] AHI/ODI,[5,54,55,72] cognitive functions,[5] psychological functions,[54] and QoL.[5,19,54] No subgroup or meta-regression analyses were conducted for any outcome. Detailed information can be found in Table 4 and **Appendix 8**.

8) Mandibular advancement devices versus tongue-retaining devices

One SR[5] included one crossover RCT that compared MADs with TRDs. A total of 22 patients had moderate OSA and were overweight. Study duration of the included primary study was one week for each intervention. Loss to follow-up in the included primary study was 19%. Outcomes reported included AHI. No subgroup or meta-regression analyses were conducted for that outcome. Detailed information can be found in Table 4, **Appendix 6**, **Appendix 7**, and **Appendix 8**.

9) Mandibular advancement devices versus lifestyle interventions

One SR[55] included studies that compared MADs with lifestyle interventions. Lifestyle interventions included diet or exercise programs. A total of 7,882 patients had mild-to-severe OSA. Patients' comorbidities, study duration, or loss to follow-up were not reported. Outcomes reported included ESS and AHI. No subgroup or meta-regression analyses were conducted for any outcome. Detailed information can be found in Table 4, **Appendix 6**, **Appendix 7**, and **Appendix 8**.

10) Diet versus exercise

One SR[55] included studies that compared diet with exercise programs. A total of 7,882 patients had mild-to-severe OSA. Patients' comorbidities, study duration, or loss to follow-up were not reported. Outcomes reported included ESS and AHI. No subgroup or meta-regression analyses were conducted for any outcome. Detailed information can be found in Table 4, **Appendix 6**, **Appendix 7**, and **Appendix 8**.

11) Tongue-retaining devices plus positional therapy versus inactive controls

One SR[5] included one RCT that compared TRD plus posture alarm with no treatment. Patients had mild-to-severe OSA. Patients' comorbidities, study duration, or loss to follow-up were not reported. Outcomes reported included AHI. No subgroup or meta-regression was done for that outcome. Detailed information can be found in Table 4, **Appendix 6**, **Appendix 7**, and **Appendix 8**.

12) Continuous positive airway pressure plus diet versus diet

One SR[19] included studies that compared CPAP plus diet programs with diet programs alone. Patients had moderate-to-severe OSA who were overweight to obese. Study duration of the included primary studies ranged from three months to six months. Loss to follow-up in the included primary studies was not reported. Outcomes reported included ESS and quality of life. No subgroup or meta-regression was done for any outcome. Detailed information can be found in Table 4, **Appendix 6**, **Appendix 7**, and **Appendix 8**.

Review of Primary Studies

The characteristics of the included primary studies, regarding the study designs used; populations, interventions, comparators, and outcomes studied; and subgroup analyses conducted are summarized in **Appendix 9**.

Study Dates, Locations, Funding, and Design

The 41 included primary studies were published between 2006 and 2016. Four studies were published in 2016,[78-81] 11 in 2015,[82-92] five in 2014,[93-97] two in 2013,[98,99] five in 2012,[100-104] five in 2011,[105-109] two in 2010,[110,111] two in 2009,[112,113] two in 2008,[114,115] two in 2007,[116,117] and one in 2006.[118]

In line with the location of the corresponding authors, six studies were conducted in the US,[79,80,93,96,106,111] six in Netherlands,[78,86,88,97,99,104] four in Australia,[90,105,109,112] four in Sweden,[83,84,107,116] three in France,[94,98,113] three in the

UK,[89,92,95] two in Brazil,[100,117] two in Canada,[101,115] two in Italy,[81,114] two in Turkey,[82,91] one in Belgium,[87] one in China,[103] one in Israel,[118] one in Japan,[110] one in South Korea,[108] one in Switzerland,[102] and one in Taiwan.[85]

Thirteen primary studies[79,81,87,89,91,94,95,98,109,111,114,117,118] did not report their sources of funding. Five primary studies[78,82,99,103,104] reported that they did not receive any funding. The remaining 23 primary studies[80,83-86,88,90,92,93,96,97,100-102,105-108,110,112,113,115,116] reported that they received funding from non-industry sources.

Six studies were RCTs,[87,88,90,93,100,115] one of which[115] was a crossover study. Five studies[80,86,94,107,109] were cohort studies. Thirty studies[78,79,81-85,89,91,92,95-99,101-106,108,110-114,116-118] were pre-and-post studies.

Populations

The total number of patients in the primary studies varied from 10[110,117] to 198.[94] All but six studies[79,92,97,100,107,117] reported mean ages of patients, with the lowest mean age at 22 years[80] to the highest at 65 years.[81] All but five studies[79,80,92,101,107] reported that the patients included were predominantly male, with mean proportions varying from 55%[111] to 100%.[98,100,110,114]

All but four studies[79,80,89,92] reported including patients at mixed levels of OSA severity, with the lowest mean baseline AHI at 11 events/hour[88] and the highest at 64 events/hour.[111] Fourteen studies[78,81,85,86,88,90,96,97,99,102,104,108,116,118] included positional OSA patients only. All but five studies[79,80,92,114,116] reported including patients at mixed levels of obesity, with the lowest mean BMI at 24.8 kg/m^2 [85] and the highest at 41.7 kg/m^2.[111]

Comparisons, Outcomes, and Subgroups

Eleven major groups of comparisons between the interventions and comparators of interest were identified from the included primary studies. Table 5 presents the breakdown of the included primary studies into different types of comparisons, highlighting any gaps, where no SRs or primary studies were found. Table 6 summarizes the outcomes and subgroup analyses reported by the primary studies and presents them by comparison.

Table 5: Number of Included Primary Studies for Each Comparison

Interventions	Comparators											
	Inactive Control	A/Bi/CPAP	EPAP	OA (Mixed)	MAD	TRD	Surgery (Mixed)	MMA	GTA	Lifestyle (Mixed)	Weight Loss	Positional Therapy
A/Bi/CPAP	+	-	x	+	+	x	x	x	x	NA[a]	+	+
EPAP	+	-	-	x	x	x	x	x	x	x	x	x
OA (mixed)	+	-	-	-	x	x	x	x	x	x	x	x
MAD	+	-	-	-	-	1[109]	x	1[94]	x	x	+	x
TRD	3[92,113,115]	-	-	-	-	-	x	x	x	x	x	x
Surgery (mixed)	NA[a]	-	-	-	-	-	-	x	x	x	x	x
MMA	3[89,98,103b]	-	-	-	-	-	-	-	x	x	x	x
GTA	+[c]2[91,117]	-	-	-	-	-	-	-	-	x	x	x
Lifestyle (mixed)	NA[a]	-	-	-	-	-	-	-	-	-	x	x
Weight loss	+	-	-	-	-	-	-	-	-	-	+	x
Positional therapy	20[78,79,81-86,88,90,96,97,99,102,104,105,108,112,116,118]	-	-	-	-	-	-	-	-	-	-	-
Combination therapy	6[80,95,101,110,111,114d]	4[93,100,106,107e]	x	x	2[87,106f]	x	x	x	x	x	1[93g]	1[87h]

APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; NA = not applicable; OA = oral appliance; TRD = tongue-retaining device.

Note: Dark grey cells, marked with -, identify duplicate combinations. Cells, marked with + identify the presence of systematic reviews. Light grey cells, marked with x, identify gaps, where no systematic reviews or primary studies were found.

[a] Because literature on individual interventions was found, there was no need for literature on mixed interventions.

[b] These primary studies were on facial aesthetics.

[c] While GTA versus inactive controls had been identified as an area of gap, a systematic review on the comparison[24] was identified from a search alert. Both of the primary studies[91,117] had been included in the systematic review,[24] which was acknowledged in the presentation of the results.

[d] Two primary studies were on CPAP plus weight loss, one was on MADs plus TRDs, and three were on MMA plus GTA, all of the pre-versus-post design.

[e] One primary study was on CPAP plus MADs, one was on CPAP plus exercise, one was on CPAP versus diet, and one was on CPAP plus weight loss, all versus CPAP.

[f] One primary study was on CPAP plus MADs, and one was on MADs plus positional therapy, both versus MADs.

[g] One primary study was on CPAP plus weight loss versus weight loss.

[h] One primary study was on MADs plus positional therapy versus positional therapy.

Table 6: Summary of Outcomes and Subgroup Analyses in Included Primary Studies by Comparison

Comparisons (Number of Studies)	Outcomes	Subgroup Analyses (Outcomes)
1. TRDs versus inactive controls (n = 3)	ESS, AHI, adherence Missing: success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
2. MMA versus inactive controls (n = 3)	Facial aesthetics Missing: mortality	None
3. GTA versus inactive controls (n = 2)	ESS, AHI Missing: success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
4. Positional therapy versus inactive controls (n = 20)	ESS, AHI, success rate, BP, QoL, adherence, snoring Missing: diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, mortality, AEs, fatigue	• Baseline AHI (i.e., mild, moderate, or severe) • Baseline weight (AHI, adherence, snoring) • Positional OSA (AHI) • Sleep position (AHI)
5. Combination therapy versus inactive controls (n = 6)	ESS, AHI, mortality, AEs Missing: success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, AEs, adherence, snoring, fatigue	None
6. MADs versus TRDs (n = 1)	AHI Missing: ESS, success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
7. MADs versus MMA (n = 1)	AHI Missing: ESS, success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
8. Combination therapy versus CPAP (n = 4)	ESS, AHI, BP, adherence Missing: success rate, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, snoring, fatigue	None
9.Combination therapy versus MADs (n = 2)	ESS, AHI Missing: success rate, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None

Table 6: Summary of Outcomes and Subgroup Analyses in Included Primary Studies by Comparison

Comparisons (Number of Studies)	Outcomes	Subgroup Analyses (Outcomes)
10. Combination therapy versus weight loss (n=1)	BP Missing: ESS, AHI, success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	None
11. Combination therapy versus positional therapy (n=1)	AHI Missing: ESS, success rate, BP, diabetes, CVEs, stroke, accidents, cognitive functions, psychological functions, QoL, mortality, AEs, adherence, snoring, fatigue	• Sleep position (AHI)

AE = adverse event; AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; CVE = cardiovascular event; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; MAD = mandibular advancement device; OA = oral appliance; QoL = quality of life; TRD = tongue-retaining device.

1) Tongue-retaining devices versus inactive controls

Three pre-and-post studies[92,113,115] compared TRDs with pre-treatment. On average, patients had moderate[115] or severe[113] OSA and were overweight,[113,115] as classified by BMI. One study did not report any patient characteristics.[92] Study duration, reported by one study,[92] was four months. Loss to follow-up, reported by all three studies, ranged from 10%[92] to 25%.[113] Outcomes reported included ESS,[92,113,115] AHI/RDI,[113,115] and adherence.[92,113] No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

2) Maxillomandibular advancement versus inactive controls

Three pre-and-post studies[89,98,103] compared MMA with pre-treatment. On average, patients had severe OSA[98,103] and were overweight,[89,98,103] as classified by BMI. One study did not report OSA severity.[89] Study duration, reported by one study,[103] was six months. Loss to follow-up was not reported. Outcomes reported included facial aesthetics. No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

3) Genial tubercle advancement versus inactive controls

Two pre-and-post studies[91,117] compared GTA with pre-treatment. Patients had mild-to-severe[117] or, on average, severe[91] OSA and were obese,[91,117] as classified by BMI. Study duration and loss to follow-up were not reported. Outcomes reported included ESS[91] and AHI.[91,117] No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

While GTA versus inactive controls had been identified as an area of gap, an SR on the comparison[24] was identified from a search alert. Both of the primary studies[91,117] had been included in the SR,[24] which was acknowledged in the presentation of the results.

4) Positional therapy versus inactive controls

Two RCTs,[88,90] one cohort study,[86] and 17 pre-and-post studies[78,79,81-85,96,97,99,102,104,105,108,112,116,118] compared positional therapy with inactive controls. Interventions varied across the studies from mattresses or pillows[82-85] to sleep position trainers,[78,90,97,99,116] tennis balls,[88,102,112,118] neck-positioning devices,[79,81,96] waistbands,[86] vests,[108] vibration devices,[104] or supine avoidance devices.[78,81,105] Control groups varied across the studies from pre-treatment[78,79,81-86,88,96,97,99,102,104,105,108,112,116,118] to supportive care.[90] While two studies[86,88] had control groups in their RCT[88] or cohort study design,[86] they compared different types of positional therapy,[86,88] which was out of scope for this report. Instead, the pre-and-post data were extracted from the two studies.[86,88]

Patients had mild,[85,86,88,97] moderate,[81-83,90,96,99,102,104,105,108,116,118] or severe[84,112] OSA, as classified by mean AHI; one study[78] included patients with moderate AHI, as classified by median AHI. Patients were overweight,[78,81,82,84,86,88,96,97,99,102,104,105,108,112,118] normal weight,[85] or obese,[90] as classified by mean BMI. One study[79] did not report patient characteristics. Two studies[83,116] did not report BMI. Study duration, reported by all but four studies,[86,88,108,112] ranged from two nights[82,84] to 30 months.[105] Loss to follow-up, reported by all but three studies,[79,82,85] ranged from 0%[82,85,104,108,118] to 38%.[112]

Outcomes reported included ESS,[78,82,83,86,88,90,96,97,99,102,116] AHI/ODI/RDI,[78,81-86,88,90,96,96,99,102,104,105,108,116,118] success rates,[78] blood pressure,[90] QoL,[78] adherence[78,79,83,85,86,88,96,97,99,102,112,118] and snoring.[79,85,105] For AHI/ODI, 11 studies[78,84-86,88,96,99,102,104,108,118] conducted subgroup analyses on baseline AHI,[96] baseline weight,[85] positional OSA,[84] and sleep position.[78,86,88,96,99,102,104,108,118] For adherence and snoring, one study[85] conducted subgroup analyses on baseline weight. Detailed information can be found in Table 6 and **Appendix 9**.

5) Combination therapy versus inactive controls

Six pre-and-post studies[80,95,101,110,111,114] compared combination therapy with pre-treatment. Interventions varied across the studies from CPAP plus weight-loss programs,[110,111] MADs plus TRDs,[101] or MMA plus GTA.[80,95,114] On average, patients had severe OSA[95,101,110,111,114] and were overweight[80,95] or obese,[101,110,111] as classified by BMI. One study[80] did not report OSA severity. One study[114] did not report BMI. Study duration, reported by three studies,[101,110,111] ranged from 12 weeks[111] to four months.[110] Loss to follow-up, reported by all but one study,[95] ranged from 0%[80,110,111,114] to 6.8%.[101] Outcomes reported included ESS[95,101,110,111] AHI,[95,101,114] mortality,[80] and adverse events.[80] No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

6) Mandibular advancement devices versus tongue-retaining devices

One cohort study[109] compared MADs with TRDs. On average, patients had moderate OSA and were overweight, as classified by BMI. No patient was lost to follow-up. Study duration was not reported. Outcomes reported included AHI. No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

7) Mandibular advancement devices versus maxillomandibular advancement

One cohort study[94] compared MADs with MMA. Patients had moderate-to-severe OSA. Of the patients in the MADs and MMA groups, 17.4% and 16.2%, respectively, were obese, as classified by BMI. Study duration and loss to follow-up were not reported. Outcomes reported included AHI. No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

8) Combination therapy versus continuous positive airway pressure

Two RCTs,[93,100] one cohort study,[107] and one three-intervention pre-and-post study[106] compared combination therapy with CPAP. Interventions varied across the studies from CPAP plus MADs[106] to CPAP plus diet,[107] exercise,[100] or weight loss[93] programs. Control groups across the studies were CPAP. On average, patients had moderate[106] or severe[93,100,107] OSA and were overweight[100,106] or obese,[93,107] as classified by BMI. Study durations, reported by all studies, ranged from eight weeks[106] to one year.[107] Loss to follow-up, reported by all but one study,[107] ranged from 7.1%[106] to 31.9%.[100] Outcomes reported included ESS,[100,106,107] AHI,[100,106,107] and blood pressure.[93] No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

9) Combination therapy versus mandibular advancement devices

One RCT[87] and one three-intervention pre-and-post study[106] compared combination therapy with MADs. Interventions varied across the studies from CPAP plus MADs[106] to MADs plus positional therapy (i.e., sleep position trainers).[87] Control groups across the studies were MADs. On average, patients had moderate OSA and were overweight,[87,106] as classified by BMI. Study duration, reported by one study,[106] was eight weeks. Loss to follow-up, reported by both studies, ranged from 0%[87] to 7.5%.[106] Outcomes reported included ESS[106] and AHI/ODI.[87,106] No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

10) Combination therapy versus weight-loss programs

One RCT[93] compared CPAP plus weight-loss programs with weight-loss programs alone. On average, patients had severe OSA and were obese, as classified by BMI. Study duration was 24 weeks, and loss to follow-up was 19.3%. Outcomes reported included blood pressure. No subgroup analyses were conducted. Detailed information can be found in Table 6 and **Appendix 9**.

11) Combination therapy versus positional therapy

One RCT[87] compared MADs plus positional therapy (i.e., sleep position trainers) with positional therapy alone. On average, patients had moderate OSA and were overweight, as classified by BMI. No patient was lost to follow-up. Study duration was not reported. Outcomes reported included AHI/ODI. For AHI, the study conducted subgroup analyses on sleep position. Detailed information can be found in Table 6 and **Appendix 9**.

Quality Assessment

Overview of Reviews

All of the SRs included in this report, with the exception of one SR,[47] assessed the quality of, or risk of bias (RoB) in, their included studies. Seven SRs[10,19,50,57,65,66,119] used the Jadad scale. Fourteen SRs[51,54-56,62-64,71-77] used the Cochrane RoB tool, whereas two SRs[53,70] used select criteria from the Cochrane tool. Other SRs used the Agency for Healthcare Research and Quality (AHRQ) methods guide,[5] the Cochrane Effective Practice and Organisation of Care (EPOC) RoB tool,[76] the *Cochrane Handbook for Systematic Reviews of Interventions*,[67] the CONSORT criteria,[58] the Downs and Black checklist,[69] the Effective Public Health Practice Project's (EPHPP's) quality assessment tool,[51] the Newcastle–Ottawa scale[52] or a modified version of it,[61] the National Institute for Health and Care Excellence (NICE) quality assessment tool,[24,68] RoBANS,[56] a quality control questionnaire,[60] and undefined quality criteria.[72] Five SRs also used Grading of Recommendations Assessment, Development and Evaluation (GRADE).[10,51,54,71,74] For the SR[47] with no quality assessment, two reviewers of this report performed quality assessment using RoBANS.

The quality assessment of the included studies conducted by the SRs, as well as descriptions of the different quality assessment tools used, are summarized in **Appendix 10**. The overall quality of the studies included in each of the SRs was rated as very low to low in one SR,[54] low in six SRs,[5,24,47,64,71,77] low to moderate in three SRs,[5,10,74] moderate in seven SRs,[5,59,60,62,67,70,72] moderate to high in three SRs,[51,52,58] high in 10 SRs,[53,55-57,63,65,66,68,69,73] or mixed in seven SRs.[5,19,50,56,61,75,76] Two of the SRs provided multiple ratings, separately for RCTs versus non-RCTs[56] or for each intervention-comparator combination.[5]

The quality assessment of the 33 SRs, conducted with the ROBIS tool and four additional criteria from AMSTAR, is summarized in **Appendix 11**. Across the SRs, substantial concerns regarding specifications of study eligibility criteria (i.e., Domain 1) were identified, with the rating of moderate or high concerns in 18 SRs, of low concerns in 14 SRs, and of unclear concerns in one SR, where concerns were unclear if relevant information had not been reported. Concerns regarding methods used to identify or select studies (i.e., Domain 2), methods used to collect data and appraise studies (Domain 3), or the synthesis of findings (i.e., Domain 4) were generally low, with the rating (presented for Domains 2, 3, and 4, respectively) of low concerns in 24, 25, and 24 SRs, of moderate concerns in nine, six, and seven SRs, of high concerns in no, two, and two SRs. On a per-SR basis, nine SRs[51,54,62,63,67,68,71,75,76] were rated as having low concerns across the four domains, and 12 SRs[5,10,19,47,50,53,55-57,59,64,74] as having low concerns across three domains. Three SRs[24,60,65,66] were rated as having low-to-moderate concerns across the four domains, and one SR[58] as having moderate-to-high concerns across the four domains. All other SRs[52,61,69,70,72,73,77] were rated as having mixed levels of concerns across the four domains. Except for one SR,[70] with high concerns in two domains, none of the SRs were rated as having high concerns in more than one domain. Of the 33 SRs, one SR included grey literature as an inclusion criterion, and two SRs provided a list of excluded studies. All 33 SRs provided a list of included studies, and 32 SRs disclosed conflicts of interests, noting no concerns.

The quality assessment of the three NMAs,[55,62,63] conducted with the ISPOR questionnaire, is summarized in **Appendix 12**. In terms of relevance (Domain 1), while all three NMAs had relevant populations and applicable contexts, not all relevant interventions and outcomes were included. In terms of credibility (Domain 2), all three NMAs

made attempts to identify and include all relevant RCTs, and the included RCTs formed a connected network. Further, no bias was induced by selective outcome reporting. However, while two NMAs[62,63] conducted an analysis on study quality, excluding poor-quality studies, and identified systematic differences in treatment effect modifiers, the other NMA[55] conducted no such analyses. In terms of analysis (Domain 3), all three NMAs used statistical methods to preserve within-study randomization, evaluated consistency, included both direct and indirect comparisons, and provided a valid rationale for the use of random-effects models. However, while two NMAs[62,63] handled inconsistency in the analysis and conducted meta-regression analyses to account for heterogeneity, the other NMA[55] did neither. In terms of reporting quality and transparency (Domain 4), two NMAs,[62,63] but not the other NMA,[55] provided the numbers of RCTs per comparison; reported individual study results, as well as results of both direct and indirect comparisons; and evaluated some patient characteristics on the outcomes. One NMA,[55] but not the other two NMAs,[62,63] provided rankings, albeit without uncertainty. In terms of interpretation (Domain 5) and conflict of interest (Domain 6), two NMAs[62,63] drew appropriate conclusions and declared no conflict of interest, whereas it was not clear for the other NMA[55] whether the conclusions for CPAP comparisons were appropriate and how the potential for conflict of interest regarding past funding from OSA device companies was mitigated.

Review of Primary Studies

The quality assessment of the 41 primary studies, conducted with the Cochrane Risk of Bias tool[49] on six RCTs[87,88,90,93,100,115] or the RoBANS tool[48] on 35 non-randomized controlled or pre-and-post studies,[78-86,89,91,92,94-99,101-114,116-118] is summarized in **Appendix 13** and **Appendix 14**, respectively.

For the six RCTs,[87,88,90,93,100,115] the Cochrane Risk of Bias rating was low risk for two studies[88,90] and unclear risk for four studies,[87,93,100,115] on a scale of low to high risk, where concerns were unclear if relevant information had not been reported. Across the included studies, sequence generation and allocation concealment were assessed to largely be at unclear risk. Blinding of participants and personnel was mostly not applicable, but blinding of outcome assessment was assessed to be largely low risk. Incomplete outcome and selective reporting were assessed to be largely low risk. Other potential threats to validity remained largely unclear throughout the studies.

For the 35 non-randomized controlled or pre-and-post studies,[78-86,89,91,92,94-99,101-114,116-118] the RoBANS rating was low risk for five criteria, mixed for one criterion, high risk for one criterion, and not applicable for one criterion, on a scale of low to high risk. For comparability, exposure measurement, outcome assessment, incomplete outcome data, and selective outcome reporting, 34, 23, 28, 25, and 31 of the 35 studies were rated as having low risk of bias, respectively. For selection of patients, a third of the studies were rated as having low risk of bias, another third was rated as unclear, and the last third was rated as having high risk of bias, where risk was unclear if relevant information had not been reported. For confounding, most of the studies were rated as having high risk of bias. For blinding of assessors, this domain was not applicable in all but one study,[94] where risk of bias was unclear. Twenty-eight studies[78-86,91,92,94-99,101-110,117] had low risk of bias, two studies[111,113] had moderate risk of bias, four studies[89,112,116,118] had high risk of bias, and one study[114] had unclear risk of bias.

Overall, the 41 studies were assessed to be at a low risk of bias. Further to risk of bias, it is important to note that the majority of the studies included small samples (i.e., fewer than 20 patients) and did not reach statistical significance or did not provide results of statistical tests and may not have been adequately powered. Moreover, 30 of the 41 studies were of the pre-and-post design, with no controls, making it difficult to draw definitive conclusions.

Data Analysis and Synthesis

The findings are presented below, first from the overview of reviews and then from the review of primary studies. For each outcome, a summary of results is provided at the end of each section.

Excessive Daytime Sleepiness

Information on the validity and reliability of EDS, as measured by the ESS, can be found in **Appendix 15**.

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Seven SRs,[5,53-55,59,62,70] including two NMAs,[55,62] reported on EDS in adults with mild-to-severe[5,54,55,59,62,70] or moderate-to-severe[5,53,70] OSA. Five SRs[5,53,54,59,62] included overweight-to-obese patients. One SR[70] included patients with nocturia only. One SR[55] provided no information on comorbidities.

All seven SRs,[5,53-55,59,62,70] with sample sizes ranging from 131 patients[70] to 7,882 patients[55] from two studies[70] to 80 studies,[55] reported significantly greater reductions in ESS with CPAP, compared with controls[5,53-55,59,62] or pre-treatment.[54,70] The mean difference in ESS, reported by all seven SRs, ranged from –5.88[70] to –0.61,[54] with five SRs[5,53,55,59,62] reporting mean differences around –2. Study duration of the included primary studies, reported by all seven SRs, ranged from one week[5,62] to 157 weeks.[62] I^2 scores, reported by all six applicable SRs,[5,53,54,59,62,70] ranged from 0%[54] to 99%[70] and were greater than 75% in four SRs.[5,53,59,70] The SRs reported the quality of the included studies as very low to low,[54] low to moderate,[5] moderate,[59,62,70] or high[53,55] (**Appendix 10**).

From subgroup or meta-regression analyses, two SRs[59,62] reported that the effect of CPAP versus controls on ESS increased with increasing EDS and OSA severity at baseline.[59,62] However, while one of the two SRs[59] reported that the effect of CPAP versus controls on ESS decreased with longer treatment duration, the other SR[62] reported no significant differences in the effect of CPAP versus controls on ESS with varying levels of follow-up duration, CPAP adherence, or age.

Across the seven SRs, 84 primary studies had been included, 34 of which had been included in one SR, 13 in two SRs, 12 in three SRs, 21 in four SRs, and four in five SRs (**Appendix 16.1**). No two SRs completely overlapped on ESS as the outcome.

The findings of the SRs are summarized in Table 7.

2) Expiratory positive airway pressure versus inactive controls

One SR[68] reported on EDS in adults with mild-to-severe OSA who were overweight to obese. The SR,[68] with a sample size of 359 patients from five studies, reported significantly greater reductions in ESS with EPAP, compared with pre-treatment. The mean difference in ESS was −2.61. Study duration of the included primary studies ranged from one month to three months. I^2 scores ranged from 0% to 18%. The SR[68] reported the quality of the included studies as high (**Appendix 10**). The findings of the SR are summarized in Table 8.

3) Oral appliances versus inactive controls

Seven SRs,[5,55,58,59,62,71,74] including two NMAs,[55,62] reported on EDS in adults with mild-to-severe[55,58,59,62] or moderate-to-severe[5,71,74] OSA. Four SRs[5,58,59,62] included overweight[58] or overweight-to-obese[5,59,62] patients. Three SRs[55,71,74] provided no information on comorbidities.

Six of the seven SRs,[5,55,58,59,62,71] with sample sizes ranging from 397 patients[58] to 7,882 patients[55] from nine studies[58] to 80 studies,[55] reported significantly greater reductions in ESS with MADs[5,55,58,59,62] or undefined OAs,[71] compared with controls[5,55,59,62,71,74] or pre-treatment.[58] The mean difference in ESS, reported by all six SRs, ranged from –3.65[58] to −1.17,[5] with five SRs[5,55,59,62,71] reporting mean differences around –2. Study duration of the included primary studies, reported by all six SRs, ranged from one week[62,71] to 157 weeks.[62] I^2 scores, reported by all four applicable SRs,[5,59,62,71] ranged from 0%[5] to 90%[71] and were greater than 75% in one SR.[71] The SRs reported the quality of the included studies as low,[71] moderate,[5,59,62] moderate to high,[58] or high[55] (**Appendix 10**).

One of the seven SRs,[74] with a sample size of 106 patients from three studies, reported no significant differences in change in ESS between undefined OAs and control appliances. Study duration of the included studies ranged from

one month to six months. The I^2 score was 81%. The SR[74] reported the quality of the included studies as low to moderate (**Appendix 10**).

From subgroup analyses, one SR[74] reported that the effect of MADs versus controls on ESS increased with increasing EDS at baseline but decreased with longer treatment durations. Two SRs[59,71] reported no significant differences in the effect of MADs[59] or undefined OAs[71] versus controls on ESS with varying OSA severity at baseline.

Across the seven SRs, 26 primary studies had been included, 15 of which had been included in one SR, two in two SRs, two in three SRs, three in four SRs, three in five SRs, and one in six SRs (**Appendix 16.2**). No two SRs completely overlapped on ESS as the outcome.

The findings of the SRs are summarized in Table 9.

4) Surgery versus inactive controls

Two SRs[24,60] reported on EDS in adults with moderate[24] or severe[60] OSA who were obese.[60] The SRs,[24,60] with sample sizes of 20 patients[24] to 113 patients[60] from two studies[24] or an unknown number of studies,[60] reported greater reductions in ESS with GP,[24] GTA,[24] or MMA with or without GTA,[60] compared with pre-treatment. The mean difference in ESS was –5.8 with GP and –2.9 with GTA.[24] The mean ESS decreased from 13.5 at baseline to 3.2 at follow-up with MMA with or without GTA.[60] Study duration of the included primary studies, reported by one SR,[60] ranged from two months to six months. I^2 scores were not applicable. The SRs[24,60] reported the quality of the included studies as low[24] or moderate[60] (**Appendix 10**). The findings of the SRs are summarized in Table 10.

5) Lifestyle interventions versus inactive controls

Six SRs,[5,19,50,55,73,76] including one NMA,[55] reported on EDS in adults with mild-to-severe[19,55,76] or moderate-to-severe[5,50,73] OSA. Five SRs[5,53,54,59,62] included overweight[19] or overweight-to-obese[5,50,73,76] patients. One SR[55] provided no information on comorbidities.

Five of the six SRs,[5,50,55,73,76] with sample sizes ranging from 120 patients[50] to 7,882 patients[55] from two studies[5,19,73] to 80 studies,[55] reported significantly greater reductions in ESS with diet[5,55,73,76] or exercise[5,50,55,76] programs, compared with controls[5,50,55,73] or pre-treatment.[76] The mean difference in ESS, reported by all five SRs, ranged from –4[5] to –1,[5] with three SRs[55,73,76] reporting mean differences around –2. Study duration of the included primary studies, reported by all five SRs, ranged from two weeks[55] to 144 weeks.[55] I^2 scores, reported by the two applicable SRs,[50,76] ranged from 0%[50] to 37%.[76] The SRs reported the quality of the included studies as moderate,[5] high,[55,73] or mixed[50,76] (**Appendix 10**).

Two of the six SRs,[19,76] with sample sizes ranging from 114 patients[19] to 142 patients[76] from two studies[19] to three studies,[76] reported no significant differences in change in ESS with diet and exercise programs, compared with controls. Study duration of the included primary studies, reported by both SRs, ranged from three months[19] to two years.[76] I^2 scores, reported by both SRs, ranging from 6%[76] to 33.5%.[19] The SRs[19,76] reported the quality of the included studies as mixed (**Appendix 10**).

Across the six SRs, 15 primary studies had been included, 11 of which had been included in one SR, two in three SRs, one in four SRs, and one in five SRs (**Appendix 16.3**). Two SRs[5,73] completely overlapped on ESS as the outcome. One SR[55] included all primary studies included in three other SRs[5,19,73] on ESS as the outcome.

The findings of the SRs are summarized in Table 11.

6) Continuous positive airway pressure versus oral appliances

Seven SRs,[5,54,55,59,62,74,77] including two NMAs,[55,62] reported on EDS in adults with mild-to-severe[54,55,62,77] or moderate-to-severe[5,59,74] OSA. Four SRs[5,54,59,62] included overweight-to-obese patients. Three SRs[55,74,77] provided no information on comorbidities.

Six of the seven SRs,[5,54,55,59,74,77] with sample sizes ranging from 139 patients[54] to 7,882 patients[55] from two studies[54] to 80 studies,[55] reported no significant differences in change in ESS[5,54,55,59,74,77] or Stanford Sleepiness Scale (SSS)[54]

between CPAP and MADs[5,55,59] or undefined OAs.[54,74,77] Study duration of the included primary studies, reported by all six SRs, ranged from two weeks[55] to 144 weeks.[55] I^2 scores, reported by the five applicable SRs,[5,54,59,74,77] ranged from 0%[54,74,77] to 89.4%[5] and were greater than 75% in two SRs.[5,77] The SRs reported the quality of the included studies as very low to low,[54] low,[77] low to moderate,[5,74] moderate,[59] or high[55] (**Appendix 10**).

One of the seven SRs,[62] with a sample size of 6,873 patients from 67 studies, reported significantly greater reductions in ESS with CPAP, compared with MADs. The mean difference in ESS ranged from –0.9 to –0.8 from network and pairwise comparisons, respectively. Study duration of the included studies ranged from one week to 157 weeks. The I^2 score for the pairwise comparison was 67%. The SR[62] reported the quality of the included studies as moderate (**Appendix 10**).

From subgroup analyses, one SR[59] reported no significant differences in the effect of CPAP versus MADs on ESS with varying EDS or OSA severity at baseline or study duration. However, severe cases of OSA may benefit more from CPAP than from MADs.

Across the seven SRs, 16 primary studies had been included, five of which had been included in one SR, one in two SRs, two in three SRs, two in four SRs, three in five SRs, and three in six SRs (**Appendix 16.4**). One SR[55] included all primary studies included in four other SRs[5,54,62,74] on ESS as the outcome.

The findings of the SRs are summarized in Table 12.

7) Continuous positive airway pressure versus lifestyle interventions

Three SRs,[5,54,55] including one NMA,[55] reported on EDS in adults with mild-to-severe[55] or moderate[5,54] OSA. Two SRs[5,54] included overweight[54] or obese[5] patients. One SR[55] provided no information on comorbidities.

Two of the three SRs,[5,55] with sample sizes ranging from 94 patients[5] to 7,882 patients[55] from three studies[5] to 80 studies,[55] reported no significant differences in the effect of CPAP versus diet[55] or exercise[55] programs or positional therapy.[5] Study duration of the included primary studies, reported by both SRs, ranged from two weeks[5,55] to 144 weeks.[55] I^2 scores were not applicable. The SRs reported the quality of the included studies as moderate[5] or high[55] (**Appendix 10**).

One of the three SRs,[54] with a sample size of 16 patients from one study, reported significantly greater reductions in ESS with CPAP, compared with exercise. The ESS Hedges' g was −0.71. Study duration of the included primary study was 60 days. I^2 scores were not applicable. The SR[54] reported the quality of the included studies as very low to low (**Appendix 10**).

Across the three SRs, six primary studies had been included, five of which had been included in one SR, and one in two SRs (**Appendix 16.5**). Two SRs[54,55] completely overlapped on ESS as the outcome.

The findings of the SRs are summarized in Table 13.

8) Mandibular advancement devices versus lifestyle interventions

One SR,[55] which included an NMA, reported on EDS in adults with mild-to-severe OSA, with no information on comorbidities. The SR,[55] with a sample size of 7,882 patients from 80 studies, reported no significant differences in change in ESS between MADs and diet or exercise programs. Study duration of the included primary studies ranged from two weeks to 144 weeks. I^2 scores were not applicable. The SR[55] reported the quality of the included studies as high (**Appendix 10**). The findings of the SR are summarized in Table 14.

9) Diet versus exercise

One SR,[55] which included an NMA, reported on EDS in adults with mild-to-severe OSA, with no information on comorbidities. The SR,[55] with a sample size of 7,882 patients from 80 studies, reported no significant differences in change in ESS between diet and exercise programs. Study duration of the included primary studies ranged from two weeks to 144 weeks. I^2 scores were not applicable. The SR[55] reported the quality of the included studies as high (**Appendix 10**). The findings of the SR are summarized in Table 15.

10) Combination therapy versus active controls

One SR[19] reported on EDS in adults with moderate-to-severe OSA who were overweight to obese. The SR,[19] with a sample size of 114 patients from two studies, reported significantly greater reductions in ESS with CPAP plus diet programs, compared with diet programs alone. The mean difference in ESS was –3.2. Study duration of the included primary studies ranged from three months to six months. The I^2 score was 82.7%. The SR[19] reported the quality of the included studies as mixed (**Appendix 10**). The findings of the SR are summarized in Table 16.

Review of Primary Studies

1) Tongue-retaining devices versus inactive controls

Three studies[92,113,115] reported on EDS in adults with moderate[115] or severe[113] OSA, providing mean AHI. Two studies[113,115] included overweight pateints,[113,115] providing mean BMI. One study[92] provided no information on comorbidities.

All three studies,[92,113,115] with sample sizes ranging from 20 patients[92] to 84 patients,[113] reported reductions in ESS with TRDs, compared with pre-treatment, with two of the studies[113,115] reporting statistical significance. The mean difference in ESS, reported by all three studies, ranged from –4.8[92] to –1.5.[115] One study[115] reported that using TRDs with suction led to better outcomes than using TRDs without suction. Concerns with the quality of the three studies were assessed to be low,[92] moderate,[113] or unclear[115] (**Appendix 13** and **Appendix 14**).

The findings of the primary studies are summarized in Table 17.

2) Genial tubercle advancement versus inactive controls

One study[91] reported on EDS in adults with moderate OSA who were obese, providing mean AHI and BMI. The study,[91] with a sample size of 17 patients, reported a significant reduction in ESS with GTA, compared with pre-treatment. The mean difference in ESS was –2.9. However, the study authors cautioned that only individuals with less severe OSA may benefit from this type of surgery. The study[91] had been included in, and its findings reported by, the SR on the comparison[24] that was later identified from a search alert. Concerns with the quality of the study were assessed to be low[91] (**Appendix 14**). The findings of the primary study are summarized in Table 18.

3) Positional therapy versus inactive controls

Eleven studies[78,82,83,86,88,90,96,97,99,102,116] reported on EDS in adults with mild,[87,88,97] moderate,[78,82,83,96,99,102,116] or severe OSA,[84] providing mean[78,82-84,87,88,96,102,116] or median AHI.[97,99] Nine studies[78,86,88,90,96,97,99,102,116] included positional OSA patients only. Ten studies included patients who were overweight,[78,82-84,87,88,96,97,99,102] providing mean[78,82-84,87,88,96,102] or median BMI.[97,99] One study[116] provided no information on comorbidities.

Eight of the 11 studies,[78,83,86,96,97,99,102,116] with sample sizes ranging from 14 patients[83] to 145 patients,[97] reported reductions in ESS with positional therapy (i.e., with tennis balls,[102] pillows,[83] an apparatus designed to prevent sleep in the supine position,[78,96,97,99,116] or an apparatus designed to mimic the tennis ball technique[86]), compared with pre-treatment, with seven of the studies[78,83,86,97,99,102,116] reporting statistical significance. The mean difference in ESS, reported by all eight studies, ranged from –4[97] to –1.6,[116] with five studies[86,96,99,102,116] reporting mean differences around –2. Concerns with the quality of the eight studies were assessed to be low[78,83,86,96,97,99,102] or high[116] (**Appendix 14**).

Three of the 11 studies,[82,88,90] with sample sizes ranging from 29 patients[82] to 86 patients,[90] reported little change in ESS with positional therapy (i.e., with tennis balls,[90] pillows,[82] or an apparatus designed to prevent sleep in the supine position[88]), compared with controls[90] or pre-treatment.[82,88] Concerns with the quality of the 11 studies were assessed to be low[82,88,90] (**Appendix 13** and **Appendix 14**).

The findings of the primary studies are summarized in Table 19.

4) Combination therapy versus inactive controls

Four studies[95,101,110,111] reported on EDS in adults with severe OSA[95,101,110,111] providing mean[95,101,110,111] AHI/RDI. moderate-to-severe[95,101] or severe[110,111] OSA. The studies included overweight[95] or obese patients,[101,110,111] providing mean[95,101,110,111] BMI.

One of the four studies,[111] with a sample size of 11 patients, reported non-significant reductions in ESS with CPAP plus weight loss, compared with pre-treatment. The mean difference in ESS was –3. However, another study,[110] with a sample size of 10 patients, reported no difference in ESS between CPAP plus weight loss and pre-treatment. The other two studies,[95,101] with sample sizes ranging from 41 patients[101] to 51 patients,[95] reported significant reductions in ESS with TRDs plus MADs[101] or MMA plus GP,[95] compared with pre-treatment. The mean difference in ESS, reported by both studies, ranged from –9[95] to –3.1.[101] Concerns with the quality of the four studies were assessed to be low[95,101,110] or moderate[111] (**Appendix 14**).

The findings of the primary studies are summarized in Table 20.

5) Combination therapy versus active controls

Three studies[100,106,107] reported on EDS in adults with moderate[106] or severe[100,107] OSA, providing mean[100,106,107] AHI. The studies included overweight[100,106] or obese[107] patients, providing mean[100,106,107] BMI.

All three studies,[100,106,107] with sample sizes ranging from 10 patients[106] to 63 patients,[107] reported greater reductions in ESS with CPAP plus MADs,[106] CPAP plus exercise,[100] or CPAP plus diet programs,[107] compared with CPAP alone, with two of the studies[106,107] reporting statistical significance. The mean difference in ESS, reported by two studies,[106,107] ranged from –2.2[106] to –2.[107] One of the three studies,[106] with a sample size of 10 patients, also reported a significantly greater reduction in ESS with CPAP plus MADs, compared with MADs alone. Concerns with the quality of the three studies were assessed to be low,[106,107] or unclear[100] (**Appendix 13** and **Appendix 14**).

The findings of the primary studies are summarized in Table 21.

Summary of Results on Excessive Daytime Sleepiness

For ESS, evidence was found on inactive comparisons with CPAP, EPAP, OAs (i.e., MADs, TRDs, and undefined OAs), surgery (MMA and GTA), lifestyle interventions (i.e., diet, exercise, and positional therapy), and combination therapy (i.e., CPAP plus weight loss, MADs plus TRDs, and MMA plus GTA). Evidence was also found on active comparisons between CPAP and OAs (i.e., MADs and undefined OAs), CPAP and lifestyle interventions (i.e., diet, exercise, and positional therapy), MADs and lifestyle interventions (i.e., diet and exercise), diet and exercise, and combination therapy and other interventions (i.e., CPAP plus MADs versus MADs alone, CPAP plus diet versus CPAP alone, and CPAP plus exercise versus CPAP alone).

Compared with inactive controls or pre-treatment, CPAP, EPAP, MADs, TRDs, undefined OAs, MMA, GTA, diet, exercise, positional therapy, CPAP plus weight loss, MADs plus TRDs, and MMA plus GTA were all effective at reducing EDS, commonly measured by ESS. While there is no commonly accepted clinically important difference for ESS (**Appendix 15**), effect sizes across the interventions were similar, with mean differences around –2. Mean differences in ESS around –10 were observed with MMA with or without GTA from small, uncontrolled studies on severe cases of OSA.[60,95] The findings on EPAP were also from uncontrolled studies.[68] The similarity in effect sizes is also reflected in the findings on active comparisons, where no significant differences in ESS scores were found between CPAP and MADs or undefined OAs; CPAP and diet, exercise, or positional therapy; MADs and diet or exercise; and diet and exercise. These findings suggest that the various interventions may be comparable in their effectiveness in improving EDS, although no formal statistical testing was conducted. MMA with or without GTA demonstrated the largest effect size for severe cases OSA, who are eligible for surgery. Some of the findings on CPAP or MADs versus inactive controls and CPAP versus OAs were associated with high heterogeneity.

Combination therapy was more effective at reducing EDS, compared with the interventions alone, specifically for CPAP plus diet programs versus CPAP or diet programs alone, CPAP plus exercise programs versus CPAP alone, and CPAP plus MADs versus MADs alone. Effect sizes were similar, with mean differences in ESS across the

comparisons around –2. These findings suggest that the various interventions in combination may have additive effects in their effectiveness in improving EDS.

Patients with nocturia experienced reduced EDS after CPAP. Subgroup and meta-regression analyses suggest that patients with higher EDS at baseline experienced greater effects with CPAP, MADs, or undefined OAs. Patients with more severe OSA at baseline experienced greater effects with CPAP but not with MADs or undefined OAs. Longer study duration was associated with lower effects with CPAP and MADs. Age and CPAP adherence levels were not significantly associated with the effects of CPAP. No subgroup or meta-regression analyses were found on sex or BMI.

Table 7: Summary of Change in ESS From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Guo 2016[53]	*CPAP versus inactive controls*				ESS was significantly decreased in the CPAP group, compared with the inactive control group.
	2,743 patients from 7 RCTs (2010 to 2015): • Moderate-to-severe OSA (mean AHI range: 28 to 45 events/hour) • Overweight to obese (mean BMI range: 28 to 34 kg/m^2) • Diabetes (% range: 29% to 38%, where reported) • Smoking (% range: 23% to 84%, where reported) • 2 to 48 months of study duration	• ESS MD (95% CI) = –1.78 (–2.31 to –1.24); $P < 0.00001$; $I^2 = 76\%$	None	High	
Gupta 2016[54]	*CPAP pre versus post*				The effect size was high for CPAP, compared with pre-treatment. The effect size was moderate for CPAP, compared with oral placebo.
	832 patients from 16 studies (1998 to 2013): • Mild-to-severe OSA (mean AHI range: 11 to 71.5 events/hour, where reported) • Overweight to obese (mean BMI range: 27.8 to 38 kg/m^2, where reported) • 11 days to 2 years of study duration	• ESS Hedges' *g* (95% CI) = –1.02 (–1.33 to –0.70); $P < 0.001$; $I^2 = 0\%$	None	Very low to low	
	CPAP versus oral placebo				
	187 patients from 4 studies (1997 to 2004): • Mild-to-severe OSA (mean AHI range: 11 to 43 events/hour)	• ESS Hedges' *g* (95% CI) = –0.61 (–1.13 to –0.09); $P = 0.021$; $I^2 = 0\%$	None	Very low to low	

Table 7: Summary of Change in ESS From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Overweight to obese (mean BMI range: 29.8 to 31.3 kg/m^2) • 4 weeks to 3 months of study duration				
Iftikhar 2016[55]	*CPAP versus inactive controls*				ESS was significantly decreased with CPAP, compared with inactive controls.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• ESS MD (95% CI) = −2.43 (–2.95 to –1.92); *P* = NR	None	High	
Sharples 2016[59]	*CPAP versus inactive controls*				Overall, ESS was significantly decreased in the CPAP group, compared with the inactive control group. The effect of CPAP on ESS increased with baseline OSA severity, as judged by baseline AHI, and in sleepier patients, as judged by baseline ESS. Longer treatment durations were associated
	4,894 patients from 38 RCTs (1997 to 2012): • Mild-to-severe OSA (AHI or DI: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 35.1 kg/m^2) • 3 to 156 weeks of study duration	• ESS MD (95% CI) = −2.23 (–2.76 to –1.71); *P* < 0.001; I^2 = 83%	Subgroup analysis: • Baseline AHI:[a] ○ Mild: ESS MD (95% CI) = –1.23 (–2.19 to -0.27); *P* = 0.012; I^2 = 59% ○ Moderate: ESS MD (95% CI) = –1.82 (–2.73 to –0.92); *P* < 0.001; I^2 = 60% ○ Severe: ESS MD (95% CI) = –2.64 (–3.44 to –1.84); *P* < 0.001; I^2 = 86% • Baseline ESS:[b] ○ Normal/mild: ESS MD (95%	Moderate	

Table 7: Summary of Change in ESS From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			CI) = –0.83 (–1.16 to –0.51); $P < 0.001$; $I^2 = 30\%$ ○ Moderate: ESS MD (95% CI) = –2.19 (–2.84 to –1.53); $P < 0.001$; $I^2 = 76\%$ ○ Severe: ESS MD (95% CI) = –4.99 (–6.51 to –3.47); $P < 0.001$; $I^2 = 46\%$ • Treatment duration: ○ 2 to 4 weeks: ESS MD (95% CI) = –2.58 (–3.66 to –1.51); $P <0.001$; $I^2 = 75\%$ ○ 5 to 12 weeks: ESS MD (95% CI) = –2.20 (–3.02 to –1.39); $P < 0.001$; $I^2 = 68\%$ ○ > 12 weeks: ESS MD (95% CI) = –1.87 (–2.83 to –0.90); $P < 0.001$; $I^2 = 93\%$		with decreasing treatment effects.
Bratton 2015[62]	*CPAP versus inactive controls*				Overall, CPAP was associated with significant reductions in ESS, when compared with inactive controls. The effect of CPAP was greater in patients with severe OSA. The effect of CPAP was not different with greater CPAP adherence, longer
	Pairwise MA: 6,142 patients from 54 RCTs (1997 to 2015): • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension) • 1 to 157 weeks of study duration	Pairwise MA: • ESS MD (95% CI) = −2.4 (–2.8 to –2.0); $P < 0.0001$; $I^2 =$ 74%	Meta-regression: • The effect of CPAP on ESS was greater in sleepier patients (i.e., –0.2 (95% CI = –0.4 to –0.1) for each unit increase in baseline ESS, $P = 0.003$). • There was a trend that the effect of CPAP on ESS was greater in patients with increasing OSA severity (i.e., –0.0 (95% CI = –0.1 to 0.0) for each event/hour increase in baseline AHI, $P =$	Moderate	

Table 7: Summary of Change in ESS From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	Network MA: 6,873 patients from 67 RCTs (1997 to 2015): • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension) • 1 to 157 weeks of study duration	Network MA: • ESS MD (95% CI) = −2.5 (–2.9 to –2.0); P < 0.0001	0.05 or –0.1 (95% CI = –0.1 to -0.0) for each dip/hour increase in baseline ODI, P = 0.02). • There was no evidence of larger treatment effect of CPAP on ESS with greater CPAP adherence (P = 0.70), longer follow-up (P = 0.50), or aging (P = 0.80).		follow-up, or aging.
Wang 2015[70]	*CPAP pre versus post*				CPAP was associated with a significant reduction in ESS, when compared with pre-treatment.
	131 patients from 2 RCTs (2004, 2014): • Mild-to-moderate OSA (mean AHI range: 11.4 to 14.4 events/hour) • Nocturia (100%) • 1 to 12 months of study duration	• ESS MD (95% CI) = −5.88 (–6.56 to –5.21); P < 0.00001; I^2 = 99%	None	High	
Balk 2011[5]	*CPAP versus inactive controls*				CPAP was associated with a significant reduction in ESS, when compared with inactive controls and when compared with sham CPAP.
	1,067 patients from 12 RCTs (1997 to 2010): • Mild-to-severe OSA (mean AHI range: 10 to 58 events/hour) • Overweight to obese (mean BMI range: 27.3 to 37 kg/m^2) • 1 to 12 months of study duration	• ESS MD (95% CI) = –2.37 (–3.23 to –1.51); P < 0.001; I^2 = 66%	None	Low to moderate	

Table 7: Summary of Change in ESS From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	CPAP versus sham CPAP				
	904 patients from 16 RCTs (1999 to 2010): • Moderate-to-severe OSA (mean AHI range: 22 to 65 events/hour, where reported) • Overweight to obese (mean BMI range: 27.3 to 37.8 kg/m^2) • 1 week to 3 months of study duration	• ESS MD (95% CI) = −2.50 (–3.54 to –1.45); $P < 0.001$; $I^2 = 80.1\%$	None	Mixed	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CBD = cerebrovascular disease; CI = confidence interval; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; DI = desaturation index; ESS = Epworth Sleepiness Scale; HF = heart failure; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SR = systematic review.

[a] Baseline AHI: mild, 5 to 14; moderate, 15 to 30; severe, > 30 events/hour.

[b] Baseline ESS: normal/mild, 0 to 9; moderate, 10 to 15; severe, 16 to 24.

Table 8: Summary of Change in ESS From EPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MA Analyses		
Riaz 2015[68]	*EPAP pre versus post*				EPAP was associated with a significant, but moderate, decrease in ESS post-treatment, when compared with pre-treatment.
	359 patients from 5 studies (2009 to 2015): • Mild-to-severe OSA (mean AHI range: 14.4 to 43.3 events/hour) • Overweight to obese (mean BMI range: 29.4 to 34.9 kg/m^2, where reported) • 1 to 3 months of study duration, where reported	• ESS MD (95% CI) = −2.61 (–3.29 to -1.94); $P < 0.00001$, $I^2 = 0\%$ • ESS SMD (95% CI) = –0.52 (–0.71 to –0.33); $P < 0.00001$, $I^2 = 18\%$	None	High	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MD = mean difference; MR = meta-regression; OSA = obstructive sleep apnea; SMD = standardized mean difference.

Table 9: Summary of Change in ESS From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Iftikhar 2016[55]	*MADs versus inactive controls*				ESS was significantly decreased with MADs, compared with inactive controls.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• ESS MD (95% CI) = –2.70 (–3.62 to –1.78); *P* = NR	None	High	

Table 9: Summary of Change in ESS From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Serra-Torres 2016[58]	*MADs pre versus post*				MADs were associated with a decrease in ESS post-treatment, when compared with pre-treatment.
	397 patients from 9 studies (2005 to 2014): • Mild-to severe OSA (mean AHI range: 14 to 45.5 events/hour) • Overweight (mean BMI range: 25.9 to 29.2 kg/m^2) • 1 to 24 months of study duration	• Mean ESS range: ○ Baseline: 7 to 13 ○ Follow-up: 4.2 to 8.5 • No MA	None	Moderate to high	
Sharples 2016[59]	*MADs versus inactive controls*				Overall, ESS was significantly decreased in the MAD group, compared with the inactive control group. The effect of MADs on ESS increased in sleepier patients, as judged by baseline ESS. The effect of MADs on ESS may have been stronger in trials of shorter treatment durations. Baseline AHI did not appear to have a significant effect on ESS by MADs.
	485 patients from 9 RCTs (1997 to 2014): • Mild-to-severe OSA (AHI or DI: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 35.1 kg/m^2) • 4 to 26 weeks of study duration, where reported	• ESS MD (95% CI) = –1.64 (–2.46 to –0.82); P < 0.001; I^2 = 48.2%	Subgroup analysis: • Baseline AHI:[a] ○ Mild (from 1 RCT): –2.01 (–2.70 to −1.32); P < 0.001; I^2 = NA ○ Moderate: –1.38 (−2.48 to –0.27); P = 0.15; I^2 = 42.0% ○ Severe: –2.68 (–5.89 to 0.54); P = 0.103; I^2 = 73.0% • Baseline ESS:[b] ○ Moderate: –1.36 (−2.07 to –0.64); P < 0.001; I^2 = 55% ○ Severe (from 1 RCT): –8.50 (–13.64 to –3.36); P = 0.001; I^2 = NA • Treatment duration: ○ 2 to 12 weeks: –1.75 (–2.22 to –1.28);	Moderate	

Table 9: Summary of Change in ESS From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			$P < 0.001$; $I^2 = 0\%$ ○ >12 weeks: –3.26 (−13.15 to 6.63); $P = 0.518$; $I^2 = 90\%$		
Pairwise MA: 515 patients from 8 RCTs (2002 to 2014): • Mild-to-severe OSA (mean AHI range: 14 to 42 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities: NR 4 to 13 weeks of study duration	Pairwise MA: ESS MD (95% CI) = −1.7 (−2.5 to −1.0); $P < 0.0001$; $I^2 = 17\%$				MADs were associated with a significant reduction in ESS, when compared with inactive controls.
	•	•	None	Moderate	
	Network MA: 6,873 patients from 67 RCTs (1997 to 2015): • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension) • 1 to 157 weeks of study duration	Network MA: • ESS MD (95% CI) = –1.7 (–2.3 to –1.1); $P < 0.0001$	None		
Zhu 2015[71]	*OAs versus inactive controls*				OAs were associated with a significant reduction in ESS, when compared with inactive controls. Baseline OSA severity did not appear to have any significant effect on ESS by OAs.
	557 patients from 11 RCTs and 1 cohort study (1997 to 2015): • (for the 840 patients included in the SR) Moderate-to-severe OSA (mean AHI ± SD: 23.15 ± 8.18 events/hour [for the OA groups] and 22.55 ± 7.59 events/hour [for the control groups]) • Comorbidities: NR	• ESS MD (95% CI) = –1.76 (–2.57 to –0.94); $P < 0.0001$; $I^2 = 90\%$	Subgroup analysis: • Baseline AHI:[a] ○ Mild-to-moderate: ESS MD (95% CI) = –1.85 (–2.94 to −0.77); P =NR; I^2 = NR ○ Mild-to-severe: ESS MD (95% CI) = –1.59 (–2.87 to –0.31); P =NR;	Low	

Table 9: Summary of Change in ESS From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 1 week to 3 months of study duration		I^2 = NR		
Okuno 2014[74]	*OAs versus control appliances*				There was no significant difference in change in ESS between OAs and control appliances.
	106 patients from 3 RCTs (2005 to 2011): • Moderate-to-severe OSA (mean AHI range: 22.1 to 39.1 events/hour [for the OA groups] and 20.1 to 32.6 events/hour [for the control groups]) • Comorbidities: NR • 1 to 6 months of study duration	• ESS MD (95% CI) = –2.26 (–6.82 to 2.31); P = 0.33; I^2 = 81%	None	Low to moderate	
Balk 2011[5]	*MADs versus inactive controls*				MADs were associated with a significant reduction in ESS, when compared with inactive controls or sham OAs.
	283 patients from 3 RCTs (2004 to 2008): • Moderate-to-severe OSA (mean AHI range: 19-34 events/hour) • Overweight to obese (mean BMI range: 27.3 to 31.3 kg/m^2); exclusion of patients with heart disease and diabetes • 4 weeks to 3 months of study duration	• ESS MD (95% CI) = –1.17 (–1.74 to −0.61); P = NR; I^2 = 45.0%	None	Moderate	
	MADs versus sham OAs				
	216 patients from 3 RCTs (1997 to 2005): • Moderate-to-severe OSA (mean AHI range: 25 to 36 events/hour) • Overweight to obese (mean BMI range: 29 to 32 kg/m^2)	• ESS MD (95% CI) = –1.95 (–2.93 to −0.97); P = NR; I^2 = 0.0%	None	Moderate	

Table 9: Summary of Change in ESS From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 2 weeks to 6 weeks of study duration				
	MADs versus inactive controls and sham OAs				
	499 patients from 6 RCTs (1997 to 2008): • Moderate-to-severe OSA (mean AHI range: 19 to 36 events/hour) • Overweight to obese (mean BMI range: 27.3 to 32 kg/m^2) • 2 weeks to 3 months of study duration	• ESS MD (95% CI) = –1.36 (–1.88 to −0.83); *P* = NR; I^2 = 34.7%	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CBD = cerebrovascular disease; CI = confidence interval; CVD = cardiovascular disease; DI = desaturation index; ESS = Epworth Sleepiness Scale; HF = heart failure; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NA = not applicable; NR = not reported; OA = oral appliances; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SR = systematic review.

[a] Baseline AHI: mild, 5 to 14; moderate, 15 to 30; severe, > 30 events/hour.

[b] Baseline ESS: normal/mild, 0 to 9; moderate, 10 to 15; severe, 16 to 24.

Table 10: Summary of Change in ESS From Surgery Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Song 2016[24]	*GP or GTA pre versus post*				GP and GTA can improve OSA outcomes.
	20 patients from 2 studies (2015): • Moderate OSA (mean AHI range: 19.9 to 27.5 events/hour) • Comorbidities: NR • Study duration: NR	• ESS MD: ○ GP (1 study): –5.8, *P* < 0.0001 ○ GTA (1 study): –2.9, *P* < 0.0001	None	Low	
Zaghi 2016[60]	*MMA ± GTA pre versus post*				MMA with or without GTA was associated with a significant improvement in EDS,
	113 patients from an unknown number of studies:	• Mean ESS score[a] ±SD: ○ Baseline: 13.5 ± 5.2 ○ Follow-up: 3.2 ± 3.2	None	Moderate	

Table 10: Summary of Change in ESS From Surgery Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• (for 455 of the 518 patients included in the SR) Severe OSA (mean AHI: 57.2 events/hour) • (for 82 of the 518 patients included in the SR) Obese (mean BMI: 33.8 kg/m^2) • (for the 45 studies included in the SR) 2 to 6 months of study duration	○ $P < 0.001$ • No MA			when pre- and post-treatment were compared.

AHI = Apnea–Hypopnea Index; BMI = body mass index; EDS = excessive daytime sleepiness; ESS = Epworth Sleepiness Scale; GP = genioplasty; GTA = genial tubercle advancement; MA = meta-analysis; MMA = maxillomandibular advancement; MR = meta-regression; OSA = obstructive sleep apnea; NR = not reported; SD = standard deviation; SR = systematic review.
[a] ESS scores range from 0 to 24, with lower scores indicating improvement.

Table 11: Summary of Change in ESS From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Aiello 2016[50]	*Exercise programs versus inactive controls*				Exercise programs were associated with having a greater decrease in ESS, compared with inactive controls.
	120 patients from 4 RCTs (2009 to 2013): • Moderate-to-severe OSA (mean AHI range: 15.4 to 32.2 events/hour) • Overweight to obese (mean BMI range: 25.9 to 35.5 kg/m^2) • 2 to 6 months of study duration (for the 180 patients included in the SR)	• ESS MD (95% CI) = –1.25 (–2.40 to –0.10); P = NR; I^2 = 0%	None	Mixed	
Iftikhar 2016[55]	*Exercise programs versus inactive controls*				ESS was significantly decreased with diet and exercise programs,
	Network MA: 7,882 patients from 80	• ESS MD (95% CI) = –3.08	None	High	

Table 11: Summary of Change in ESS From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	(–5.48 to –0.68); *P* = NR			compared with inactive controls.
	Diet programs versus inactive controls				
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR	• ESS MD (95% CI) = –2.12 (–4.22 to –0.01); *P* = NR	None	High	
Mitchell 2014[73]	*Weight-loss programs versus inactive controls*				The effect of intensive weight-loss programs on ESS was inconclusive, when compared with inactive controls.
	135 patients from 2 RCTs (2009): • Moderate-to-severe OSA (AHI threshold: ≥ 15 events/hour) or documented OSA • Overweight to obese (BMI range: 28 to 40 kg/m^2) • 9 weeks to 12 months of study duration	• Intensive intervention versus conservative intervention as control: change in ESS ± SD = –3.1 ± 4 versus –2.1 ± 2.9 • Intensive intervention versus usual diet as control: change in ESS ± SD =	None	High (for the RCTs included in the MA)	

Table 11: Summary of Change in ESS From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
		–3 ± 5 versus 1 ± 3 • No MA			
Araghi 2013[76]	*Weight-loss programs versus inactive controls or pre versus post*				Weight-loss programs were associated with an improvement in ESS, when pre- and post-treatment were compared but not when compared with inactive controls.
	142 patients from 3 RCTs (2009 to 2011) and 108 patients from 3 before-and-after studies (2009 to 2011): • Mild-to-severe OSA (mean AHI range: 10.0 to 43.0 events/hour) • Overweight to obese (mean BMI range: 29.7 to 40.0 kg/m^2) • 1 to 2 years of study duration, where reported	• Overall effect: ESS MD (95% CI) = –2.01 (–3.22 to –0.79); P = 0.001; I^2 = 50% • RCTs only: ESS MD (95% CI) = –1.04 (–2.31 to 0.23); P = 0.11; I^2 = 6% • Before-and-after studies only: ESS MD (95% CI) = –2.87 (–4.30 to –1.44); P < 0.0001; I^2 = 37%	None	Mixed	
Thomasouli 2013[19]	*Weight-loss programs versus inactive controls*				There was no significant difference in change in ESS between intensive weight-loss programs and usual care.
	114 patients from 2 RCTs (2009 and 2011): • Mild-to-moderate OSA (mean AHI range: 9.7 to 28.3 events/hour) • Obese (mean BMI range: 33.4 to 34.8 kg/m^2) • 3 to 12 months of study duration	• ESS MD (95% CI) = –0.31 (–2.03 to 1.40); P = 0.22; I^2 = 33.5%	None	Mixed	
Balk 2011[5]	*Weight-loss programs versus inactive controls*				The effect of intensive weight-loss programs on ESS was inconclusive, when compared with inactive control.
	144 patients from 2 RCTs (2009): • Moderate-to-severe OSA (mean AHI range: 9 to 37 events/hour) • Obese (mean BMI range: 31.4 to 34.8 kg/m^2) • 9 weeks to 1 year of study duration	• Intensive intervention versus conservative intervention as control: change in ESS (95% CI) = –1 (–2.7 to 0.7); P = 0.25 • Intensive intervention versus usual diet as control:	None	Moderate	

Table 11: Summary of Change in ESS From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
		change in ESS (95% CI) = –4 (–6 to –2); $P < 0.001$ • No MA			

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SD = standard deviation; SR = systematic review.

Table 12: Summary of Change in ESS/SSS From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus OAs*				There was no significant difference between CPAP and OAs in their effects on ESS.
	139 (included) or 132 (analyzed) patients from 2 RCTs (2004 and 2013): • Moderate OSA (mean AHI range: 21.3 to 26.2 events/hour) • Overweight to obese (mean BMI range: 27.8 to 31.1 kg/m^2) • 60 days to 3 months of study duration	• ESS/SSS Hedges' *g* (95% CI) = –0.06 (–0.24 to 0.12); $P = 0.53$; $I^2 = 0\%$	None	Very low to low	
Iftikhar 2016[55]	*CPAP versus MADs*				There was no significant difference between CPAP and MADs in their effects on ESS.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups])	• ESS MD (95% CI) = 0.26 (–0.64 to 1.18); P = NR	None	High	

Table 12: Summary of Change in ESS/SSS From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Comorbidities: NR • 2 to 144 weeks of study duration				
Sharples 2016[59]	*CPAP versus MADs*				Any treatment effect of CPAP over MADs on ESS was small, with clinically significant differences likely only for those with severe baseline AHI. No significant effects of baseline ESS or study durations on ESS were identified between CPAP and MADs.
	675 (included) or 664 (analyzed) patients from 10 RCTs (1997 to 2013): • Moderate-to-severe OSA (mean AHI/DI range: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 35.1 kg/m^2) • 4 to 26 weeks of study duration	• ESS MD (95% CI) = –0.67 (–1.44 to 0.11); P = 0.093; I^2 = 45.2%	Subgroup analysis: • Baseline AHI:[a] ○ Moderate: ESS MD (95% CI) = –0.06 (−0.72 to 0.61); P = 0.86; I^2 = 0% ○ Severe: ESS MD (95% CI) = –1.42 (–3.08 to 0.24); P = 0.09; I^2 = 68% • Baseline ESS:[b] ○ Moderate: ESS MD (95% CI) = –0.81 (−1.65 to 0.04); P = 0.06; I^2 = 49% • Study duration: ○ 2 to 12 weeks: ESS MD (95% CI) = –0.82 (–1.73 to 0.09); P = 0.078; I^2 = 55% ○ >12 weeks: ESS MD (95% CI) = 0.06 (–1.54 to 1.66); P = 0.94; I^2 = 0%	Moderate	
Bratton 2015[62]	*CPAP versus MADs*				CPAP was estimated to further reduce ESS, when compared with MADs.
	Pairwise MA: 704 patients from 11 RCTs (1997 to 2014): • Moderate-to-severe OSA (mean AHI range: 21 to 42 events/hour)	Pairwise MA: • ESS MD (95% CI) = −0.9 (−1.8 to 0.0); P = 0.06;	None	Moderate	

Table 12: Summary of Change in ESS/SSS From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Overweight to obese (mean BMI range: 27 to 33 kg/m^2) • Other comorbidities: NR • 4 to 26 weeks of study duration	I^2 = 67%			
	Network MA: 6,873 patients from 67 RCTs (1997 to 2015): • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension) • 1 to 157 weeks of study duration	Network MA: • ESS MD (95% CI) = −0.8 (−1.4 to −0.1); P = 0.015	None		
Okuno 2014[74]	*CPAP versus OAs*				There was no significant difference between CPAP and OAs in their effects on ESS.
	278 (included) or 205 (analyzed) patients from 3 RCTs (2007 to 2011): • Moderate-to-severe OSA (mean AHI range: 20.9 to 40.3 events/hour) • Comorbidities: NR • 8 weeks to 6 months of study duration	• ESS MD (95% CI) = −1.28 (−2.74 to 0.18); P = 0.09; I^2 = 0%	None	Low to moderate	
Li 2013[77]	*CPAP versus OAs*				There was no significant difference between CPAP and OAs in their effects on ESS.
	460 patients from 8 RCTs (1997 to 2009): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 8 to 16 weeks of study duration	Crossover trials (from 5 RCTs): • ESS MD (95% CI) = −0.74 (−2.17 to 0.69); P = 0.31; I^2 = 88% Parallel-group trials (from 3 RCTs): • ESS MD (95% CI)	None	Low	

Table 12: Summary of Change in ESS/SSS From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
		= −1.33 (−2.85 to 0.19); *P* = 0.09; I^2 = 0%			
Balk 2011[5]	*CPAP versus MADs*				There was no significant difference between CPAP and MADs in their effects on ESS.
	361 patients from 7 RCTs (2002 to 2009): • Moderate-to-severe OSA (mean AHI range: 21 to 40 events/hour) • Overweight to obese (mean BMI range: 26.7 to 34.1 kg/m^2) • 1 to 3 months of study duration	• ESS MD (95% CI) = −1.27 (−2.77 to 0.23); *P* = 0.098; I^2 = 89.4%	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CBD = cerebrovascular disease; CI = confidence interval; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; DI = desaturation index; ESS = Epworth Sleepiness Scale; HF = heart failure; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliances; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SSS = Stanford Sleepiness Scale.

[a] Baseline AHI: mild, 5 to 14; moderate, 15 to 30; severe, > 30 events/hour.

b Baseline ESS: normal/mild, 0 to 9; moderate, 10 to 15: severe, 16 to 24.

Table 13: Summary of Change in ESS From CPAP Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus exercise programs*				CPAP was moderately more effective than exercise at reducing ESS.
	16 patients from 1 RCT (2013): • Moderate OSA (mean AHI: 26.2 events/hour) • Overweight (mean BMI: 27.8 kg/m^2) • 60 days of study duration	• ESS Hedges' *g* (SE) = –0.71 (0.49)	None	Very low to low	
Iftikhar 2016[55]	*CPAP versus exercise programs*				There was no significant difference between CPAP and diet or exercise in reducing ESS.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-	• ESS MD (95% CI) = 0.64 (–1.79 to 3.08); *P* = NR	None	High	

Table 13: Summary of Change in ESS From CPAP Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary Overall	Subgroup or MR Analyses	Quality of Included Studies	Conclusions
	severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration				
	CPAP versus diet programs				
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• ESS MD (95% CI) = –0.31 (–2.48 to 1.85); *P* = NR	None	High	
Balk 2011[5]	*CPAP versus positional therapy (i.e., shoulder-head elevation pillows or devices worn on the back)*				There was no significant difference between CPAP and positional therapy in reducing ESS.
	94 patients from 3 RCTs (1999 to 2008): • Moderate OSA (mean AHI range: 18 to 27 events/hour) • Obese (mean BMI range: 30 to 34 kg/m^2) • 2 weeks to 1 month of study duration	• ESS MD: no significant differences between CPAP and positional therapy • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SE = standard error; SR = systematic review.

Table 14: Summary of Change in ESS From OAs Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Iftikhar 2016[55]	*MADs versus exercise programs*				There was no significant difference between MADs and diet or exercise in reducing ESS.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• ESS MD (95% CI) = 0.37 (–2.15 to 2.90); *P* = NR	None	High	
	MADs versus diet programs				
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• ESS MD (95% CI) = –0.58 (–2.88 to 1.71); *P* = NR	None	High	

AHI = Apnea–Hypopnea Index; CI = confidence interval; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliances; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SR = systematic review.

Table 15: Summary of Change in ESS From Diet Versus Exercise

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Iftikhar 2016[55]	*Diet programs versus exercise programs*				There was no significant difference between diet and exercise in reducing ESS.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 64 RCTs provided ESS: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• ESS MD (95% CI) = 0.96 (–2.23 to 4.15); *P* = NR	None	High	

AHI = Apnea–Hypopnea Index; CI = confidence interval; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SR = systematic review.

Table 16: Summary of Change in ESS From Combination Therapy Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Thomasouli 2013[19]	*CPAP plus diet programs versus diet programs alone*				CPAP plus diet programs was associated with a significant reduction in ESS, compared with diet programs alone.
	230 patients from 2 RCTs (1999 and 2001): • Moderate-to-severe OSA (mean AHI range: 20 to 56 events/hour) • Overweight to obese (mean BMI range: 29 to 32 kg/m^2) • 3 to 6 months of study duration	• ESS MD (95% CI) = −3.20 (–6.62 to –0.23); *P* = NR; I^2 = 82.7%	None	Mixed	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

Table 17: Summary of Change in ESS From TRDs Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Roplekar 2015[92]	*TRDs pre versus post*			TRDs were associated with a reduction in ESS, although no statistical testing was conducted.
	20 patients: • Patient characteristics: NR	• Mean ESS (n = 11): ○ Before: 11.9 (range 3 to 24) ○ After 4 months: 7.1 (range 2 to 13)	None	
Lazard 2009[113]	*TRDs pre versus post*			TRDs were associated with a significant reduction in ESS.
	84 patients: • Mean AHI ± SD: 37 ± 19.5 events/hour • Mean BMI ± SD: 26 ± 3.8 kg/m^2	• Mean ESS ± SD (n = 24): ○ Before: 9 ± 5.0 ○ After: 6 ± 3.7 ○ Difference: $P < 0.05$	None	
Dort 2008[115]	*TRDs pre versus post*			TRDs with or without suction were both associated with significant reductions in ESS. There was no significant difference between TRDs with suction and TRDs without suction.
	38 patients: • Mean RDI ± SD: 15.5 ± 17.7 events/hour • Mean BMI ± SD: 29.4 ± 5.7 kg/m^2	• Mean ESS ± SD (n = 32): ○ Before: 12.4 ± 4.5 ○ After: - No suction: 10.3 ± 4.9 - Suction: 10.9 ± 4.4 ○ Difference (before versus after): - No suction: $P = 0.017$ - Suction: $P = 0.025$ ○ Difference (no suction versus suction): –0.65 (95% CI = –1.8 to 0.47), $P = 0.25$	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; ESS = Epworth Sleepiness Scale; NR = not reported; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; SD = standard deviation; TRD = tongue-retaining device.

Table 18: Summary of Change in ESS From GTA Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Kuscu 2015[91]	*GTA pre versus post*			GTA resulted in significant reductions in ESS.
	17 patients: • Mean AHI ± SD: 27.5 ± 8 events/hour • Mean BMI ± SD: 30.2 ± 4 kg/m^2	• Mean ESS ± SD: ○ Before: 7.7 ± 1.6 (range: 5-9) ○ After: 4.8 ± 1.9 (range: 2-8) ○ Difference: *P* = 0.001	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; ESS = Epworth Sleepiness Scale; GTA = genial tubercle advancement; OSA = obstructive sleep apnea; SD = standard deviation

Table 19: Summary of Change in ESS From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Benoist 2016[78]	*Positional therapy (i.e., sleep position trainers) pre versus post*			Positional therapy with a sleep position trainer significantly improved ESS scores in patients with positional OSA.
	33 positional OSA patients: • Median AHI: 18.3 (IQR: 13.7 to 24.0) events/hour • Mean BMI ± SD: 27.9 ± 2.8 kg/m^2	• Median ESS: ○ Before (n = 33): 10.0 (IQR: 5.5 to 15.0) ○ After 3 months (n = 32): 7.0 (IQR: 5.0 to 12.0) ○ Difference: *P* = 0.029	None	
Afrashi 2015[82]	*Positional therapy (i.e., pillows for prone positioning) pre versus post*			Pillows for prone positioning saw no significant change in ESS.
	29 patients: • Mean AHI ± SD: 15.5 ± 6.2 events/hour • Mean BMI ± SD: 28.9 ± 3.2 kg/m^2	• Mean ESS ± SD: ○ Before: 7.3 ± 5.1 (range: 1-18) ○ After 2 nights: - Respondents[a] (n = 15): 6 (range: 3 to 12) - Non-respondents[a] (n = 14): 6 (range: 2 to 11.25) ○ Difference (respondents versus non-respondents): *P* = 0.58	None	

Table 19: Summary of Change in ESS From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Bidarian-Moniri 2015[83]	*Positional therapy (i.e., mattresses and pillows for prone positioning) pre versus post*			Positional therapy with mattresses and pillows for prone positioning significantly improved ESS scores.
	14 patients: • Mean AHI: 26 events/hour (range: 6 to 53 events/hour) • Mean ODI: 21 events/hour (range: 5-51 events/hour) • Mean BMI: 26 kg/m^2	• Mean ESS (n = 10): ○ Before: 12 ○ After 4 weeks: 9 ○ Difference: *P* = 0.007	None	
Eijsvogel 2015[88]	*Positional therapy (i.e., tennis balls or sleep position trainers) pre versus post*			No significant change in ESS was found between baseline and 1 month after positional therapy.
	26 (TBT) or 29 (SPT) positional OSA patients: • Mean AHI ± SD: 13.1 ± 9.1 (TBT) or 11.4 ± 4.9 (SPT) events/hour • Mean BMI ± SD: 26.8 ± 3.0 (TBT) or 27.6 ± 4.5 (SPT) kg/m^2	• Mean ESS ± SD: ○ TBT patients: - Before (n = 26): 7.3 ± 4.2 - After 1 month (n = 21): 7.8 ± 4.3 ○ SPT patients: - Before (n = 29): 6.4 ± 3.4 - After 1 month (n = 27): 6.0 ± 3.6 ○ Difference: *P* = non-significant	None	
de Vries 2015[86]	*Positional therapy (i.e., commercial devices or self-made constructions) pre versus post*			Short-term positional therapy was associated with a significant reduction in ESS and may be an easy and effective method in patients with positional OSA. The commercial device and self-made construction had similar effects.
	40 positional OSA patients: • Median AHI: 14.5 events/hour (IQR: 10.7 to 19.6 events/hour) • Mean BMI ± SD: 28.0 ± 4.1 kg/m^2	• Mean ESS ± SD: ○ Before: 12.2 ± 5.4 ○ After: 10.2 ± 5.5 ○ Difference: *P* < 0.01	None	
Jackson 2015[90]	*Positional therapy (i.e., sleep position modification devices) versus inactive controls*			A significant reduction in ESS was found in the active group but not in the control group.
	47 (in the intervention group) or 39 (in the control group) positional OSA patients: • Mean AHI ± SD: 20.1 ± 8.8 (in the intervention group) or 21.8 ± 10.1 (in the control group) events/hour • Mean BMI ± SD: 30.0 ± 5.3 (in the intervention group) or 30.9 ± 7.7 (in	• Mean ESS ± SD (intervention versus control): ○ Before: 9.9 ± 4.7 versus 10.0 ± 5.9 ○ After 4 weeks: 8.1 ± 4.1 versus 9.4 ± 6.6 ○ Difference: *P* < 0.005 versus *P* = non-significant	None	

Table 19: Summary of Change in ESS From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
	the control group) kg/m^2			
Levendowski 2014[96]	*Positional therapy (i.e., neck position devices) pre versus post*			Patients showed non-significant improvements in ESS.
	30 positional OSA patients: • Mean AHI ± SD: 24.7 ± 14.7 events/hour • Mean BMI ± SD: 28 ± 3.4 kg/m^2	• Mean ESS ± SD: ○ Before: 11.3 ± 4.6 ○ After 30 nights: 9.5 ± 4.6 ○ Difference: *P* = 0.064	None	
van Maneen 2014[97]	*Positional therapy (i.e., sleep position trainers) pre versus post*			There was a significant decrease in median ESS.
	145 positional OSA patients: • Median AHI: 11.5 events/hour (IQR: 2.5 to 20.5 events/hour) • Median BMI: 27.0 kg/m^2 (IQR: 23.0 to 31.0 kg/m^2)	• Median ESS ± IQR (n = 53): ○ Before: 11 ± 6 ○ After 1, 3, and 6 months: 9 ± 8, 8 ± 8, 7 ± 6 ○ Difference after 1, 3, and 6 months: *P* < 0.001	None	
van Maanen 2013[99]	*Positional therapy (i.e., sleep position trainers) pre versus post*			Sleep position trainers significantly decreased median ESS.
	31 positional OSA patients: • Median AHI: 16.4 events/hour (IQR: 6.6 to 29.9 events/hour) • Mean BMI ± SD: 27.0 ± 3.7 kg/m^2	• Median ESS: ○ Before: 11 (IQR: 2 to 20) ○ After: 9 (IQR: 0 to 19) ○ Difference: *P* = 0.004	None	
Heinzer 2012[102]	*Positional therapy (i.e., tennis balls) pre versus post*			There was a significant decrease in sleepiness after three months of device use.
	16 positional OSA patients: • Mean AHI ± SD: 26.7 ± 17.5 events/hour • Mean BMI ± SD: 25.4 ± 4.1 kg/m^2	• Mean ESS ± SD: ○ Before: 9.4 ± 4.5 ○ After 3 months: 6.6 ± 4.7 ○ Difference: *P* = 0.02	None	
Loord 2007[116]	*Positional therapy (i.e., the Positioner) pre versus post*			The mean ESS score decreased significantly during treatment.
	18 positional OSA patients: • Mean AHI ± SD: 21.8 ± 12.0 events/hour • Mean BMI: NR	• Mean ESS ± SD: ○ Before: 11.8 ± 4.2 ○ After 29 ± 2 nights: 10.2 ± 5.2 ○ Difference: *P* = 0.02	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; ESS = Epworth Sleepiness Scale; IQR = interquartile range; NR = not reported; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; SD = standard deviation; SPT = sleep position trainer; TBT = tennis ball technique.

[a] Respondents and non-respondents to treatment.

Table 20: Summary of Change in ESS From Combination Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Islam 2014[95]	*MMA plus GTA pre versus post*			Maxillomandibular and mandibular advancement surgery had a significant impact on decreasing ESS.
	51 patients: • Mean AHI ± SD: 42 ± 17 events/hour • Mean BMI: 29 ± 3.4 kg/m^2	• Mean ESS ± SD: ○ Before: 14 ± 4 ○ After: 5 ± 4 ○ Difference: *P* < 0.001	None	
Dort 2012[101]	*MADs plus TRDs pre versus post*			The combination of mandibular advancement and tongue retention was an effective treatment for moderate-to-severe OSA by significantly decreasing ESS scores post-treatment.
	41 patients: • Mean RDI ± SD: 33.5 ± 15.9 events/hour • Mean BMI ± SD: 32.2 ± 5.8 kg/m^2	• Mean ESS ± SD: ○ Before: 12.3 ± 5.4 ○ After 20 weeks: - 6 mm mandibular advancement: 9.2 ± 4.3 - 8 mm mandibular advancement: 9.0 ± 4.6 ○ Difference: - 6 mm mandibular advancement: *P* = 0.001 - 8 mm mandibular advancement: *P* = 0.009	None	
Fujii 2010[110]	*CPAP plus weight-loss programs pre versus post*			Weight-loss programs had no significant impact on ESS scores.
	10 patients: • Mean AHI ± SD: 59.0 ± 20.9 events/hour • Mean BMI ± SD: 30.7 ± 2.5 kg/m^2	• Mean ESS ± SD: ○ Before: 9.1 ± 4.0 ○ After 4 months: 9.2 ± 4.4 ○ Difference: *P* = 0.89	None	
McDoniel 2010[111]	*CPAP plus weight-loss programs pre versus post*			Patients had improved ESS scores, but it was not significant.
	11 patients: • Mean AHI ± SD: 64.2 ± 28.2 events/hour	• Mean ESS ± SD: ○ Before: 10.7 ± 3.2 ○ After 12 weeks: 7.7 ± 4.1	None	

Table 20: Summary of Change in ESS From Combination Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
	• Mean BMI ± SD: 41.7 ± 6.8 kg/m^2	○ Difference: *P* = 0.09		

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; SD = standard deviation

Table 21: Summary of Change in ESS From Combination Therapy Versus Active Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Ackel-D'Elia 2012[100]	*CPAP plus exercise programs versus CPAP alone*			CPAP plus exercise and CPAP alone were both effective at significantly reducing ESS.
	13 (CPAP plus exercise) or 19 (CPAP) patients: • Mean AHI ± SD: 40.5 ± 22.9 (CPAP plus exercise) or 42.3 ± 21.6 (CPAP) events/hour • Mean BMI ± SD: 28.0 ± 3.1 (CPAP plus exercise) or 28.5 ± 2.2 (CPAP) kg/m^2	• Mean ESS ± SD: ○ Before: - CPAP plus exercise: 14.0 ± 4.1 - CPAP:13.0 ± 4.8 ○ After 2 months: - (data presented as a graph) CPAP plus exercise more effective than CPAP alone ○ Difference: - CPAP plus exercise: *P* < 0.05 - CPAP: *P* < 0.05	None	
El-Solh 2011[106]	*CPAP plus MADs versus MADs alone*			The combination therapy of CPAP plus MADs and MADs alone were both effective in significantly reducing ESS.
	10 patients: • Mean AHI ± SD: 23.5 ± 13.4 events/hour • Mean BMI ± SD: 26.9 ± 3.2 kg/m^2	• Mean ESS ± SD: ○ Before: 12.7 ± 2.1 ○ After 8 weeks: - CPAP plus MADs: 7.5 ± 4.1 - MADs: 9.7 ± 3.1 ○ Difference: - CPAP plus MADs: *P* = 0.007 - MADs: *P* = 0.04	None	

Table 21: Summary of Change in ESS From Combination Therapy Versus Active Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Johansson 2011[107]	*CPAP plus diet programs versus CPAP alone*			After CPAP with a weight-loss program and low-energy diet, patients had a significant decrease in ESS.
	63 patients: • Mean AHI ± SD: 36 ± 15 events/hour • BMI range: 30 to 40 kg/m^2	• Mean ESS ± SD: ○ Before: 8 ± 5 ○ After 1 year of study duration: - CPAP plus very-low-energy diet (0 to 9 weeks): 5 ± 4 - After full program (0 to 52 weeks): 6 ± 5 ○ Difference (MD ± SD, 95% CI): - CPAP plus very-low-energy diet (0 to 9 weeks): –2 ± 4, –1 to –3, *P* < 0.001 - After full program (0 to52 weeks): −2 ± 3, –1 to –3, *P* < 0.001	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; ESS = Epworth sleepiness score; CPAP = continuous positive airway pressure; MAD = mandibular advancement device therapy; MD = mean difference; OSA = obstructive sleep apnea; SD = standard deviation.

OSA Severity

Information on the validity and reliability of measurement of OSA severity by AHI can be found in **Appendix 15**.

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Five SRs,[5,54,55,59,70] including one NMA,[55] reported on OSA severity in adults with mild-to-severe[55,59] or moderate-to-severe[5,54,70] OSA. Three SRs[5,54,59] included overweight-to-obese patients. One SR[70] included patients with nocturia only. One SR[55] provided no information on comorbidities.

All five SRs,[5,54,55,59,70] with sample sizes ranging from 84 patients[54] to 7,882 patients[55] from two studies[54,70] to 80 studies,[55] reported significantly greater reductions in AHI,[5,54,55,59,70] ODI,[55] or RDI,[54] with CPAP, compared with controls[5,54,55,59] or pre-treatment.[54,70] The mean difference in AHI, reported by four SRs,[5,55,59,70] ranged from –46.39 events/hour[5] to –19.85 events/hour,[5] with three SRs[5,55,59] reporting mean differences around –20 events/hour. Study duration of the included primary studies, reported by all five SRs, ranged from one week[5] to 156 weeks.[59] I^2 scores, reported by the four applicable SRs,[5,54,59,70] ranged from 0%[54] to 98%[70] and were greater than 75% in three SRs.[5,59,70] The SRs reported the quality of the included studies as very low to low,[54] low to moderate,[5] moderate,[59,70] or high[55] (**Appendix 10**).

From subgroup analyses, one SR[59] reported that the effect of CPAP versus controls on AHI increased with increasing EDS and OSA severity at baseline but decreased with longer treatment durations.

Across the five SRs, 66 primary studies had been included, 42 of which had been included in one SR, 15 in two SRs, seven in three SRs, and two in four SRs (**Appendix 16.6**). No two SRs completely overlapped on AHI as the outcome.

The findings of the SRs are summarized in Table 22.

2) Expiratory positive airway pressure versus inactive controls

One SR[68] reported on OSA severity in adults with moderate-to-severe OSA who were overweight to obese. The SR,[68] with a sample size of 345 patients from 10 studies, reported significantly greater reductions in AHI and ODI with EPAP, compared with pre-treatment. The mean difference in AHI was –14.78 events/hour. Study duration of the included primary studies ranged from one night to two months. I^2 scores ranged from 72% to 80%. The SR[68] reported the quality of the included studies as high (**Appendix 10**). The findings of the SR are summarized in Table 23.

3) Oral appliances versus inactive controls

Six SRs,[5,55,58,59,71,74] including one NMA,[55] reported on OSA severity in adults with mild-to-severe[55,58,59] or moderate-to-severe[5,71,74] OSA. Three SRs[5,58,59] included overweight-to-obese patients. Three SRs[55,71,74] provided no information on comorbidities.

All six SRs,[5,55,58,59,71,74] with sample sizes ranging from 106 patients[5,74] to 7,882 patients[55] from three studies[74] to 80 studies,[55] reported significantly greater reductions in AHI[5,55,58,59,71,74] or ODI[55] with MADs[5,55,58,59] or undefined OAs,[71,74] compared with controls[5,55,59,71,74] or pre-treatment.[58] The mean difference in AHI, reported by all six SRs, ranged from –15.20 events/hour[55] to –7.05 events/hour,[74] with four SRs[5,58,59,71] reporting mean differences around –10 events/hour. Study duration of the included primary studies, reported by all six SRs, ranged from one week[5,74] to 84 months.[58] I^2 scores, reported by the four applicable SRs,[5,59,71,74] ranged from 0%[5] to 90%[71] and were greater than 75% in one SR.[71] The SRs reported the quality of the included studies as low,[71] low to moderate,[74] moderate,[5,59] moderate to high,[58] or high[55] (**Appendix 10**).

From subgroup analyses, one SR[59] reported that the effect of MADs versus controls on AHI was greater with moderate versus severe ESS at baseline[59] and with shorter treatment durations.[59] However, two SRs[59,71] reported no significant differences in the effect of MADs[59] or undefined OAs[71] versus controls on AHI with varying levels of OSA severity at baseline.

Across the six SRs, 37 primary studies had been included, 25 of which had been included in one SR, four in two SRs, three in three SRs, four in four SRs, and one in five SRs (**Appendix 16.7**). Three SRs[55,59,71] included all primary studies included in another SR[74] on AHI as the outcome.

The findings of the SRs are summarized in Table 24.

4) Surgery versus inactive controls

Two SRs[24,60] reported on OSA severity in adults with moderate-to-severe[24] or severe[60] OSA who were obese.[60] The SRs,[24,60] with sample sizes of 61 patients[24] or 455 patients[60] from nine studies[24] to 36 studies,[60] reported greater reductions in AHI[24,60] or RDI[60] with GP,[24] GTA,[24] or MMA with or without GTA,[60] compared with pre-treatment. The mean difference in AHI was −7.78 events/hour with GP,[24] –11.1 events/hour with GTA,[24] and –47.8 events/hour with MMA with or without GTA.[60] Study duration of the included primary studies, reported by one SR,[60] ranged from two months to six months. I^2 scores, reported by both SRs,[24,60] ranged from 0%[24] to 61.3%.[60] The SR[60] reported the quality of the included studies as low[24] or moderate[60] (**Appendix 10**). From subgroup analyses, one SR[60] reported that the effect of MMA with or without GTA versus pre-treatment on AHI increased with increasing OSA severity at baseline. The findings of the SRs are summarized in Table 25.

5) Lifestyle interventions versus inactive controls

Seven SRs[5,19,50,55,61,73,76] reported on OSA severity in adults with mild-to-severe OSA. Six SRs[5,19,50,61,73,76] included overweight-to-obese patients. One SR[55] provided no information on comorbidities.

All seven SRs,[5,19,50,55,61,73,76] with sample sizes ranging from 184 patients[50] to 7,882 patients[55] from three studies[5] to 80 studies,[55] reported significantly greater reductions in AHI[5,19,50,55,61,73,76] and ODI[55,73,76] with diet[5,19,55,61,73,76] or exercise[5,19,50,55,61,76] programs, compared with controls[5,19,50,55,73,76] or pre-treatment.[61,76] The mean difference in AHI, reported by all seven SRs, ranged from –23 events/hour[5] to –0.54 events/hour,[50] with four SRs[55,61,73,76] reporting mean differences between –17 events/hour and –11 events/hour. Study duration of the included primary studies, reported by all seven SRs, ranged from two weeks[55] to 94.3 months.[61] I^2 scores, reported by the five applicable SRs,[19,50,61,73,76] ranged from 5%[76] to 92.2%[73] and were greater than 75% in three SRs.[61,73,76] The SRs reported the quality of the included studies as moderate,[5] high,[55,73] or mixed[19,50,61,76] (**Appendix 10**).

From subgroup analyses, one SR[76] reported that the effect of diet or exercise programs on AHI increased with increasing OSA severity at baseline and was greater with shorter treatment durations in before-and-after, but not controlled, studies. The SR[76] also reported that the greatest source of heterogeneity appeared to be studies with higher baseline AHI and also those with greater change in BMI.

Across the seven SRs, 39 primary studies had been included, 24 of which had been included in one SR, nine in two SRs, one in three SRs, four in four SRs, and one in five SRs (**Appendix 16.8**). One SR[73] included all primary studies included in another SR[5] on AHI as the outcome.

The findings of the SRs are summarized in Table 26.

6) Combination therapy versus inactive controls

One SR[5] reported on OSA severity in adults with mild-to-severe OSA, with no information on comorbidities. The SR,[5] with a sample size of 60 patients from one study, reported no significant differences in change in AHI between TRDs plus positional therapy and no treatment. Study duration was not reported. I^2 scores were not applicable. The SR[5] reported the quality of the included study as low (**Appendix 10**). The findings of the SR are summarized in Table 27.

7) Continuous positive airway pressure versus oral appliances

Six SRs[5,54,55,59,74,77] reported on OSA severity in adults with mild-to-severe,[55,77] moderate,[54] or moderate-to-severe[5,59,74] OSA. Three SRs[5,54,59] included overweight-to-obese patients. Three SRs[55,74,77] provided no information on comorbidities.

All six SRs,[5,54,55,59,74,77] with sample sizes ranging from 139 patients[54] to 7,882 patients[55] from two studies[54] to 80 studies,[55] reported significantly greater reductions in AHI[5,54,55,59,74,77] and ODI[55] with CPAP compared with MADs[5,55,59] or undefined OAs.[54,74,77] The mean difference in AHI, reported by all six SRs, ranged from –10.06 events/hour[55] to –0.9 events/hour,[54] with four SRs[5,59,74,77] reporting mean differences between –8 events/hour and –5 events/hour. Study duration of the included primary studies, reported by all six SRs,[5,54,59,74,77] ranged from two weeks[5,55] to 144 weeks.[55] I^2 scores, reported by the five applicable SRs, ranged from 0%[54] to 68%.[77] The SRs reported the quality of the included studies as very low to low,[54] low,[77] low to moderate,[5,74] moderate,[59] or high[55] (**Appendix 10**).

From subgroup analyses, one SR[59] reported no significant differences in the effect of CPAP versus undefined OAs on AHI with varying EDS or OSA severity at baseline or treatment durations.

Across the six SRs, 17 primary studies had been included, five of which had been included in one SR, two in two SRs, three in three SRs, four in four SRs, and three in five SRs (**Appendix 16.9**). One SR[55] included all primary studies included in three other SRs[54,74,77] on AHI as the outcome. Another SR[59] also included all primary studies included in two other SRs[74,77] on AHI as the outcome.

The findings of the SRs are summarized in Table 28.

8) Continuous positive airway pressure versus lifestyle interventions

Four SRs[5,54,55,72] reported on OSA severity in adults with mild-to-moderate[55,72] or moderate[5,54] OSA. Three SRs[5,54,72] included overweight[54] or obese[5,72] patients. One SR[55] provided no information on comorbidities.

All four SRs,[5,54,55,72] with sample sizes ranging from 16 patients[54] and 7,882 patients[55] from one study[54] to 80 studies,[55] reported significantly greater reductions in AHI with CPAP, compared with diet,[19,55] exercise,[54] or positional therapy.[5,72] The mean difference in AHI, reported by all four SRs, ranged from –16 events/hour[5] to –2.01 events/hour.[54] However, one of the four SRs,[55] with a sample size of 7,882 patients from 80 studies, reported no significant differences in the effect of CPAP versus exercise. Study duration of the included primary studies, reported by all four SRs, ranging from three nights[72] to 144 weeks.[55] The I^2 score, reported by the one applicable SR,[72] was 70%. The SRs reported the quality of the included studies as very low to low,[54] moderate,[5,72] or high[55] (**Appendix 10**).

Across the four SRs, five primary studies had been included, two of which had been included in one SR, and three in two SRs (**Appendix 16.10**). Two SRs[54,55] completely overlapped on AHI as the outcome.

The findings of the SRs are summarized in Table 28.

9) Mandibular advancement devices versus tongue-retaining devices

One SR[5] reported on OSA severity in adults with moderate OSA who were overweight. The SR,[5] with a sample size of 22 patients from one study, reported no significant differences in change in AHI between MADs and TRDs. Study duration of the included primary study was one week. I^2 scores were not applicable. The SR[5] reported the quality of the included study as moderate (**Appendix 10**). The findings of the SR are summarized in Table 30.

10) Mandibular advancement devices versus lifestyle interventions

One SR[55] reported on OSA severity in adults with mild-to severe OSA, with no information on comorbidities. The SR,[55] with a sample size of 7,882 patients from 80 studies, reported no significant differences in change in AHI between MADs and diet or exercise programs. Study duration of the included primary studies ranged from two weeks to 144 weeks. I^2 scores were not applicable. The SR[55] reported the quality of the included studies as high (**Appendix 10**). The findings of the SR are summarized in Table 31.

11) Diet versus exercise

One SR[55] reported on OSA severity in adults with mild-to severe OSA, with no information on comorbidities. The SR,[55] with a sample size of 7,882 patients from 80 studies, reported no significant differences in change in AHI between diet and exercise programs. Study duration of the included primary studies ranged from two weeks to 144

weeks. I^2 scores were not applicable. The SR[55] reported the quality of the included studies as high (**Appendix 10**). The findings of the SR are summarized in Table 32.

Review of Primary Studies

1) Tongue-retaining devices versus inactive controls

Two studies[113,115] reported on OSA severity in adults with moderate[115] or severe[113] OSA, providing mean[113,115] AHI. The studies included overweight[113,115] patients, providing mean[113] BMI. Both studies,[113,115] with sample sizes ranging from 38 patients[115] to 84 patients,[113] reported significant reductions in AHI[115] or RDI[113] with TRDs[113] or TRDs with and without suction,[115] compared with pre-treatment. The mean difference, reported by both studies, was –24 events/hour in AHI[115] or –6.6 events/hour to –2 events/hour in RDI.[113] Concerns with the quality of the two studies were assessed to be moderate[113] or unclear[115] (**Appendix 13** and **Appendix 14**). The findings of the primary studies are summarized in Table 33.

2) Genial tubercle advancement versus inactive controls

Two studies[91,117] reported on OSA severity in adults with mild-to-moderate[117] OSA, providing AHI ranges, or moderate[91] OSA, providing mean AHI. The studies included obese[91] patients, providing mean[91] AHI, or patients with a BMI under 30 in another study,[117] normal-to-overweight[117] or overweight-to-obese[91] patients. Both studies,[91,117] with sample sizes ranging from 10 patients[117] to 17 patients,[91] reported significant reductions in AHI with GTA, compared with pre-treatment. The mean difference in AHI, reported by both studies, ranged from –10.2 events/hour[117] to –7.98 events/hour.[91] However, the authors of one study[91] cautioned that only individuals with less severe OSA may benefit from this type of surgery. The studies[91,117] had been included, and their findings reported, by the SR on the comparison[24] that was later identified from a search alert. Concerns with the quality of the two studies were assessed to be low[91,117] (**Appendix 14**). The findings of the primary studies are summarized in Table 34.

3) Positional therapy versus inactive controls

Seventeen studies[78,81-86,88,90,96,99,102,104,105,108,116,118] reported on OSA severity in adults with mild,[85,86,88] moderate,[78,81-83,90,96,99,102,104,105,108,116,118] or severe OSA,[84] providing mean[81-84,88,90,96,102,104,105,108,116,118] or median AHI.[78,85,86,99] Ten studies included patients who were normal weight,[85] overweight,[78,81-84,86,88,96,99,102,104,105,108,118] or obese,[90] providing mean[78,81-84,86,88,90,96,102,104,105,108,118] or median BMI.[85,99] Twelve studies[78,81,85,86,90,96,99,102,104,108,116,118] included positional OSA patients only. Fourteen studies included normal-to-overweight,[85,102,108] normal-to-obese,[78,81,83,84,90,99,118] or overweight-to-obese[78,82,86,88,96,104,105] patients. One study[116] provided no information on comorbidities.

Sixteen of the 17 studies,[78,81-84,86,88,90,96,99,102,104,105,108,116,118] with sample sizes ranging from 14 patients[83] to 86 patients,[90] reported significantly greater reductions in AHI,[78,81-84,86,88,90,96,99,102,104,105,108,116,118] ODI,[78,81] or RDI[81] with positional therapy (i.e., with tennis balls,[88,90,102,118] pillows,[83,84] an apparatus designed to mimic the tennis ball technique,[86] or an apparatus designed to avoid sleep in the supine position[78,81,82,96,99,104,105,108,116]), compared with controls[90] or pre-treatment.[78,81-84,86,88,96,99,102,104,105,108,116,118] One of the 17 studies,[85] with a sample size of 25 patients, also reported a reduction in ODI with positional therapy (i.e., with pillows), compared with pre-treatment, but the reduction was not significant. One of the 17 studies[102] reported higher reductions in AHI from tennis balls with shorter duration (i.e., one night) than longer duration (i.e., three months). The mean difference in AHI, reported by all but one study,[105] ranged from –29 events/hour[118] to –0.7 events/hour,[85] with seven SRs[82,86,88,90,99,108,116] reporting mean differences between –15 events/hour and –5 events/hour. Concerns with the quality of the 17 studies were assessed to be low[78,81-86,88,90,96,99,102,104,105,108] or high[116,118] (**Appendix 13** and **Appendix 14**).

From subgroup analyses, two studies[85,96] reported that the effect of positional therapy versus pre-treatment on AHI[96] or ODI[85] was greater with mild or moderate OSA, compared with severe OSA,[96] but was indifferent between normal-weight and overweight patients.[85] Nine studies[78,86,88,96,99,102,104,108,118] conducted subgroup analyses on supine versus non-supine sleep position, seven of which[86,88,96,99,102,104,108] reported significant reductions in AHI in the supine sleep position but not in non-supine sleep positions, whereas one reported significant reductions in AHI in both supine and

non-supine sleep positions.[78] One study[84] conducted subgroup analyses on positional versus non-positional OSA and reported reductions in AHI and ODI in patients with positional or non-positional OSA.

The findings of the primary studies are summarized in Table 35.

4) Combination therapy versus inactive controls

Three studies[95,101,114] reported on OSA severity in adults with severe[95,101] OSA provided with a mean AHI, or with an initial RDI of 35 or greater.[114] Two studies included overweight[95] or obese[101] patients, provided with a mean BMI. One study[114] provided no information on comorbidities.

All three studies,[95,101,114] with sample sizes ranging from four patients[114] to 51 patients,[95] reported reductions in AHI[95] or RDI[114] after MMA plus GP[95,114] or a reduction in RDI after MADs plus TRDs,[101] compared with pre-treatment, with two studies[95,101] reporting statistical significance. The mean difference, reported by all three studies, was –34 events/hour in AHI[95] or –25 events/hour[114] to –14.3 events/hour[101] in RDI. Concerns with the quality of the three studies were assessed to be low[95,101] or unclear[114] (**Appendix 14**).

The findings of the primary studies are summarized in Table 36.

5) Mandibular advancement devices versus tongue-retaining devices

One study[109] reported on OSA severity in overweight adults with moderate OSA, provided with mean AHI and BMI. The study, with a sample size of 39 patients, reported reductions in AHI with the use of both MADs and TRDs but a greater reduction with TRDs, compared with MADs, with a mean difference of –0.8 events/hour. Concerns with the quality of the study were assessed to be low[109] (**Appendix 14**). The findings of the primary study are summarized in Table 37.

6) Mandibular advancement devices versus maxillomandibular advancement

One study[94] reported on OSA severity in adults with moderate-to-severe OSA, with 17.2% of the patients being obese. The study, with a sample size of 198 patients, reported a significantly greater reduction in AHI with MMA, compared with MADs, with a mean difference of –13.59 events/hour. Concerns with the quality of the study were assessed to be low[94] (**Appendix 14**). The findings of the primary study are summarized in Table 38.

7) Combination therapy versus active controls

Four studies[87,100,106,107] reported on OSA severity in patients with moderate[87,106] or severe,[100,107] provided by mean AHI. The studies included overweight patients[87,100,106] provided by mean BMI, or obese patients[107] provided by a BMI range.

Three of the four studies,[87,106,107] with sample sizes ranging from 10 patients[106] to 63 patients,[107] reported reductions in AHI[87,106,107] or ODI[87] with CPAP plus MADs[106] or CPAP plus diet programs,[107] compared with CPAP alone, or with MADs plus positional therapy (i.e., sleep position trainers), compared with MADs or positional therapy alone,[87] with two studies[106,107] reporting statistical significance. The mean difference in AHI, reported by all three studies, was –21 events/hour[107] or –5.5 events/hour,[87] with two studies[87,106] reporting mean differences between –5 and –7. Concerns with the quality of the three studies were assessed to be low[106,107] or unclear[87] (**Appendix 13** and **Appendix 14**).

The other study,[100] with a sample size of 32 patients, reported similar reductions in AHI for both CPAP plus exercise programs and CPAP alone. Concerns with the quality of the study were assessed to be unclear[100] (**Appendix 13**).

From subgroup analyses, one study[107] reported that the effect of CPAP plus diet programs versus CPAP alone on AHI was greater in the supine sleep position, compared with the combination of supine and non-supine positions.

The findings of the primary studies are summarized in Table 39.

Summary of Results on Obstructive Sleep Apnea Severity

For OSA severity, evidence was found on inactive comparisons with CPAP, EPAP, OAs (i.e., MADs, TRDs, and undefined OAs), surgery (MMA and GTA), lifestyle interventions (i.e., diet, exercise, and positional therapy), and combination therapy (i.e., MADs plus TRDs, TRDs plus positional therapy, and MMA plus GTA). Evidence was also found on active comparisons between CPAP and OAs (i.e., MADs and undefined OAs), CPAP and lifestyle interventions (i.e., diet, exercise, and positional therapy), MADs and TRDs, MADs and MMA, MADs and lifestyle interventions (i.e., diet and exercise), diet and exercise, and combination therapy and other interventions (i.e., CPAP plus MADs versus MADs alone, CPAP plus diet programs versus CPAP alone, CPAP plus exercise programs versus CPAP alone, and MADs plus positional therapy versus MADs or positional therapy alone).

Compared with inactive controls or pre-treatment, CPAP, EPAP, MADs, TRDs, undefined OAs, MMA, GTA, diet, exercise, positional therapy, MADs plus TRDs, TRDs plus positional therapy, and MMA plus GTA were all effective at reducing OSA severity, commonly measured by AHI. The minimal clinically important difference for AHI is five events/hour (**Appendix 15**). While effect sizes varied across the interventions, they tended to be above this threshold. The highest of the mean differences in AHI was around –20 events/hour for CPAP, followed by –15 events/hour for EPAP, –10 events/hour for MADs or undefined OAs, and –8 events/hour to –11 events/hour for GTA. Mean differences in AHI around –48 were observed with MMA with or without GTA from small, uncontrolled studies on severe cases of OSA.[60] The findings on EPAP were also from uncontrolled studies.[68] Wide ranges of effect sizes were observed for TRDs, diet, exercise, and positional therapy. Some of the differences in effect sizes are reflected in the findings on active comparisons, where significant differences in AHI values were found between CPAP and MADs or undefined OAs and also between CPAP and diet, exercise, or positional therapy. No significant differences in effect sizes were found between MADs and diet or exercise programs and also between diet and exercise programs. Mixed findings were reported for the comparison between MADs and TRDs, where a 2011 SR[5] reported comparable effects between the two interventions, while a 2011 study[109] reported superior effects of TRDs, compared with MADs. These findings suggest that CPAP, compared with other interventions, may be most effective at improving OSA severity, while the largest effect was observed for MMA with or without GTA for severe cases OSA, who are eligible for surgery. The majority of studies on MMA and GTA, however, were in highly selected patients in uncontrolled pre-and-post studies with sample sizes of fewer than 10 patients. The results, therefore, must be interpreted with great caution, especially given the invasiveness of the procedures and potential adverse events. Some of the findings on CPAP, EPAP, MADs, diet, or exercise versus inactive controls were associated with high heterogeneity.

For combination therapy, CPAP plus MADs compared with MADs alone, CPAP plus diet programs compared with CPAP alone, and MADs plus positional therapy compared with MADs or positional therapy alone were more effective at reducing OSA severity. However, CPAP plus exercise programs, compared with CPAP alone, was not effective at reducing OSA severity. In general, these findings suggest that the various interventions in combination may have additive effects in their effectiveness in improving OSA severity.

Patients with nocturia experienced reduced OSA severity after CPAP. Subgroup and meta-regression analyses suggest that patients with higher EDS at baseline experienced greater effects with CPAP but lower effects with MADs or undefined OAs. Patients with more severe OSA at baseline experienced greater effects with CPAP, MMA, diet, and exercise but lower effects with MADs or undefined OAs and positional therapy. Longer study duration was associated with lower effects with CPAP, MADs, diet, exercise, and positional therapy. Baseline weight was not significantly associated with the effects of positional therapy. No subgroup or meta-regression analyses were found on sex, age, or adherence.

Table 22: Summary of Change in AHI/ODI/RDI From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP pre versus post*				There was a large effect size on AHI/RDI in favour of CPAP, compared with pre-treatment and when compared with sham CPAP.
	278 patients from 6 studies (1999 to 2013): • Moderate-to-severe OSA (mean AHI range: 21.3 to 63.6 events/hour) • Overweight to obese (mean BMI range: 27.8 to 37 kg/m^2, where reported) • 11 days to 6 months of study duration	• AHI/RDI Hedges' *g* (95% CI) = –1.48 (–1.68 to –1.28); *P* < 0.001; I^2 = 5.5%	None	Very low to low	
	CPAP versus sham CPAP				
	84 patients from 2 studies (1999 to 2007): • Severe OSA (mean AHI range: 40.6 to 63.6 events/hour) • Obese (mean BMI: 33.1 kg/m^2, where reported) • 2 to 3 months of study duration	• AHI/RDI Hedges' *g* (95% CI) = –1.88 (–2.39 to –1.37); *P* < 0.001; I^2 = 0%	None	Very low to low	
Iftikhar 2016[55]	*CPAP versus inactive controls*				AHI and ODI were significantly decreased with CPAP, compared with inactive controls.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI and 15 RCTs provided ODI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR	• AHI MD (95% CI) = –25.27 (–28.52 to –22.03); *P* = NR • ODI MD (95% CI) = –20.40 (–25.19 to –15.62); *P* = NR	None	High	

Table 22: Summary of Change in AHI/ODI/RDI From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 2 to 144 weeks of study duration				
Sharples 2016[59]	*CPAP versus inactive controls*				Overall, AHI was significantly decreased in the CPAP group, compared with the inactive control group. The effect of CPAP on AHI increased with baseline OSA severity, as judged by baseline AHI, and in sleepier patients, as judged by baseline ESS (i.e., moderate versus severe). Longer treatment durations were associated with decreasing treatment effects.
	1,596 patients from 25 RCTs (2001 to 2013): • Mild-to-severe OSA (AHI or DI: NR) • (for the 6,757 patients included in the SR) Overweight-to-obese (mean BMI range: 28.3 to 35.1 kg/m^2) • 3 to 156 weeks of study duration	• AHI MD (95% CI) = –25.37 events/hour (–30.67 to –20.07); $P < 0.001$; $I^2 = 96.1\%$	Subgroup analysis: • Baseline AHI:[a] ○ Mild: AHI MD (95% CI) = –2.40 (–3.67 to –1.13); $P < 0.001$; I^2 = NA ○ Moderate: AHI MD (95% CI) = –13.67 (–16.13 to –11.20); $P < 0.001$; $I^2 = 47\%$ ○ Severe: AHI MD (95% CI) = –33.04 (–39.75 to –26.34); $P < 0.001$; $I^2 = 90\%$ • Baseline ESS:[b] ○ Normal/mild: AHI MD (95% CI) = –32.50 (−43.55 to –21.45); $P < 0.001$; I^2 = NA ○ Moderate: AHI MD (95% CI) = –17.54 (–22.51 to –12.56); $P < 0.001$; $I^2 = 95\%$ ○ Severe: AHI MD (95% CI) = –34.73 (–58.90 to –10.57); $P = 0.005$; $I^2 = 95\%$	Moderate	

Table 22: Summary of Change in AHI/ODI/RDI From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			• Study duration: ○ 2 to 4 weeks: AHI MD (95% CI) = –32.90 (−43.78 to –22.02); $P < 0.001$; $I^2 = 93\%$ ○ 5 to 12 weeks: AHI MD (95% CI) = –22.34 (−29.84 to –14.85); $P < 0.001$; $I^2 = 96\%$ ○ >12 weeks: AHI MD (95% CI) = –14.25 (−19.03 to –9.46); $P < 0.001$; $I^2 = 82\%$		
Wang 2015[70]	*CPAP pre versus post*				CPAP was associated with a significant reduction in AHI, when compared with pre-treatment.
	85 patients from 2 RCTs (2004, 2015): • Moderate-to-severe OSA (mean AHI range: 24.0 to 51.5 events/hour) • Nocturia (100%) • 1 month of study duration	• AHI MD (95% CI) = –31.57 (−33.87 to −29.28); $P < 0.00001$; $I^2 = 98\%$	None	Moderate	
Balk 2011[5]	*CPAP versus inactive controls*				CPAP was associated with a significant reduction in AHI, when compared with inactive controls and when compared with sham CPAP.
	417 patients from 7 RCTs (2001 to 2007): • Moderate-to-severe OSA (mean AHI range: 19 to 46 events/hour) • Overweight to obese (mean BMI range: 27.3 to 33.5 kg/m^2) • 1 to 6 months of study duration	• AHI MD (95% CI) = –19.85 (–26.06 to –13.65); $P < 0.001$; $I^2 = 86\%$	None	Low to moderate	

Table 22: Summary of Change in AHI/ODI/RDI From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	CPAP versus sham CPAP				
	311 patients from 8 RCTs (1999 to 2008): • Severe OSA (mean AHI range: 35 to 65 events/hour) • Overweight to obese (mean BMI range: 27.5 to 33.4 kg/m^2) • 1 week to 3 months of study duration	• AHI MD (95% CI) = –46.39 (–56.97 to –35.81); $P < 0.001$; $I^2 = 69.6\%$	None	Mixed	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; DI = desaturation index; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; RDI = respiratory disturbance index; SR = systematic review.

[a] Baseline AHI: mild, 5 to 14; moderate, 15 to 30; severe, > 30 events/hour.

[b] Baseline ESS: normal/mild, 0 to 9; moderate, 10 to 15; severe, 16 to 24.

Table 23: Summary of Change in AHI/ODI From EPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Riaz 2015[68]	*EPAP pre versus post*				EPAP was associated with a significant, and large, decrease in AHI post-treatment, when compared with pre-treatment. EPAP was associated with a significant, but moderate, decrease in ODI post-treatment, when compared with pre-treatment.
	345 patients from 10 studies (2008 to 2015): • Moderate-to-severe OSA (mean AHI range: 18.1 to 43.3 events/hour) • Overweight to obese (mean BMI range: 28.2 to 34.9 kg/m^2, where reported)	• AHI MD (95% CI) = –14.78 (–19.12 to –10.45); $P < 0.00001$, $I^2 = 72\%$ • AHI SMD (95% CI) = −0.94 (–1.31 to –0.57); $P < 0.00001$, $I^2 = 80\%$	None	High	

Table 23: Summary of Change in AHI/ODI From EPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 1 night to 2 months of study duration, where reported				
	247 patients from 7 studies (2008 to 2015): • Moderate-to-severe OSA (mean AHI range: 18.1 to 43.3 events/hour) • Overweight to obese (mean BMI range: 28.2 to 34.9 kg/m^2, where reported) • 1 night to 2 months of study duration, where reported	• ODI MD (95% CI) = –7.69 (–11.78 to –3.60); P = 0.0002, I^2 = 67% • ODI SMD (95% CI) = −0.58 (–0.91 to –0.25); P = 0.0006, I^2 = 69%	None		

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; EPAP = expiratory positive airway pressure; MA = meta-analysis; MD = mean difference; MR = meta-regression; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; SMD = standardized mean difference.

Table 24: Summary of Change in AHI/RDI From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Iftikhar 2016[55]	*MADs versus inactive controls*				ESS was significantly decreased with MADs, compared with inactive controls.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI and 15 RCTs provided ODI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups])	• AHI MD (95% CI) = –15.20 (–19.50 to –10.91); P = NR • ODI MD (95% CI) = –12.58 (–18.84 to –6.32); P = NR	None	High	

Table 24: Summary of Change in AHI/RDI From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Comorbidities: NR • 2 to 144 weeks of study duration				
Serra-Torres 2016[58]	*MADs pre versus post*				MADs were associated with a decrease in AHI post-treatment, compared with pre-treatment.
	1,505 patients from 18 studies (2004 to 2014): • Mild-to severe OSA (mean AHI range: 14 to 45.5 events/hour) • Overweight to obese (mean BMI range: 25.9 to 32.3 kg/m^2, where reported) • 0.5 to 84 months of study duration	• Mean AHI range: ○ Baseline: 14 to 45.5 events/hour ○ Follow-up: 4.1 to 19.6 events/hour • Mean AHI % reduction range: 21% to 80% • No MA	None	Moderate to high	
Sharples 2016[59]	*MADs versus inactive controls*				Overall, AHI was significantly decreased in the MAD group, compared with the inactive control group. Baseline AHI and baseline ESS did not appear to have any effect on the reduction of AHI by MADs. The effect of MADs on AHI was greater in trials of shorter durations.
	557 patients from 11 RCTs (1997 to 2014): • Mild-to-severe OSA (AHI or DI: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 5.1 kg/m^2) • 4 to 26 weeks of study duration, where reported	• AHI MD (95% CI) = –9.29 (–12.28 to –6.30); $P < 0.001$; $I^2 = 60.4\%$	Subgroup analysis: • Baseline AHI:[a] ○ Mild: –7.79 (–16.38 to 0.79); $P = 0.075$; $I^2 = 65.1\%$ ○ Moderate: –10.72 (−14.59 to –6.85); $P < 0.001$; $I^2 = 52.0\%$ ○ Severe: –7.95 (–15.94 to 0.05); $P = 0.051$; $I^2 = 31.6\%$ • Baseline ESS:[b] ○ Moderate: –6.69 (−8.98 to –4.41); $P < 0.001$; $I^2 = 35\%$ ○ Severe (from 1 RCT): –2.10 (–12.33 to 8.13); $P = 0.687$; I^2 = NA	Moderate	

Table 24: Summary of Change in AHI/RDI From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			• Treatment duration: ○ 2 to 12 weeks: –9.69 (–13.27 to –6.12); $P < 0.001$; $I^2 = 68\%$ ○ >12 weeks: –6.78 (−13.24 to –0.33); $P = 0.039$; $I^2 = 23\%$		
Zhu 2015[71]	*OAs versus inactive controls*				OAs were associated with a significant reduction in AHI, when compared with inactive controls. Baseline OSA severity did not appear to have any significant effect on AHI by OAs.
	679 patients from 12 RCTs and 1 cohort study (2002 to 2015): • (for the 840 patients included in the SR) Moderate-to-severe OSA (mean AHI ± SD: 23.15 ± 8.18 events/hour [for OA group] and 22.55 ± 7.59 events/hour [for control group]) • Comorbidities: NR • 4 weeks to 6 months of study duration	• AHI MD (95% CI) = −10.26 (–12.59 to −7.93); $P < 0.00001$; $I^2 = 90\%$	Subgroup analysis: • Baseline AHI:[a] ○ Mild-to-moderate: AHI MD (95% CI) = –8.13 (–10.69 to –5.57); P = NR; I^2 = NR ○ Mild-to-severe: AHI MD (95% CI) = –13.54 (–15.75 to –11.36); P = NR; I^2 = NR	Low	
Okuno 2014[74]	*OAs versus control appliances*				OAs were associated with a significant reduction in AHI, when compared with control appliances.
	106 patients from 3 RCTs (2005 to 2011): • Moderate-to-severe OSA (mean AHI range: 22.1 to 39.1 events/hour [for OA group] and 20.1 to 32.6 events/hour [for control group]) • Comorbidities: NR • 1 to 6 months of study duration	• AHI MD (95% CI) = −7.05 (–12.07 to −2.03); $P = 0.006$; $I^2 = 0\%$	None	Low to moderate	
Balk 2011[5]	*MADs versus inactive controls*				MADs were associated with a significant reduction in AHI, when compared with inactive controls or sham
	331 patients from 4 RCTs (2000 to 2008):	• AHI MD (95% CI) = −11.39 (–15.21 to −7.58); P = NR;	None	Moderate	

Table 24: Summary of Change in AHI/RDI From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Moderate-to-severe OSA (mean AHI range: 19 to 34 events/hour) • Overweight to obese (mean BMI range: 27.3 to 31.3 kg/m^2); exclusion of patients with heart disease and diabetes • 1 to 10 weeks of study duration	I^2 = 55.3%			OAs.
	MADs versus sham OAs				
	234 patients from 3 RCTs (2001 to 2005): • Moderate-to-severe OSA (mean AHI range: 25 to 31 events/hour) • Overweight to obese (mean BMI range: 29 to 32 kg/m^2) • 1 to 6 weeks of study duration	• AHI MD (95% CI) = −14.04 (–20.06 to −8.02); *P* = NR; I^2 = 0.0%	None	Moderate	
	MADs versus control and sham OAs				
	565 patients from 7 RCTs (2000 to 2008): • Moderate-to-severe OSA (mean AHI range: 19 to 34 events/hour) • Overweight to obese (mean BMI range: 27.3 to 32 kg/m^2) • 1 to 10 weeks of study duration	• AHI MD (95% CI) = −11.76 (–14.64 to −8.87); *P* = NR; I^2 = 30.8%	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; DI = desaturation index; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliance; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; RDI = respiratory disturbance index; SD = standard deviation; SR = systematic review.

[a] Baseline AHI: mild, 5 to 14; moderate, 15 to 30; severe, > 30 events/hour.

[b] Baseline ESS: normal/mild, 0 to 9; moderate, 10 to 15; severe, 16 to 24.

Table 25: Summary of Change in AHI/RDI From Surgery Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Song 2016[24]	*GP or GTA pre versus post*				Standard GP and GTA can improve OSA outcomes.
	61 patients from 9 studies (1994 to 2015): • Moderate-to-severe OSA (mean AHI range: 13.0 to 88.2 events/hour) • Comorbidities: NR • Study duration: NR	• AHI % change before and after: ○ Standard GP: –43.8% ○ Modified GP: +37.3% ○ GTA: –45.7% • AHI MD (95% CI): ○ GP (from 2 studies): –7.78 events/hour (−9.84 to –5.72); $P < 0.00001$; $I^2 = 0\%$ ○ GTA (from 3 studies): –11.1 events/hour (–17.9 to –4.25); $P = 0.001$; $I^2 = 0\%$ • AHI SMD (95% CI): ○ GP: –2.97 (–4.31 to –1.63); $P < 0.0001$; $I^2 = 0\%$ ○ GTA: –0.94 (–1.59 to –0.28); $P = 0.005$; $I^2 = 0\%$	None	Low	
Zaghi 2016[60]	*MMA ± GTA pre versus post*				MMA with or without GTA was associated with a significant decrease on AHI and RDI, when pre- and post-treatment were compared. The effect of MMA with or without GTA on AHI increased with baseline OSA severity.
	455 patients from 36 studies (1986 to 2014): • (for 455 of the 518 patients included in the SR) Severe OSA (mean AHI: 57.2 events/hour) • (for 82 of the 518 patients included in the SR) Obese (mean BMI: 33.8 kg/m^2) • (for the 45 studies included in the SR) 2 to 6 months of	• AHI MD ± SD = –47.8 ± 25.0; $P < 0.001$; $I^2 = 61.3\%$	Subgroup analysis: • Baseline AHI: ○ < 30 events/hour: AHI MD ± SD = –14.1 ± 11.6 ○ 30 to 60 events/hour: AHI MD = –37.4 ○ 60 to 90 events/hour: AHI MD = –61.0 ○ ≥ 90 events/hour: AHI MD ± SD = –94.5 ± 23.5	Moderate	

Table 25: Summary of Change in AHI/RDI From Surgery Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	study duration				
	68 patients from 11 studies (2001 to 2013): • (for 455 of the 518 patients included in the SR) Severe OSA (mean AHI: 57.2 events/hour) • (for 82 of the 518 patients included in the SR) Obese (mean BMI: 33.8 kg/m^2) • (for the 45 studies included in the SR) 2 to 6 months of study duration	• RDI MD ± SD = –44.4 ± 33.0; P < 0.001; I^2 = 41.3%	None		

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; GP = genioplasty; GTA = genial tubercle advancement; MA = meta-analysis; MD = mean difference; MMA = maxillomandibular advancement; MR = meta-regression; NR = not reported; RDI = respiratory disturbance index; OSA = obstructive sleep apnea; SD = standard deviation; SR = systematic review.

Table 26: Summary of Change in AHI/ODI From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Aiello 2016[50]	*Exercise programs versus inactive controls*				Exercise was associated with having a greater decrease in AHI, when compared with inactive control.
	184 patients from 7 RCTs (2000 to 2014): • Mild-to-severe OSA (mean AHI range: 3.5 to 42.3 events/hour, where reported) • Overweight to obese (mean BMI range: 25.9 to 35.5 kg/m^2,	• AHI MD (95% CI) = −0.54 (–0.86 to –0.21); P = NR; I^2 = 20% • AHI decrease of 4 events/hour OR (95% CI) = 77.33 (27.91 to	None	Mixed	

Table 26: Summary of Change in AHI/ODI From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	where reported) • 2 to 6 months of study duration (for the 8 RCTs included in the SR)	187.49) • AHI decrease of 4 events/hour RR (95% CI) = 7.29 (4.07 to 13.06)			
Iftikhar 2016[55]	*Exercise programs versus inactive controls*				AHI, but not ODI, was significantly decreased with diet and exercise, compared with inactive controls.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI and 15 RCTs provided ODI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• AHI MD (95% CI) = −17.23 (–25.82 to −8.64); *P* = NR • ODI MD (95% CI) = −9.99 (–22.01 to 2.02); *P* =NR	None	High	
	Diet programs versus inactive controls				
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR	• AHI MD (95% CI) = −12.27 (–18.79 to −5.75); *P* = NR	None	High	

Table 26: Summary of Change in AHI/ODI From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 2 to 144 weeks of study duration				
Ashrafian 2015[61]	*Weight-loss programs pre versus post*				Non-surgical weight-loss programs were associated with a significant reduction in AHI, when pre- and post-treatment were compared.
	825 patients from 20 studies (1987 to 2014): • Mild-to-severe OSA (mean AHI range: 10 to 90 events/hour) • Overweight to obese (mean BMI range: 29.8 to 54 kg/m^2) • 1 to 94.3 months of study duration	• AHI MD (95% CI) = −11.39 (–14.98 to −7.81); $P < 0.00001$; $I^2 = 82\%$	None	Mixed	
Mitchell 2014[73]	*Weight-loss programs versus inactive controls*				Intensive weight-loss programs were associated with a significant reduction in AHI, when compared with inactive controls.
	410 patients from 4 RCTs (2008 to 2009): • Mild-to-severe OSA (AHI threshold range: ≥ 5 to ≥ 15 events/hour) • Overweight to obese (BMI range: 28 to 40 kg/m^2) • 8 weeks to 12 months of study duration	• AHI MD (95% CI) = −16.09 (–25.64 to −6.54); $P = 0.001$; $I^2 = 92.2\%$ • ODI MD (95% CI) = −14.18 (–24.23 to −4.13); $P = 0.006$; $I^2 = 83.5\%$	None	High (for the RCTs included in the MA)	
Araghi 2013[76]	*Weight-loss programs versus inactive controls or pre versus post*				Weight-loss programs were associated with a significant reduction in AHI, when compared with inactive control and when pre- and post-treatment were compared. There was evidence of greater effects of weight-loss programs on
	519 patients from 7 RCTs (2006 to 2011) and 256 patients from 9 before-and-after studies (1987 to 2011): • Mild-to-severe OSA (mean AHI range: 10.0 to 66.5 events/hour)	• RCTs only: AHI MD (95% CI) = –6.04 (−11.18 to –0.90); $P = 0.02$; $I^2 = 86\%$ • Before-and-after studies only: ○ AHI MD (95% CI) =	Subgroup analysis: • Baseline AHI: ○ RCTs only: - < 15 events/hour: AHI MD (95% CI) = –1.99 (–5.58 to 1.61); $I^2 = 48\%$	Mixed	

Table 26: Summary of Change in AHI/ODI From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Overweight to obese (mean BMI range: 26.5 to 54.6 kg/m^2) • 1 to 2 years of study duration, where reported	–12.26 (–18.51 to −6.02); *P* =0.0001; I^2 = 88% ○ ODI MD (95% CI) = –18.91 (–23.40 to −14.43); *P* < 0.00001; I^2 = 5%	- 15 to 25 events/hour: AHI MD (95% CI) = −9.08 (–12.87 to −5.30); I^2 = 0% - ≥ 25 events/hour: AHI MD (95% CI) = –4.91 (–21.97 to 12.15); I^2 = 93% ○ Before-and-after studies only: - < 15 events/hour: −4.90 (–6.43 to −3.37); I^2 = NA - 15 to 25 events/hour: –8.72 (–14.19 to –3.25); I^2 = 0% - ≥ 25 events/hour: −15.60 (–22.95 to −8.24); I^2 = 71% • Change in BMI: ○ RCTs only: - 0 to 3 kg/m^2: –7.12 (–9.14 to –5.10); I^2 = 12% - 3 to 5 kg/m^2: –4.11 (–5.89 to –2.33); I^2 = 0% - ≥ 5 kg/m^2: –13.74 (−35.10 to 7.61); I^2 = 95%		AHI with increasing baseline AHI and shorter treatment durations, when pre- and post-treatment were compared but not when compared with inactive controls. The greatest source of heterogeneity appeared to be studies with higher baseline AHI and also those with greater change in BMI.

Table 26: Summary of Change in AHI/ODI From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			○ Before-and-after studies only: - 0 to 3 kg/m^2: –10.50 (–16.46 to –4.53); I^2 = 0% - 3 to 5 kg/m^2: –15.00 (–25.44 to –4.56); I^2 = NA - ≥ 5 kg/m^2: –12.30 (−20.92 to –3.68); I^2 = 92% • Treatment duration: ○ RCTs only: - ≤ 12 weeks: –8.78 (–15.65 to –1.87); I^2 = 88% - < 12 weeks: –0.67 (–11.18 to 9.83); I^2 = 88% ○ Before-and-after studies only: - ≤ 12 weeks: –14.79 (–24.41 to –5.17); I^2 = 69% - < 12 weeks: –12.66 (–19.85 to –5.47); I^2 = 76% Meta-regression analysis: • For every event/hour increase in baseline AHI,		

Table 26: Summary of Change in AHI/ODI From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			change in AHI was additionally reduced by 0.41 event/hour (P = 0.001). • There was no significant association between weight loss and change in AHI (P = 0.186).		
Thomasouli 2013[19]	*Weight-loss programs versus inactive controls*				Intensive weight-loss programs were associated with a significant reduction in AHI, when compared with usual care.
	554 patients from 6 RCTs (2008 to 2012): • Mild-to-severe OSA (mean AHI range: 9.7 to 46.2 events/hour) • Overweight to obese (mean BMI range: 28.2 to 36.7 kg/m^2) • 2 to 12 months of study duration	• AHI MD (95% CI) = −4.55 (–7.12 to –1.98); P =0.041; I^2 = 54.4%	None	Mixed	
Balk 2011[5]	*Weight-loss programs versus inactive controls*				Intensive weight-loss programs were associated with a significant reduction in AHI, when compared with inactive controls.
	345 patients from 3 RCTs (2009): • Mild-to-severe OSA (mean AHI range: 9 to 37 events/hour) • Overweight to obese (BMI range: 31.4 to 36.7 kg/m^2) • (in 1 RCT) 100% diabetes • 9 weeks to 1 year of study duration	• Intensive intervention versus conservative intervention as control: change in AHI (95% CI) = –4.4 (–7.6 to −1.0); P = 0.011 • Intensive intervention versus usual diet as control: change in AHI (95% CI) = –23 (–30 to –15); P < 0.001	None	Moderate	

Table 26: Summary of Change in AHI/ODI From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
		• Intensive intervention versus diabetes support and education as control: change in AHI (95% CI) = –9.7 (−13.6 to –5.7); *P* < 0.001 • No MA			

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; MA = meta-analysis; MD = mean difference; MR = meta-regression; NA = not applicable; NR = not reported; ODI = oxygen desaturation index; OR = odds ratio; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; RDI = respiratory disturbance index; RR = risk ratio; SR = systematic review.

Table 27: Summary of Change in AHI From Combination Therapy Versus No Treatment

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*TRDs plus positional therapy (i.e., posture alarm) versus no treatment*				There was no significant difference between TRDs plus posture alarm and no treatment in reducing AHI.
	60 patients from 1 RCT (1991): • Mild-to-severe OSA (AHI threshold: > 12.5 events/hour) • Comorbidities: NR • Study duration: NR	• AHI MD: no significant differences between combination therapy and no treatment • No MA	None	Low	

AHI = Apnea–Hypopnea Index; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCT = randomized controlled trial; TRD = tongue-retaining device.

Table 28: Summary of Change in AHI/ODI From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus OAs*				There was a moderate effect size, favouring CPAP over OAs, for the reduction of AHI.
	139 (included) or 132 (analyzed) patients from 2 RCTs (2004 and 2013): • Moderate OSA (mean AHI range: 21.3 to 26.2 events/hour) • Overweight to obese (mean BMI range: 27.8 to 31.1 kg/m^2) • 60 days to 3 months of study duration	• AHI Hedges' g (95% CI) = –0.90 (–1.11 to –0.69); P < 0.001; I^2 = 0%	None	Very low to low	
Iftikhar 2016[55]	*CPAP versus MADs*				AHI and ODI were significantly decreased with CPAP, compared with MADs.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI and 15 RCTs provided ODI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• AHI MD (95% CI) = –10.06 (−14.21 to –5.91); P = NR • ODI MD (95% CI) = –7.82 (−13.04 to –2.59); P = NR	None	High	
Sharples 2016[59]	*CPAP versus MADs*				CPAP had a significantly greater effect in reducing AHI, compared with MADs, regardless of baseline OSA severity, baseline ESS, or treatment durations.
	746 (included) or 735 (analyzed) patients from 13 RCTs (1996 to 2013): • Moderate-to-severe OSA (mean AHI or DI range: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 35.1 kg/m^2) • 4 to 26 weeks of study duration	• AHI MD (95% CI) = –7.03 (−8.66 to –5.41); P < 0.001; I^2 = 51.9%	Subgroup analysis: • Baseline AHI:[a] ○ Moderate: AHI MD (95% CI) = –7.48 (−9.19 to –5.77); P < 0.001; I^2 = 28% ○ Severe: AHI MD (95% CI) = –7.22 (–11.25 to –3.20); P < 0.001;	Moderate	

Table 28: Summary of Change in AHI/ODI From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			I^2 =74% • Baseline ESS:[b] ○ Moderate: AHI MD (95% CI) = –6.70 (−8.54 to –4.86); P < 0.001; I^2 = 57% • Treatment duration: ○ 2 to 12 weeks: AHI MD (95% CI) = –7.19 (−9.12 to –5.25); P < 0.001; I^2 = 59% ○ > 12 weeks: AHI MD (95% CI) = –6.78 (−10.31 to –3.25); P < 0.001; I^2 = 42%		
Okuno 2014[74]	*CPAP versus OAs*				CPAP was significantly more effective than OAs in reducing AHI.
	278 (included) or 200 (analyzed) patients from 3 RCTs (2007 to 2011): • Moderate-to-severe OSA (mean AHI range: 20.9 to 40.3 events/hour) • Comorbidities: NR • 8 weeks to 6 months of study duration	• AHI MD (95% CI) = –6.11 (−8.98 to 3.24); P < 0.0001; I^2 = 63%	None	Low to moderate	
Li 2013[77]	*CPAP versus OAs*				CPAP was significantly more effective than OAs in reducing AHI.
	471 patients from 9 RCTs (1996 to 2011): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 6 to 48 weeks of study duration	Crossover trials (from 6 RCTs): • AHI MD (95% CI) = –8.25 (−10.61 to −5.89); P < 0.001; I^2 = 68%	None	Low	

Table 28: Summary of Change in AHI/ODI From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
		Parallel-group trials (from 3 RCTs): • AHI MD (95% CI) = –5.96 (−8.51 to –3.40); P < 0.001; I^2 = 0%			
Balk 2011[5]	*CPAP versus MADs*				CPAP was significantly more effective than OAs in reducing AHI.
	393 patients from 9 RCTs (1996 to 2009): • Moderate-to-severe OSA (mean AHI range: 18 to 40 events/hour) • Overweight to obese (mean BMI range: 26.7 to 34.1 kg/m^2) • 2 weeks to 4 months of study duration	• AHI MD (95% CI) = –7.69 (−10.09 to −5.29); P < 0.001; I^2 = 60.3%	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; DI = desaturation index; ESS = Epworth Sleepiness Scale; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliances; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; RCT = randomized controlled trial; RDI = respiratory disturbance index; SR = systematic review.

[a] Baseline AHI: mild, 5 to 14; moderate, 15 to 30; severe, > 30 events/hour.

[b] Baseline ESS: normal/mild, 0 to 9; moderate, 10 to 15: severe, 16 to 24.

Table 29: Summary of Change in AHI/ODI From CPAP Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus exercise programs*				CPAP was substantially more effective than exercise at reducing AHI.
	16 patients from 1 RCT (2013): • Moderate OSA (mean AHI range: 26.2 events/hour)	• AHI Hedges' g (SE) = –2.01 (0.59)	None	Very low to low	

Table 29: Summary of Change in AHI/ODI From CPAP Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Overweight (mean BMI range: 27.8 kg/m^2) • 60 days of study duration				
Iftikhar 2016[55]	*CPAP versus exercise programs*				AHI was significantly decreased with CPAP, compared with diet programs. However, there was no significant difference between CPAP and exercise programs in reducing AHI or ODI.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI and 15 RCTs provided ODI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• AHI MD (95% CI) = –8.04 (–17.00 to 0.92); *P* = NR • ODI MD (95% CI) = –10.41 (–23.35 to 2.52); *P* = NR	None	High	
	CPAP versus diet programs				
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9	• AHI MD (95% CI) = –13.00 (–20.28 to –5.72); *P* = NR	None	High	

Table 29: Summary of Change in AHI/ODI From CPAP Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration				
Ha 2014[72]	*CPAP versus positional therapy (i.e., backpacks, thoracic anti-spine bands, or the Zzoma positional sleeper)*				CPAP was associated with a significant reduction in AHI, compared with positional therapy.
	71 patients from 3 RCTs (1999 to 2010): • Mild-to-moderate OSA (mean AHI range: 13 to 22.7 events/hour) • Obese (mean BMI range: 30 to 31 kg/m^2) • 3 nights to 9 weeks of study duration	• AHI MD (95% CI) = –4.28 (–7.83 to –0.72); P = 0.02; I^2 = 70%	None	Moderate	
Balk 2011[5]	*CPAP versus positional therapy (i.e., shoulder-head elevation pillows or devices worn on the back)*				CPAP was associated with a significant reduction in AHI, compared with positional therapy.
	94 patients from 3 RCTs (1999 to 2008): • Moderate OSA (mean AHI range: 18 to 27 events/hour) • Obese (mean BMI range: 30 to 34 kg/m^2) • 2 weeks to 1 month of study duration	• AHI MD: significant reductions, ranging from 6.1 to 16 events/hour, associated with CPAP compared with positional therapy • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; MA = meta-analysis; MD = mean difference; MR = meta-regression; NA = not applicable; NR = not reported; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; RDI = respiratory disturbance index; SE = standard error; SR= systematic review.

Table 30: Summary of Change in AHI From MADs Versus TRDs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*MADs versus TRDs*				There was no significant difference between MADs and TRDs in reducing AHI.
	22 patients from 1 RCT (2009): • Moderate OSA (mean AHI: 27.0 events/hour) • Overweight (mean BMI: 29.3 kg/m^2) • 1 week of study duration	• AHI MD (95% CI) = –1 (–9.7 to 7.7); *P* = NR	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCT = randomized controlled trial; TRD = tongue-retaining device.

Table 31: Summary of Change in AHI/ODI From MADs Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Iftikhar 2016[55]	*MADs versus exercise programs*				There was no significant difference between MADs and diet or exercise in reducing AHI or ODI.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI and 15 RCTs provided ODI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• AHI MD (95% CI) = 2.02 (–7.31 to 11.37); *P* = NR • ODI MD (95% CI) = 2.59 (–16.14 to 10.96); *P* = NR	None	High	
	MADs versus diet programs				
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI:	• AHI MD (95% CI) = –2.93	None	High	

Table 31: Summary of Change in AHI/ODI From MADs Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	(–10.73 to 4.87); *P* = NR			

AHI = Apnea–Hypopnea Index; CI = confidence interval; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; ODI = oxygen desaturation index; SR = systematic review.

Table 32: Summary of Change in AHI From Diet Versus Exercise

Study	Patient Characteristics	Pooled Estimates from MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Iftikhar 2016[55]	*Diet programs versus exercise programs*				There was no significant difference between diet and exercise programs in reducing AHI.
	Network MA: 7,882 patients from 80 RCTs (1985 to 2015), where 56 RCTs provided AHI: • (for the 7,882 patients included in the SR) Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • 2 to 144 weeks of study duration	• AHI MD (95% CI) = 4.96 (–5.82 to 15.74); *P* = NR	None	High	

AHI = Apnea–Hypopnea Index; CI = confidence interval; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OSA = obstructive sleep apnea; RCTs = randomized controlled trials.

Table 33: Summary of Change in AHI/RDI From TRDs Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Lazard 2009[113]	*TRDs pre versus post*			TRDs were associated with a significant reduction in AHI.
	84 patients: • Mean AHI ± SD: 37 ± 19.5 events/hour • Mean BMI ± SD: 26 ± 3.8 kg/m^2	• Mean AHI ± SD (n=55): ○ Before: 38 ± 22.2 events/hour ○ After: 14 ± 13.2 events/hour ○ Difference: *P* < 0.001	None	
Dort 2008[115]	*TRDs pre versus post*			TRDs with suction had significant reductions in RDI; TRDs without suction had non-significant reductions in RDI. TRDs with suction had greater reductions in RDI than TRDs without suction.
	38 patients: • Mean RDI ± SD: 15.5 ± 17.7 • Mean BMI ± SD: 29.4 ± 5.7 kg/m^2	• Mean RDI ± SD (n = 32): ○ Before: 15.5 ± 17.6 events/hour ○ After: - No suction: 13.5 ± 15.4, *P* = 0.391 - Suction: 8.9 ± 7.6, *P* = 0.006 ○ Difference: - No suction: *P* = 0.391 - Suction: *P* = 0.006 - Suction versus no suction: 4.9 (95% CI: 0.85 to 8.9), *P* = 0.019	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; SD = standard deviation; TRD = tongue-retaining device.

Table 34: Summary of Change in AHI From GTA Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Kuscu 2015[91]	*GTA pre versus post*			Genioglossus advancement surgery was associated with a significant reduction in AHI.
	17 patients: • Mean AHI ± SD: 27.5 ± 8 events/hour • Mean BMI ± SD: 30.2 ± 4 kg/m^2	• Mean AHI ± SD: ○ Before: 27.5 ± 8 events/hour (range: 15.6 to 44.3) ○ After: 17.3 ± 12.6 events/hour (range: 4.1 to 40.4) ○ Difference: *P* = 0.002	None	
Santos Junior 2007[117]	*GTA pre versus post*			Genioplasty for genioglossus advancement significantly reduced OSA severity and may provide an alternate treatment for non-obese OSA patients with hypopharynx obstruction.
	10 patients: • AHI range: 5 to 30 events/hour • BMI threshold: < 30 kg/m^2	• Mean AHI ± SD: ○ Before: 12.38 ± 4.62 events/hour ○ After: 4.40 ± 5.7 events/hour ○ Difference: *P* < 0.001	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; GTA = genial tubercle advancement; OSA = obstructive sleep apnea; SD = standard deviation.

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Benoist 2016[78]	*Positional therapy (i.e., sleep position trainers) pre versus post*			Positional therapy with a sleep position trainer significantly improved AHI and ODI in patients with positional OSA.
	33 positional OSA patients: • Median AHI: 18.3 (IQR: 13.7 to 24.0) events/hour • Mean BMI ± SD: 27.9 ± 2.8 kg/m^2	• Median AHI: ○ Before (n = 33): 18.3 (IQR: 13.7 to 24.0) events/hour ○ After 3 months (n = 32): 12.5 (IQR: 4.5 to 21.8) events/hour	• Sleep position: ○ Supine median AHI: - Before (n = 33): 43.0 (IQR: 24.2 to 59.6) events/hour - After 3 months (n = 32): 32.4 (IQR: 14.2 to 66.2) events/hour	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
		○ Difference: *P* = 0.034 • Median ODI: ○ Before (n = 33): 21.0 (IQR: 14.7 to 29.2) events/hour ○ After 3 months (n = 32): 12.9 (IQR: 5.5 to 23.3) events/hour ○ Difference: *P* = 0.011	- Difference: *P* = 0.023 ○ Non-supine median AHI: - Before (n = 33): 4.8 (IQR: 2.3 to 8.6) events/hour - After 3 months (n = 32): 7.9 (IQR: 3.3 to 16.3) events/hour - Difference: *P* = 0.002	
Scarlata 2016[81]	*Positional therapy (i.e., neck position devices) pre versus post*			The neck position device was effective at significantly improving AHI, ODI, and RDI in patients with positional OSA.
	20 positional OSA patients: • Mean AHI ± SD: 16.8 ± 9.5 events/hour • Mean BMI ± SD: 28.9 ± 4.0 kg/m^2	• Mean AHI ± SD: ○ Before: 16.8 ± 9.5 events/hour ○ After 3 nights: 4.4 ± 5.5 events/hour ○ Difference: *P* < 0.001 • Mean ODI ± SD: ○ Before: 13.7 ± 7.5 events/hour ○ After 3 nights: 3.8 ± 5.2 events/hour ○ Difference: *P* < 0.001 • Mean RDI ± SD: ○ Before: 20.0 ± 9.5 events/hour ○ After 3 nights: 5.2 ± 5.6 events/hour ○ Difference: *P* < 0.001	None	
Afrashi 2015[82]	*Positional therapy (i.e., pillows for prone positioning) pre versus post*			A pillow for prone positioning significantly improved AHI and ODI in patients with mild-to-moderate OSA.
	29 patients: • Mean AHI ± SD: 15.5 ± 6.2 events/hour	• Mean AHI ± SD: ○ Before: 15.5 ± 6.2 events/hour	None	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
	• Mean BMI ± SD: 28.9 ± 3.2 kg/m^2	○ After 2 nights: 10.3 ± 12.8 events/hour ○ Difference (95% CI): –5.2 (–0.1 to −10.3) events/hour, *P* = 0.04 • Mean ODI (95% CI): ○ Before: 13.0 (10.0 to 16.1) events/hour ○ After 2 nights: 4.0 (1.5 to 7.6) events/hour ○ Difference: –6.7 (−11.8 to –1.4) events/hour, *P* = 0.04		
Bidarian-Moniri 2015[83]	*Positional therapy (i.e., mattresses and pillows for prone positioning) pre versus post*			Positional therapy with a mattress and pillow for prone positioning significantly improved AHI and ODI levels in patients with OSA.
	14 patients: • Mean AHI: 26 events/hour (range: 6 to 53 events/hour)	• Mean AHI: ○ Before: 26 events/hour (range 6 to 53) ○ After 4 weeks: 8 events/hour (range 1 to 26) ○ Difference: *P* < 0.001 • Mean ODI: ○ Before: 21 events/hour (range 6 to 51) ○ After 4 weeks: 7 events/hour (range 1 to 25) ○ Difference: *P* < 0.001	None	
Bidarian-Moniri 2015[84]	*Positional therapy (i.e., mattresses and pillows for prone positioning) pre versus post*			Positional therapy with the mattress and a pillow for prone positioning significantly improved AHI and ODI levels in patients with OSA.
	27 patients: • Mean AHI: 31 events/hour (range: 5 to 93 events/hour)	• Median AHI: ○ Before: 23 events/hour ○ After 2 nights: 7	• Positional OSA: ○ Positional OSA: - Median AHI:	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
	• Mean BMI: 28 kg/m^2 (range: 23 to 36 kg/m^2)	events/hour ○ Difference: *P* < 0.001 • Median ODI: ○ Before: 21 events/hour ○ After 2 nights: 6 events/hour ○ Difference: *P* < 0.001	▪ Before: 20 events/hour ▪ After 2 nights: 5 events/hour ▪ Difference: *P* < 0.001 - Median ODI ▪ Before: 19 events/hour ▪ After 2 nights: 5 events/hour ▪ Difference: *P* < 0.001 ○ Non-positional OSA: - Median AHI: ▪ Before: 45 events/hour ▪ After 2 nights: 22 events/hour ▪ Difference: NR - Median ODI: ▪ Before: 22 events/hour ▪ After 2 nights: 11 events/hour ▪ Difference: NR	
Chen 2015[85]	*Positional therapy (i.e., head-positioning pillows) pre versus post*			The use of a head-positioning pillow had no significant impact on reducing ODI in patients with positional OSA.
	25 patients: • Median AHI: 7.0 events/hour (IQR: 6.0 to 15.2 events/hour) • Median BMI: 24.8 kg/m^2 (IQR: 23.1 to 26.4 kg/m^2)	• Median ODI: ○ Before (regular pillow): 4.2 events/hour (IQR: 1.5 to 8.9) ○ After 3 nights (head-positioning pillow): 3.5 events/hour (IQR: 1.6 to 8.5) ○ Difference: *P* = 0.247	• Baseline weight: ○ Normal-weight patients (n = 13) median ODI: - Before (regular pillow): 4.0 events/hour (IQR: 1.3 to 7.7) - After 3 nights (head-positioning pillow): 3.4 events/hour (IQR: 1.0 to 9.1) - Difference: *P* = 0.366 ○ Overweight patients (n = 12) median ODI: - Before (regular pillow): 4.4 events/hour (IQR: 2.7 to 9.1) - After 3 nights (head-	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
			positioning pillow): 4.3 (IQR: 2.3 to 8.6) - Difference: *P* = 0.346	
de Vries 2015[86]	*Positional therapy (i.e., commercial devices or self-made constructions) pre versus post*			Commercial devices or self-made constructions significantly reduced median AHI.
	40 positional OSA patients: • Median AHI: 14.5 events/hour (IQR: 10.7 to 19.6 events/hour) • Mean BMI ± SD: 28.0 ± 4.1 kg/m^2	• Median AHI: ○ Before: 14.5 events/hour (IQR: 10.7 to 19.6) ○ After: 5.9 (IQR: 3.1-8.5) ○ Difference: *P* < 0.001	• Sleep position: ○ Supine median AHI: - Before: 38.0 (IQR: 24.0 to 52.4) - After: 8.5 (IQR: 0 to 21.5) - Difference: *P* < 0.001 ○ Non-supine median AHI: - Before: 3.9 (IQR: 2.2 to 7.1) - After: 4.3 (IQR: 1.4 to 8.9) - Difference: *P* = 0.2	
Eijsvogel 2015[88]	*Positional therapy (i.e., tennis balls or sleep position trainers) pre versus post*			Both tennis balls and sleep position trainers significantly reduced AHI, ODI, and RDI in patients with positional OSA.
	26 (TBT) or 29 (SPT) positional OSA patients: • Mean AHI ± SD: 13.1 ± 9.1 (TBT) or 11.4 ± 4.9 (SPT) events/hour • Mean BMI ± SD: 26.8 ± 3.0 (TBT) or 27.6 ± 4.5 (SPT) kg/m^2	TBT patients: • Mean AHI: ○ Baseline AHI ± SD: - TBT: 13.1 ± 9.1 events/hour - SPT: 11.4 ± 4.9 events/hour ○ After 1 month AHI (95% CI): - TBT: 5.8 (0.2 to 23.1) events/hour - SPT: 3.9 (0.4 to 30.8) events/hour ○ Difference: - TBT: *P* < 0.05 - SPT: *P* < 0.05 • Mean ODI:	• Sleep position: ○ Supine: - Before AHI ± SD: ▪ TBT: 37.3 ± 24.0 events/hour ▪ SPT: 30.7 ± 15.3 events/hour - After 1 month AHI (95% CI): ▪ TBT: 0.0 (0.0 to 116) events/hour ▪ SPT: 0.0 (0.0 to 64.2) events/hour - Difference: ▪ TBT: *P* < 0.01 ▪ SPT: *P* < 0.01 ○ Non-supine: - Before AHI (95% CI):	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
		○ Baseline ODI ± SD: - TBT: 10.9 ± 7.7 events/hour - SPT: 9.9 ± 5.0 events/hour ○ After 1 month ODI (95% CI): - TBT: 5.4 (0.4 to 15.1) events/hour - SPT: 4.4 (0.5 to 33.8) events/hour ○ Difference: - TBT: $P < 0.01$ - SPT: $P < 0.05$ • Mean RDI: ○ Baseline RDI ± SD: - TBT: 13.3 ± 9.1 events/hour - SPT: 11.9 ± 4.6 events/hour ○ After 1 month RDI (95% CI): - TBT: 6.0 (0.2 to 14.2) events/hour - SPT: 3.9 (0.4 to 30.8) events/hour ○ Difference: - TBT: $P < 0.01$ - SPT: $P < 0.01$	▪ TBT: 3.3 (0.0 to 13.7) events/hour ▪ SPT: 3.9 (0.5 to 13.0) events/hour - After 1 month: ▪ TBT: 5.0 (0.2 to 14.2) events/hour ▪ SPT: 3.6 (0.4 to 30.8) events/hour - Difference: ▪ TBT: not significant ▪ SPT: not significant	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Jackson 2015[90]	*Positional therapy (i.e., sleep position modification devices) versus inactive controls*			A sleep position modification device was significantly more effective in reducing AHI, compared with sleep hygiene advice.
	47 (sleep position modification device) or 39 (sleep hygiene advice) positional OSA patients: • Mean AHI ± SD: 20.1 ± 8.8 (sleep position modification device) or 21.8 ± 10.1 (sleep hygiene advice) events/hour • Mean BMI ± SD: 30.0 ± 5.3 (sleep position modification device) or 30.9 ± 7.7 sleep hygiene advice) kg/m^2	• Mean AHI ± SD: ○ Before: - Sleep position modification device: 20.1 ± 8.8 events/hour - Sleep hygiene advice: 21.8 ± 10.1 events/hour ○ After 4 weeks: - Sleep position modification device: 10.8 ± 9.9 events/hour - Sleep hygiene advice: 16.8 ± 15.9 events/hour ○ Difference (device versus advice): *P* = 0.013	None	
Levendowski 2014[96]	*Positional therapy (i.e., neck position devices) pre versus post*			Neck position devices were effective at significantly reducing supine sleep and improving AHI in patients with positional OSA.
	30 positional OSA patients: • Mean AHI ± SD: 24.7 ± 14.7 events/hour • Mean BMI ± SD: 28 ± 3.4 kg/m^2	• Mean AHI ± SD: ○ Before: 24.7 ± 14.7 ○ After 30 nights: 7.5 ± 7.7 ○ Difference: *P* < 0.00001	• Sleep position: ○ Supine: - Mean AHI ± SD: ▪ Before: 44.9 ± 25.5 events/hour ▪ After 30 nights: 4.5 ± 12.7 events/hour ▪ Difference: *P* < 0.00001	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
			○ Non-supine: - Mean AHI ± SD: ▪ Before: 8.1 ± 7.9 events/hour ▪ After 30 nights: 7.1 ± 7.8 events/hour ▪ Difference: *P* = 0.300 • OSA severity: ○ Mild OSA (n = 11): - AHI < 10 and > 50% decrease: 81.8% (n = 9) - AHI > 50% reduction: 0% (n = 0) - AHI > 35% reduction: 9.1% (n = 1) - No response: 9.1% (n = 1) ○ Moderate OSA (n = 10): - AHI < 10 and > 50% decrease: 80.0% (n = 8) - AHI > 50% reduction: 0% (n = 0) - AHI > 35% reduction: 0% (n = 0) - No response: 20.0 (n = 2) ○ Severe OSA (n = 9): - AHI < 10 and > 50% decrease: 55.6% (n = 5) - AHI > 50% reduction: 33.3% (n = 3) - AHI > 35% reduction: 11.1% (n = 1) - No response: 0% (n = 0)	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
van Maanen 2013[99]	*Positional therapy (i.e., sleep position devices) pre versus post*			Sleep position trainers proved to be a significantly effective treatment for patients with positional OSA.
	31 positional OSA patients: • Median AHI: 16.4 events/hour (IQR: 6.6 to 29.9 events/hour) • Mean BMI ± SD: 27.0 ± 3.7 kg/m^2	• Median AHI: ○ Before: 16.4 events/hour (IQR: 6.6 to 29.9) ○ After 29 ± 2 nights: 5.2 events/hour (IQR: 0.5 to 46.5) ○ Difference: *P* < 0.001	• Sleep position: ○ Supine median AHI: - Before: 35.7 (IQR: 9.3 to 81.0) - After 29 ± 2 nights: 0.0 (IQR: 0.0 to 100.7) - Difference: *P* < 0.001 ○ Non-supine median AHI: - Before: 3.2 (IQR: 0.0 to 16.2) - After 29 ± 2 nights: 4.3 (IQR: 0.1 to 48.0) - Difference: *P* = 0.052	
Heinzer 2012[102]	*Positional therapy (i.e., tennis balls) pre versus post*			After 1 night of device use, there was a significant decrease in AHI. After 3 months of device use, there was no significant decrease in AHI, when compared with the first night of device use.
	16 positional OSA patients: • Mean AHI ± SD: 26.7 ± 17.5 events/hour • Mean BMI ± SD: 25.4 ± 4.1 kg/m^2	• Mean AHI: ○ Before: 26.7 ± 17.5 events/hour ○ After first night with positional device: 6.0 ± 3.4 events/hour ○ After 3 months: 10.3 ± 8.2 ○ Difference: - Before versus T0: *P* = 0.0002 - T0 versus T3: *P* = 0.58	• Sleep position: ○ Supine: - Mean AHI ± SD: ▪ Before: 54.0 ± 21.2 events/hour ▪ After first night with positional device (T0): 32.9 ± 19.2 events/hour ▪ After 3 months (T3): 39.4 ± 24.6 ○ Non-supine: - Mean AHI ± SD: ▪ Baseline: 5.6 ± 5.0 events/hour ▪ After first night with positional device (T0): 5.0 ± 3.6 events/hour ▪ After 3 months (T3): 8.7 ± 7.4 events/hour	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
van Maanen 2012[104]	*Positional therapy (i.e., sleep position modification devices) pre versus post*			Patients with the device in the on or off modes experienced significantly more reductions on OSA severity than wearing no device.
	30 positional OSA patients: • Mean AHI ± SD: 27.7 ± 2.4 events/hour • Mean BMI ± SD: 27.7 ± 3.6 kg/m^2	• Mean AHI: ○ Before (i.e., no device): 27.7 ± 2.4 events/hour ○ After: - Device attached in OFF mode: 23.5 ± 2.6 events/hour - Device attached in ON mode: 12.8 ± 2.2 ○ Difference: - Before versus device in OFF mode: *P* = 0.04 - Before versus device in ON mode: *P* = 0.00 - Device in ON versus OFF mode: *P* = 0.00	• Sleep position: ○ Supine: - Mean AHI ± SD: ▪ Baseline (no device): 59.7 ± 3.6 events/hour ▪ Device attached in OFF mode: 45.0 ± 4.8 events/hour ▪ Difference between baseline versus device in OFF mode: *P* = 0.00 ▪ Device attached in ON mode: 12.5 ± 3.1 events/hour ▪ Difference between baseline versus device in ON mode: *P* = 0.50 ▪ Difference between ON versus OFF modes: *P* = 0.00 ○ Non-supine: - Mean AHI ± SD: ▪ Baseline (no device): 6.7 ± 1.2 events/hour ▪ Device attached in OFF mode: 13.4 ± 2.7 events/hour ▪ Difference between baseline versus device in OFF mode: *P* = 0.03	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
			▪ Device attached in ON mode: 11.2 ± 2.2 events/hour ▪ Difference between baseline versus device in ON mode: *P* = 0.03 ▪ Difference between ON versus OFF modes: *P* = 0.49	
Bignold 2011[105]	*Positional therapy (i.e., sleep position modification devices) pre versus post*			Position recording and supine avoidance devices significantly reduced AHI.
	15 patients: • Mean AHI ± SD: 24.1 ± 10.5 events/hour • Mean BMI ± SD: 28.8 ± 2.5 kg/m^2	• AHI: ○ Difference: 45% reduction with active treatment, *P* = 0.03	None	
Kim 2011[108]	*Positional therapy (i.e., sleep position modification devices) pre versus post*			There was a significant improvement in AHI and ODI in patients with positional OSA.
	14 positional OSA patients: • Mean AHI ± SD: 22.8 ± 9.3 events/hour • Mean BMI ± SD: 26.3 ± 3.6 kg/m^2	• Mean AHI: ○ Baseline: 22.8 ± 9.3 events/hour ○ Experimental examination: 9.3 ± 8.3 events/hour ○ Control examination: 13.5 ± 9.0 ○ Differences: *P* < 0.001 • Mean ODI: ○ Baseline: 19.0 ± 9.9 ○ Experimental examination: 8.6 ± 8.2 ○ Control examination: 10.4 ± 8.1 ○ Differences: *P* < 0.001	• Sleep position: ○ Supine: - Mean AHI ± SD: ▪ Baseline: 33.2 ± 13.9 events/hour ▪ Experimental examination: 25.6 ± 22.0 events/hour ▪ Control examination: 7.6 ± 13.1 ▪ Differences: *P* < 0.001 ○ Non-supine: - Mean AHI ± SD: ▪ Baseline: 5.6 ± 7.0 events/hour ▪ Experimental examination: 6.7 ± 7.1 events/hour	

Table 35: Summary of Change in AHI/RDI/ODI From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
			▪ Control examination: 1.1 ± 7.3 ▪ Differences: *P* = 0.585	
Loord 2007[116]	*Positional therapy (i.e., the Positioner) pre versus post*			The Positioner used in this study significantly reduced OSA symptoms in patients with OSA.
	18 positional OSA patients: • Mean AHI ± SD: 21.8 ± 12.0 events/hour	• Mean AHI ± SD: ○ Before: 21.8 ± 12.0 events/hour ○ After 10 months: 14.3 ± 15.2 events/hour ○ Difference: *P* = 0.02	None	
Oksenberg 2006[118]	*Positional therapy (i.e., tennis balls) pre versus post*			Most of the patients who used tennis balls had significant reductions in AHI.
	78 positional OSA patients: • Mean AHI ± SD: 25.5 ± 17.3 events/hour • Mean BMI ± SD: 28.1 ± 3.7 kg/m^2	• Mean AHI ± SD: ○ Before (n = 12): 46.5 ± 19.9 events/hour ○ After (n = 12): 17.5 ± 19.4 events/hour ○ Difference: *P* < 0.002	• Sleep position: ○ Supine: - Mean AHI ± SD: ▪ Before (n = 12): 57.0 ± 22.4 events/hour ▪ After (n = 12): 44.4 ± 28.7 events/hour ▪ Differences: *P* = NR ○ Non-supine: - Mean AHI ± SD: ▪ Before (n = 12): 11.6 ± 8.2 events/hour ▪ After (n = 12): 13.8 ± 22.0 events/hour ▪ Differences: *P* = NR	

AHI = Apnea–Hypopnea Index; AI = Apnea Index; BMI = body mass index; CI = confidence interval; HI = hypopnea index; HPP = head-positioning pillow; IQR = interquartile range; NR = not reported; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; SD = standard deviation; SPT = sleep position trainer; TBT = tennis ball technique.

Table 36: Summary of Change in AHI/RDI From Combination Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Islam 2014[95]	*MMA plus GTA pre versus post*			Maxillomandibular and mandibular advancement surgery was successful at significantly decreasing AHI values post-surgery.
	51 patients: • Mean AHI ± SD: 42 ± 17 • Mean BMI ± SD: 26.4 ± 3.0 kg/m^2	• Mean AHI ± SD: ○ Before: 42 ± 17 events/hour ○ After: 8 ± 7 events/hour ○ Difference: *P* < 0.001	None	
Dort 2012[101]	*MADs plus TRDs pre versus post*			The combination of mandibular advancement and tongue retention had a significant decrease in RDI values post-treatment.
	41 patients: • Mean RDI ± SD: 33.5 ± 15.9 events/hour • Mean BMI ± SD: 32.2 ± 5.8 kg/m^2	• Mean RDI (95% CI): ○ Before (n = 41): 33.5 events/hour (28.6 to 38.4) ○ After 20 weeks: - 6 mm MADs + TRDs (n = 28): 19.2 events/hour (13.9 to 24.5) - 8 mm MADs + TRDs (n = 26): 18.1 events/hour (13.3 to 23.0) ○ Difference: - 6 mm MADs + TRDs: *P* = NR - 8 mm MADs + TRDs *P* = 0.001	None	
Bruno 2008[114]	*MMA plus GTA pre versus post*			MMA plus modified genioplasty surgery reduced RDI values, but no statistical test was conducted.
	4 patients: • RDI threshold: > 35 events/hour • Mean BMI: NR	RDI thresholds: • Before: > 35 events/hour • After: < 10 events/hour	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; NR = not reported; OSA = obstructive sleep apnea; RDI = respiratory disturbance index; SD = standard deviation; TRD = tongue-retaining device.

Table 37: Summary of Change in AHI From MADs Versus TRDs

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Sutherland 2011[109]	*MADs versus TRDs*			Both MADs and TRDs reduced AHI, but no statistical testing was conducted.
	39 patients: • Mean AHI ± SD: 26.9 ± 17.1 events/hour • Mean BMI ± SD: 29.2 ± 5.5 kg/m^2	• Mean AHI ± SD (events/hour): ○ Baseline: - MADs: 26.9 ± 17.1 - TRDs: 26.8 ± 18.1 ○ After: - MADs: 12.0 ± 12.6 - TRDs: 11.0 ± 9.1	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; MAD = mandibular advance device; SD = standard deviation; TRD = tongue-retaining device.

Table 38: Summary of Change in AHI From MADs versus MMA

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Garreau 2014[94]	*MADs versus MMA*			For patients with moderate-to-severe OSA, MMA surgery was significantly more effective than MAD treatment and may be an alternative for those who refuse or do not tolerate CPAP.
	161 (MADs) or 37 (MMA) patients: • Moderate-to-severe OSA (46.6% moderate and 53.4% severe [MADs] or 27.0% moderate and 72.1% severe [MMA]) • 17.4% (MADs) or 16.2% (MMA) obese	MMA patients: • Mean AHI ± SD: ○ Before: - MADs: 32.45 ± 15.0 events/hour - MMA: 42.76 ± 22.72 events/hour - Difference: $P < 0.001$ ○ After: - MADs: 14.88 ± 11.4 events/hour - MMA: 11.59 ± 12.11 events/hour - Difference: $P = 0.120$	None	

Table 38: Summary of Change in AHI From MADs versus MMA

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
		○ Change in AHI: - MADs: -17.57 ± 14.16 events/hour, - MMA: -31.16 ± 21.19 events/hour - Difference: *P* < 0.001		

AHI = Apnea–Hypopnea Index; CPAP = continuous positive airway pressure; MAD = mandibular advancement device therapy; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; SD = standard deviation.

Table 39: Summary of Change in AHI/ODI From Combination Therapy Versus Active Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Dieltjens 2015[87]	*MADs plus positional therapy (i.e., sleep position trainers) versus MADs or positional therapy (i.e., sleep position trainers) alone*			A combination of MADs plus a sleep position trainer led to more significant reductions in AHI than either intervention alone.
	20 patients: • Mean AHI ± SD: 24.6 ± 10.2 events/hour • Mean BMI ± SD: 26.4 ± 3.0 kg/m^2	• Mean AHI (IQR): ○ Before: - MADs plus SPT: 20.9 events/hour (17.0 to 34.0) - MADs: 20.9 events/hour (17.0 to 34.0) - SPT: 20.9 events/hour (17.0 to 34.0) ○ After: - MADs plus SPT: 5.5 events/hour (3.4 to 7.2) - MADs: 11.0 events/hour (6.6 to 14.0) - SPT: 12.8 events/hour (3.9 to 17.9) ○ Differences:	None	

Table 39: Summary of Change in AHI/ODI From Combination Therapy Versus Active Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
		- MADs plus SPT: $P < 0.008$ - MADS: $P < 0.008$ - SPT: $P < 0.008$ - MADS plus SPT, compared with MAD: $P < 0.001$ - MADS plus SPT, compared with SPT: $P < 0.008$ • Mean ODI (IQR): ○ Before: - MADs plus SPT: 7.7 events/hour (6.6 to.5) - MADs: 7.7 events/hour (6.6 to 16.5) - SPT: 7.7 events/hour (6.6 to 16.5) ○ After: - MADs plus SPT: 1.8 events/hour (1.0 to 3.0) - MADs: 3.8 events/hour (1.2 to 5.5) - SPT: 2.6 events/hour (1.0 to 4.6) ○ Difference: - MADs plus SPT: $P < 0.008$ - MADS: $P < 0.008$ - SPT: $P < 0.008$ - MADS plus SPT, compared with MAD:		

Table 39: Summary of Change in AHI/ODI From Combination Therapy Versus Active Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
		P < 0.001 - MADS plus SPT, compared with SPT: *P* = non-significant		
Ackel-D'Elia 2012[100]	*CPAP plus exercise programs versus CPAP alone*			CPAP plus exercise and CPAP both significantly reduced AHI.
	13 (CPAP plus exercise) or 19 (CPAP) patients: • Mean AHI ± SD: 40.5 ± 22.9 (CPAP plus exercise) or 42.3 ± 21.6 (CPAP) events/hour • Mean BMI ± SD: 28.0 ± 3.1 (CPAP plus exercise) or 28.5 ± 2.2 (CPAP) kg/m^2	• Mean AHI ± SD: ○ Before: - CPAP plus exercise: 40.5 ± 22.9 events/hour - CPAP: 42.3 ± 21.6 events/hour ○ After 2 months: - CPAP plus exercise: 5.9 ± 4.4, *P* < 0.05 - CPAP: 6.2 ± 4.4 ○ Difference: - CPAP plus exercise: *P* < 0.05 - CPAP: *P* < 0.05	None	
El-Solh 2011[106]	*CPAP plus MADs versus MADs alone*			The combination therapy of CPAP plus MADs and MADs alone significantly reduced AHI. The combination of CPAP plus MADs reduced AHI more so than MADs alone.
	10 patients: • Mean AHI ± SD: 23.5 ± 13.4 events/hour • Mean BMI ± SD: 26.9 ± 3.2 kg/m^2	• Mean AHI ± SD: ○ Before: 23.5 ± 13.4 ○ After 8 weeks: - CPAP plus MADs: 4.8 ± 2.8 events/hour - MADs: 11.4 ± 4.8 events/hour ○ Difference: - CPAP plus MADs: *P* < 0.05 - MADs: *P* < 0.05	None	

Table 39: Summary of Change in AHI/ODI From Combination Therapy Versus Active Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Johansson 2011[107]	*CPAP plus diet programs versus CPAP alone*			After CPAP plus a weight-loss program, patients with severe OSA experienced greater reductions in AHI, compared with CPAP alone. However, both treatments had significant reductions in AHI.
	63 patients: • Mean AHI ± SD: 36 ± 15 events/hour • BMI range: 30 to 40 kg/m^2	• Mean AHI ± SD: ○ Before: 36 events/hour ○ After 1 year of study duration: - CPAP with very-low-energy diet (0 to 9 weeks): 15 ± 9 events/hour - After full program (0 to 52 weeks): 19 ± 14 events/hour ○ Difference (MD ± SD, 95% CI): - After very-low-energy diet (0 to 9 weeks): −21 ± 16 (95% CI, −17 to −25), *P* < 0.001 - After full program (0 to 52 weeks): –17 ± 16 (95% CI, 13 to –21), *P* < 0.001	• Mean supine AHI ± SD: ○ Before: 36 events/hour ○ After 1 year of study duration: - CPAP with very-low-energy diet (0 to 9 weeks): 25 ± 17 events/hour - After full program (0 to 52 weeks): 27 ± 18 events/hour ○ Difference (MD ± SD, 95% CI): - After very-low-energy diet (0 to 9 weeks): –23 ± 21 (95% CI, –18 to −29), *P* < 0.001 - After full program (0 to 52 weeks): –21 ± 3 (95% CI, –16 to –27), *P* < 0.001	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; IQR = interquartile range; MAD = mandibular advancement device therapy; MD = mean difference; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PSG = polysomnography; SD = standard deviation; SPT = sleep position trainer.

Success or Cure Rate

Overview of Reviews

1) Oral appliances versus inactive controls

One SR[51] reported on rates of success, defined as ([mean AHI at baseline – mean AHI after treatment] / mean AHI at baseline), in adults with moderate-to-severe OSA who were overweight to obese. The SR,[51] with a sample size of 484 patients from 13 studies, reported significantly positive success rates of 0.62 with MADs, compared with pre-treatment. Study duration of the included primary studies ranged from three weeks to one year. No I^2 scores were reported. The SR[51] reported the quality of the included studies as moderate to high (**Appendix 10**). The findings of the SR are summarized in Table 40.

2) Surgery versus inactive controls

One SR[60] reported on rates of success and cure, defined as greater than 50% reductions in AHI to fewer than 10, 15, or 20 events/hour or AHI levels of fewer than five events/hour, respectively, in adults with severe OSA who were obese. The SR,[60] with a sample size of 518 patients from 45 studies, reported significantly positive success rates with MMA with or without GTA, compared with pre-treatment. Overall success rates of achieving AHI values of 10, 15, or 20 events/hour were 63.3%, 80.4%, and 85.5%, respectively. Overall cure rates of achieving AHI values of five events/hour were 38.5%. Study duration of the included primary studies ranged from two months to six months. No I^2 scores were reported. The SR[60] reported the quality of the included studies as moderate (**Appendix 10**). From subgroup analyses, the SR[60] reported that patients with a higher preoperative AHI are less likely to achieve surgical success and cure with MMA with or without GTA, compared with pre-operation. The findings of the SR are summarized in Table 41.

3) Lifestyle interventions versus inactive controls

One SR[5] reported on rates of cure, defined as AHI levels of fewer than five events/hour, in adults with moderate OSA who were obese. The SR,[5] with a sample size of 72 patients from one study, reported significantly positive cure rates with very-low-calorie diets, compared with controls, with an odds ratio of 4.17. Study duration of the included primary study was one year. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as moderate (**Appendix 10**). The findings of the SR are summarized in Table 42.

4) Continuous positive airway pressure versus oral appliances

One SR[5] reported on treatment response in adults with severe OSA who were overweight to obese. The SR,[5] with a sample size of 131 patients from two studies, reported that CPAP was significantly more effective at achieving AHI levels of fewer than five events/hour, compared with MADs, with risk differences ranging from 20% to 28.6%. Study duration of the included primary studies ranged from two months to 78 days. No I^2 scores were reported. The SR[5] reported the quality of the included studies as low to moderate (**Appendix 10**). From subgroup analyses, the SR[5] reported that the effect of CPAP, compared with MADs, was specific to patients with baseline AHI greater than 30 events/hour. The findings of the SR are summarized in Table 43.

Review of Primary Studies

1) Positional therapy versus inactive controls

One study[78] reported on treatment response and success rates in adults with moderate OSA, provided by median AHI. The study[78] included positional OSA patients only who were overweight, provided by mean BMI. The study,[78] with a sample size of 33 patients, reported treatment response, defined as greater than 50% reductions in AHI, in 37.5% of the patients with an apparatus designed to prevent sleep in the supine position. The study[78] also reported treatment success, defined as greater than 50% reductions in AHI to fewer than five events/hour, in 31.3% of the patients with the apparatus. Concerns with the quality of the study[78] were assessed to be low (**Appendix 14**). The findings of the primary study are summarized in Table 44.

Summary of Results on Success or Cure Rate

For success or cure rates, evidence was found on inactive comparisons with MADs, MMA, and lifestyle interventions (i.e., weight-loss programs and positional therapy). Evidence was also found on active comparisons between CPAP and MADs. Compared with inactive controls or pre-treatment, MADs, MMA, weight-loss programs, and positional therapy were associated with positive success or cure rates, although success and cure rates were not always identically defined, and it is unclear if these results are clinically important. CPAP was associated with higher cure rates, compared with MADs. Subgroup analyses suggest that patients with more severe OSA at baseline were less likely to achieve success and cure with MMA. No subgroup or meta-regression analyses were found on comorbidities, baseline EDS, sex, age, BMI, adherence, or study duration.

Table 40: Summary of Success Rates From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Bartolucci 2016[51]	*MADs pre versus post*				MADs were associated with a significant improvement in AHI, when compared with pre-treatment.
	484 patients from single arms in 13 RCTs (2000 to 2010): • Moderate-to-severe OSA (mean AHI range: 16.2 to 50.4 events/hour) • Overweight to obese (mean BMI range: 25.9 to 32.3 kg/m^2) • 3 weeks to 1 year of study duration	• Mean success rate[a] (95% CI) = 0.62 (0.56 to 0.68)	None	Moderate to high	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; MA = meta-analysis; MAD = mandibular advancement device; MR = meta-regression; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

[a] Defined as ([mean AHI at baseline – mean AHI after treatment] / mean AHI at baseline).

Table 41: Summary of Success and Cure Rates from Surgery Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary	Quality of Included Studies	Conclusions
Zaghi 2016[60]	*MMA ± GTA pre versus post*			Patients with a higher preoperative AHI are less likely to achieve surgical success and cure from MMA with or without GTA.
	518 patients from 45 studies (1986 to 2013): • (for 455 of the 518 patients included in the SR) Severe OSA (mean AHI: 57.2 events/hour) • (for 82 of the 518 patients included in the SR) Obese (mean BMI: 33.8 kg/m^2) • (for the 45 studies included in the SR) 2 to 6 months of study duration	Overall cure[a] rate = 38.5% (175/455) Overall success-10[b] rate = 63.3% (288/455) Overall success-15[c] rate = 80.4% (366/455) Overall success-20[d] rate = 85.5% (388/455)	Moderate	

Surgical success (%)	Preoperative AHI in events/hour			
	< 30 (n = 61)	30- < 60 (n = 192)	60- < 90 (n = 161)	≥90 (n = 41)
Cure[a]	55.7[e]	45.8[e]	28.0	19.5

Table 41: Summary of Success and Cure Rates from Surgery Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary					Quality of Included Studies	Conclusions
		Success-10[b]	77.0[e]	72.9[e]	47.8	58.5		
		Success-15[c]	83.6[f]	88.0[f]	72.7	70.7		
		Success-20[d]	83.6[g]	91.7[g]	80.7[g]	75.6		

AHI = Apnea–Hypopnea Index; BMI = body mass index; GTA = genial tubercle advancement; OSA = obstructive sleep apnea; MA = meta-analysis; MMA = maxillomandibular advancement; SR = systematic review.

[a] AHI levels of fewer than 5 events/hour after MMA.

[b] > 50% reduction in AHI to < 10 events/hour after MMA.

[c] > 50% reduction in AHI to < 15 events/hour after MMA.

[d] > 50% reduction in AHI to < 20 events/hour after MMA.

[e] $P < 0.001$.

[f] $P = 0.009$.

[g] $P = 0.003$

Table 42: Summary of Cure Rates From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*Weight-loss programs versus inactive controls*				Treatment with a very-low-calorie diet was associated with a four-fold increase in the odds of being cured from OSA, when compared with inactive controls.
	72 patients from 1 RCT (2009): • Moderate OSA (mean AHI = 9 events /hour) • Obese (mean BMI = 31.4 kg/m^2) • 1 year of study duration	• Cure[a] rate OR (95% CI) = 4.17 (1.41 to 12.34); *P* = 0.011	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; MA = meta-analysis; MD = mean difference; OR = odds ratio; OSA = obstructive sleep apnea; RCT = randomized controlled trial.
[a] OSA was considered objectively cured when AHI < 5 events/hour.

Table 43: Summary of Treatment Response From CPAP Versus MADs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*CPAP versus MADs*				CPAP appeared to be more effective than MADs in achieving AHI below 5 events/hour.
	131 patients from 2 RCTs (2008 and 2009): • Severe OSA (mean AHI range: 34 to 40 events/hour) • Overweight to obese (mean BMI range: 26.7 to 33.3 kg/m^2) • 2 months to 78 days of study duration	From 1 RCT: • Complete response:[a] ○ RD (95% CI) = 28.6% (3.8% to 53%); *P* = 0.02 • Partial response:[b] ○ No significant difference between CPAP and MADs • Overall (i.e., combined complete and partial) response: ○ No significant	Subgroup analysis: • Baseline AHI (from 1 RCT): ○ ≤ 30 events/hour: – Complete response[e] RD (95% CI) = –4% (–25% to 18%); *P* = NS – Effective treatment[f] RD (95% CI) = 4% (–25% to 18%); *P* = NS ○ > 30 events/hour: – Complete response[e] RD (95% CI) = 43.3% (17% to 62%); *P* < 0.001	Moderate	

Table 43: Summary of Treatment Response From CPAP Versus MADs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
		difference between CPAP and MADs From 1 RCT: • Complete response:[c] ○ RD (95% CI) = 20% (1.9% to –37%); *P* = 0.02 • Effective treatment:[d] ○ No significant difference between CPAP and MAD	– Effective treatment[f] RD (95% CI) = 1.6% (–6.8% to 37%); *P* = NS		

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; MA = meta-analysis; MAD = mandibular advancement device; MR = meta-regression; NS = not significant; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; RD = risk difference.

[a] Defined as ≥50% reductions in AHI to < 5 events/hour

[b] Defined as ≥50% reductions in AHI to > 5 events/hour

[c] Defined as achieving AHI < 5 events/hour

[d] Defined as achieving AHI < 5 events/hour or > 50% reductions in AHI to < 20 events/hour.

[e] Defined as achieving AHI < 5 events/hour

[f] Defined as achieving AHI < 5 events/hour or > 50% reduction in AHI to < 20 events/hour

Table 44: Summary of Treatment Response and Success Rates From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Benoist 2016[78]	*Positional therapy (i.e., sleep position trainers) pre versus post*			Levels of response and success with positional therapy, using a sleep position trainer, were 37.5% and 31.3%, respectively, in patients with positional OSA.
	33 positional OSA patients: • Median AHI: 18.3 (IQR: 13.7 to 24.0) events/hour • Mean BMI ± SD: 27.9 ± 2.8 kg/m^2	• Treatment response:[a] ○ 37.5% (i.e., 12 of 32 patients) • Treatment success:[b] ○ 31.3% (i.e., 10 of 32 patients)	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; IQR = interquartile range; OSA = obstructive sleep apnea; SD = standard deviation.
[a] Defined as > 50% reductions in AHI.
[b] Defined as > 50% reductions in AHI to < 5 events/hour.

Blood Pressure

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Six SRs,[5,10,53,57,63,65] including one NMA,[63] reported on blood pressure in adults with mild-to-severe[5,10,63] or moderate-to-severe[53,57,65] OSA. The SRs[5,10,53,57,63,65] included overweight-to-obese[5,10,53,57,63] or obese[65] patients. Two SRs[57,65] included patients with hypertension[65] or resistant hypertension only.[57,65]

Four of the six SRs,[10,53,63,65] with sample sizes ranging from 794 patients[65] to 4,888 patients[63] from seven studies[65] to 51 studies,[63] reported significantly greater reductions in most[10,53,65] or all[63] systolic blood pressure (SBP) and diastolic blood pressure (DBP) measures included (e.g., daytime, nighttime, or 24-hour) with CPAP, compared with controls. The mean difference in blood pressure, reported by all four SRs, ranged from –4.39 mm Hg[53] to –1.41 mm Hg[53] with 14 of the 22 mean differences in SBP and DBP measures around –2 mm Hg. Study duration of the included primary studies, reported by all four SRs, ranged from one week[63] to 157 weeks.[63] I^2 scores, reported by three of the four applicable SRs,[53,63,65] ranged from 0%[53,65] to 89%[65] and were greater than 75% in two SRs.[57,65] The SRs reported the quality of the included studies as low to moderate[10] or high[53,63,65] (**Appendix 10**).

Two of the six SRs,[5,57] with sample sizes ranging from 446 patients[57] to 586 patients[5] from five studies[57] to seven studies,[5] reported mixed findings, including significantly greater reductions in some SBP and DBP measures (e.g., 24-hour SBP and DBP[57] or unspecified SBP and DBP in a subset of studies[5]) but not others (e.g., daytime and nighttime SBP and DBP[5,57]) with CPAP, compared with controls. Study duration of the included primary studies, reported by both studies, ranged from one week[5] to 12 months.[5] I^2 scores, reported by the one applicable study,[57] ranged from 0% to 87%. The SRs reported the quality of the included studies as low to moderate[5] or high[57] (**Appendix 10**).

Results of subgroup or meta-regression analyses conducted by four SRs[10,57,63,65] were also mixed. The effect of CPAP versus controls on blood pressure was reported to decrease,[57] increase,[10] or not change[65] with increasing EDS at baseline; decrease,[57] increase,[10,65] or not change[63] with increasing OSA severity at baseline; decrease,[63] increase,[65] or not change[57] with increasing blood pressure at baseline; decrease[57] or increase[10,63,65] with greater CPAP adherence; and decrease[10,57,63] or increase[65] with longer study durations. The effect of CPAP versus controls on blood pressure was also reported to not change with increasing BMI at baseline;[57,65] be higher in patients with hypertension versus no hypertension[10] and higher in patients with resistant hypertension versus hypertension;[65] increase with age;[10,65] and not depend on sex.[65]

Across the six SRs, 53 primary studies had been included, 17 of which had been included in one SR, 17 in two SRs, 14 in three SRs, four in four SRs, and one in five SRs (**Appendix 16.11**). No two SRs completely overlapped on blood pressure as the outcome.

The findings of the SRs are summarized in Table 45.

2) Oral appliances versus inactive controls

Two SRs,[5,63] including one NMA,[63] reported on blood pressure in adults with mild-to-severe[63] or moderate[5] OSA. The SRs[5,63] included overweight[5] or overweight-to-obese[63] patients. Both SRs,[5,63] with sample sizes ranging from 146 patients[5] to 4,888 patients[63] from one study[5] to 51 studies,[63] reported significantly greater reductions in overall[63] or 24-hour[5] SBP and DBP with MADs, compared with controls. The mean difference in blood pressure, reported by both SRs, ranged from –2.1 mm Hg[63] to –1.5 mm Hg.[5] Study duration of the included studies, reported by both SRs, ranged from one week[63] to 157 weeks.[63] I^2 scores, reported by one of the two applicable SRs,[63] ranged from 0% to 45%. The SRs reported the quality of the included studies as moderate[5] or high[63] (**Appendix 10**).

Across the two SRs, seven primary studies had been included, all of which had been included in one or the other SR, with no overlap between the two SRs (**Appendix 16.12**).

The findings of the SRs are summarized in Table 46.

3) Lifestyle interventions versus inactive controls

One SR[5] reported on blood pressure in adults with mild OSA who were obese. The SR,[5] with a sample size of 81 patients from one study, reported no significant differences in change in SBP or DBP with diet and exercise programs, compared with controls. Study duration of the included primary study was one year. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as moderate (**Appendix 10**). The findings of the SR are summarized in Table 47.

4) Continuous positive airway pressure versus oral appliances

Two SRs,[63,77] including one NMA,[63] reported on blood pressure in adults with mild-to-severe OSA. One SR[63] included overweight-to-obese patients. The other SR[77] provided no information on comorbidities.

Both SRs,[63,77] with sample sizes ranging from 128 patients[77] to 4,888 patients[63] from three studies[77] to 51 studies,[63] reported no significant differences in change in SBP or DBP between CPAP and MADs[63] or undefined OAs,[77] except the findings of one RCT that nighttime DBP was significantly lower with OAs, compared with CPAP.[77] Study duration of the included primary studies, reported by both SRs, ranged from one week[63] to 157 weeks.[63] I^2 scores, reported by the one applicable SR,[63] ranged from 0% to 5%. The SRs reported the quality of the included studies as low[77] or high[63] (**Appendix 10**).

Across the two SRs, six primary studies had been included, five of which had been included in one or the other SR, and one in both SRs (**Appendix 16.13**). The two SRs did not completely overlap on blood pressure as the outcome.

The findings of the SRs are summarized in Table 48.

Review of Primary Studies

1) Positional therapy versus inactive controls

One study[90] reported on blood pressure in obese adults with mild OSA, provided by mean AHI and BMI. The study,[90] with a sample size of 86 patients, reported marginal differences in blood pressure between positional therapy (i.e., an apparatus designed to avoid sleep in the supine position) and sleep hygiene advice. Concerns with the quality of the study were assessed to be low[90] (**Appendix 13**). The findings of the primary study are summarized in Table 49.

2) Combination therapy versus active controls

One study[93] reported on blood pressure in obese adults with severe OSA, provided by mean AHI and BMI. The study,[93] with a sample size of 181 patients, reported mixed findings, including significantly greater reductions in SBP with CPAP plus weight loss, compared with either intervention alone, in patients who lost 5% or more of their baseline weight and adhered to CPAP but no significant differences in SBP among the interventions in intention-to-treat analyses. CPAP plus weight loss was more effective with longer study duration (i.e., 24 versus eight weeks), CPAP was less effective with longer study duration (i.e., 24 versus eight weeks), and weight loss was more effective with longer study duration (i.e., 24 versus eight weeks).[93] Concerns with the quality of the study were assessed to be unclear[93] (**Appendix 13**). The findings of the primary study are summarized in Table 50.

Summary of Results on Blood Pressure

For blood pressure, evidence was found on inactive comparisons with CPAP, MADs, and lifestyle interventions (i.e., diet, exercise, and positional therapy). Evidence was also found on active comparisons between CPAP and OAs (i.e., MADs and undefined OAs) and combination therapy and other interventions (i.e., CPAP plus weight loss versus CPAP or weight loss alone).

Compared with inactive controls, CPAP and MADs were effective at reducing blood pressure. Effect sizes across the interventions were similar, with mean differences in blood pressure around –2 mm Hg, although it is unclear whether these results are clinically important. The similarity in effect sizes is reflected in the findings on active comparisons, where no significant differences in blood pressure were found between CPAP and MADs or undefined OAs. For diet, exercise, and positional therapy, compared with inactive controls, non-significant reductions in blood pressure were

found. These findings suggest that CPAP and MADs or undefined OAs may be comparable in their effectiveness in improving blood pressure, while lifestyle interventions may not significantly improve blood pressure. Some of the findings on CPAP versus inactive controls were associated with high heterogeneity.

Combination therapy was more effective at reducing blood pressure, compared with the interventions alone, specifically for CPAP plus weight loss versus CPAP or weight loss alone, in a subset of patients achieving tangible weight loss and CPAP adherence but not in intention-to-treat analyses. These findings suggest that the various interventions in combination have additive effects in their effectiveness in improving blood pressure in cases of high adherence.

Patients with hypertension or resistant hypertension experienced greater effects with CPAP. Subgroup and meta-regression analyses suggest that older patients experienced greater effects with CPAP. Findings on the role of baseline EDS, OSA severity, and blood pressure, as well as CPAP adherence levels and study duration on the effect of CPAP were mixed and inconclusive. However, longer study duration was associated with greater effects with weight-loss programs. Sex and BMI were not significantly associated with the effects of CPAP.

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Guo 2016[53]	*CPAP versus inactive controls*				CPAP was associated with significantly lowered 24-hour blood pressure (for both SBP and DBP), daytime blood pressure (for DBP only), and nighttime blood pressure (for both SBP and DBP), when compared with inactive controls.
	1,171 patients from 7 RCTs (2006 to 2015): • Moderate-to-severe OSA (mean AHI range: 24 to 60 events/hour) • Overweight to obese (mean BMI range: 28 to 40 kg/m^2) • Diabetes (% range: 28% to 47%, where reported) • Smoking (% range: 12% to 84%, where reported) • 3 to 6 months of study duration	• 24-hour SBP MD (95% CI) = –2.03 mm Hg (–3.64 to –0.42); *P* = 0.01; I^2 = 0% • 24-hour DBP MD (95% CI) = –1.79 mm Hg (–2.89 to –0.68); *P* = 0.001; I^2 = 0% • Daytime SBP MD (95% CI) = –1.41 mm Hg (–3.80 to 0.97); *P* = 0.25; I^2 = 43% • Daytime DBP MD (95% CI) = –1.43 mm Hg (–2.67 to –0.19); *P* = 0.02; I^2 = 0% • Nighttime SBP MD (95% CI) = –4.39 mm Hg (–6.85 to –1.93); *P* = 0.0005; I^2 = 34% • Nighttime DBP MD (95% CI) = –1.64 mm Hg (–2.88 to –0.40); *P* = 0.009; I^2 = 0%	None	High	

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Liu 2016[57]	*CPAP versus inactive controls*				In patients with OSA and resistant hypertension, CPAP was associated with significantly lowered 24-hour blood pressure (for both SBP and DBP) but not daytime blood pressure (for both SBP and DBP) or nighttime blood pressure (for SBP only), when compared with inactive controls. The effect of CPAP on 24-hour DBP decreased with severe OSA, sleepier patients, obese patients, longer CPAP usage at night, and longer follow-up durations but was not influenced by baseline SBP/DBP.
	446 patients from 5 RCTs (2010 to 2015): • Moderate-to-severe OSA (mean AHI range: 20 to 52.7 events/hour) • Overweight to obese (mean BMI range: 29.8 to 34.1 kg/m^2) • Resistant hypertension (100%) • 3 to 8 months of study duration	• 24-hour SBP MD (95% CI) = –4.78 mm Hg (–7.95 to –1.61); P = 0.003; I^2 = 48% • 24-hour DBP MD (95% CI) = –2.95 mm Hg (–5.37 to –0.53); P = 0.02; I^2 = 69% • Daytime SBP MD (95% CI) = –3.15 mm Hg (–9.20 to 2.89); P = 0.31; I^2 = 87% • Daytime DBP MD (95% CI) = –2.51 mm Hg (–6.23 to 1.22); P = 0.19; I^2 = 84% • Nighttime SBP MD (95% CI) = –1.89 mm Hg (–4.14 to 0.35); P = 0.10; I^2 = 0% • Nighttime DBP MD (95% CI) = –1.53 mm Hg (–3.07 to 0.00); P = 0.05; I^2 = 0%	Subgroup analysis: • Baseline ESS: ○ < 10: 24-hour DBP MD (95% CI) = –3.24 (–5.21 to –1.28); P = 0.001; I^2 = 0% ○ ≥ 10: 24-hour DBP MD (95% CI) = –2.44 (–8.32 to 3.43); P = 0.41; I^2 = 89% • Baseline AHI: ○ < 30 events/hour: 24-hour DBP MD (95% CI) = –5.3 (–7.29 to –3.31); P < 0.0001; I^2 = 0% ○ > 30 events/hour: 24-hour DBP MD (95% CI) = –1.99 (–4.51 to –0.2); P = 0.12; I^2 = 52% • Baseline SBP/DBP: ○ < 140/90 mm Hg: 24-hour DBP MD (95% CI) = –2.9 (–6.41 to 0.61); P = 0.11; I^2 = 0% ○ ≥ 140/90 mm Hg: 24-hour DBP MD (95% CI) = –2.89 (–6.03 to 0.25); P = 0.07; I^2 = 79% • Baseline BMI: ○ ≤ 32 kg/m^2: 24-hour DBP MD (95% CI) = –4.55 (–6.73 to –2.38); P < 0.0001; I^2 = 26% ○ > 32 kg/m^2: 24-hour DBP MD (95% CI) = –1.51 (–5.51 to 2.5); P = 0.46; I^2 = 75%	High	

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			• Follow-up duration: ○ ≤ 3 months: 24-hour DBP MD (95% CI) = –3.24 (–5.21 to –1.28); P = 0.001; I^2 = 0% ○ > 3 months: 24-hour DBP MD (95% CI) = –2.44 (–8.32 to 3.43); P = 0.41; I^2 = 89% • CPAP adherence: ○ ≤ 5 hours/night: 24-hour DBP MD (95% CI) = –4.55 (–6.73 to –2.38); P < 0.0001; I^2 = 26% ○ > 5 hours/night: 24-hour DBP MD (95% CI) = –1.51 (–5.51 to 2.5); P = 0.46; I^2 = 75%		
Bratton 2015[63]	*CPAP versus inactive controls*				CPAP was associated with significantly lowered blood pressure (for both SBP and DBP), when compared with inactive controls. The association of CPAP with reductions in both SBP and DBP was greater in patients using CPAP for longer periods at night or in those with higher baseline blood pressure but less with longer follow-up durations.
	Pairwise MA: 4,533 patients from 47 RCTs (1996 to 2015): • Mild-to-severe OSA (mean AHI range: 13 to 64 events/hour) • Overweight to obese (mean BMI range: 26 to 37 kg/m^2) • Other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder)	Pairwise MA: • Overall SBP MD (95% CI) = –2.6 mm Hg (–3.6 to –1.6); P < 0.001; I^2 = 54% • Overall DBP MD (95% CI) = –2.1 mm Hg (–2.8 to –1.4); P < 0.001; I^2 = 52%	Meta-regression: • For every mm Hg of increase in baseline SBP and DBP, SBP and DBP were additionally reduced by 0.2 mm Hg (95% CI = –0.3 to 0; P = 0.04) and 0.2 mm Hg (95% CI = –0.4 to 0; P = 0.01), respectively. • For every week of increase in the length of follow-up, SBP and DBP was additionally raised by 0.2 mm Hg (95% CI = 0.1 to 0.3; P = 0.003) and 0.1 mm Hg (95% CI = 0 to 0.2; P = 0.006), respectively. • For every 1-hour/night increase in CPAP use, SBP and DBP were additionally reduced by 1.5 mm Hg	High	

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 1 to 157 weeks of study duration		(95% CI = 0.8 to 2.3; $P < 0.001$) and 0.9 mm Hg (95% CI = 0.3 to 1.4; $P = 0.001$), respectively. • There was no significant association between OSA severity (i.e., baseline AHI or ODI) and CPAP treatment effect on SBP ($P = 0.24$) or DBP ($P = 0.17$).		
	Network MA: 4,888 patients from 51 RCTs (1996 to 2015): • Mild-to-severe OSA (mean AHI range: 13 to 64 events/hour) • Overweight to obese (mean BMI range: 26 to 37 kg/m^2) • Other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder) • 1 to 157 weeks of study duration	Network MA: • Overall SBP MD (95% CI) = –2.5 mm Hg (–3.5 to –1.5); $P < 0.001$ • Overall DBP MD (95% CI) = –2.0 mm Hg (–2.7 to –1.3); $P < 0.001$			
Hu 2015[65]	*CPAP versus inactive controls*				In patients with OSA and hypertension or resistant hypertension, CPAP was associated with significantly lowered 24-hour blood pressure (for both SBP and DBP), and nighttime blood pressure (for both SBP and DBP), when compared with inactive controls. The effect of CPAP on 24-hour blood pressure (for both SBP and DBP) was higher in patients with resistant hypertension, compared with those with
	794 patients from 7 RCTs (2006 to 2014): • Moderate-to-severe OSA (mean AHI range: 28.1 to 58.3 events/hour) • Obese (mean BMI range: 30.8 to 35.7 kg/m^2) • Hypertension (100% in 3 RCTs) or	• 24-hour SBP MD (95% CI) = –2.32 mm Hg (–3.65 to –1.00); $P = 0.001$; $I^2 = 0\%$ • 24-hour DBP MD (95% CI) = –1.98 mm Hg (–2.82 to –1.14); $P < 0.001$; $I^2 = 21\%$ • Daytime SBP MD	Subgroup analysis: • Hypertension: ○ Hypertension: - 24-hour SBP MD (95% CI) = –1.81 mm Hg (–3.34 to –0.29); $P = 0.02$; I^2 = NR - 24-hour DBP MD (95% CI) = –1.28 mm Hg (–2.28 to –0.27); $P = 0.01$; I^2 = NR ○ Resistant hypertension: - 24-hour SBP MD (95% CI) =	High	

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	resistant hypertension (100% in 4 RCTs) • 1 to 6 months of study duration	(95% CI) = –3.58 mm Hg (–8.04 to 0.89); *P* = 0.12; I^2 = 89% • Daytime DBP MD (95% CI) = –2.85 mm Hg (–5.58 to –0.12); *P* = 0.04; I^2 = 88% • Nighttime SBP MD (95% CI) = –2.74 mm Hg (–4.26 to –1.23); *P* < 0.001; I^2 = 0% • Nighttime DBP MD (95% CI) = –1.75 mm Hg (–2.79 to –0.71); *P* = 0.001; I^2 = 0%	–3.88 mm Hg (–6.55 to –1.22); *P* = 0.004; I^2 = NR - 24-hour DBP MD (95% CI) = –3.65 mm Hg (–5.19 to –2.10); *P* < 0.001; I^2 = NR Meta-regression: • CPAP adherence (*P* = 0.016), age (*P* = 0.024), and baseline SBP (*P* = 0.036) were positively correlated with reductions in 24-hour DBP by CPAP. • CPAP adherence (*P* < 0.001), age (*P* < 0.05), OSA severity (*P* < 0.001), study duration (*P* < 0.001), and baseline SBP (*P* < 0.001) were positively correlated with reductions in daytime SBP and daytime DBP by CPAP. • Sex, BMI, and baseline ESS were not significantly correlated with reductions in 24-hour or daytime SBP or DBP.		hypertension. CPAP adherence, age, and baseline SBP were positively correlated with a reduction in 24-hour DBP, but not SBP, by CPAP. CPAP adherence, age, OSA severity, study durations, and baseline SBP were positively correlated with reductions in daytime blood pressure (for both SBP and DBP) by CPAP.
Fava 2014[10]	*CPAP versus inactive controls*				CPAP was associated with significantly lowered overall blood pressure (for both SBP and DBP), as well as daytime and nighttime blood pressure (for both SBP and DBP), when compared with inactive controls. The effect of CPAP in lowering both SBP and DBP was significantly larger in
	1,820 patients from 29 RCTs (1996 to 2012): • Mild-to-severe OSA (mean AHI range: 12.9 to 63.8 events/hour) • Overweight to obese (mean BMI range:	• Overall SBP MD (95% CI) = –2.56 mm Hg (–3.68 to –1.44); *P* < 0.001; I^2 = NR • Overall DBP MD (95% CI) = –2.00 mm Hg (–2.81 to	Subgroup analysis: • Hypertension: ○ Yes: - SBP WMD ± SE = –1.9 ± 0.7 (*P* < 0.01) - DBP WMD ± SE = –1.6 ± 0.4 (*P* < 0.001) ○ No:	Low to moderate	

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	27.2 to 37.0 kg/m^2) • Hypertension (% range: 0% to 100%, where reported) • 2 to 52 weeks of study duration	–1.19); *P* < 0.001; I^2 = NR • Daytime SBP MD (95% CI) = –2.19 mm Hg (–3.50 to 0.89); *P* = 0.001; I^2 = NR • Daytime DBP MD (95% CI) = –1.89 mm Hg (–3.05 to −0.73); *P* = 0.001; I^2 = NR • Nighttime SBP MD (95% CI) = –3.77 mm Hg (–5.33 to −2.21); *P* < 0.001; I^2 = NR • Nighttime DBP MD (95% CI) = –1.78 mm Hg (–2.90 to −0.65); *P* = 0.002; I^2 = NR	- SBP WMD ± SE = –1.0 ± 0.9 (NS) - DBP WMD ± SE = –1.3 ± 0.6 (*P* < 0.05) • Baseline ESS: ○ < 10: - SBP WMD ± SE = –1.3 ± 1.2 (NS) - DBP WMD ± SE = –1.6 ± 0.9 (NS) ○ ≥ 10: - SBP WMD ± SE = –2.4 ± 0.6 (*P* < 0.001) - DBP WMD ± SE = –1.9 ± 0.5 (*P* < 0.001) • Baseline AHI: ○ ≤ 30 events/hour: - SBP WMD ± SE = –0.5 ± 1.0 (NS) - DBP WMD ± SE = –0.4 ± 0.9 (NS) ○ > 30 events/hour: - SBP WMD ± SE = –2.6 ± 0.6 (*P* = 0.001) - DBP WMD ± SE = –2.1 ± 0.5 (*P* < 0.001) • Age: ○ < 50 years: - SBP WMD ± SE = –2.0 ± 0.7 (*P* < 0.01) - DBP WMD ± SE = –1.7 ± 0.5 (*P* < 0.001) ○ ≥ 50 years: - SBP WMD ± SE = –3.6 ± 1.0 (*P* < 0.001) - DBP WMD ± SE = –2.7 ± 0.8 (*P* < 0.001)		patients with hypertension (versus no hypertension), patients with severe OSA, sleepier patients, older patients, shorter study durations, and higher CPAP adherence.

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			• Study duration: ○ ≤ 9 weeks: - SBP WMD ± SE = –2.9 ± 0.8 (*P* < 0.001) - DBP WMD ± SE = –2.5 ± 0.6 (*P* = 0.001) ○ > 9 weeks: - SBP WMD ± SE = –2.3 ± 0.9 (*P* < 0.01) - DBP WMD ± SE = –1.6 ± 0.6 (*P* < 0.01) • CPAP adherence: ○ < 4 hours/night: - SBP WMD ± SE = –2.0 ± 1.0 (NS) - DBP WMD ± SE = –1.9 ± 0.7 (*P* < 0.05) ○ ≥ 4 hours/night: • SBP WMD ± SE = –2.8 ± 0.7 (*P* < 0.001) • DBP WMD ± SE = –2.0 ± 0.5 (*P* < 0.001) Meta-regression: • For each 10 event/hour increase in baseline AHI, a 1 mm Hg decrease in SBP by CPAP was observed (*P* < 0.01).		

Table 45: Summary of Change in Blood Pressure From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*CPAP versus inactive controls*				No significant differences were found between CPAP and inactive controls in their effect on blood pressure.
	586 patients from 7 RCTs (1996 to 2010): • Mild-to-severe OSA (mean AHI range: 13 to 65 events/hour) • Overweight to obese (mean BMI range: 29.4 to 36 kg/m^2) • 1 to 12 months of study duration	• Daytime or nighttime SBP or DBP (from 7 RCTs): no significant differences between CPAP and control in any RCT • No MA	None	Low to moderate	
	CPAP versus sham CPAP				The effect of CPAP on blood pressure was inconsistent across studies, when compared with sham CPAP.
	608 patients from 12 RCTs (2001 to 2010): • Moderate-to-severe OSA (mean AHI range: 30 to 65 events/hour, where reported) • Overweight to obese (mean BMI range: 27.2 to 42.6 kg/m^2) • 1 week to 3 months of study duration	• SBP (from 10 RCTs): significant decreases associated with CPAP in 2 RCTs • DBP (from 10 RCTs): significant decreases associated with CPAP in 3 RCTs • No MA	None	Mixed	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; DBP = diastolic blood pressure; ESS = Epworth Sleepiness Scale; HF = heart failure; MA = meta-analysis; MAP = mean arterial pressure; MD = mean difference; MR = meta-regression; NR = not reported; NS = not significant; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; SBP = systolic blood pressure; SE = standard error; WMD = weighted mean difference.

Table 46: Summary of Change in Blood Pressure From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Bratton 2015[63]	*MADs versus inactive controls*				MADs were associated with significant reductions in blood pressure (for both SBP and DBP), compared with inactive controls.
	Pairwise MA: 473 patients from 6 RCTs (2004 to 2014): • Mild-to-severe OSA (mean AHI range: 14 to 42 events/hour) • Overweight to obese (mean BMI range: 27 to 31 kg/m^2) • 4 to 13 weeks of study duration	Pairwise MA: • Overall SBP MD (95% CI) = –1.9 mm Hg (–3.2 to –0.6); *P* = 0.004; I^2 = 0% • Overall DBP MD (95% CI) = –1.1 mm Hg (–2.4 to 0.2); *P* = 0.11; I^2 = 45%	None	High	
	Network MA: 4,888 patients from 51 RCTs (1996 to 2015) • Mild-to-severe OSA (mean AHI range: 13 to 64 events/hour) • Overweight to obese (mean BMI range: 26 to 37 kg/m^2) • Other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder) • 1 to 157 weeks of study duration	Network MA: • Overall SBP MD (95% CI) = –2.1 mm Hg (–3.4 to –0.8); *P* = 0.002 • Overall DBP MD (95% CI) = –1.9 mm Hg (–3.2 to –0.5); *P* = 0.008	None		
Balk 2011[5]	*MADs versus sham OAs*				MADs were associated with significant reductions in blood pressure (for both SBP and DBP), compared with sham OAs.
	146 patients from 1 RCT (2002): • Moderate OSA (mean AHI: 25 events/hour)	• 24–hour SBP MD (95% CI) = –1.5 (–3.0 to –0.0); *P* = 0.05 • 24–hour DBP MD (95%	None	Moderate	

Table 46: Summary of Change in Blood Pressure From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Overweight (BMI: 29 kg/m^2) • 4 weeks of study duration	CI) = –1.6 (–2.5 to –0.6); *P* = 0.001			

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CVD = cardiovascular disease; DBP = diastolic blood pressure HF = heart failure; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; OA = oral appliance; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SBP = systolic blood pressure; SE = standard error.

Table 47: Summary of Change in Blood Pressure From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*Weight-loss programs versus inactive controls*				No significant differences were found between weight-loss programs and inactive controls for blood pressure (for both SBP and DBP).
	81 patients from 1 RCT (2009): • Mild OSA (mean AHI = 9 events /hour) • Obese (mean BMI = 31.4 kg/m^2) • 1 year of study duration	• SBP MD (95% CI) = –0.6 (–8.4 to 7.2); *P* = 0.88 • DBP MD (95% CI) = –1.5 (–7.4 to 4.4); *P* = 0.62	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; DBP = diastolic blood pressure; MA = meta-analysis; MD = mean difference; MR = meta-regression; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; SBP = systolic blood pressure.

Table 48: Summary of Change in Blood Pressure From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Bratton 2015[63]	*CPAP versus MADs*				There was no significant difference between CPAP and MADs in their effect on SBP and DBP.
	Pairwise MA: 370 patients from 4 RCTs (2004 to 2014): • Moderate-to-severe OSA (mean AHI range: 21 to 42 events/hour)	Pairwise MA: • Overall SBP MD (95% CI) = 0.3 mm Hg (–1.0 to 1.5); *P* = 0.68; I^2 = 5%	None	High	

Table 48: Summary of Change in Blood Pressure From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Overweight to obese (mean BMI range: 27 to 31 kg/m^2) • 4 to 13 weeks of study duration	• Overall DBP MD (95% CI) = 0.2 mm Hg (–0.6 to 0.9); *P* = 0.68; I^2 = 0%			
	Network MA: 4,888 patients from 51 RCTs (1996 to 2015): • Mild-to-severe OSA (mean AHI range: 13-64 events/hour) • Overweight to obese (mean BMI range: 26 to 37 kg/m^2) • Other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder) • 1 to 157 weeks of study duration	Network MA: • Overall SBP MD (95% CI) = –0.5 mm Hg (–2.0 to 1.0); *P* = 0.55 • Overall DBP MD (95% CI) = –0.2 mm Hg (–1.6 to 1.3); *P* = 0.82	None		
Li 2013[77]	*CPAP versus OAs*				The findings on blood pressure were mixed but generally indifferent between CPAP and OA.
	128 patients from 3 RCTs (2002 to 2009): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 8 to 10 weeks of study duration	• 24-hour SBP and DBP (from 1 RCT): no significant difference between CPAP and OAs • Nighttime DBP (from 1 RCT): significantly lower with OAs, compared with CPAP (*P* < 0.05) • Undefined blood pressure (from 2 RCTs): no significant difference between CPAP and OAs • No MA	None	Low	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; DBP = diastolic blood pressure; HF = heart failure; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliances; OSA = obstructive sleep apnea; RCTs = randomized controlled trials; SBP = systolic blood pressure.

Table 49: Summary of Change in Blood Pressure From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Jackson 2015[90]	*Positional therapy (i.e., sleep position modification devices) versus inactive control*			Marginal differences were found in blood pressures in the active group compared with the control group.
	47 (in the intervention group) or 39 (in the control group) positional OSA patients: • Mean AHI ± SD: 20.1 ± 8.8 (in the intervention group) or 21.8 ± 10.1 (in the control group) events/hour • Mean BMI ± SD: 30.0 ± 5.3 (in the intervention group) or 30.9 ± 7.7 (in the control group) kg/m^2	• Systolic BP ± SD: ○ Before: - Sleep position modification device: 128.3 ± 15.5 mm Hg - Sleep hygiene advice: 127.6 ± 15.4 mm Hg ○ After 4 weeks: - Sleep position modification device: 125.7 ± 9.6 mm Hg - Sleep hygiene advice: 133.4 ± 15.2 mm Hg ○ Difference: - Sleep position modification device: *P* = non-significant - Sleep hygiene advice: *P* = non-significant • Diastolic BP ± SD: ○ Before: - Sleep position modification device: 77.6 ± 9.2 mm Hg - Sleep hygiene advice: 78.1 ± 10.6 mm Hg ○ After 4 weeks: - Sleep position modification device: 75.1 ± 9.2 mm Hg - Sleep hygiene advice: 79.4 ± 9.8 mm Hg ○ Difference: - Sleep position modification device: *P* < 0.05 - Sleep hygiene advice: *P* = non-significant	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; BP = blood pressure; OSA = obstructive sleep apnea; SD = standard deviation.

Table 50: Summary of Change in Blood Pressure From Combination Therapy Versus Active Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Chirinos 2014[93]	*CPAP plus weight-loss programs versus CPAP or weight-loss programs alone*			A combination of CPAP and weight loss may result in slight but significant reductions in blood pressure than either intervention alone.
	62 (CPAP plus weight loss), 58 (CPAP), or 61 (weight loss) patients: • Mean AHI ± SD: 47.1 ± 26.86 (CPAP plus weight loss), 41.2 ± 20.96 (CPAP), or 39.7 ± 20.3 (weight loss) events/hour • Mean BMI ± SD: 38.4 ± 6.4 (CPAP plus weight loss), 39.8 ± 7.1 (CPAP), or 38.1 ± 5.8 (weight loss) kg/m^2	CPAP plus weight-loss patients: • Per cent change in systolic BP (95% CI): ○ CPAP plus weight loss: - Modified ITT[a] at week 8: –5.4 (–8.7 to –2.1) mm Hg - Modified ITT[a] at week 24: –7.8 (–11.4 to –4.3) mm Hg - Adherence[b] at week 8: –2.5 (–7.1 to 2.1) mm Hg - Adherence[b] at week 24: –14.1 (–18.7 to –9.5) mm Hg ○ CPAP: - Modified ITT[a] at week 8: –6.6 (–9.8 to –3.4) mm Hg - Modified ITT[a] at week 24: –4.2 (–7.7 to –0.6) mm Hg - Adherence[b] at week 8: –5.6 (–9 to –2.1) mm Hg - Adherence[b] at week 24: –3 (–6.5 to 0.5) mm Hg - Difference between CPAP and CPAP plus weight loss: $P < 0.001$ ○ Weight loss: - Modified ITT[a] at week 8: –4.5 (–7.9 to –1.1) mm Hg - Modified ITT[a] at week 24: –5.1 (–8.7 to –1.4) mm Hg - Adherence[b] at week 8: –3.5 (–7.9 to 0.8) mm Hg - Adherence[b] at week 24: -6.8 (–10.8 to –-2.7) mm Hg - Difference between weight loss and CPAP plus weight loss: $P = 0.02$	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure; ITT = intention-to-treat; SD = standard deviation.

[a] Defined as all patients who were randomly assigned to a study group, with ≥ 1 observation after being randomized.

[b] Included participants who met minimum requirements for weight loss (i.e., ≥ 5% of baseline weight) and adhered to CPAP therapy (i.e., on average, used ≥ 4 hours/night on at least 70% of the total number of nights).

Diabetes

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Two SRs[5,64] reported on diabetes in adults with diabetes and moderate[5] or unknown severity[64] OSA. Both SRs[5,64] included obese patients.

Both SRs,[5,64] with sample sizes ranging from 13 patients[5] to 128 patients[64] from one study[5] to six studies,[64] reported no significant differences in change in A1C with CPAP, compared with controls[5] or pre-treatment.[64] Study duration of the included primary studies, reported by both SRs, ranged from four weeks[5] to four months.[64] The I^2 score, reported by the one applicable SR,[64] was 0%. One of the two SRs,[64] with a sample size of 128 patients from six studies, reported a significant improvement in insulin sensitivity with CPAP, compared with pre-treatment, with a mean difference of 0.33. Study duration of the included primary studies ranged from one month to four months. The I^2 score was 86.4%. The SRs reported the quality of the included studies as low[64] or low to moderate[5] (**Appendix 10**).

From subgroup analyses, one SR[64] reported that the effect of CPAP versus pre-treatment on A1C did not vary with CPAP adherence levels.

Across the two SRs, seven primary studies had been included, all of which had been included in one or the other SR, with no overlap between the two SRs (**Appendix 16.14**).

The findings of the SRs are summarized in Table 51.

2) Lifestyle interventions versus inactive controls

One SR[5] reported on diabetes in adults with diabetes and moderate OSA who were obese. The SR,[5] with a sample size of 264 patients from one study, reported significantly greater reductions in A1C with diet and exercise programs, compared with controls, with a mean difference of –0.5. Study duration was one year. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as moderate (**Appendix 10**). The findings of the SR are summarized in Table 52.

Review of Primary Studies

No primary studies on any of the comparisons were found that reported on diabetes.

Summary of Results on Diabetic Outcomes

For diabetic outcomes, evidence was found on inactive comparisons with CPAP and lifestyle interventions (i.e., diet and exercise programs). No evidence was found on active comparisons. Compared with inactive controls, diet and exercise, but not CPAP, were effective at reducing A1C levels in patients with diabetes, although it is unclear if these results are clinically important. However, the studies on CPAP were shorter in duration (i.e., up to four months), compared with the study on diet and exercise (i.e., one year). Compared with pre-treatment, CPAP was effective at improving insulin sensitivity in patients with diabetes. However, this finding was associated with high heterogeneity. Subgroup analyses suggest that CPAP adherence levels were not significantly associated with the effects of CPAP. No subgroup or meta-regression analyses were found on comorbidities, baseline EDS or OSA severity, sex, age, BMI, or study duration.

Table 51: Summary of Change in Diabetic Outcomes From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Feng 2015[64]	*CPAP pre versus post*				CPAP had no significant effect on A1C but significantly improved insulin sensitivity, when compared with pre-treatment. There was no significant difference in change in A1C with change in CPAP adherence levels.
	128 patients from 2 RCTs and 4 observational studies (1994 to 2012): • OSA severity: NR • Obese (mean BMI range: 33.6 to 42.7 kg/m^2) • Diabetes (100%) • 1 to 4 months of study duration	• A1C (from 2 RCTs and 4 observational studies) MD (95% CI) = –0.07 (–0.25 to 0.10); P = 0.42; I^2 = 0% • Insulin sensitivity[a] (from 1 RCT and 2 observational studies) MD (95% CI) = 0.33 (0.001 to 0.66); P = 0.05; I^2 = 86.4%	Subgroup analysis: • CPAP adherence: ○ ≤ 5 hours/night: A1C MD (95% CI) = -0.12 (-0.41 to 0.18); P = 0.44; I^2 = 0% ○ > 5 hours/night: A1C MD (95% CI) = -0.06 (-0.28 to 0.18); P = 0.64; I^2 = 0%	Low	
Balk 2011[5]	*CPAP versus inactive controls*				No significant difference was found between CPAP and inactive controls in their effect on A1C.
	13 patients from 1 RCT (2009): • Moderate OSA (mean AHI: 28 events/hour) • Obese (mean BMI: 31.1 kg/m^2) • 4 weeks of study duration	• A1C MD (95% CI) = 0.04 (–0.27 to 0.34)	None	Low to moderate	

A1C = glycated hemoglobin; AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; = MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OR = odds ratio; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

[a] Measured by the hyperinsulinemic–euglycemic clamp.

Table 52: Summary of Change in Diabetic Outcomes From Lifestyle Interventions Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*Weight-loss programs versus inactive controls*				Intensive weight-loss programs were associated with a significant reduction in A1C in patients with type 2 diabetes, when compared with inactive controls.
	264 patients from 1 RCT (2009): • Moderate OSA (mean AHI = 24 events /hour) • Obese (mean BMI = 36.7 kg/m^2) • Diabetes (100%) • 1 year of study duration	• A1C MD (95% CI) = –0.5 (–0.8 to –0.2); *P* < 0.001	None	Moderate	

A1C = glycated hemoglobin; AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; = MA = meta-analysis; MD = mean difference; MR = meta-regression; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

Cardiovascular Events

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Four SRs[53,56,67,69] reported on cardiovascular events (CVEs) in adults with mild-to-severe[56,67] or moderate-to-severe[53,69] OSA. Two SRs[53,67] included overweight-to-obese patients. Two SRs[56,67] included patients with previous cardiovascular disease (CVD)[56] or atrial fibrillation (AF).[67]

Three of the four SRs,[56,67,69] with sample sizes ranging from 1,247 patients[67] to 35,323 patients[56] from five studies[56] to eight studies,[67] reported significantly reduced risk of CVEs,[56,69] cardiac disease (including recurrent),[56] or recurrent AF,[67] with CPAP, compared with no treatment[56] or no CPAP.[67,69] The relative risk of the events, reported by all three SRs, ranged from 0.46[56] to 0.57.[69] Study duration of the included primary studies, reported by one of the three SRs,[56] ranged from 49 months to 132 months. I^2 scores, reported by all three SRs, ranged from 0%[56,67] to 42.4%.[69] The SRs reported the quality of the included studies as moderate,[67] high,[69] or high to mixed[56] (**Appendix 10**).

Two of the four SRs,[53,56] with sample sizes ranging from 2,669 patients[53] to 35,323 patients[56] from five studies[56] to six studies,[53] reported no significant differences in the risk of major adverse cardiac events,[53] hypertension and CVEs,[56] or myocardial infarction (MI),[56] with CPAP, compared with controls[53] or no treatment.[56] Study duration of the included studies, reported by both SRs, ranged from three months[53] to 132 months.[56] The I^2 score, reported by the one applicable SR,[53] was 0%. The SRs reported the quality of the included studies as high[53] or high to mixed[56] (**Appendix 10**).

From subgroup or meta-regression analyses, three SRs[53,56,67] reported that the effect of CPAP versus controls on reducing the risk of CVEs was greater with higher CPAP adherence,[56] older age,[67] lower BMI,[67] and female patients[67] but did not vary with study durations[53] or having hypertension or diabetes.[67]

Across the four SRs, 21 primary studies had been included, 18 of which had been included in one SR, two in two SRs, and one in three SRs (**Appendix 16.15**). No two SRs completely overlapped on CVEs as the outcome.

The findings of the SRs are summarized in Table 53.

Review of Primary Studies

No primary studies on any of the comparisons were found that reported on CVEs.

Summary of Results on Cardiovascular Events

For CVEs, evidence was found on inactive comparisons with CPAP. No evidence was found on active comparisons. Compared with inactive controls, CPAP was effective at reducing the risk of CVEs, cardiac disease (including recurrent), and recurrent AF, but not that of major adverse cardiac events, hypertension and CVEs, or MI. Subgroup and meta-regression analyses suggest that patients who were male, older, with lower BMI, or with higher CPAP adherence experienced greater effects with CPAP. Having diabetes or hypertension (versus not having those conditions) and study duration were not significantly associated with the effects of CPAP. No subgroup or meta-regression analyses were found on baseline EDS or OSA severity.

Table 53: Summary of Change in Cardiovascular Events From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Guo 2016[53]	*CPAP versus inactive controls*				CPAP did not significantly reduce the risk of CVEs, when compared with inactive controls. There was no significant difference in the risk of CVEs between short and long-term follow-up.
	2,669 patients from 6 RCTs (2012 to 2015): • Moderate-to-severe OSA (mean AHI range: 24 to 42 events/hour) • Overweight to obese (mean BMI range: 28 to 40 kg/m^2) • Diabetes (% range: 28% to 47%, where reported) • Smoking (% range: 26% to 84%, where reported) • 3 to 60 months of study duration	• MACEs[a] OR (95% CI) = 0.84 (0.62 to 1.13); $P = 0.25$; $I^2 = 0\%$	Subgroup analysis: • Study duration: ○ < 12 months: MACE OR (95% CI) = 0.68 (0.26 to 1.79); $I^2 = 29\%$ ○ ≥ 12 months: MACE OR (95% CI) = 0.80 (0.55 to 1.16); $I^2 = 0\%$	High	
Kim 2016[56]	*CPAP versus no treatment*				The effect of CPAP on the incidence of CVEs varied across studies and across different sets of outcomes, when compared with no treatment. There was evidence that greater CPAP adherence might improve the effect of CPAP on reducing the risk of hypertension and CVEs.
	35,323 patients from 1 RCT, 3 cohort studies, and 1 administrative database study (2005 to 2014): • Mild-to-severe OSA (AHI threshold range: ≥ 5 to ≥ 20 events/hour) • Previous CVD (excluded from the RCT and one cohort study but included in the other studies)	• Hypertension and CVEs[b] (from 1 RCT) adjusted IDR (95% CI) = 0.81 (0.61 to 1.06) • CVEs[b] (from 3 cohort studies) RR (95% CI) = 0.46 (0.35 to 0.61); $P < 0.00001$; $I^2 = 0\%$ • Cardiac disease[b] (from 3 cohort studies) RR (95% CI) = 0.54 (0.38 to 0.75);	Subgroup analysis: • CPAP adherence: ○ ≥ 4 hours/night (from 1 RCT): hypertension and CVEs adjusted IDR (95% CI) = 0.69 (0.50 to 0.94)	High (for the RCT) or mixed (for the non-RCTs)	

Table 53: Summary of Change in Cardiovascular Events From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 48 to 132 months of study duration	$P = 0.0003$; $I^2 = 0\%$ • MI (from 1 administrative database study) adjusted IRR (95%) = 0.99 (0.85 to 1.15)			
Qureshi 2015[67]	*CPAP versus no CPAP*				CPAP was associated with significantly reduced risk of recurrence of AF in patients with OSA and AF, when compared with no CPAP. The treatment effect of CPAP may be higher for older, slimmer, and female patients. Having hypertension or diabetes was not significantly associated with the risk of recurrence of AF by CPAP.
	1,247 patients from 1 RCT and 7 cohorts (2003 to 2013): • Mild-to-severe OSA (% severe OSA range: 10% to 100%) • Overweight to obese (mean BMI range: 25 to 35 kg/m^2) • 100% AF • Hypertension (% range: 24% to 70%) • Diabetes (% range: 15% to 24%, where reported) • Study duration: NR	• CVEs[c] RR (95% CI) = 0.56 (0.47 to 0.68); $P < 0.001$; $I^2 = 0\%$	Meta-regression: • In univariate analysis, decreasing age (slope = –0.06; $P = 0.03$), male sex (slope = 0.07; $P = 0.01$), and increasing BMI (slope = 0.07; $P = 0.04$) were significantly correlated with increasing risk of recurrence of AF by CPAP. Having hypertension or diabetes was not significantly associated with the risk of recurrence of AF by CPAP. • In multivariate analysis, none of the above associations were significant.	Moderate	
Wang 2015[69]	*CPAP versus no CPAP*				CPAP was associated with significantly reduced risk of non-fatal CVEs, compared with no CPAP.
	2,255 patients from 6 studies (2005 to 2015): • Moderate-to-severe OSA (in 4 studies) or unselected OSA	• CVEs[d] OR (95% CI) = 0.57 (0.43 to 0.75); $P < 0.0001$; $I^2 = 42.4\%$	None	Moderate	

Table 53: Summary of Change in Cardiovascular Events From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	(in 2 studies) • Comorbidities: NR • Study duration: NR				

AF = atrial fibrillation; AHI = Apnea–Hypopnea Index; BMI = body mass index; CABG = coronary artery bypass grafting; CI = confidence interval; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; CVE = cardiovascular event; IDR = incidence density ratio; IRR = incidence rate ratio; MA = meta-analysis; MACE = major adverse cardiac event; MI = myocardial infarction; MR = meta-regression; NR = not reported; OR = odds ratio; OSA = obstructive sleep apnea; PCI = percutaneous coronary intervention; RCT = randomized controlled trial; RR = relative risk.

[a] Including mortality, non-fatal MI, HF, and non-fatal stroke.

[b] Included events not specified.

[c] Including recurrence of AF.

[d] Non-fatal CVEs, including MI, stroke, CABG, and PCI.

Cerebrovascular Events

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Two SRs[53,56] reported on cerebrovascular events (CBEs) in adults with mild-to-severe[56] or moderate-to-severe[53] OSA. One SR[53] included overweight-to-obese patients. The other SR[56] included patients with previous CVD.[56]

One of the two SRs,[56] with a sample size of 34,600 patients from four studies, reported significantly reduced risk of stroke (including recurrent), but not of ischemic stroke (IS), with CPAP, compared with controls, with the relative risk of stroke reported as 0.27. Study duration of the included primary studies ranged from 72 months to 132 months. The I^2 score was 0%. The SR[56] reported the quality of the included studies as high to mixed (**Appendix 10**).

The other SR,[53] with a sample size of 922 patients from four studies, reported no significant differences in the risk of stroke with CPAP, compared with controls. Study duration of the included primary studies ranged from three months to 60 months. The I^2 score was 12%. The SR[56] reported the quality of the included studies as high (**Appendix 10**).

From subgroup analyses, one SR[53] reported that the effect of CPAP versus controls on the risk of stroke did not vary with study durations.

Across the two SRs, eight primary studies had been included, all of which had been included in one or the other SR, with no overlap between the two SRs (**Appendix 16.16**).

The findings of the SRs are summarized in Table 54.

Review of Primary Studies

No primary studies on any of the comparisons were found that reported on CBEs.

Summary of Results on Cerebrovascular Events

For CBEs, evidence was found on inactive comparisons with CPAP. No evidence was found on active comparisons. Compared with inactive controls, CPAP was effective at reducing the risk of stroke in patients with previous CVD but not that of stroke in other patients or IS in patients with previous CVD. Subgroup analyses suggest that study duration was not significantly associated with the effects of CPAP. No subgroup or meta-regression analyses were found on baseline EDS or OSA severity, sex, age, BMI, or adherence.

Table 54: Summary of Change in Cerebrovascular Events From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Guo 2016[53]	*CPAP versus inactive controls*				CPAP did not significantly reduce the risk of stroke, when compared with inactive controls. There was no significant difference in the risk of stroke between short and long-term follow-up.
	922 patients from 4 RCTs (2012 to 2015): • Moderate-to-severe OSA (mean AHI range: 24 to 42 events/hour) • Overweight to obese (mean BMI range: 28 to 35 kg/m^2) • Diabetes (% range: 33% to 47%, where reported) • Smoking (% range: 26% to 66%, where reported) • 3 to 60 months of study duration	• Stroke OR (95% CI) = 0.56 (0.18 to 1.73); *P* = 0.32; I^2 = 12%	Subgroup analysis: • Study duration: ○ < 12 months: stroke OR (95% CI) = 0.36 (0.01 to 8.84); I^2 = NR ○ ≥ 12 months: stroke OR (95% CI) = 0.56 (0.18 to 1.73); I^2 = 11.8%	High	
Kim 2016[56]	*CPAP versus no treatment*				The effect of CPAP on the risk of stroke was inconsistent across studies and across different outcomes, when compared with no treatment.
	34,600 patients from 3 cohort studies and 1 administrative database study (2005 to 2014): • Mild-to-severe OSA (AHI threshold range: ≥ 5 to ≥ 15 events/hour) • Previous CVD (excluded from one cohort study but included in the other studies) • 72 to 132 months of study duration	• Stroke (from 3 cohort studies) RR (95% CI) = 0.27 (0.14 to 0.53); *P* < 0.0001; I^2 = 0% • IS (from 1 administrative database study) adjusted IRR (95%) = 0.99 (0.82 to 1.19)	None	High (for the RCT) or mixed (for the non-RCTs)	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; IRR = incidence rate ratio; IS = ischemic stroke; MA = meta-analysis; MR = meta-regression; NR = not reported; OR = odds ratio; OSA = obstructive sleep apnea; RCT = randomized controlled trial; RR = relative risk.

Accidents

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

One SR[47] reported on MVAs in adults with severe OSA who were overweight to obese. The SR,[47] with a sample size of 1,221 patients from 10 studies, reported significant reductions in the risk of real and near-miss accidents with CPAP, compared with pre-treatment, with the odds ratios (ORs) of the accidents reported as 0.21 and 0.09, respectively. Study duration of the included primary studies ranged from six months to 36 months. I^2 scores ranged from 26% to 85%. The SR[47] reported the quality of the included studies as low (**Appendix 10**). The findings of the SR are summarized in Table 55.

Review of Primary Studies

No primary studies on any of the comparisons were found that reported on accidents.

Summary of Results on Accidents

For accidents, evidence was found on inactive comparisons with CPAP. No evidence was found on active comparisons. Compared with pre-treatment, CPAP was effective at reducing the risk of real and near-miss accidents. However, the findings on CPAP were from uncontrolled studies of low quality and associated with high heterogeneity.[47] No subgroup or meta-regression analyses were found.

Table 55: Summary of Road Traffic Accidents From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Antonopoulos 2011[47]	*CPAP pre versus post*				CPAP was associated with significant reductions in the risk of real and near-miss road traffic accidents, when compared with pre-treatment.
	1,221 patients from 10 studies (1992 to 2007): • Severe OSA (mean AHI range: 37.9 to 60 events/hour, where reported) • Overweight to obese (mean BMI range: 29.5 to 35.5 kg/m^2, where reported) • 6 to 36 months of study duration	• Real accidents (from 10 studies): ○ OR (95% CI) = 0.21 (0.12 to 0.35); I^2 = 48% ○ IRR (95% CI) = 0.45 (0.34 to 0.59); I^2 = 26% ○ RD (95% CI) = –0.22 (–0.32 to –0.13) ○ NNT (95% CI) = 5 patients (3 to 8) • Near– miss accidents (from 5 studies): ○ OR (95% CI) = 0.09 (0.04 to 0.21); I^2 = 67% ○ IRR (95% CI) = 0.23 (0.08 to 0.67); I^2 = 85% ○ RD (95% CI) = –0.47 (– 0.69 to – 0.25) ○ NNT (95% CI) = 2 patients (1 to 4)	None	Low	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; IRR = incidence rate ratio; MA = meta-analysis; MR = meta-regression; NNT = number needed-to-treat; NR = not reported; OR = odds ratio; OSA = obstructive sleep apnea; RD = risk difference.

Cognitive Functions

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Two SRs[5,66] reported on cognitive functions in adults with mild-to-severe OSA who were overweight to obese.

One of the SRs[5] with sample sizes ranging from 291 patients to 382 patients from seven studies to eight studies, reported significantly greater increases in various neurocognitive and psychological outcomes[5] with CPAP, compared with controls, with no effect sizes reported. Study duration of the included primary studies ranged from 11 days to 12 months. I^2 scores were not applicable. The SR reported the quality of the included studies as low to moderate[5] (**Appendix 10**).

The other SR,[66] with a sample size of 1,744 patients from 13 studies, reported significantly greater increases in one domain of cognitive function (i.e., vigilance), but not others (i.e., attention, processing speed, working memory, memory, verbal fluency, and visuoconstructive skills) with CPAP, compared with controls. The standardized mean difference in vigilance was –0.12. Study duration of the included primary studies ranged from one week to 24 weeks. I^2 scores ranged from 0% to 85%. The SR reported the quality of the included studies as high[66] (**Appendix 10**).

Across the two SRs, 20 primary studies had been included, 12 of which had been included in one SR, and eight in two SRs (**Appendix 16.17**). The two SRs did not completely overlap on cognitive functions as the outcome.

The findings of the SRs are summarized in Table 56.

2) Oral appliances versus inactive controls

One SR[5] reported on cognitive functions in adults with moderate OSA who were overweight. The SR,[5] with 146 patients from one study, reported significantly greater increases in speed and vigilance with MADs, compared with controls, with no effect sizes reported. Study duration of the included primary study was four weeks. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as moderate (**Appendix 10**). The findings of the SR are summarized in Table 57.

3) Continuous positive airway pressure versus oral appliances

Two SRs[5,77] reported on cognitive functions in adults with mild-to-severe[77] or severe[5] OSA. One SR[5] included overweight-to-obese patients. The other SR[77] provided no information on comorbidities.

Both SRs,[5,77] with sample sizes ranging from 76 patients[5] to 221 patients[77] from two studies[5] to three studies,[77] reported no significant differences in change in cognitive functions, including intelligence quotient, executive function, and processing speed, between CPAP and MADs[5] or undefined OAs.[77] Study duration of the included primary studies, reported by both SRs, ranged from eight weeks[5,77] to 12 weeks.[77] I^2 scores were not applicable. The SRs reported the quality of the included studies as low[77] or low to moderate[5] (**Appendix 10**).

Across the two SRs, three primary studies had been included, one of which had been included in one or the other SR, and two in both SRs (**Appendix 16.18**). One SR[77] included all primary studies included in another SR[5] on cognitive functions as the outcome.

The findings of the SRs are summarized in Table 68.

4) Continuous positive airway pressure versus lifestyle interventions

One SR[5] reported on cognitive functions in adults with moderate OSA who were obese. The SR,[5] with a sample size of 26 patients from one study, reported no significant differences in change in cognitive functions, including executive function and processing speed, with CPAP, compared with positional therapy. Study duration of the included primary study was two weeks. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as moderate (**Appendix 10**). The findings of the SR are summarized in Table 59.

Review of Primary Studies

No primary studies on any of the comparisons were found that reported on cognitive functions.

Summary of Results on Cognitive Functions

For cognitive functions, evidence was found on inactive comparisons with CPAP and OAs (i.e., MADs and undefined OAs). Evidence was also found on active comparisons between CPAP and MADs or undefined OAs and between CPAP and positional therapy. Findings on CPAP were mixed, where one SR reported improved cognitive functions with CPAP, compared with inactive controls, while another SR reported improvement in one of seven domains. Further, it is unclear if these results are clinically important, and some of the findings were associated with high heterogeneity. Compared with inactive controls, MADs were effective at improving speed and vigilance. No significant differences in cognitive functions were found between CPAP and MADs or undefined OAs and between CPAP and positional therapy. However, the findings on CPAP versus positional therapy were based on one study of 26 patients that was two weeks in duration. No subgroup or meta-regression analyses were found.

Table 56: Summary of Change in Cognitive Functions From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Pan 2015[66]	*CPAP versus inactive controls*				Out of seven domains of cognitive function, only vigilance was found significantly improved by CPAP, compared with inactive controls.
	1,744 patients from 13 RCTs (1994 to 2012): • Mild-to-severe OSA (mean AHI range: 10.0 to 55.4 events/hour) • Overweight to obese (mean BMI range: 27.8 to 37.1 kg/m^2) • 1 to 24 weeks of study duration	• Attention SMD (95% CI) = –0.10 (–0.27 to 0.07); P = 0.24; I^2 = 85% • Vigilance SMD (95% CI) = – 0.12 (–0.23 to –0.01); P = 0.04; I^2 = 11% • Processing speed SMD (95% CI) = –0.08 (–0.20 to 0.03); P = 0.16; I^2 = 20% • Working memory SMD (95% CI) = 0.00 (–0.14 to 0.15); P = 0.95; I^2 = 70% • Memory SMD (95% CI) = – 0.04 (–0.11 to 0.04); P = 0.30; I^2 = 10% • Verbal fluency SMD (95% CI) = –0.06 (–0.19 to 0.07); P = 0.34; I^2 = 12% • Visuoconstructive skills SMD (95% CI) = –0.01 (−0.15 to 0.14); P = 0.92; I^2 = 0%	None	High	
Balk 2011[5]	*CPAP versus inactive controls*				Four RCTs reported significant increases in some neurocognitive and psychological functions with CPAP, compared with inactive controls.
	382 patients from 8 RCTs (1994 to 2004): • Mild-to-severe OSA (mean AHI range: 10 to 43 events/hour) • Overweight to obese (mean BMI range: 29.4 to 33 kg/m^2) • 4 weeks to 12 months of study duration	• Wide variety of neurocognitive and psychological outcomes (from 8 RCTs): significant increases in cognitive performance, executive function, processing speed, and semantic fluency with CPAP, compared with control, in 4 RCTs • No MA	None	Low to moderate	
	CPAP versus sham CPAP				One RCT reported significant increases in some neurocognitive and psychological functions with CPAP, compared with sham CPAP.
	291 patients from 7 RCTs (1999 to 2007): • Moderate-to-severe OSA (mean AHI	• Wide variety of neurocognitive and psychological outcomes (from 7 RCTs): significant increases in digital vigilance with CPAP, compared with sham CPAP,	None	Mixed	

Table 56: Summary of Change in Cognitive Functions From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	range: 22-68 events/hour) • Overweight to obese (mean BMI range: 29 to 42.6 kg/m^2) • 11 days to 6 weeks of study duration	in 1 RCT • No MA			

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SMD = standardized mean difference.

Table 57: Summary of Change in Cognitive Functions From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates from MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*MADs versus sham OAs*				MADs were associated with significant improvements in speed and vigilance on the neuropsychological test, compared with sham OAs.
	146 patients from 1 RCT (2002): • Moderate OSA (mean AHI: 25 events/hour) • Overweight (BMI: 29 kg/m^2) • 4 weeks of study duration	• Speed and vigilance:[a] significant improvements in MADs compared with sham OAs ($P < 0.001$) • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; MA = meta-analysis; MAD = mandibular advancement device; MR = meta-regression; OA = oral appliance; OSA = obstructive sleep apnea; RCT = randomized controlled trial.
[a] Measured by a choice reaction time task.

Table 58: Summary of Change in Cognitive Functions From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates from MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Li 2013[77]	*CPAP versus OAs*				There was no significant difference between CPAP and OAs for cognitive functions.
	221 patients from 3 RCTs (2002 to 2009): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 8 to 12 weeks of study duration	• No significant differences in cognitive functions between CPAP and OAs, measured by the following: ○ (from 1 RCT) performance IQ decrement score, Trail-Making test B, Steer Clear Performance Test, and Paced Auditory Serial Addition Test 2s ○ (from 1 RCT) Paced Auditory Serial Addition Test 1.2 ○ (from 1 RCT) Trail-Making tests A and B • No MA	None	Low	
Balk 2011[5]	*CPAP versus MADs*				There were no significant differences between CPAP and MADs for various neurocognitive tests.
	76 patients from 2 RCTs (2002 and 2009): • Severe OSA (mean AHI range: 31 to 34 events/hour) • Overweight (mean BMI: 26.7 kg/m^2, where reported) • 8 weeks to 2 months of study duration	• No significant differences between CPAP and MADs in a range of tests of cognitive performance (IQ), executive function (Trail-Making), processing speed (Paced Auditory Addition Test), error making (Oxford sleep resistance), and driving skills (SteerClear) • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; IQ = intelligence quotient; MA = meta-analysis; MAD = mandibular advancement device; MR = meta-regression; NR = not reported; OA = oral appliances; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

Table 59: Summary of Change in Cognitive Functions From CPAP Versus Lifestyle Intervention

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	*CPAP versus positional therapy (i.e., devices worn on the back)*				There was no significant difference in cognition between CPAP and positional therapy.
	26 patients from 1 RCT (1999): • Moderate OSA (mean AHI = 18 events /hour) • Obese (mean BMI = 30 kg/m^2) • 2 weeks of study duration	• No significant differences between CPAP and positional therapy in cognition assessed by various scales[a] • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

[a] Including Wechsler Memory Scale, Purdue Pegboard, Trail-Making Test, Symbol Digit Modalities, Consonant Trigram, or Concentration Endurance Test scores.

Psychological Functions

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Three SRs[5,54,75] reported on psychological functions in adults with mild-to-severe OSA. The SRs included normal-to-obese[75] or overweight-to-obese[5,54] patients.

All three SRs,[5,54,75] with sample sizes ranging from 169 patients[54] to 1,314 patients[75] from four studies[54] to 19 studies,[75] generally reported significantly greater reductions in depression[5,54,75] and anxiety[5,54] with CPAP, compared with controls[5,54,75] or pre-treatment.[54] The depression or anxiety Hedges' g, reported by one of the three SRs,[54] ranged from –0.23 to –0.52. Study duration of the included primary studies, reported by all three SRs, ranged from one week[75] to two years.[54] I^2 scores, reported by the two applicable SRs, ranged from 0%[54] to 71.3%.[75] The SRs reported the quality of the included studies as very low to low,[54] moderate,[5] or mixed[75] (**Appendix 10**).

From subgroup analyses, one SR[75] reported that the effect of CPAP versus controls on depressive symptoms was significantly greater in patients with depression at baseline. However, the SR[75] reported that OSA severity at baseline, trial lengths, and CPAP adherence were not significant factors for the effect of CPAP on depression.

Across the three SRs, 36 primary studies had been included, 26 of which had been included in one SR, seven in two SRs, and three in three SRs (**Appendix 16.19**). No two SRs completely overlapped on psychological functions as the outcome.

The findings of the SRs are summarized in Table 60.

2) Oral appliances versus inactive controls

Two SRs[5,75] reported on psychological functions in adults with moderate[5] or moderate-to-severe[75] OSA. The SRs[5,75] included normal-to-obese[75] and overweight-to-obese[5] patients.

Both SRs,[5,75] with sample sizes ranging from 146 patients[5] to 418 patients[75] from one study[5] to five studies,[75] reported mixed findings, including significant improvements in some scales (e.g., somatic items on the Beck Depression Inventory [BDI] scale in one study) but not others (e.g., Short Form [36] Health Survey [SF-36] mental health in three studies) with MADs, compared with controls. Study duration of the included primary studies, reported by both SRs, ranged from four weeks[5,75] to three months.[5] The I^2 score, reported by the one applicable SR,[75] was 0%. The SRs reported the quality of the included studies as moderate[5] or mixed[75] (**Appendix 10**).

Across the two SRs, six primary studies had been included, five of which had been included in one or the other SR, and one in both SRs (**Appendix 16.20**). The two SRs did not completely overlap on psychological functions as the outcome.

The findings of the SRs are summarized in Table 61.

3) Continuous positive airway pressure versus oral appliances

Two SRs[54,77] reported on psychological functions in adults with mild-to-severe[77] or moderate[54] OSA. One SR[54] included overweight-to-obese patients. The other SR[77] provided no information on comorbidities.

One of the two SRs,[54] with a sample size of 132 patients from two studies, reported mixed findings, including a significant improvement in anxiety but no improvement in depression with CPAP, compared with undefined OAs. Study duration of the included primary studies ranged from 60 days to three months. The I^2 score was 0%. The SR[54] reported the quality of the included studies as very low to low (**Appendix 10**).

The other SR,[77] with a sample size of 151 patients from two studies, reported no significant differences in change in psychological functions between CPAP and undefined OAs. Study duration of the included studies ranged from eight weeks to 12 weeks. I^2 scores were not applicable. The SR[77] reported the quality of the included studies as low (**Appendix 10**).

Across the two SRs, four primary studies had been included, all of which had been included in one or the other SR, with no overlap between the two SRs (**Appendix 16.21**).

The findings of the SRs are summarized in Table 62.

4) Continuous positive airway pressure versus lifestyle interventions

One SR[54] reported on psychological functions in adults with moderate OSA who were overweight. The SR,[54] with a sample size of 16 patients from one study, reported significant improvements in anxiety and depression with CPAP, compared with exercise, with the depression and anxiety Hedges' g reported as –0.09 and –0.35, respectively. Study duration of the included primary study was 60 days. I^2 scores were not applicable. The SR[54] reported the quality of the included studies as very low to low (**Appendix 10**). The findings of the SR are summarized in Table 63.

Review of Primary Studies

No primary studies on any of the comparisons were found that reported on psychological functions.

Summary of Results on Psychological Functions

For psychological functions, evidence was found on inactive comparisons with CPAP and MADs. Evidence was also found on active comparisons between CPAP and undefined OAs and between CPAP and exercise. Compared with inactive controls or pre-treatment, CPAP was effective at reducing depression and anxiety severity, although it is unclear if these results are clinically important. Findings on MADs were mixed, including improvements in some scales, but not others, of psychological functions. Findings on CPAP versus undefined OAs were mixed, where one SR reported an improvement in anxiety but not in depression, while another SR reported no significant differences between the two interventions. CPAP may be more effective at improving anxiety and depression, compared with exercise. Subgroup analyses suggest that patients with baseline depression, compared with those without depression, experienced greater effects with CPAP. Baseline OSA severity, adherence, and study duration were not significantly associated with the effects of CPAP. No subgroup or meta-regression analyses were found on baseline EDS, sex, age, or BMI.

Table 60: Summary of Change in Psychological Functions From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP pre versus post*				Depression and anxiety severity was significantly decreased with CPAP, compared with oral placebo and when pre- and post-treatment were compared. There was no significant difference between CPAP and sham CPAP in their effects on depression and anxiety severity.
	803 patients from 21 studies (1988 to 2013): • Mild-to-severe OSA (mean AHI range: 11 to 71.5 events/hour, where reported) • Overweight to obese (mean BMI range: 27.8 to 38 kg/m^2, where reported) • 11 days to 2 years of study duration	• Depression Hedges' *g* (95% CI) = – 0.52 (–0.65 to –0.40); *P* < 0.001; I^2 = 4.3%	None	Very low to low	
	406 patients from 12 studies (1988 to 2013): • Moderate-to-severe OSA (mean AHI range: 21.3 to 67 events/hour, where reported) • Overweight to obese (mean BMI range: 27.8 to 33.1 kg/m^2, where reported) • 11 days to 12 months of study duration	• Anxiety Hedges' *g* (95% CI) = −0.41 (–0.56 to –0.26); *P* < 0.001; I^2 = 3.6%	None		
	CPAP versus oral placebo				
	219 patients from 5 studies (1994 to 2004): • Mild-to-severe OSA (mean AHI range: 11 to 43 events/hour)	• Depression Hedges' *g* (95% CI) = –0.36 (–0.52 to –0.19); *P* < 0.001; I^2 = 0.29% • Anxiety Hedges' *g* (95% CI) = −0.23 (–0.36 to –0.09);	None	Very low to low	

Table 60: Summary of Change in Psychological Functions From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• Overweight to obese (mean BMI range: 27.8 to 33 kg/m^2) • 4 weeks-3 months of study duration	P = 0.001; I^2 = 0%			
	CPAP versus sham CPAP				
	169 patients from 4 studies (1999 to 2012): • Moderate-to-severe OSA (mean AHI range: 21.6 to 63.6 events/hour) • Overweight to obese (mean BMI range: 29.2 to 33.1 kg/m^2, where reported) • 4 weeks to 3 months of study duration	• Depression Hedges' g (95% CI) = 0.05 (–0.19 to 0.29); P = 0.69; I^2 = 0% • Anxiety Hedges' g (95% CI) = 0.07 (–0.17 to 0.32); P = 0.55; I^2 = 0%	None	Very low to low	
Povitz 2014[75]	*CPAP versus inactive controls*				CPAP resulted in an improvement in depressive symptoms, compared with inactive controls. However, the overall effect size was small, and there was significant heterogeneity among the included studies. The effect of CPAP on depressive symptoms was significantly larger in patients with depression at baseline. OSA severity, trial length, and CPAP adherence were not significant factors for the effect of CPAP on depression.
	1,314 patients from 19 RCTs (1998 to 2013): • Mild-to-severe OSA (mean AHI range: 10 to 65.1 events/hour, where reported) • (for the 1,732 patients included in the SR) Normal-to-obese (mean BMI range: 24.7 to 42.5 kg/m^2) • 1 to 24 weeks of study	• Depression[a] SMD (95% CI) = −0.31 (–0.53 to –0.10); P = 0.004; I^2 = 71.3%	Subgroup analysis: • Baseline depression: ○ Yes: depression SMD (95% CI) = −2.00 (–2.62 to −1.39); I^2 = 12% ○ No: depression[a] SMD (95% CI) = −0.20 (–0.33 to −0.06); I^2 = 30% • Baseline AHI: ○ < 30 events/hour:	Mixed	

Table 60: Summary of Change in Psychological Functions From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	duration		depression[a] SMD (95% CI) = –0.46 (–0.85 to –0.06); I^2 = 84% ○ ≥ 30 events/hour: depression[a] SMD (95% CI) = –0.23 (–0.46 to 0.002); I^2 = 48% • Trial length: ○ < 4 weeks: depression[a] SMD (95% CI) = –0.31 (–0.73 to 0.11); I^2 = 58% ○ 4 to 8 weeks: depression[a] SMD (95% CI) = –0.39 (–0.81 to 0.04); I^2 = 83% ○ > 8 weeks: depression[a] SMD (95% CI) = –0.20 (–0.36 to –0.04); I^2 = 0% • CPAP adherence: ○ < 4 hours/night: depression[a] SMD (95% CI) = –0.47 (–0.81 to –0.13); I^2 = 80%		

Table 60: Summary of Change in Psychological Functions From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
			○ ≥ 4 hours/night: depression[a] SMD (95% CI) = –0.16 (–0.32 to 0.001); I^2 = 0%		
Balk 2011[5]	*CPAP versus inactive controls*				Four RCTs reported significant increases in some neurocognitive and psychological functions with CPAP, compared with inactive controls.
	382 patients from 8 RCTs (1994 to 2004): • Mild-to-severe OSA (mean AHI range: 10 to 43 events/hour) • Overweight to obese (mean BMI range: 29.4 to 33 kg/m^2) • 4 weeks to 12 months of study duration	• Wide variety of neurocognitive and psychological outcomes (from 8 RCTs): significant increases in anxiety and depression scores with CPAP, compared with control, in 4 RCTs • No MA	None	Low to moderate	

AHI = Apnea–Hypopnea Index; BDI = Beck depression index; BMI = body mass index; BSI = Brief Symptom Inventory; CI = confidence interval; CPAP = continuous positive airway pressure; HADS-D = Hospital Anxiety and Depression Scale–Depression Subscale; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea; POMS-D = Profile of Mood States–Depression Subscale; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; SMD = standardized mean difference; SR = systematic review.

[a] Measured by BDI, BSI, HADS-D, POMS-D, or SF-36.

Table 61: Summary of Change in Psychological Functions From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Povitz 2014[75]	*MADs versus inactive controls*				There was a significant improvement in depressive symptoms with MADs, compared with inactive controls.
	418 patients from 5 RCTs (2004 to 2008): • Moderate-to-severe OSA (mean AHI range: 21.3 to 34.7	Depression: • BDI or SF–36 Mental Health (from 5 RCTs) SMD (95% CI) =–0.21 (–0.40 to –0.03);	None	Mixed	

Table 61: Summary of Change in Psychological Functions From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	events/hour) • (for the 1,732 patients included in the SR) Normal-to-obese (mean BMI range: 24.7 to 42.5 kg/m^2) • 4 to 12 weeks of study duration	P = 0.025; I^2 = 0% • SF–36 Mental Health (from 3 RCTs) MD (95% CI) = –2.98 (−7.78 to 1.81); P = NR; I^2 = 0% • BDI (from 2 RCTs) MD (95% CI) = –0.80 (–1.52 to –0.08); P = NR; I^2 = 0%			
Balk 2011[5]	*MADs versus inactive controls*				There was no significant difference between MADs and inactive controls on the BDI scale.
	160 patients from 1 RCT (2004) • Moderate OSA (mean AHI: 21 events/hour) • Obese (mean BMI: 31.1 kg/m^2) • 3 months of study duration	• BDI (from 1 RCT): no significant differences between MADs and controls	None	Moderate	
	MADs versus sham OAs				MADs were associated with significant improvements in somatic items on the BDI scale, compared with sham OAs.
	146 patients from 1 RCT (2002): • Moderate OSA (mean AHI: 25 events/hour) • Overweight (mean BMI: 29 kg/m^2) • 4 weeks of study duration	• Somatic items on the BDI scale (P < 0.05)	None	Moderate	

AHI = Apnea–Hypopnea Index; BDI = Beck Depression Inventory; BMI = body mass index; CI = confidence interval; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliance; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SF = Short Form Health Survey; SMD = standardized mean difference; SR = systematic review.

Table 62: Summary of Change in Psychological Functions From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus OAs*				There was a small effect size, favouring CPAP over OAs, for anxiety. There was no significant difference between CPAP and OAs for depression.
	132 patients from 2 RCTs (2004 and 2013): • Moderate OSA (mean AHI range: 21.3 to 26.2 events/hour) • Overweight to obese (mean BMI range: 27.8 to 31.1 kg/m^2) • 60 days to 3 months of study duration	• Anxiety[a] Hedges' *g* (95% CI) = –0.10 (–0.28 to –0.08); *P* = 0.27; I^2 = 0% • Depression[a] Hedges' *g* (95% CI) = –0.11 (–0.29 to 0.72); *P* = 0.24; I^2 = 0%	None	Very low to low	
Li 2013[77]	*CPAP versus OAs*				There was no significant difference between CPAP and OAs for anxiety and depression.
	151 patients from 2 RCTs (2002 and 2008) using Hospital Anxiety and Depression Scale: • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 8 to 12 weeks of study duration	Hospital Anxiety and Depression Scale (from 2 RCT): • No significant differences between CPAP and OAs	None	Low	

AHI = Apnea–Hypopnea Index; BDI = Beck depression index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; MA = meta-analysis; MR = meta-regression; NR = not reported; OA = oral appliances; OSA = obstructive sleep apnea; POMS = profile of mood states; RCT = randomized controlled trial.

[a] Measured by BDI or POMS.

Table 63: Summary of Change in Psychological Functions From CPAP Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus exercise programs*				CPAP was marginally more effective than exercise at reducing depression and anxiety.
	16 patients from 1 RCT (2013): • Moderate OSA (mean AHI: 26.2 events/hour) • Overweight (mean BMI: 27.8 kg/m^2) • 60 days of study duration	• POMS–depression Hedges' *g* (SE) = –0.09 (0.48) • POMS–tension and anxiety Hedges' *g* (SE) = –0.35 (0.48)	None	Very low to low	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea; POMS = profile of mood states; RCT = randomized controlled trial; SE = standard error.

Quality of Life

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Two SRs[5,54] reported on QoL in adults with mild-to-severe OSA who were overweight to obese.

One of the SRs,[54] with sample sizes ranging from 219 patients from five controlled studies to 365 patients from nine pre-and-post studies, reported significantly greater increases in QoL with CPAP, compared with oral placebo or pre-treatment. The QoL Hedges' g ranged from 0.44 to 0.49. Study duration of the included primary studies ranged from four weeks to eight months. I^2 scores ranged from 4% to 50%. The SR[54] reported the quality of the included studies as very low to low (**Appendix 10**).

The other SR,[5] with sample sizes ranging from 347 patients to 618 patients from six studies to 11 studies, reported in general no significant differences in change in QoL between CPAP and inactive controls. Study duration of the included studies ranged from three weeks to six months. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as low to moderate (**Appendix 10**).

Across the two SRs, 22 primary studies had been included, 16 of which had been included in one or the other SR, and six in both SRs (**Appendix 16.22**). The two SRs did not completely overlap on QoL as the outcome.

The findings of the SRs are summarized in Table 64.

2) Oral appliances versus inactive controls

Two SRs[5,74] reported on QoL in adults with moderate-to-severe OSA. One SR[5] included overweight-to-obese patients. The other SR[5] provided no information on comorbidities.

Both SRs,[5,74] with sample sizes ranging from 52 patients[5] to 227 patients[5] from one study[5] to two studies,[5,74] reported in general no significant differences in change in QoL between OAs[74] or MADs,[5] compared with controls. Study duration of the included primary studies, reported by both SRs, ranged from four weeks[5] to three months.[5,74] I^2 scores, reported by the one applicable SR,[74] ranged from 0% to 65%. The SRs reported the quality of the included studies as low to moderate[74] or moderate[5] (**Appendix 10**).

Across the two SRs, four primary studies had been included, three of which had been included in one or the other SR, and one in both SRs (**Appendix 16.23**). The two SRs did not completely overlap on QoL as the outcome.

The findings of the SRs are summarized in Table 65.

3) Continuous positive airway pressure versus oral appliances

Four SRs[5,54,74,77] reported on QoL in adults with mild-to-severe[77] or moderate-to-severe[5,54,74] OSA. Two SRs[5,54] included overweight-to-obese patients. Two SRs[74,77] provided no information on comorbidities.

Three of the four SRs,[5,74,77] with sample size ranging from 161 patients[5] to 376 patients[77] from two studies[74,77] to seven studies,[77] reported mixed findings, including significantly greater increases in some components of QoL[74,77] or some scales of QoL,[5] but not others, with CPAP, compared with OAs. Study duration of the included studies, reported by all three SRs, ranged from one month[5] to 48 weeks.[77] I^2 scores, reported by the two applicable SRs,[74,77] ranged from 30%[74] to 86%[77] and were greater than 75% in one SR.[77] The SRs reported the quality of the included studies as very low[77] or low to moderate[5,74] (**Appendix 10**).

The other SR,[54] with a sample size of 132 patients from two studies, reported no significant differences in change in QoL between CPAP and OAs. Study duration of the included primary studies ranged from 60 days to three months. The I^2 score was 0%. The SR[54] reported the quality of the included studies as very low to low (**Appendix 10**).

Across the four SRs, nine primary studies had been included, five of which had been included in one SR, one in two SRs, and three in three SRs (**Appendix 16.24**). Two SRs[5,77] included all primary studies included in another SR[74] on QoL as the outcome.

The findings of the SRs are summarized in Table 66.

4) Continuous positive airway pressure versus lifestyle interventions

Two SRs[5,54] reported on QoL in adults with moderate OSA who were overweight[54] or obese.[5]

One of the two SRs,[54] with a sample size of 16 patients from one study, reported significantly greater increases in QoL with CPAP, compared with exercise,[54] with the QoL Hedges' g of 1.23. Study duration of the included primary study was 60 days. I^2 scores were not applicable. The SR[54] reported the quality of the included studies as very low to low (**Appendix 10**).

The other SR,[5] with a sample size of 94 patients from three studies, reported no significant differences in the effect of CPAP versus positional therapy. Study duration of the included primary studies ranged from two weeks to one month. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as moderate (**Appendix 10**).

Across the two SRs, six primary studies had been included, all of which had been included in one or the other SR, with no overlap between the two SRs (**Appendix 16.25**).

The findings of the SRs are summarized in Table 67.

5) Combination therapy versus active controls

One SR[19] reported on QoL in adults with moderate-to-severe OSA who were overweight to obese. The SR,[19] with a sample size of 230 patients from two studies, reported no significant differences in the effect of CPAP plus diet programs, compared with diet programs alone. Study duration of the included primary studies ranged from three months to six months. The I^2 score was 0%. The SR[19] reported the quality of the included studies as mixed (**Appendix 10**). The findings of the SR are summarized in Table 68.

Review of Primary Studies

1) Positional therapy versus inactive controls

One study[78,81-86,88,90,96,99,102,104,105,108,116,118] reported on QoL in adults with mild-to-moderate OSA. The study[78,81,85,86,90,96,99,102,104,108,116,118] included positional OSA patients only who were overweight, provided by mean BMI. The study,[78,81-84,86,88,90,96,99,104,105,108,116,118] with a sample size of 33 patients, reported no significant change in QoL with an apparatus designed to prevent sleep in the supine position, compared with pre-treatment. Concerns with the quality of the study[78,81-84,86,88,90,96,99,104,105,108,116,118] were assessed to be low (**Appendix 14**). The findings of the primary study are summarized in Table 69.

Summary of Results on Quality of Life

For QoL, evidence was found on inactive comparisons with CPAP, OAs (i.e., MADs and undefined OAs), and positional therapy. Evidence was also found on active comparisons between CPAP and MADs or undefined OAs and between CPAP and lifestyle interventions (i.e., diet, exercise, and positional therapy). Findings on CPAP were mixed, where one SR reported improved QoL with CPAP, compared with inactive controls, while another SR reported no significant differences between CPAP and inactive controls, although it is unclear if these results are clinically important. No significant differences between MADs, undefined OAs, or positional therapy and inactive controls were reported. Findings on CPAP versus MADs or undefined OAs, as well as those on CPAP versus diet, exercise, and positional therapy, were mixed, and some of the findings were associated with high heterogeneity. No significant differences between CPAP plus diet programs and diet programs alone were reported. No subgroup or meta-regression analyses were found.

Table 64: Summary of Change in Quality of Life From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP pre versus post*				CPAP was associated with improved QoL, when pre- and post-treatment were compared and when compared with oral placebo.
	365 patients from 9 studies (1998 to 2013): • Moderate-to-severe OSA (mean AHI range: 21.3 to 54.5 events/hour) • Overweight to obese (mean BMI range: 27.8 to 34.4 kg/m^2, where reported) • 4 weeks to 8 months of study duration	• QoL[a] Hedges' *g* (95% CI) = 0.44 (0.24 to 0.63); *P* < 0.001; I^2 = 4.32% • FOSQ Hedges' *g* (95% CI) = 0.51 (0.22 to 0.80); *P* = 0.001; I^2 = 49.9%	None	Very low to low	
	CPAP versus oral placebo				
	219 patients from 5 studies (1994 to 2004): • Mild-to-severe OSA (mean AHI range: 11 to 43 events/hour) • Overweight to obese (mean BMI range: 27.8 to 33 kg/m^2) • 4 weeks to 3 months of study duration	• QoL[a] Hedges' *g* (95% CI) = 0.49 (0.13 to 0.86); *P* = 0.008; I^2 = 34%	None	Very low to low	
Balk 2011[5]	*CPAP versus inactive controls*				In general, no significant differences were found between CPAP and inactive controls in FOSQ. The effect of CPAP on QoL is uncertain, when compared with inactive controls.
	618 patients from 11 RCTs (1994 to 2007): • Mild-to-severe OSA (mean AHI range: 13 to 58 events/hour) • Overweight to obese (mean BMI range: 27.3 to 33.5 kg/m^2)	• FOSQ (from 4 RCTs): no significant differences between CPAP and control in any RCT • QoL[b] (from 10 RCTs): inconsistent findings across RCTs • No MA	None	Low to moderate	

Table 64: Summary of Change in Quality of Life From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 4 weeks to 6 months of study duration				
	CPAP versus sham CPAP				
	347 patients from 6 RCTs (2001 to 2008): • Moderate-to-severe OSA (mean AHI range: 22 to 57 events/hour) • Overweight to obese (mean BMI range: 29 to 35.2 kg/m^2) • 3 weeks to 3 months of study duration	• FOSQ (from 3 RCTs): no significant differences between CPAP and sham CPAP in any RCT • QoL[c] (from 6 RCTs): significant increases in SF-36 physical and mental health and SAQLI with CPAP, compared with sham CPAP, in 1 RCT • No MA	None	Mixed	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; FOSQ = Functional Outcomes of Sleep Questionnaire; GHQ = General Health Questionnaire; GQL = glaucoma quality of life; MA = meta-analysis; MR = meta-regression; NHP = Nottingham Health Profile; NR = not reported; OSA = obstructive sleep apnea; QoL = quality of life; RCT = randomized controlled trial; SAHS = sleep apnea/hypopnea syndrome; SAQLI = the Calgary Sleep Apnea Quality of Life Index; SF = Short Form (36) Health Survey; UMACL Energetic Arousal Score = energetic arousal score of the University of Wales Mood Adjective Checklist, WHO = World Health Organization.

[a] Measured by SF-36, GQL, SF-12, WHOQOL, NHP-2, GHQ-28, WHO-5, or FOSQ.

[b] Measured by SF-36, NHP, GHQ-28, UMACL, SAHS-related symptoms questionnaire, or SAQLI.

[c] Measured by SF-36 or SAQLI.

Table 65: Summary of Change in Quality of Life From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Okuno 2014[74]	*OAs versus control appliances*				There was no significant difference in the change in SF-63 General Health, Mental Health, or Vitality between OAs and control appliances.
	67 patients from 2 RCTs (2005 and 2008): • Moderate-to-severe OSA (mean AHI: 33.8 and 39.1 events/hour	• SF-36 General Health MD (95% CI) = 1.34 (-8.16 to 10.85); P = 0.78; I^2 = 0% • SF-36 Mental Health MD (95% CI) = −3.04 (–9.82 to 3.73); P = 0.38; I^2 = 0%	None	Low to moderate	

Table 65: Summary of Change in Quality of Life From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	[for OA group] and 24 and 32.6 events/hour [for control group]) • Comorbidities: NR • 1 to 3 months of study duration	• SF-36 Vitality MD (95% CI) = 3.76 (−13.77 to 21.29); $P = 0.67$; $I^2 = 65\%$			
Balk 2011[5]	*MADs versus inactive controls*				There was no significant difference in the overall quality of life between MADs and inactive controls.
	227 patients from 2 RCTs (2004 and 2007): • Moderate OSA (mean AHI range: 19 to 21 events/hour) • Overweight to obese (mean BMI range: 27.3 to 31.1 kg/m^2) • 10 weeks-3 months of study duration	• SAQLI score (from 1 RCT) MD (95% CI) = 0.7 (0.6 to 0.8); $P < 0.001$ • FOSQ social domain outcome (from 1 RCT): no significant differences between MAD and control • SAQLI–social interactions treatment-related symptoms or SF-36 mean score and physical and mental components (from 1 RCT): no significant differences between MAD and control • No MA	None	Moderate	
	MADs versus sham OAs				MADs were associated with a significant improvement in SF-36 Vitality domain but not in the other domains, when compared when sham OAs.
	52 patients from 1 RCT (2008): • Severe OSA (mean AHI: 35 events/hour) • Obese (mean BMI: 31 kg/m^2) • 4 weeks of study duration	• SF-36: ○ Vitality: net difference = 18.7; $P = 0.001$ ○ Other domains: no significant differences between MADs and sham OAs • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass inventory; CI = confidence interval; FOSQ = Functional Outcomes of Sleep Questionnaire; MA = meta-analysis; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliance; OSA = obstructive sleep apnea; RCT = randomized controlled trial; SAQLI = Calgary Sleep Apnea Quality of Life Index; SF = Short Form (36) Health Survey.

Table 66: Summary of Change in Quality of Life From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus OAs*				There was no significant difference between CPAP and OAs for QoL.
	132 patients from 2 RCTs (2004 and 2013): • Moderate OSA (mean AHI range: 21.3-26.2 events/hour) • Overweight to obese (mean BMI range: 27.8 to 31.1 kg/m^2) • 60 days to 3 months of study duration	SF-36: • All subscales Hedges' *g* (95% CI) = −0.02 (–0.20 to 0.16); *P* = 0.82; I^2 = 0%	None	Very low to low	
Okuno 2014[74]	*CPAP versus OAs*				CPAP was significantly more effective at improving mental health, measured by SF-36, when compared with OAs. However, there were no significant differences between CPAP and OAs at improving general health and vitality, measured by SF-36.
	214 (included) or 167 (analyzed) patients from 2 RCTs (2007 and 2008): • Moderate-to-severe OSA (mean AHI range: 20.9 to 40.3 events/hour) • Comorbidities: NR • 8 to 10 weeks of study duration	SF-36: • General Health MD (95% CI) = 0.61 (−1.03 to 2.24); *P* = 0.47; I^2 = 30% • Mental Health MD (95% CI) = 1.80 (0.42 to 3.17); *P* = 0.01; I^2 = 44% • Vitality MD (95% CI) = 2.68 (–5.32 to 10.69); *P* = 0.51; I^2 = 75%	None	Low to moderate	
Li 2013[77]	*CPAP versus OAs*				The findings on quality of life were mixed but generally indifferent between CPAP and OAs.
	162 patients from 2 RCTs (2002 and 2004) using FOSQ or 376 patients from 5 RCTs (2002 to 2011) using SF-36: • Mild-to-severe OSA (AHI threshold: ≥5 events/hour) • Comorbidities: NR • 8-48 weeks of study	FOSQ: • MD (95% CI): 0.43 (–0.54 to 1.41); *P* = 0.38; I^2 = 86% SF-36: • Components analyzed separately (from 1 RCT): significantly higher health transition (*P* = 0.001) and mental components (*P* = 0.008) with CPAP	None	Low	

Table 66: Summary of Change in Quality of Life From CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	duration	versus OAs and no significant difference in physical component between CPAP and OAs • Components analyzed or reported together (from 4 RCTs): no significant differences between CPAP and OAs • No MA			
Balk 2011[5]	*CPAP versus MADs*				The findings on QoL were inconsistent between CPAP and MADs.
	161 patients from 3 RCTs (2002 to 2008) using FOSQ or 361 patients from 7 RCTs (2002 to 2009) using various QoL scales:[a] • Moderate-to-severe OSA (mean AHI range: 21 to 40 events/hour) • Overweight to obese (mean BMI range: 26.7 to 34.1 kg/m^2) • 1 to 3 months of study duration	FOSQ: • MD (95% CI) = –0.86 (–2.49 to 0.77) Various QoL scales:[a] • (from 5 RCTs) no significant difference between CPAP and MADs • (from 2 RCTs) components of SF-36 favouring CPAP versus MADs • (from 1 RCT) greater improvement on SALQI but more treatment-related symptoms with CPAP versus MADs • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BDI = Beck Depression Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; FOSQ = Functional Outcomes of Sleep Questionnaire; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NHP = the Nottingham Health Profile; NR = not reported; OA = oral appliances; OSA = obstructive sleep apnea; QoL = quality of life; RCT = randomized controlled trial; SAQLI = the Calgary Sleep Apnea Quality of Life Index; SF-36 = Short Form (36) Health Survey.

[a] Including SF-36, Hospital Anxiety and Depression Scale, BDI, SAQLI, NHP, a "General Health" measure, and the Scottish National Sleep Laboratory symptom questionnaire.

Table 67: Summary of Change in Quality of Life From CPAP Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Gupta 2016[54]	*CPAP versus exercise programs*				CPAP was substantially more effective than exercise at improving QoL.
	16 patients from 1 RCT (2013): • Moderate OSA (mean AHI: 26.2 events/hour) • Overweight (mean BMI: 27.8 kg/m^2) • 60 days of study duration	• SF-36 Hedges' *g* (SE) = 1.23 (0.52)	None	Very low to low	
Balk 2011[5]	*CPAP versus positional therapy (i.e., shoulder-head elevation pillows or devices worn on the back)*				There was no significant difference in QoL between CPAP and positional therapy.
	94 patients from 3 RCTs (1999 to 2008): • Moderate OSA (mean AHI range: 18 to 27 events/hour) • Obese (mean BMI range: 30 to 34 kg/m^2) • 2 weeks to 1 month of study duration	• (from 3 RCTs) no significant differences between CPAP and positional therapy in QoL assessed by various scales[a] • (from 1 RCT) significantly higher NPH energy subscale with CPAP compared with positional therapy (difference = 1; *P* = 0.04) • No MA	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; FOSQ = Functional Outcomes of Sleep Questionnaire; GHQ = General Health Questionnaire; MA = meta-analysis; MR = meta-regression; NPH = Nottingham Health Profile; OSA = obstructive sleep apnea; QoL = quality of life; RCT = randomized controlled trial; SF-36 = Short Form (36) Health Survey; UWIST = University of Wales Institute of Science and Technology.

[a] Including SF-36 Mental and Physical Component Summaries, FOSQ, Hospital Anxiety and Depression Scale, UWIST mood adjective checklist, and GHQ.

Table 68: Summary of Change in Quality of Life From Combination Therapy Versus Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Thomasouli 2013[19]	*CPAP plus diet programs versus diet programs alone*				There was no significant difference in QoL between CPAP plus diet programs and diet programs alone.
	230 patients from 2 RCTs (1999 and 2001): • Moderate-to-severe OSA (mean AHI range: 20 to 56 events/hour) • Overweight to obese (mean BMI range: 29 to 32 kg/m^2) • 3 to 6 months of study duration	• NHP MD (95% CI) = −0.93 (–5.93 to 4.06); *P* = NR; I^2 = 0%	None	Mixed	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; MA = meta-analysis; MD = mean difference; MR = meta-regression; NHP = the Nottingham Health Profile; NR = not reported; OSA = obstructive sleep apnea; QoL = quality of life; RCT = randomized controlled trial.

Table 69: Summary of Change in Quality of Life From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Benoist 2016[78]	*Positional therapy (i.e., sleep position trainers) pre versus post*			Positional therapy with a sleep position trainer did not improve quality of life in patients with positional OSA.
	33 positional OSA patients: • Median AHI: 18.3 (IQR: 13.7 to 24.0) events/hour • Mean BMI ± SD: 27.9 ± 2.8 kg/m^2	• Median FOSQ score: ○ Before (n = 33): 15.8 (IQR: 10.5 to 17.0) ○ After 3 months (n = 32): 16.0 (IQR: 10.8 to 18.2) ○ Difference: *P* = 0.616	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; FOSQ = Functional Outcomes of Sleep Questionnaire; IQR = interquartile range; OSA = obstructive sleep apnea; SD = standard deviation.

Mortality

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Four SRs[52,53,56,69] reported on mortality in adults with mild-to-severe,[56] moderate-to-severe,[53,69] or unknown severity[52] OSA. One SR[53] included overweight-to-obese patients. One SR[56] included patients with previous CVD. Two SRs[52,69] provided no information on comorbidities.

Three of the four SRs,[52,56,69] with sample sizes ranging from 1,455 patients[56] to 3,112,644 patients[52] from three studies[56] to 11 studies,[52,69] reported significantly greater reductions in the risk of death from stroke,[56] cardiac disease,[56] and CVEs overall[52,56,69] with CPAP, compared with controls. The risk of the events, reported by all three SRs,[52,56,69] ranged from 0.37 in hazard ratio (HR),[52] 0.06 to 0.19 in relative risk,[56] and 0.32 in OR.[69] One of the SRs[52] also reported significantly greater reductions in the risk of death from all causes, with an HR reported as 0.66. Study duration of the included primary studies, reported by one of the three SRs,[56] ranged from 72 months to 89 months. I^2 scores, reported by all three SRs,[52,56,69] ranged from 0%[56] to 48%.[56] The SRs reported the quality of the included studies as moderate to high,[52] high,[69] or high to mixed[56] (**Appendix 10**).

The other SR,[53] with a sample size of 2,020 patients from four studies, reported no significant differences in the risk of death from all causes with CPAP, compared with controls. Study duration of the included primary studies ranged from six months to 60 months. The I^2 score was 0%. The SR[53] reported the quality of the included studies as high (**Appendix 10**).

From subgroup analyses, one SR[53] reported no significant differences in the effect of CPAP versus controls on mortality with varying levels of follow-up durations.

Across the four SRs, 19 primary studies had been included, 11 of which had been included in one SR, six in two SRs, and two in three SRs (**Appendix 16.26**). No two SRs completely overlapped on mortality as the outcome.

The findings of the SRs are summarized in Table 70.

Review of Primary Studies

1) Combination therapy versus inactive controls

One study[80] reported on mortality in adults with unknown severity OSA who were overweight, provided by mean BMI. The study,[80] with a sample size of 28 patients, concluded that MMA plus genioglossus advancement (GA) may be a safe method for treating OSA, as no mortality was reported. Concerns with the quality of the study were assessed to be low[80] (**Appendix 14**). The findings of the primary study are summarized in Table 71.

Summary of Results on Mortality

For mortality, evidence was found on inactive comparisons with CPAP and combination therapy (i.e., MMA plus GTA). No evidence was found on active comparisons. Compared with inactive controls, CPAP was effective at reducing death from specific causes, including stroke, cardiac disease, and CVEs, in patients with or without previous CVD. Findings on death from all causes were mixed, where one SR reported significant risk reductions with CPAP, compared with inactive controls, whereas another SR reported no differences. For MMA plus GTA, no mortality was reported, either from the surgical procedure or from OSA, although this study included a small number of patients. Subgroup analyses suggest that baseline OSA severity and study duration were not significantly associated with the effects of CPAP. No subgroup or meta-regression analyses were found on baseline EDS, sex, age, BMI, or adherence.

Table 70: Summary of Mortality Outcomes From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Fu 2016[52]	*CPAP versus inactive controls*				All-cause mortality and cardiovascular mortality were significantly lower in CPAP-treated patients than in untreated patients.
	3,112,644 patients from 11 cohort studies (2005 to 2015): • OSA severity: NR • Comorbidities: NR • 5 to 10.3 years of study duration	• All-cause mortality HR (95% CI) = 0.66 (0.59 to 0.73); I^2 = 12.7% • Cardiovascular mortality HR (95% CI) = 0.37 (0.16 to 0.54); I^2 = 5.7%	None	Moderate to high	
Guo 2016[53]	*CPAP versus inactive controls*				There was no difference in the incidence of all-cause mortality between CPAP and inactive controls. There was no significant difference in the incidence of mortality between short and long-term follow-up.
	2,020 patients from 4 RCTs (2012 to 2015): • Moderate-to-severe OSA (mean AHI range: 28 to 42 events/hour) • Overweight to obese (mean BMI range: 28 to 32 kg/m^2) • Diabetes (% range: 33% to 38%, where reported) • Smoking (% range: 26% to 62%, where reported) • 6 to 60 months of study duration	• All-cause mortality OR (95% CI) = 0.85 (0.35 to 2.06); P = 0.72; I^2 = 0%	Subgroup analysis: • Study duration: ○ < 12 months: all-cause mortality OR (95% CI) = 0.97 (0.14 to 6.94); I^2 = NR ≥ 12 months: all-cause mortality OR (95% CI) = 0.82 (0.31 to 2.22); I^2 = 0%	High	
Kim 2016[56]	*CPAP versus no treatment*				CPAP was associated with significantly decreased mortality from stroke, cardiac diseases, or overall CVEs, when compared with no treatment.
	1,455 patients from 3 cohort studies (2005 to 2012): • Mild-to-severe OSA (AHI threshold range:	• Mortality from stroke (from 2 cohort studies): RR (95% CI) = 0.06 (0.01 to 0.34); P = 0.001; I^2 = 0% • Mortality from cardiac disease	None	High (for the RCT) or mixed (for the non-RCTs)	

Table 70: Summary of Mortality Outcomes From CPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	≥ 5 to ≥ 15 events/hour) • Previous CVD (included in all 3 cohort studies) • 72 to 89 months in study duration	(from 2 cohort studies): RR (95% CI) = 0.19 (0.09 to 0.40); $P < 0.00001$; $I^2 = 0\%$ • Mortality from overall CVEs (from 3 cohort studies): RR (95% CI) = 0.19 (0.11 to 0.34); $P < 0.00001$; $I^2 = 48\%$			
Wang 2015[69]	*CPAP versus no CPAP*				CPAP was associated with significantly decreased mortality from CVEs, when compared with no treatment. Baseline AHI did not seem to affect the study findings.
	4,620 patients from 11 studies (2005 to 2015): • Moderate-to-severe OSA (in 5 studies) or unselected OSA (in 6 studies) • Comorbidities: NR • Study duration: NR	• Mortality from CVEs: OR (95% CI) = 0.32 (0.24 to 0.41); $P < 0.0001$; $I^2 = 19.9\%$	Subgroup analysis: • OSA severity: ○ Moderate-to-severe: mortality from CVEs: OR (95% CI) = 0.29 (0.18 to 0.47); $P < 0.0001$; $I^2 = 0\%$	High	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; CVE = cardiovascular event; HR = hazard ratio; MA = meta-analysis; MR = meta-regression; NR = not reported; OR = odds ratio; OSA = obstructive sleep apnea; RCT = randomized controlled trial; RR = risk ratio.

Table 71: Summary of Mortality Outcomes From Combination Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Passeri 2016[80]	*MMA plus GTA pre versus post*			MMA plus GTA is a safe method for OSA treatment in terms of mortality, but patients need to be cautioned on potential complications.
	28 patients: • OSA severity: NR • Mean BMI ± SD: 29.6 ± 4.7 kg/m^2	• No incidence of mortality	None	

BMI = body mass index; GTA = genial tubercle advancement; MMA = maxillomandibular advancement; NR = not reported; OSA = obstructive sleep apnea; SD = standard deviation.

Adverse Events

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

One SR[5] reported on adverse events associated with CPAP use, with no information on OSA severity or comorbidities. The adverse events reported by the SR,[5] with a sample size of 368 patients from six studies, included claustrophobia, epistaxis, excessive nasal dryness, excessive pressure, excessive salivation, gums and lip problems, and pressure intolerance. The authors reported that in general, 5% to 15% of patients reported specific adverse events they considered to be a major problem while using CPAP; however, no study reported a severe adverse event that would not resolve quickly upon discontinuing CPAP or that may be amenable to alleviation with ancillary treatments (e.g., humidification). The SR[5] reported the quality of the included studies as low to moderate (**Appendix 10**). The findings of the SR are summarized in Table 72.

2) Oral appliances versus inactive controls

Two SRs[5,58] reported on adverse events associated with MAD or undefined OA use. One SR[58] included adults with moderate-to-severe OSA who were overweight to obese. The other SR[5] provided no information on OSA severity or comorbidities. The adverse events reported by the SRs,[5,58] with sample sizes ranging from 168 patients[5] to 361 patients[58] from five studies,[58] included dental crown damage, dry mouth, excessive salivation, mouth muscle and joint discomfort, occlusal changes, and tooth discomfort. The SRs reported the quality of the included studies as moderate[5] or moderate to high[58] (**Appendix 10**).

Across the two SRs, 10 primary studies had been included, all of which had been included in one or the other SR, with no overlap between the two SRs (**Appendix 16.27**).

The findings of the SRs are summarized in Table 73.

3) Lifestyle interventions versus inactive controls

One SR[5] reported on adverse events associated with diet programs in adults with severe OSA who were obese. The adverse events reported by the SR,[5] with a sample size of 30 patients from one study, included gout and transient elevation of alanine amino transferase. The authors reported that adverse events associated with diet programs were transient and rare. The SR[5] reported the quality of the included studies as moderate (**Appendix 10**). The findings of the SR are summarized in Table 74.

4) Continuous positive airway pressure versus oral appliances

One SR[77] reported on adverse events associated with CPAP and undefined OAs in adults with mild-to-severe OSA, with no information on comorbidities. The adverse events associated with CPAP use included eye irritation, nasal congestion, rhinorrhea, a sense of suffocation or pressure on face, stuffy nose, and mask problems. The adverse events associated with OA use included discomfort in mouth, excessive salivation, and sore teeth and jaw muscles. The SR,[77] with a sample size of 289 patients from seven studies, reported that although the adverse events associated with CPAP might be more severe than those with undefined OAs, all adverse events for both CPAP and undefined OAs were generally mild. The SR[77] reported the quality of the included studies as low (**Appendix 10**). The findings of the SR are summarized in Table 75.

Review of Primary Studies

1) Combination therapy versus inactive controls

One study[80] reported on AEs in overweight patients with unknown OSA severity, provided by mean BMI. All 28 patients in the study reported having complications after MMA plus GTA, including 13.9% of patients having major complications, defined as any complication requiring readmission or operation under general anesthesia. Concerns

with the quality of the study were assessed to be low[80] (**Appendix 14**). The findings of the primary study are summarized in Table 76.

Summary of Results on Adverse Events

Lists of adverse events associated with CPAP, OAs (i.e., MADs and undefined OAs), diet, and combination therapy (i.e., MMA plus GTA) were identified. Although common, adverse events associated with both CPAP and OAs were deemed mild and resolvable, even if the adverse events associated with CPAP were more serious than those associated with OAs. Adverse events associated with diet programs were deemed transient and rare. Some of the adverse events associated with MMA plus GTA were deemed major. No subgroup or meta-regression analyses were found.

Table 72: Summary of Adverse Events Associated With PAP Use

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	368 patients from 6 studies (2003 to 2009): • 4 weeks to 4 months of study duration	AEs with PAP reported: • CPAP (from 1 study): ○ Claustrophobia (1.4%) ○ Pressure intolerance (9.2%) • APAP (from 3 studies): ○ Claustrophobia (2.9%) ○ Pressure intolerance (3.6%) ○ Epistaxis (0% for humidified; 9.1% for non-humidified) • Nasal CPAP (from 2 studies): ○ Claustrophobia (4.8% to 23%) ○ Excessive pressure (13%) ○ Epistaxis (12%) ○ Excessive nasal dryness (12%) • Oral CPAP (from 2 studies): ○ Excessive pressure (19%) ○ Excessive oral dryness (14% to 52%) ○ Major gums/lip problems (9.5% to 14%) ○ Excessive salivation (4.8%) Other AEs reported: skin irritation, nasal irritation or obstruction, minor aerophagia, abdominal distention, minor chest wall discomfort, and pressure discomfort.	None	Low to moderate or mixed	Generally, 5% to 15% of patients reported specific AEs they considered to be a major problem while using CPAP. However, no study reported a severe AE that would not resolve quickly upon discontinuing CPAP or that may be amenable to alleviation with ancillary treatments (e.g., humidification).

AE = adverse event; APAP = autotitrating positive airway pressure; CPAP = continuous positive airway pressure; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea; PAP = positive airway pressure.

Table 73: Summary of Adverse Events Associated With OA Use

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Serra-Torres 2016[58]	361 patients from 5 studies (2005 to 2013): • Moderate-to-severe OSA (mean AHI range: 26.4 to 45.5 events/hour, where reported) • Overweight to obese (mean BMI range: 26.7 to 31.4 kg/m^2) • 1 to 64 months of study duration	AEs with MADs reported: • Muscle discomfort (19% to 56%) • Joint discomfort (19% to 69%) • Excessive salivation (19% to 44%) • Dry mouth (25% to 75%) • Occlusal changes (35% to 56%)	None	Moderate to high	The main AEs associated with MAD use were mouth muscle and joint discomfort, excessive salivation, dry mouth, and occlusal changes.
Balk 2011[5]	168 patients from 5 RCTs (1996 to 2008): • 4 weeks to 4 years of study duration	AEs with OAs reported: • Dental crown damage (6.3%) • Tooth or joint discomfort (2.2% to 5.2%) Other AEs reported: teeth loosening, pressure sensation of the mouth, transient morning mouth and TMJ discomfort or sounds, minor sore teeth or jaw, transient mild mucosal erosions, minor excessive salivation, tooth grinding, and sleep disruption.	None	Moderate	Dental crown damage and tooth or joint discomfort are major AEs associated with OA use.

AE = adverse event; AHI = Apnea–Hypopnea Index; BMI = body mass index; MA = meta-analysis; MAD = mandibular advancement device; MR = meta-regression; OA = oral appliance; OSA = obstructive sleep apnea; RCT = randomized controlled trial; TMJ = temporal mandibular joint.

Table 74: Summary of Adverse Events Associated With Lifestyle Interventions

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Balk 2011[5]	30 patients from 1 RCT (2009): • Severe OSA (mean AHI = 37 events /hour) • Obese (mean BMI = 34.8 kg/m^2) • 9 weeks of study duration	AEs with weight-loss programs reported: • Gout (3.3%) • Transient elevation of alanine amino transferase (6.7%) Other AEs reported: dizziness, dry lips, and constipation	None	Moderate	AEs associated with a very low-energy diet were transient and rare.

AE = adverse event; AHI = Apnea–Hypopnea Index; BMI = body mass index; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

Table 75: Summary of Adverse Events Associated With CPAP Versus OA Use

Study	Patient Characteristics	Pooled Estimates from MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Li 2013[77]	289 patients from 7 RCTs (1996 to 2011): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 6 to 48 weeks of study duration	AEs associated with CPAP: • Nasal congestion • Rhinorrhea • Eye irritation • Sense of suffocation • Sense of pressure on face • Stuffy nose • Mask problems AEs associated with OAs: • Sore teeth • Sore jaw muscles • Excessive salivation • Early morning discomfort in mouth 1 RCT reported that patients using CPAP reported moderate-	None	Low	There were various and specific side effects associated with CPAP and OAs.

Table 75: Summary of Adverse Events Associated With CPAP Versus OA Use

Study	Patient Characteristics	Pooled Estimates from MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
		to-severe side effects, while those using OAs reported that all side effects were mild and acceptable. 4 RCTs reported that side effects were common but mild and acceptable for both CPAP and OAs.			

AE = adverse event; AHI = Apnea–Hypopnea Index; CPAP = continuous positive airway pressure; MA = meta-analysis; MR = meta-regression; NR = not reported; OA = oral appliance; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

Table 76: Summary of Adverse Events Associated with Combination Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Passeri 2016[80]	28 patients: • OSA severity: NR • Mean BMI ± SD: 29.6 ± 4.7 kg/m^2	AEs associated with MMA plus GTA: • Total number of complications: 108 • 13.9% of the complications were major[a] • 100% (28/28) of patients had complications[b]	None	MMA plus GTA is a safe method for OSA treatment in terms of mortality, but patients need to be cautioned on potential complications.

AE = adverse event; BMI = body mass index; GTA = genial tubercle advancement; MMA = maxillomandibular advancement; NR = not reported; OSA = obstructive sleep apnea; SD = standard deviation.
[a] Defined as any complication requiring readmission or operation under general anesthesia.
[b] All major complications in this study were caused by infections.

Adherence

Overview of Reviews

1) Continuous positive airway pressure versus inactive controls

Nine SRs[5,10,53,56,57,64-66,75] reported on CPAP adherence in adults with mild-to-severe,[10,56,66,75] moderate-to-severe,[53,57,65] severe,[5] or unknown severity[64] OSA. Eight SRs included normal-weight-to-obese,[75] overweight-to-obese,[10,53,57,66] or obese[5,64,65] patients. Three SRs[56,64,65] included patients with hypertension or resistant hypertension,[65] diabetes,[64] or previous CVD.[56]

Eight of the nine SRs,[5,10,53,57,64-66,75] with sample sizes ranging from 118 patients[64] to 4,146[53] patients from two studies[5] to 29 studies,[10] reported that the mean CPAP adherence ranged from 2.3 hours/night[75] to 6.6 hours/night.[75] One of the nine SRs,[56] with a sample size of 4,194 patients from four studies, reported that the proportion of patients using CPAP for at least four hours/night ranged from 64.6% to 100% across the included studies. One of the nine SRs,[5] with a sample size of 2,160 patients from five studies, reported rates of CPAP discontinuation between 16% at one year and 32% at four years of CPAP use. Study duration of the included primary studies, reported by all nine SRs, ranged from one week[66,75] to 80 months.[56] I^2 scores were not applicable. The SRs reported the quality of the included studies as low,[64] low to moderate,[5,10] high[53,57,65,66] or mixed[56,75] (**Appendix 10**).

The findings of the SRs are summarized in Table 77.

2) Mandibular advancement devices versus inactive controls

One SR[75] reported on MAD adherence in adults with mild-to-severe OSA who were normal-weight-to-obese. The SR,[75] with a sample size of 325 patients from four studies, reported that the mean MAD adherence ranged from 5.5 hours/night to 7.7 hours/night. Study duration of the included studies ranged from four weeks to 12 weeks. The SR[75] reported the quality of the included studies as mixed[75] (**Appendix 10**). The findings of the SRs are summarized in Table 78.

3) Continuous positive airway pressure versus oral appliances

Two SRs[5,77] reported on adherence with CPAP versus MADs[5] or undefined OAs[77] in adults with mild-to-severe[77] or moderate-to-severe[5] OSA. One SR[5] included overweight-to-obese patients. The other SR[77] provided no information on comorbidities.

One of the two SRs,[5] with a sample size of 28 patients from one study, reported significantly greater adherence with MADs, compared with CPAP, in terms of nightly durations (i.e., seven hours/night versus six hours/night) and numbers of nights (i.e., 98% versus 90%) of the device use. Study duration ranged from one month to three months. I^2 scores were not applicable. The SR[5] reported the quality of the included studies as low to moderate (**Appendix 10**).

The other SR,[77] with sample sizes ranging from 290 patients to 409 patients from five studies to six studies, reported no significant differences in adherence with CPAP versus MADs, in terms of nightly durations and numbers of nights of the device use, as well as study withdrawals. Study duration ranged from eight weeks to 48 weeks. I^2 scores ranged from 22% to 95%. The SR[5] reported the quality of the included studies as low (**Appendix 10**).

Across the two SRs, eight primary studies had been included, all of which had been included in one or the other SR, with no overlap between the two SRs (**Appendix 16.28**).

The findings of the SRs are summarized in Table 79.

Review of Primary Studies

1) Tongue-retaining devices versus inactive controls

Two studies[92,113] reported on adherence in adults with moderate-to-severe[113] or unknown severity[92] OSA. One study[113] included normal-to-overweight patients. The other study[92] provided no information on comorbidities. Both studies,[92,113] with sample sizes ranging from 20 patients[92] to 84 patients,[113] reported rates of discontinuation with TRDs, ranging from 35% at four months[92] to 48% at five years.[113] One of the two studies[92] suggested that TRDs may be a possible alternative to MADs. Concerns with the quality of the two studies were assessed to be low,[92] or moderate[113] (**Appendix 14**). The findings of the primary studies are summarized in Table 80.

2) Positional therapy versus inactive controls

Twelve studies[78,79,83,85,86,88,96,97,99,102,112,118] reported on adherence in adults with mild,[85,86,88,97,102] moderate,[78,79,96,99,118] or severe OSA,[112] providing mean[78,88,96,102,112,118] or median AHI.[85,86,97,99] Studies included patients who were normal weight[85] or overweight[78,79,86,88,96,97,99,102,112,118]providing mean[78,79,86,88,96,102,112,118] or median BMI.[85,97,99] One study[79] provided no information on comorbidities.

The findings on adherence across the studies, with sample sizes ranging from 14 patients[83] to 145 patients,[97] were mixed. Eight studies[78,79,83,85,86,96,99,102] reported good adherence with neck-positioning devices,[79,96] mattresses and pillows,[83,85] commercial or self-made bands,[86] sleep positioning trainers,[78,99] or tennis balls.[102] One study[97] reported that adherence with a sleep position trainer was higher when measured by a self-reported questionnaire, compared with the device itself. One study[88] reported higher adherence with sleep position trainers, compared with tennis balls. Three studies[86,112,118] reported high rates of discontinuation with tennis balls[112,118] or commercial or self-made bands,[86] especially long-term.[86,112] The quality of the 12 studies was assessed to be low[78,79,83,85,86,88,96,97,99,102] or high[112,118] (**Appendix 13** and **Appendix 14**).

From subgroup analyses, one study[85] reported 100% adherence in both normal-weight and overweight patients.

The findings of the primary studies are summarized in Table 81.

3) Combination therapy versus inactive controls

One study[107] reported on adherence with CPAP plus diet programs in adults with severe OSA who were obese, provided by mean AHI and a BMI range. The study,[107] with a sample size of 63 patients, reported that 69.8% of all patients completed the full CPAP plus diet programs. Concerns with the quality of the study were assessed to be low[107] (**Appendix 14**). The findings of the primary studies are summarized in Table 82.

Summary of Results on Adherence

Adherence levels associated with CPAP, OAs (i.e., MADs and TRDs), positional therapy, and combination therapy (i.e., CPAP plus diet) were identified. Evidence was also found on active comparisons between CPAP and MADs or undefined OAs. The mean adherence ranged from 2.3 hours/night to 6.6 hours/night for CPAP and 5.5 hours/night to 7.7 hours/night for MADs. Greater adherence with MADs versus CPAP was also reported in terms of nightly durations (i.e., seven hours/night versus six hours/night) and numbers of nights (i.e., 98% versus 90%) of device use, although it is unclear if these results are clinically important. Discontinuation was reported to be 16% of patients at one year and 32% of patients at four years for CPAP, 35% of patients at four months and 48% of patients at five years for TRDs, and 31.2% at some unknown follow-up time for CPAP plus diet programs. The findings on adherence with positional therapy across different devices were mixed, with no notable trends. No subgroup or meta-regression analyses were found.

Table 77: Summary of Adherence With CPAP

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Guo 2016[53]	4,146 patients from 18 RCTs (2006 to 2015): • Moderate-to-severe OSA (mean AHI range: 24 to 60 events/hour) • Overweight to obese (mean BMI range: 28 to 40 kg/m^2) • 22.3% diabetes (% range: 28% to 63%, where reported); 34.7% smoking (% range: 12% to 84%, where reported) • 2 to 60 months of study duration	• Mean CPAP adherence: 5 hours/night (range: 4 to 7 hours/night)	None	High	The mean CPAP adherence was 5 hours/night.
Kim 2016[56]	4,194 patients from 1 RCT and 3 cohort studies (2007 to 2014): • Mild-to-severe OSA (AHI threshold range: ≥ 5 to ≥ 20 events/hour) • Previous CVD (excluded from the RCT and 1 cohort study but included in the other studies) • 48 to 80 months of study duration	• % CPAP adherence range:[a] 64.4-100% of patients	None	High (for the RCT) or mixed (for the non-RCTs)	The proportion of patients using CPAP for at least 4 hours/night ranged from 64.6% to 100% across the included studies.
Liu 2016[57]	446 patients from 5 RCTs (2010 to 2015): • Moderate-to-severe OSA	• Mean CPAP adherence range: 4 to 6 hours/night	None	High	The mean CPAP adherence ranged from 4 hours/night to 6 hours/night across the

Table 77: Summary of Adherence With CPAP

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	(mean AHI range: 20 to 52.7 events/hour) • Overweight to obese (mean BMI range: 29.8 to 34.1 kg/m^2) • Resistant hypertension (100%) • 3 to 8 months of study duration				included studies.
Feng 2015[64]	118 patients from 2 RCTs and 3 observational studies (2004 to 2012): • OSA severity: NR • Obese (mean BMI range: 33.6 to 42.7 kg/m^2) • Diabetes (100%) • 1 to 3 months of study duration	• Mean CPAP adherence range: 3.6 to 5.8 hours/night	None	Low	The mean CPAP adherence ranged from 3.6 hours/night to 5.8 hours/night across the included studies.
Hu 2015[65]	794 patients from 7 RCTs (2006 to 2014): • Moderate-to-severe OSA (mean AHI range: 28.1 to 58.3 events/hour) • Obese (mean BMI range: 30.8 to 35.7 kg/m^2) • Hypertension (100% in 3 RCTs) or resistant hypertension (100% in 4 RCTs)	• Mean CPAP adherence range: 4.5 to 6.0 hours/night	None	High	The mean CPAP adherence ranged from 4.5 hours/night to 6.0 hours/night across the included studies.

Table 77: Summary of Adherence With CPAP

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• 1 to 6 months of study duration				
Pan 2015[66]	1,698 patients from 11 RCTs (1994 to 2012): • Mild-to-severe OSA (mean AHI range: 10.0 to 55.4 events/hour) • Overweight to obese (mean BMI range: 29 to 33.0 kg/m^2) • 1 to 24 weeks of study duration	• Mean CPAP adherence range: 2.8 to 5.4 hours/night	None	High	The mean CPAP adherence ranged from 2.8 hours/night to 5.4 hours/night across the included studies.
Fava 2014[10]	1,820 patients from 29 RCTs (1996 to 2012): • Mild-to-severe OSA (mean AHI range: 12.9 to 63.8 events/hour) • Overweight to obese (mean BMI range: 27.2 to 37.0 kg/m^2) • Hypertension (% range: 0% to 100%, where reported) • 2 to 52 weeks of study duration	• Mean CPAP adherence range: 3.3 to 6.4 hours/night	None	Low to moderate	The mean CPAP adherence ranged from 3.3 hours/night to 6.4 hours/night across the included studies.
Povitz 2014[75]	1,570 patients from 21 RCTs (1998 to 2013): • Mild-to-severe OSA (mean AHI range: 10 to 65.1 events/hour)	• Mean CPAP adherence range: 2.3 to 6.6 hours/night	None	Mixed	The mean CPAP adherence ranged from 2.3 hours/night to 6.6 hours/night across the included studies.

Table 77: Summary of Adherence With CPAP

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	• (for the 1,732 patients included in the SR) Normal-to-obese (mean BMI range: 24.7 to 42.5 kg/m^2) • Study duration: 1 to 24 weeks				
Balk 2011[5]	2,160 patients from 1 RCT and 4 cohort studies (1996 to 2009): • Severe OSA (mean AHI range: 44 to 70 events/hour) • Obese (mean BMI: 30 kg/m^2) • 3 months to 4 years of study duration	• Discontinuation of CPAP use (from 2 studies): 16% at 1 year and 32% at 4 years in 1 cohort study; 14% at mean 3.2 years in 1 cohort study • CPAP use (from 2 studies): mean 5 hours/night at 3 months in 1 RCT and 1 cohort study	None	Low to moderate or mixed	Discontinuation of CPAP varied between 16% at 1 year and 32% at 4 years of CPAP use. Each study defined adherence differently.

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

[a] Defined as usage of CPAP for ≥ 4 hours/night on average.

Table 78: Summary of Adherence With MADs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Povitz 2014[75]	325 patients4 RCTs (2004 to 2007): • Moderate OSA (mean AHI range: 21.3 to 28.9 events/hour) • (for the 1,732 patients included in the SR) Normal-to-obese (mean BMI range: 24.7 to 42.5 kg/m^2) • Study duration: 4 to 12 weeks	• Mean MAD adherence range: 5.5 to 7.7 hours/night	None	Mixed	The mean MAD adherence ranged from 5.5 hours/night to 7.7 hours/night across the included studies.

AHI = Apnea–Hypopnea Index; BMI = body mass index; MA = meta-analysis; MAD = mandibular adjustment device; MR = meta-regression; OSA = obstructive sleep apnea; RCT = randomized controlled trial.

Table 79: Summary of Adherence With CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Li 2013[77]	*CPAP versus OAs*				There was no significant difference between CPAP and OAs for treatment adherence, assessed as hours of use per night, nights of use per week, or study withdrawal.
	409 patients from 6 RCTs (2002 to 2008): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 8 to 12 weeks of study duration	• Hours of use per night: ○ Crossover trials (from 2 RCTs) MD (95% CI) = –1.01 (–2.78 to 0.75); P = 0.26; I^2 = 95% ○ Parallel-groups trials (from 2 RCTs) MD (95% CI) = –0.82 (–1.91 to 0.27); P = 0.14; I^2 = 93% • Number of nights of use per week: ○ Parallel-groups trials (from 2 RCTs) MD (95% CI) = –0.16 (–0.40 to 0.08); P = 0.19; I^2 = 54%	None	Low	

Table 79: Summary of Adherence With CPAP Versus OAs

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
	290 patients from 5 RCTs (2007 to 2011): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • 10 to 48 weeks of study duration	• Study withdrawal: ○ Parallel-groups trials (from 5 RCTs) OR (95% CI) = 0.64 (0.25 to 1.61); *P* = 0.34; I^2 = 22%	None		
Balk 2011[5]	*CPAP versus MADs*				MADs were associated with higher adherence, compared with CPAP.
	28 patients from 1 RCT (2009): • Moderate-to-severe OSA (mean AHI range: 21 to 40 events/hour) • Overweight to obese (mean BMI range: 26.7 to 34.1 kg/m^2) • 1 to 3 months of study duration	• Hours of use: ○ 6.0 hours/night for CPAP ○ 7.0 hours/night for MAD ○ *P* < 0.01 • Nights of use: ○ 90% for CPAP ○ 98% for MAD ○ *P* < 0.01	None	Moderate	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CI = confidence interval; CPAP = continuous positive airway pressure; MA = meta-analysis; MAD = mandibular advancement device; MD = mean difference; MR = meta-regression; NR = not reported; OA = oral appliance; OSA = obstructive sleep apnea; SR = systematic review.

Table 80: Summary of Adherence With TRDs

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Roplekar 2015[92]	*TRDs pre versus post*			The level of adherence with TRDs was encouraging.
	20 patients: • Patient characteristics: NR	• 65% continuation after 4 months (i.e., 7/20 patients did not use the device)	None	
Lazard 2009[113]	*TRDs pre versus post*			Adherence with TRDs was shown to be quite good.
	84 patients (recruited) or 63 patients (analyzed): • Mean AHI ± SD: 37 ± 19.5 events/hour • Mean BMI ± SD: 26 ± 3.8 kg/m^2	• 52% continuation after 5 years (i.e., 30/63 patients did not use the device) ○ 79% daily adherence[a] after 5 years among the 33 users	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; NR = not reported; SD = standard deviation; TRD = tongue-retaining device.
[a] Defined as > 4 nights/week of use.

Table 81: Summary of Adherence With Positional Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Benoist 2016[78]	*Positional therapy (i.e., sleep position trainers) pre versus post*			The sleep position trainer used in this study had high adherence rates during the 3 months of use.
	33 positional OSA patients: • Median AHI: 18.3 (IQR: 13.7 to 24.0) events/hour • Mean BMI ± SD: 27.9 ± 2.8 kg/m^2	• Adherence: ○ Defined as ≥ 4 hours/night and ≥ 5 days/week of usage: - 89.0% of patients ○ Average nightly use ± SD per patients: - 6.92 ± 0.75 hours/night	None	
Levendowski 2016[79]	*Positional therapy (i.e., neck position devices) pre versus post*			The device used in this study had high adherence rates. Sleep efficiency and loud snoring varied from patient to patient.
	135 patients: • Patient characteristics: NR	• Unacceptable adherence: ○ Defined as < 50% 4-hour adherence: - 18.4% of patients ○ Defined as < 4 hours average hours of use: - 24.3% of patients	None	

Table 81: Summary of Adherence With Positional Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
		• Marginal adherence: ○ Defined as ≥ 50 and < 70% 4-hour adherence: - 22.8% of patients ○ Defined as ≥ 4 and < 5 average hours of use: - 15.4% of patients • Acceptable adherence: ○ Defined as ≥ 70 and < 80% 4-hour adherence: - 22.8% of patients ○ Defined as ≥ 5 and < 6 average hours of use: - 25.7% of patients • Excellent adherence: ○ Defined as ≥ 80% 4-hour adherence: - 36.0% of patients ○ Defined as ≥ 5 hours average hours of use: - 34.6% of patients		
Bidarian-Moniri 2015[83]	*Positional therapy (i.e., mattresses and pillows for prone positioning) pre versus post*			Positional therapy with the mattress and a pillow for prone positioning improved AHI and ODI levels patients with OSA. Adherence was satisfactory during the course of the study.
	14 patients: • Mean AHI: 26 events/hour (range: 6 to 53) • Mean BMI: 26 kg/m^2	• Adherence: ○ All 14 patients completed the study after 4 weeks, with sleep time of > 4 hours/night with the device	None	
Chen 2015[85]	*Positional therapy (i.e., head-positioning pillows) pre versus post*			The use of the head-positioning pillow in this study was associated with short-term adherence.
	25 positional OSA patients: • Median AHI: 7.0 events/hour (IQR: 6.0 to 15.2) • Median BMI: 24.8 kg/m^2	Adherence: • All patients (n = 25) ○ Regular pillow: Reference ○ Head-positioning pillow: 100% of patients using it every night	• Baseline weight: ○ Normal-weight patients (n = 13) adherence: - Before (regular pillow):	

Table 81: Summary of Adherence With Positional Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
	(IQR: 23.1 to 26.4)		Reference - After 3 nights (head-positioning pillow): 100 ○ Overweight patients (n = 12) adherence: - Before (regular pillow): Reference - After 3 nights (head-positioning pillow): 100	
de Vries 2015[86]	*Positional therapy (i.e., commercial devices or self-made constructions) pre versus post*			Short-term adherence was good. However, long-term adherence was considered disappointing.
	40 positional OSA patients: • Mean AHI: 14.5 events/hour (range: 10.7 to 19.6) • Mean BMI ± SD: 28.0 ± 4.1 kg/m^2	• Adherence: ○ Short-term: most patients used their device > 7 hours/night, > 6 days/week after < 3 months ○ Long-term: 65% (n = 26) patients stopped using their device after 13 ± 5 months	None	
Eijsvogel 2015[88]	*Positional therapy (i.e., tennis balls or sleep position trainers) pre versus post*			
	26 (TBT) or 29 (SPT) positional OSA patients: • Mean AHI ± SD: 13.1 ± 9.1 (TBT) or 11.4 ± 4.9 (SPT) events/hour • Mean BMI ± SD: 26.8 ± 3.0 (TBT) or 27.6 ± 4.5	• Effective adherence: ○ TBT: 42.3% (11/16 patients) ○ SPT: 75.9% (22/29 patients) ○ Difference: *P* = 0.01 • Median hours used per night: ○ TBT: 4.5 (IQR: 1.1 to 7.0) ○ SPT: 6.5 (IQR: 5.5 to 7.2)	None	Adherence was significantly improved with a sleep position trainer, compared with the tennis ball technique.

Table 81: Summary of Adherence With Positional Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
	(SPT) kg/m^2	○ Difference: *P* = 0.078 • Median percentage of days used: ○ TBT: 77.2 (IQR: 21.2 to 96.6) ○ SPT: 100 (IQR: 79.6 to 100) ○ Difference: *P* = 0.005 • Everyday use: ○ TBT: 15.4% (4/26 patients) ○ SPT: 51.7% (15/29 patients) ○ Difference: *P* = 0.005		
van Maanen 2014[97]	*Positional therapy (i.e., sleep position trainers) pre versus post*			Most patients using the sleep position trainer were considered compliant (64.4% of patients using the trainer more than 4 hours per night).
	145 positional OSA patients: • Median AHI: 11.5 events/hour (IQR: 2.5 to 20.5) • Median BMI: 27.0 kg/m^2 (IQR: 23.0 to 31.0)	• Average use: ○ 5.5 hours/night in 106/145 patients • Objective adherence (measured by the device as more than 4 hours of use per night over 168 nights): ○ 64.4% (106/145) • Subjective adherence (measured by an online questionnaire after 1, 3, and 6 months with the device): ○ After 1 month: 91.8% (110/145 patients) ○ After 3 months: 74.3% (101/145 patients) ○ After 6 months: 59.8% (87/145 patients)	None	
Levendowski 2014[96]	*Positional therapy (i.e., neck position devices) pre versus post*			
	30 positional OSA patients: • Mean AHI ± SD: 24.7 ± 14.7 events/hour • Mean BMI ± SD: 28 ± 3.4 kg/m^2	• Adherence: ○ Median percentage: 96% (range: 71% to 100%) ○ The device was worn in 99% of treatment nights	None	The positional therapy method used in this study (neck position device) was associated with good adherence in patients with positional OSA.
van Maanen 2013[99]	*Positional therapy (i.e., sleep position trainers) pre versus post*			
	31 positional OSA patients:	• Adherence: ○ Median percentage: 92.7% (range: 62% to	None	Short-term adherence (1 month) was high using the sleep positioning

Table 81: Summary of Adherence With Positional Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
	• Median AHI: 16.4 events/hour (IQR: 6.6 to 29.9 events/hour) • Mean BMI ± SD: 27.0 ± 3.7 kg/m^2	100%)		trainer; however, long-term adherence with the sleep positioning trainer is as yet unknown.
Heinzer 2012[102]	*Positional therapy (i.e., tennis balls) pre versus post*			Positional therapy was successful with select patients with an objective adherence of 73.7%
	16 positional OSA patients: • Mean AHI ± SD: 26.7 ± 17.5 events/hour • Mean BMI ± SD: 25.4 ± 4.1 kg/m^2	• Adherence: ○ Median percentage ± SD: 73.7 ± 29.3% ○ 62.5% (n = 10) of the patients used the device > 80% of the nights	None	
Bignold 2009[112]	*Positional therapy (i.e., tennis balls) pre versus post*			Long-term adherence was very poor with the tennis ball technique among patients with positional OSA; alternative forms of positional therapy are required.
	108 patients: • Mean AHI ± SD: 32.4 ± 35.2 events/hour • Mean BMI ± SD: 28.7 ± 4.2 (67 respondents) or 29.3 ± 8.5 (41 non-respondents) kg/m^2	• Adherence (n = 67): ○ 6% (n = 4) of patients reported still using TBT. ○ 13.4% (n = 9) reported no longer using TBT because they had learned to avoid sleeping in the supine position. ○ 80.6% (n = 54) were no longer using TBT nor avoiding sleep in the supine position. 63% (34 of the 54 patients) reported discomfort as the main reason for no longer using TBT. ○ Other reasons for non-adherence included: - Patient claims not to sleep on his/her back - Shoulder problems - Skin irritation from using TBT - Ineffectiveness on a soft mattress - Suspicion that TBT would cause back problems	None	

Table 81: Summary of Adherence With Positional Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Oksenberg 2006[118]	*Positional therapy (i.e., tennis balls) pre versus post*			The positional therapy used in this study (tennis ball technique) did not have great long-term adherence.
	78 positional OSA patients: • Mean AHI ± SD: 25.5 ± 17.3 events/hour • Mean BMI ± SD: 28.1 ± 3.7 kg/m^2	• Adherence: ○ 64.1% of patients filled out and returned the questionnaire, of whom 38% were still using TBT after 6 months	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; IQR = interquartile range; NR = not reported; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; SD = standard deviation; SPT = sleep position trainer; TBT = tennis ball technique.

Table 82: Summary of Adherence With Combination Therapy

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Johansson 2011[107]	*CPAP plus diet programs*			The level of adherence with the full program was encouraging.
	63 patients: • Mean AHI ± SD: 36 ± 15 events/hour • BMI range: 30 to 40 kg/m^2	• 69.8% of patients completed the full CPAP plus diet programs (i.e., 44/63 patients)	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; CPAP = continuous positive airway pressure; MA = meta-analysis; MR = meta-regression.

Snoring

Overview of Reviews

1) Expiratory positive airway pressure versus inactive controls

One SR[68] reported on snoring in adults with moderate OSA who were overweight to obese. The SR,[68] with a sample size of 102 patients from three studies, reported uniform reductions in snoring across its three included studies with EPAP, compared with pre-treatment, with no effect sizes reported. Study duration of the included primary studies ranged from one night to 12 months. I^2 scores were not applicable. The SR[68] reported the quality of the included studies as high (**Appendix 10**). The findings of the SR are summarized in Table 83.

2) Oral appliances versus inactive controls

One SR[58] reported on snoring in adults with mild-to-severe OSA who were overweight. The SR,[68] with a sample size of 112 patients from three studies, reported reductions in mean ranges in visual analogue scales for snoring with MADs, compared with pre-treatment, from 3-8 to 2-3. Study duration of the included primary studies ranged from one month to nine months. I^2 scores were not applicable. The SR[68] reported the quality of the included studies as moderate to high (**Appendix 10**). The findings of the SR are summarized in Table 84.

Review of Primary Studies

1) Positional therapy versus inactive controls

Three studies[79,85,105] reported on snoring in adults with mild[85,105] OSA, provided by mean[105] or median[85] AHI. Two studies included normal weight[85] or overweight[105] patients, provided by mean[105] or median[85] BMI. The other study[79] provided no information on comorbidities.

Two of the three studies,[79,105] with sample sizes ranging from 15 patients[105] to 135 patients,[79] reported no improvements in snoring with positional therapy (i.e., an apparatus designed to prevent sleep in the supine position[79,105]), compared with pre-treatment, in most patients[79] or in patients with supine-predominant OSA.[105] The other study,[85] with a sample size of 25 patients, reported that in overweight patients, subjective snoring, measured on a visual analogue scale ranging from 0 to 10, improved significantly after positional therapy (i.e., a head-positioning pillow), but objective snoring, expressed as the number of snoring events/hour measured on an acoustic analytical program, did not; in normal-weight patients, both subjective and objective snoring significantly improved. Concerns with the quality of the three studies were assessed to be low[79,85,105] (**Appendix 14**).

From subgroup analyses, one study[85] reported that, while snoring severity improved in both normal-weight and overweight patients with positional therapy, compared with pre-treatment, snoring index improved in normal-weight, and not overweight, patients only.

The findings of the primary studies are summarized in Table 85.

Summary of Results on Snoring

For snoring, evidence was found on inactive comparisons with EPAP, MADs, and positional therapy. No evidence was found on active comparisons. Compared with pre-treatment, EPAP and MADs were effective at reducing snoring. Findings on positional therapy were mixed. Two studies reported no improvement in snoring, and one study reported improvements in both subjective and objective snoring in normal-weight patients but reported improvements in subjective but not objective snoring in overweight patients. All findings were from uncontrolled studies, and it is unclear if these results are clinically important. Subgroup analyses suggest that patients with normal-weight were more likely to experience improvements in snoring, compared with those who were overweight. No subgroup or meta-regression analyses were found on comorbidities, baseline EDS or OSA severity, sex, age, adherence, or study duration.

Table 83: Summary of Change in Snoring From EPAP Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analysis		
Riaz 2015[68]	*EPAP pre versus post*				EPAP was associated with a decrease in snoring, when compared with pre-treatment.
	102 patients from 3 studies (2008 to 2015): • Moderate OSA (mean AHI range: 15.7 to 24.8 events/hour) • Overweight to obese (mean BMI range: 27 to 32.5 kg/m^2) • 1 night to 12 months of study duration	• Uniform reductions in snoring in all 3 studies	None	High	

AHI = Apnea–Hypopnea Index; BMI = body mass index; EPAP = expiratory positive airway pressure; MA = meta-analysis; MR = meta-regression; OSA = obstructive sleep apnea.

Table 84: Summary of Change in Snoring From OAs Versus Inactive Controls

Study	Patient Characteristics	Pooled Estimates From MAs or Narrative Summary		Quality of Included Studies	Conclusions
		Overall	Subgroup or MR Analyses		
Serra-Torres 2016[58]	*MADs pre versus post*				MADs were associated with a decrease in snoring, when compared with pre-treatment.
	112 patients from 3 studies (2005 to 2013): • Mild-to severe OSA (mean AHI range: 14 to 45.5 events/hour) • Overweight (mean BMI range: 27.9 to 29.2 kg/m^2) • 1 to 9 months of study duration	• Mean snoring VAS range: ○ Baseline: 3 to 8 ○ Follow-up: 2 to 3 • No MA	None	Moderate to high	

AHI = Apnea–Hypopnea Index; BMI = body mass index; MA = meta-analysis; MAD = mandibular advancement device; MR = meta-regression; NA = not applicable; NR = not reported; OA = oral appliance; OSA = obstructive sleep apnea; VAS = visual analogue scale.

Table 85: Summary of Change in Snoring From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Levendowski 2016[79]	*Positional therapy (i.e., sleep position modification devices) pre versus post*			The majority of patients did not find a difference in snoring patterns from the neck device.
	135 patients: • Patient characteristics: NR	• Snoring patterns: ○ No difference in 91.3% (105/115) of patients ○ Decrease in 4.3% (5/115) of patients ○ Increase in 4.3% (5/115) of patients	None	
Chen 2015[85]	*Positional therapy (i.e., head-positioning pillows) pre versus post*			The use of the head-positioning pillow provided improvements in snoring severity in overweight patients; a significant improvement was found in both snoring severity and snoring index in normal-weight patients.
	25 positional OSA patients: • Median AHI: 7.0 events/hour (IQR: 6.0 to 15.2 events/hour) • Median BMI: 24.8 kg/m^2 (IQR: 23.1 to 26.4 kg/m^2)	Snoring severity: • All patients (n = 25) ○ Regular pillow: 5.0 (5.0, 7.5) ○ Head-positioning pillow: 4.0 (1.5, 5.0) ○ Difference: *P* < 0.001 Snoring index: • All patients (n = 25) ○ Regular pillow: 218.0 (100.0, 288.5) events/hour ○ Head-positioning pillow: 115.0 (48.0, 260.3) events/hour ○ Difference: *P* = 0.001	• Baseline weight: ○ Normal-weight patients (n = 13) snoring severity - Before (regular pillow): 7.0 (5.0, 8.0) - After 3 nights (head-positioning pillow): 5.0 (1.5, 5.0) - Difference: *P* = 0.007 ○ Overweight patients (n = 12) snoring severity: - Before (regular pillow): 5.0 (4.3, 6.0) - After 3 nights (head-positioning pillow): 4.0 (1.3, 4.0) - Difference: *P* = 0.007 • Baseline weight: ○ Normal-weight patients (n = 13) snoring index - Before (regular pillow): 200.0 (58.5, 256.0) events/ hour	

Table 85: Summary of Change in Snoring From Positional Therapy Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
			- After 3 nights (head-positioning pillow): 107.0 (35.0, 204.3) events/hour - Difference: *P* = 0.003 ○ Overweight patients (n = 12) snoring index: - Before (regular pillow): 244.0 (169.3, 332.0) events/hour - After 3 nights (head-positioning pillow): 149.5 (62.5, 288.0) - Difference: *P* = 0.052	
Bignold 2011[105]	*Positional therapy (i.e., sleep position modification devices) pre versus post*			Positional therapy may only provide a small reduction in snoring and may be only of greatest benefit to patients who sleep alone.
	15 patients: • Mean AHI ± SD: 24.1 ± 10.5 events/hour • Mean BMI ± SD: 28.8 ± 2.5 kg/m^2	• Snoring frequency: ○ Difference: 20% reduction with treatment, no statistical significance • Mean snore duration ± SD: ○ Pre-treatment: 1126 ± 169 msec ○ Post-treatment: 1082 ± 96 msec	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; IQR = interquartile range; NR = no reported; OSA = obstructive sleep apnea; SD = standard deviation.

Fatigue

No SRs or primary studies on any of the comparisons were found that reported on fatigue.

Facial Aesthetics (for Maxillomandibular Advancement Only)

Overview of Reviews

No SRs on any of the comparisons were found that reported on facial aesthetics.

Review of Primary Studies

1) Maxillomandibular advancement versus inactive controls

Three studies[89,98,103] reported on facial aesthetics in adults with severe,[98] moderate-to-severe,[98] severe,[103] or unknown severity[89] OSA, provided by mean AHI. The studies[89,98,103] included normal weight–to-overweight patients[98] or overweight patients,[89] provided by mean BMI. All studies[89,98,103] compared MMA with pre-treatment.

All three studies,[89,98,103] with sample sizes ranging from 12 patients[103] to 51 patients,[89] reported improvements in facial aesthetics with MMA, compared with pre-treatment. Two of the three studies[98,103] reported that the post-operative profile was given preference by the majority of the panellists who evaluated the patients' profiles. The other study[89] reported that a majority of the patients had indicated that their facial appearance had improved after surgery. Concerns with the quality of the three studies were assessed to be low[98,103] or high[89] (**Appendix 14**).

The findings of the primary studies are summarized in Table 86.

Summary of Results on Facial Aesthetics

For facial aesthetics, evidence was found on inactive comparisons with MMA. Compared with pre-treatment, MMA was effective at improving facial aesthetics in patients. No subgroup or meta-regression analyses were found.

Table 86: Summary of Change in Facial Aesthetics From MMA Versus Inactive Controls

Study	Patient Characteristics	Effect Estimates		Conclusions
		Overall	Subgroup Analyses	
Islam 2015[89]	*MMA pre versus post*			Satisfaction with facial appearance improved after MMA.
	51 patients: • OSA severity: NR • Mean BMI ± SD: 28 ± 3 kg/m^2	• VAS score[a] for satisfaction with the facial appearance: ○ Before: 4.1 ○ After: 6.5	None	
Cohen-Levy 2013[98]	*MMA pre versus post*			The facial changes created by MMA were interpreted as positive changes.
	15 patients: • Mean AHI: 50.9 events/hour (range: 19 to 85 events/hour) • Mean BMI ± SD: 27.41 ± 3.5 kg/m^2	• Self-assessment questionnaires: ○ 93% (i.e., 14/15) of patients were satisfied with their aesthetic outcome ○ 73% (i.e., 11/15) of patients noted an improvement, while 20% (i.e., 3/15) did not notice or were not concerned with an improvement • Panel assessment: ○ 80% (i.e., 12/15) of patients were given preference in their post-operative profile from panellists	None	
Liu 2012[103]	*MMA pre versus post*			Thoughts on facial aesthetics post MMA were generally positive from patients.
	12 patients: • Mean AHI ± SD: 60.53 ± 12.66 events/hour • Mean BMI ± SD: 27.45 ± 2.14 kg/m^2	• Self-assessment questionnaires: ○ 67% (i.e., 8/12) of patients felt their change in facial appearance was favourable • Panel assessment: ○ 92% (i.e., 11/12) of patients were given preference in their post-operative profile from panellists	None	

AHI = Apnea–Hypopnea Index; BMI = body mass index; MMA = maxillomandibular advancement; NR = not reported; OSA = obstructive sleep apnea; SD = standard deviation; VAS = visual analogue scale.
[a] Rated on a 10-point scale, 1 representing the least attractive and 10 representing the most attractive.

Summary of Clinical Review Results

An overview of SRs, supplemented by a review of primary studies, was conducted on the clinical effectiveness, comparative clinical effectiveness, and safety of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults. Evidence was found on inactive comparisons with all interventions of interest. The effects of CPAP, MADs, and undefined OAs were most commonly reported. Limited evidence was found on active comparisons. Nevertheless, three NMAs were identified that compared CPAP and MADs or CPAP, MADs, diet, and exercise. In terms of outcomes, EDS and OSA severity were most commonly reported.

For the overview of SRs, the quality of the primary studies included and assessed by the SRs ranged widely, from very low to high and mixed. The risk of bias of the SRs themselves assessed in this report was generally low, with moderate or high concerns raised on one domain of the ROBIS tool (i.e., specifications of study eligibility criteria). Among the three NMAs, one NMA was missing information (e.g., no pairwise results were presented) and analyses (e.g., no handling of inconsistency or conducting subgroup or meta-regression analyses) that were deemed important by the ISPOR questionnaire. For the review of primary studies, the RCTs were at low or unclear risk of bias, and the non-randomized controlled or pre-and-post studies were generally rated as having low risk. However, sample sizes of 20 or fewer patients in 15 of the 41 studies and the pre-and-post design used in 30 of the 41 studies suggest that the findings need to be interpreted with caution.

Based on the analysis of the primary outcome, CPAP, EPAP, MADs, TRDs, undefined OAs, MMA, GTA, diet, exercise, and positional therapy were all effective at reducing EDS, compared with inactive controls or pre-treatment. Effect sizes across the interventions were similar, although it is unclear whether reductions of two ESS score points are clinically significant. In fact, a survey of the literature on what constitutes a clinically significant change in ESS scores did not find any relevant information (**Appendix 15**). The similarity in effect sizes across the interventions was also reflected in the findings on active comparisons, where no significant differences in ESS scores were found between some interventions, except for severe cases of OSA who may benefit more from CPAP than from MADs. However, based on the analysis using OSA severity as the outcome, effect sizes varied across the interventions, with CPAP showing the largest effect, with mean differences around –20 events/hour. A survey of the literature on what constitutes a clinically significant change in AHI scores found five events/hour to be of significance (**Appendix 15**). For severe cases with OSA, who are eligible for surgery, MMA with or without GTA may be effective at improving both EDS and OSA severity, although the findings are mostly from small, uncontrolled pre-and-post studies on highly selected patients and warrant caution, considering the invasiveness of the procedure and potential adverse events. The findings on EPAP were also from uncontrolled studies. Some of the findings on ESS (i.e., CPAP or MADs versus inactive controls and CPAP versus OAs) and AHI (i.e., CPAP, EPAP, MADs, diet, or exercise versus inactive controls) were associated with high heterogeneity.

CPAP, MADs, and undefined OAs independently demonstrated similar improvements in blood pressure, although it is unclear whether reductions of 2 mm Hg are clinically significant. Diet, exercise, and positional therapy did not significantly reduce blood pressure. Diet and exercise for one year, but not CPAP for up to four months, were effective at reducing A1C levels in patients with diabetes, although it is unclear whether reductions of 0.5 units are clinically important. While CPAP was effective at improving insulin sensitivity in patients with diabetes, this finding was associated with high heterogeneity. CPAP was effective at reducing the risk of real and near-miss accidents, although the findings were from uncontrolled studies. Findings on the effects of CPAP and MADs on cognitive and psychological functions and QoL were mixed, with generally small effect sizes, if any. CPAP was effective at reducing certain types of death (i.e., caused by stroke, cardiac disease, or CVEs), but findings on all-cause mortality were mixed. No mortality was reported for MMA plus GTA, although this outcome was reported in a single study that included a small number of participants. While long lists of adverse events associated with various interventions were identified, no major adverse events were noted, except for MMA plus GTA, where all patients had complications caused by infections. Adherence was higher with MADs than with CPAP, in terms of both nightly durations and numbers of nights of use, and discontinuation was reported as 16% and 32% of patients after one and four years of use, respectively. From uncontrolled studies, improvements in snoring were reported for EPAP and MADs, but the findings were inconsistent for positional therapy. No evidence on fatigue was identified. Facial aesthetics were

deemed more favourable after MMA compared with before. Findings on combination therapy suggest that various interventions in combination may have additive effects in their effectiveness in improving EDS, OSA severity, and blood pressure. Some of the findings on blood pressure (i.e., CPAP versus inactive controls), insulin sensitivity (i.e., CPAP versus inactive controls), accident (i.e., CPAP versus inactive controls), cognitive functions (i.e., CPAP versus inactive controls), and QoL (i.e., CPAP versus OAs) were associated with high heterogeneity.

Evidence on subgroups of interest, including different comorbidities and OSA severity, was found on some of the intervention-comparator-outcome combinations. Patients with hypertension or resistant hypertension experienced greater effects on blood pressure with CPAP. CPAP, diet, and exercise were effective at improving A1C levels or insulin sensitivity in patients with diabetes, although it is unclear whether changes were clinically significant. CPAP was effective at reducing the risk of certain CVEs (e.g., recurrent cardiac disease or AF), but not others (e.g., major adverse cardiac events or MI), and effective at reducing the risk of stroke, but not IS, in patients with previous CVD. Patients with higher EDS at baseline experienced greater effects on EDS with CPAP, MADs, or undefined OAs. Patients with more severe OSA at baseline experienced greater effects on EDS and OSA severity with CPAP, but not with MADs or undefined OAs, and were less likely to achieve success or cure with MMA. Patients with normal weight were more likely to experience improvements in snoring, compared with those who were overweight. Longer study duration was associated with lower effects on EDS and OSA severity with CPAP and MADs. Higher adherence with interventions was associated with higher effects of CPAP and weight loss on blood pressure and higher effects of CPAP on CVEs.

Economic Evaluation

This section addresses Research Question 2: What is the cost-effectiveness of PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?

Review of Economic Studies

A review of the published and grey literature was conducted to identify relevant economic evaluations that assessed therapies for sleep apnea. Thirteen unique economic evaluations were identified that addressed the cost-effectiveness of at least one or more OSA treatments of interest.[28,39,120-130] **Appendix 18** provides details on each economic evaluation.

The applicability of these studies in addressing the research question of interest in this review is limited. None of the economic evaluations reviewed all therapies of interest but rather several compared one treatment modality against no treatment,[39,121,122,125-128] which does not reflect the multiple treatment options that are available for patients with OSA. In addition, only two economic analyses addressed surgical procedures and were focused on either upper airway stimulation[128] or palatopharyngeal reconstructive surgery.[130] Of particular interest to this review are the surgical interventions involving MMA with or without GTA, for which no economic evaluation has been conducted. Some of the economic models adopted a narrower scope by characterizing only the association between OSA and MVAs[39,126] or OSA and cardiovascular morbidity or mortality.[121] As such, they do not consider the full range of clinical evidence available to estimate the economic impact of treatments for OSA, nor do they capture the broader health consequences of OSA in the pathogenesis of several major conditions.

Few economic evaluations were conducted with a Canadian setting.[39] The analysis by Tan et al.[39] compared only the effects of CPAP against no treatment on MVAs, making it difficult to adapt in order to address the research question in this review. Outside of the project's scope, one Canadian economic model[131] was identified that explored the economic impact of providing decision aids to patients with OSA. This study evaluated the relationship between decision aids to reduce rates of discontinuation from either CPAP or MADs, and concluded that the cost-effectiveness of patient decision aids will depend on contextual factors. However, it also highlighted the importance of discontinuation as a factor that affects the cost-effectiveness of treatments for OSA.

Overall, existing economic evaluations did not fully address the cost-effectiveness of treatments among different patient populations, with the exception of patients with type 2 diabetes[122] and patients intolerant to CPAP.[129] This is of particular interest given that the clinical benefit of treatments may vary depending on patient characteristics, resulting in differences in cost-effectiveness.

Given that no Canadian model was identified that would fully address Research Question 2, a de novo economic model was constructed. Identified economic models provided insights in developing the model structure, determining appropriate model assumptions, and as a source for data inputs relating to utilities and disease prognosis.

Primary Economic Evaluation

Methods

The objective of the economic analysis was to evaluate the cost-effectiveness of various treatments for adult patients with OSA, across different disease severities, within a Canadian health care system over a patient's lifetime. In addition, the cost-effectiveness in specific subgroups was explored, including sex, age, hypertensive patients, smokers, and diabetic patients. A protocol for the economic evaluation was written a priori and followed in the conduct of this review.

1. Type of Analysis

A cost-utility analysis was conducted given the broad set of adverse clinical outcomes associated with OSA. Health outcomes were expressed as quality-adjusted life-years (QALYs), which captures both the mortality and morbidity

impacts related to the condition and its treatments. The primary outcome in the economic analysis was the incremental cost per QALY gained (commonly referred to as the incremental cost-utility ratio [ICUR]).

2. Target Populations and Settings

The target population for the economic evaluation was adult Canadians with OSA, aligned with the clinical population identified from the clinical review. The base-case cohort represented patients aged 55 years (76.5% males), none of whom were current smokers or had diabetes. A stratified economic analysis was conducted by disease severity, as defined by the baseline AHI value, into mild (AHI < 15), moderate (15 ≤ AHI < 30) and severe OSA (AHI > 60). Unless specified, it was assumed that, for every analysis, the patients in the cohort comprised only those eligible for all the interventions assessed. It is important to note that not all patients with OSA may be eligible or suitable for all interventions that were being considered. Separate analyses were conducted exploring cases where the patient cohort may not be suitable for a particular intervention by excluding that intervention from the analysis.

The subgroup analyses undertaken included:

i. Sex: female vs. male
ii. Age
iii. Blood pressure: all patients were hypertensive
iv. Smoking: all patients currently smoked
v. Diabetes: all patients were diabetic

3. Time Horizon and Discount Rate

OSA is a chronic condition associated with considerable morbidities that manifest over a patient's lifetime. A lifetime time horizon was therefore adopted in which costs and health outcomes were discounted at a rate of 5% per annum as per Canadian guidelines.[132] Sensitivity analyses were conducted with a range of discount rates at 0%, 1.5%, and 3%. In addition, sensitivity analyses were further conducted over various modelled time horizons (i.e., two years, seven years, and 10 years).

4. Interventions

Interventions for OSA of interest included C/APAP devices, EPAP, MAD, MMA with or without GTA, and lifestyle modifications. In addition, a no-treatment strategy was modelled, reflecting the natural progression of OSA for untreated patients.

PAP-Based Devices: CPAP and APAP

Feedback from clinical experts suggest that CPAP and APAP devices can be grouped together as a single class of interventions, given similarities in their clinical effectiveness and safety profile. Together, these are referred to as PAP therapy throughout the economic section of this report. The clinical effectiveness was based on a pooled estimate reported in the clinical review while costs were weighted according to the assumption that 19% of patients received CPAP while the remainder received APAP.[35] It is important to note that, although APAP and CPAP were grouped together, the cost of testing for these different treatments may differ but was not considered in the economic model, given that this was considered to be outside the scope of this report.

BiPAP was excluded from the analysis given that it is primarily prescribed to a subset of patients with specific needs (e.g., those with cardiopulmonary disorders).[13,14]

EPAP

Nasal EPAP is a single-use device consisting of a small valve attached externally to each nostril, which act as one-way resistors to permit unobstructed inspiration. Utilizing a patient's own breathing, PAP is created during each expiration to prevent obstruction to breathing. Given that the mechanism of action is different from other PAP therapies, EPAP was considered as a separate strategy.

Oral Appliances

Oral appliances include MAD and TRD. Although the manner in which it prevents or minimizes upper airway obstruction differs among the classes, the clinical review found that the clinical effectiveness between oral devices were similar. Costing analysis between the two devices further suggests that the price and resource consumption for each type of oral appliance is similar. They primarily differ in adherence as, in one study comparing between the two types of oral appliances, the incidence of patients involuntarily removing MAD during the night was 9% compared with 86.4% for TRD.[133] As TRD is known to be inferior to MAD, given a similar clinical effectiveness profile and similar costs but lower adherence, MAD was modelled as the oral appliance of interest. Although both over-the-counter and customized oral appliances are commercially available, the former was not considered because patients diagnosed with OSA and seeking treatment from their health care providers would be predominately offered a customized oral appliance based on clinical experts' feedback.

Surgery

Of the numerous surgical interventions available for patients with OSA, oropharyngeal interventions have become increasingly less utilized due to its poor rates of success. According to clinical experts, orthognathic surgery (e.g., MMA with or without GTA) has replaced oropharyngeal surgery and, to reflect current treatment trends, the economic model focused solely on modelling MMA with or without GTA. In practice, the appropriate surgical procedure for OSA depends on the site of the anatomical obstruction and the patient's anatomical features. However, to model a cohort, it was assumed that the majority of patients (90%) would be suitable surgical candidates for MMA, while the remaining would be candidates for GTA. This assumption was based on clinical experts' feedback and the available literature. Among patients receiving MMA, 20% of patients would receive adjunctive GTA.

Lifestyle Modification

Lifestyle modification involves counselling patients with regard to lifestyle advice or behavioural changes in order to reduce and/or to cope with symptoms. Often, the objective of these interventions is to target specific patient characteristics that are also factors that contribute to OSA. As such, lifestyle modifications are suitable interventions for particular subgroups of patients and will be explored in subgroups analysis rather than in the base case. Strategies to modify lifestyle, assessed in this economic evaluation, reflect the interventions studied in the clinical review. This includes interventions for weight loss (via diet or exercise) or changes to sleep position (via positional therapy). In the economic analysis, weight reduction was considered a suitable treatment option in overweight or obese OSA patients, whereas positional therapy was considered a suitable treatment in patients with positional OSA (i.e., defined arbitrary as supine AHI at least twice of non-supine AHI).

Given the results of the clinical review, only single therapies were included in the economic analysis with the exception of surgery (e.g., MMA with or without GTA). A scenario analysis was conducted to explore the economic value of a weight-loss intervention when compared with the interventions included in the base case for obese patients with mild-to-moderate OSA. As the clinical review did not identify any studies that reported on the effects of EPAP or positional therapy on blood pressure, the base case compared PAP therapy, MADs, and MMA with or without GTA, with an exploratory analysis that incorporated EPAP or positional therapy. Table 87 summarizes the set of interventions that was compared in each analysis.

Table 87: Interventions Compared in the Analysis

	PAP Therapy	Nasal EPAP	MAD	MMA ± GTA	Weight Loss	Positional Therapy	No Treatment
Base case	✓		✓	✓			✓
Scenario Analysis	✓		✓	✓	✓		✓
Exploratory	✓	✓	✓	✓		✓	✓

EPAP = expiratory PAP; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; PAP = positive airway pressure.

5. Perspective

This analysis was conducted from the perspective of the publicly funded health care system. As such, direct medical costs were captured that included the cost of the medical devices, laboratory tests, emergency visits, in-patient visits, medical services, and physician fees for services covered in provincial fee schedules. Indirect costs, such as productivity losses, out-of-pocket costs, and time lost, were not included. Only medical costs pertaining to an MVA were included. Given the varying coverage for PAP therapy and dental procedures across Canada (**Appendix 17**), a secondary analysis was undertaken exploring different reimbursement schemes for oral appliances.

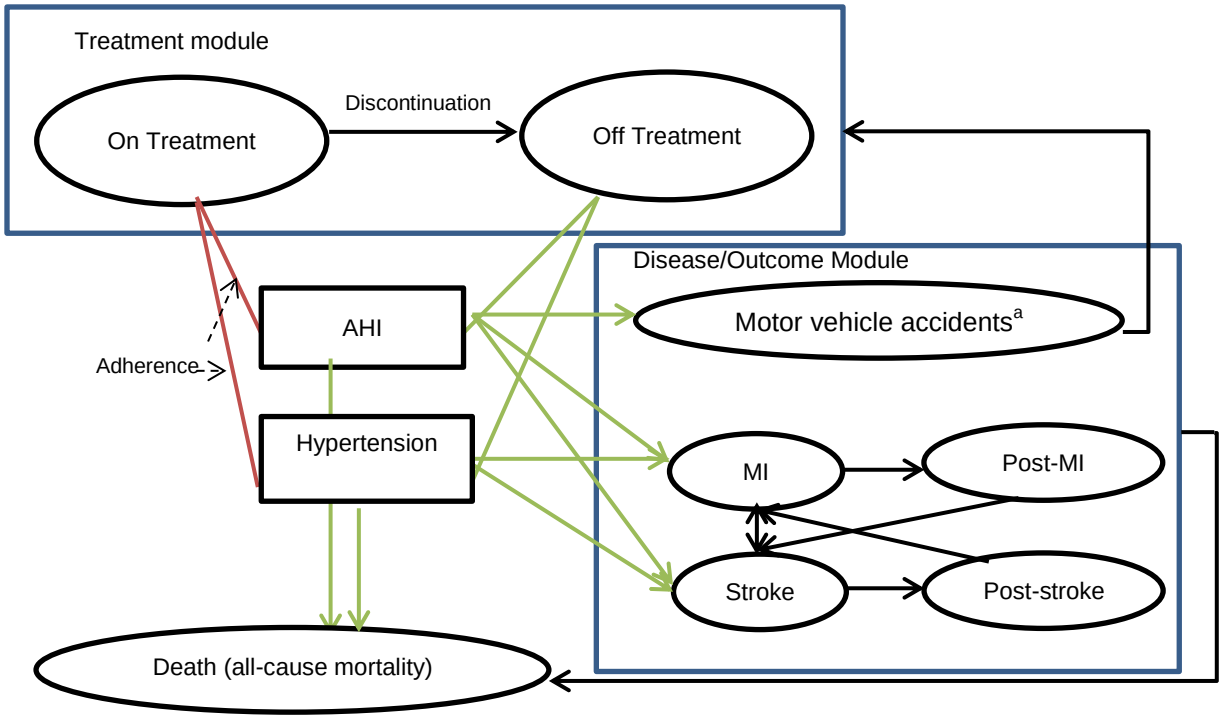
6. Decision-Analytic Model

A decision-analytic Markov model was developed to assess the effectiveness and costs of each strategy (i.e., intervention or no treatment). The clinical pathway and decision-analytic model were developed by reviewing existing clinical and economic literature. It was further validated by clinical experts from a range of medical specialities (i.e., respirology, dentistry, maxillofacial surgery) with experience managing patients with OSA.

Figure 1**Error! Reference source not found.** presents the clinical pathways of OSA, which include the associated conditions (i.e., stroke, MI, MVA, death) that have a suspected causal relationship to OSA and are considered important from both a clinical and a policy-making viewpoint. Although there is literature emerging that suggests a relationship between OSA and other conditions, such as depression or diabetes,[5,119] the clinical review reported mixed findings or results applicable to a particular patient subgroup. Given that no clear treatment effect differences were observed, these health states were not captured in the economic model. **Appendix 19** presents the decision-analytic model conceptualized from the clinical pathway presented above.

In the base case, all members of the cohort (i.e., 55 years of age, 76.5% males) start in the “at-risk” state regardless of the strategy (i.e., diagnosed with OSA but are event free). They can remain in that state, unless a transition occurs into one of a CVE health state or death. In each one-year cycle of the model, patients could experience a CVE or MVA, die from other causes, or remain event free. MVA was classified into property damage without injury, injury, or death. Patients who survive an MVA return to the health state of the previous cycle. Individuals are assumed to stop driving at the age of 80, based on clinical experts’ opinions, or upon experiencing a severe disabling stroke. CV events included MI and stroke (mild-to-moderate or severe) and could be fatal or non-fatal. Patients who survive the CV event progress into either the post-MI or post-stroke state given the increased morbidity and mortality associated with a history of CV disease. From these states, patients can remain until death or until another CVE occurs. Death is the absorbing health state.

Figure 1: Clinical Pathway Diagram Describing the Relationship Between OSA and the Pathogenesis of Cardiovascular, Cerebrovascular Morbidity, and Motor Vehicle Accidents.



AHI = Apnea–Hypopnea Index; MI = myocardial infarction.
Note: Arrows link variables that are related. Green arrows indicate a positive relationship (i.e., all else remaining equal, an increase in the source variable will lead to an increase in the resulting variable), while red arrows suggest a negative relationship. Adherence modulates the relationship between treatment and AHI value and, thus, indirectly affects clinical outcomes.
[a] In the model, a condition is incorporated whereby patients no longer experience motor vehicle accidents at the age of 80 or upon experiencing a severe disabling stroke.

Surgery differs from other treatments primarily in how AHI is incorporated into the model. The clinical review found that the treatment effects for AHI for non-surgical interventions are typically reported as a continuous measure, while surgery is reported by the following categorical definition: cure (post-operative AHI < 5), response (post-operative AHI ≤ 15 and at least a reduction in AHI by 50%) or failure.[60] The outcome for surgery in terms of AHI is categorized into these three states, which affects progression.

The model runs based on yearly transitions. All analyses were conducted using Microsoft Excel 2010.

7. Clinical Inputs

Disease Natural History
Mortality

Mortality due to other causes, by age and sex, was calculated by subtracting MI, stroke, and MVA mortality from general population mortality estimates reported in Statistics Canada lifetables.[134]

Existing literature suggests that the risk of all-cause mortality is graded in patients with OSA based on disease severity (Table 88).[135,136] Specifically, there is a statistically significant increase in all-cause mortality in patients with severe OSA compared with no OSA, even after adjustment for the increased risk in cardiovascular mortality. A similar

trend, although not statistically significant, is observed in patients with moderate OSA.[137] It is speculated that the increased risk is related to pathophysiological changes associated with OSA. Patients' risk of mortality is adjusted by disease severity using a recently published meta-analysis by Pan et al. (based on 12 prospective cohort studies of 34,382 patients with OSA).[137]

For patients with history of CVD, the model similarly adjusts for an increased risk of death. The Danish Monitoring Trends and Determinants in Cardiovascular Disease cohort study reported long-term survival following MI and stroke. To reflect the findings from this longitudinal study, a lifelong and a five-year post-event mortality risk was applied for patients with a history of stroke or MI, respectively.[138,139]

The relative risk of mortality following treatment was determined based on the post-treatment AHI value achieved. A sensitivity analysis was further conducted that assumed that patients adherent on treatment would have their mortality risk return to general population (i.e., non-OSA) rates, regardless of post-treatment AHI value. This reflects the findings of several observational studies that have reported that the mortality risks of patients with moderate-to-severe OSA who tolerated CPAP were found to return to rates similar to those of patients without OSA.[140,141]

Table 88: Relative Risk of Mortality by Health Condition

Health Condition	Variable Name (in the Model)	RR (95% CI)	Ref
Severe OSA	rrDeath_SevereOSA	1.601 (1.298 to 1.902)[a]	Pan, 2016[137]
Moderate OSA	rrDeath_ModerateOSA	1.178 (0.978 to 1.378)[a]	Pan, 2016[137]
Mild OSA	rrDeath_MildOSA	0.945 (0.810 to 1.081)[a]	Pan, 2016[137]
History of MI (first 5 yrs) Males aged 30 to 59, yr 1 to 5	rrDeath_HistoryOfMI_Yr1to5_Male	3.22 (2.65 to 3.87)[b]	Bronnum-Hansen, 2001[139]
History of MI (first 5 yrs) Males ≥ 60 age, yr 1 to 5	rrDeath_HistoryOfMI_Yr1to5_Male_Age60	1.95 (1.69 to 2.24)[b]	
History of MI (first 5 yrs) Females aged 30 to 59, yr 1 to 5	rrDeath_HistoryOfMI_Yr1to5_Female	4.41 (2.79 to 6.61)[b]	
History of MI (first 5 yrs) Females ≥ 60 age, yr 1 to 5	rrDeath_HistoryOfMI_Yr1to5_Female_Age60	2.75 (2.18 to 3.44)[b]	
History of stroke (lifelong) Males aged 25 to 69	rrDeath_HistoryOfStroke_Male	3.01 (2.63 to 3.43)[b]	Bronnum-Hansen, 2001[138]
History of stroke (lifelong) Males ≥ 70 age	rrDeath_HistoryOfStroke_Male_Age70	1.92 (1.68 to 2.18)[b]	
History of stroke (lifelong) Females aged 25 to 69	rrDeath_HistoryOfStroke_Female	3.52 (2.80 to 4.35)[b]	
History of stroke (lifelong) Females ≥ 70 age	rrDeath_HistoryOfStroke_Female_Age70	2.05 (1.81 to 2.30)[b]	

CI = confidence interval; MI = myocardial infarction; OSA = obstructive sleep apnea; RR = relative risks; yr = year.
[a] Measure reported in the publication as a hazard ratio.
[b] Measure reported in the publication as standardized mortality ratios.

Cardiovascular Outcomes

The model classified patients into either normotensive or hypertensive according to age- and sex-specific incidence and prevalence rates for hypertension based on Canadian sources.[142,143] In the Sleep Heart Health Study (SHHS; n = 2,470),[144] an elevated risk of developing hypertension was observed among patients with OSA who were

normotensive at baseline when compared with those without OSA after a mean follow-up of 5.2 years. This risk of hypertension was proportional to the disease severity and was applied to this model (Table 89).[144]

Table 89: Model Parameters Pertaining to Incident Cardiovascular Event

Event	Variable Name (in the Model)	Model Value (95% CI)	Ref
Baseline data			
Incidence rate of hypertension	(Age- and sex-dependent)		CCDSS, 2009[145]
Prevalence of hypertension	(Age- and sex-dependent)		CCDSS, 2009[145]
Hypertension			
RR hypertension in male patients with mild OSA	rrHypertens_MaleMildOSA	1.19 (0.92 to 1.53)	Calculated from O'Connor, 2009[144]
RR hypertension in male patients with moderate OSA	rrHypertens_MaleModerateOSA	1.61 (0.76 to 3.40)	
RR hypertension in male patients with severe OSA	rrHypertens_MaleSevereOSA	1.65 (0.69 to 3.96)	
RR for hypertension in female patients with mild OSA	rrHypertens_FemaleMildOSA	1.37 (0.70 to 2.70)	
RR for hypertension in female patients with moderate OSA	rrHypertens_FemaleModerateOSA	1.79 (0.80 to 4.01)	
RR for hypertension in female patients with severe OSA	rrHypertens_FemaleSevereOSA	1.90 (0.73 to 4.92)	
MI			
RR of MI occurrence, severe OSA	rrMI_SevereOSA	1.21 (0.75 to 1.96)	Wang, 2013[146]
Probability of 28-day mortality Male	(Age- and sex-dependent)	0.335 to 0.479	Smolina, 2012[147]
Probability of 28-day mortality Female		0.331 to 0.506	
RR MI is fatal in incident yr: Males aged 30 to 59	rrDeath_IncidentMI_MaleUnder60	5.84 (4.26 to 7.81)[b]	Bronnum-Hansen, 2001[139]
RR MI is fatal in incident yr: Males ≥ 60 age)	rrDeath_IncidentMI_MaleOver60	4.04 (3.31 to 4.89)[b]	
RR MI is fatal in incident yr: Females aged 30 to 59)	rrDeath_IncidentMI_FemaleUnder60	16.8 (10.3 to 25.9)[b]	
RR MI is fatal in incident yr: Females ≥ 60 age	rrDeath_IncidentMI_FemaleOver60	6.22 (8.38 to 4.50)[b]	
RR of MI being fatal, severe OSA	rrDeath_CV_SevereOSA	2.87 (1.17 to 7.51)[a]	Marin, 2015[6]
Stroke			
RR of stroke occurrence, severe OSA	rrStroke_SevereOSA	2.15 (1.42 to 3.24)	Wang, 2013[146]
Proportion of severe stroke	propSevereStroke	0.12 (0 to 0.36)	Anis, 2006[148]
Probability of 28-day mortality Male	(Age- and sex-dependent)	0.181 to 0.338	Bronnum-Hansen, 2001[138]
Probability of 28-day mortality Female		0.226 to 0.383	

Table 89: Model Parameters Pertaining to Incident Cardiovascular Event

Event	Variable Name (in the Model)	Model Value (95% CI)	Ref
RR stroke is fatal in incident yr: Males aged 25 69	rrDeath_IncidentStroke_MaleUnder70	4.64 (3.71 to 5.72)[b]	
RR stroke is fatal in incident yr: Males ≥ 70 age	rrDeath_IncidentStroke_MaleOver70	3.70 (3.15 to 4.32)[b]	
RR stroke is fatal in incident yr: Females aged 25 69	rrDeath_IncidentStroke_FemaleUnder70	9.27 (6.94 to 12.1)[b]	
RR stroke is fatal in incident yr: Females ≥ 70 age	rrDeath_IncidentStroke_FemaleOver70	5.18 (4.54 to 5.87)[b]	
RR of stroke being fatal, severe OSA	rrDeath_CV_SevereOSA	2.87 (1.17 to 7.51)[a]	Marin, 2015[6]

CCDSS = Canadian Chronic Disease Surveillance System; CI = confidence interval; MI = myocardial infarction; OSA = obstructive sleep apnea; RR = relative risk; yr = year.
[a] Measure reported in the publication as an odds ratio. Given low event risks (< 10%), the odds ratio is assumed to closely approximate relative risk.[149]
[b] Measure reported in the publication as standardized mortality ratios.

A principal morbidity associated with OSA is CV complication, as the rates are higher than in the general population.[150,151] The clinical review identified only a few studies evaluating the effect of CPAP on stroke and MI, although many studies reported on the effects of treatment on blood pressure changes. To reflect the data available from the clinical review, the Framingham risk equation was used to estimate the probability of stroke or MI given changes to blood pressure.[152] A series of published risk equations was estimated separately for men and women using the baseline characteristics shown in Table 90. Although the equation can be a function of either systolic or diastolic blood pressure, systolic blood pressure was selected in this model given that it has been found to be a more reliable predictor for stroke.[152]

Table 90: Hypothetical Baseline Characteristics for Patients in the Base-Case Scenario to Estimate Risk of Cardiovascular Events, Based on the Framingham Equation

Inputs	Age	55
	SBP[a]	118
	Smoking (0 = no; 1 = yes)	0
	Total cholesterol[a]	224
	HDL cholesterol[a]	43
	Diabetes (0 = no; 1 = yes)	0
	ECG-LVH	0
Outputs	**10-year probability of MI**	**16.3 (males); 15.9 (females)**
	10-year probability of stroke	**8.1 (males); 6.7 (females)**

ECG-LVH = electrocardiographic left ventricular hypertrophy; HDL = high-density lipoprotein; MI = myocardial infarction; SBP = systolic blood pressure.
[a] Baseline SBP, total cholesterol, HDL were taken from Weatherly.[124]

It was assumed that OSA patients diagnosed with hypertension would be treated with medication, targeting a return to blood pressure levels at entry into the model. In such a circumstance, the Framingham risk equation would predict that patients with hypertension managed by medication would have similar risks as a patient without hypertension in the model. However, a meta-analysis of patients with OSA reported that, in patients with severe OSA, the risk of stroke (relative risk [RR]: 2.15; 95% CI, 1.42 to 3.24) and MI (RR: 1.21; 95% CI, 0.75, 1.96) increased independent of

blood pressure.[146] Therefore, in patients with severe OSA, the probability of MI and stroke predicted by the Framingham risk equation was adjusted to reflect this higher risk.

The probability that a CV event was fatal reflects the findings from the Danish Monitoring Trends and Determinants in Cardiovascular Disease cohort study. These data reflect the risk of CV death in a general population. From a long-term observation of CV outcomes in men with OSA, a higher incidence of fatal CV events (defined as fatal MI and stroke) was observed in patients with untreated severe OSA compared with healthy participants (adjusted OR: 2.87; 95% CI, 1.14 to 7.51). The risk of a fatal CV event in patients untreated with mild-to-moderate OSA was found to be at levels similar to a healthy population.

Patient prognosis following a non-fatal CV event was based on several long-term observational studies.[147,153-155]

Table 91 lists the inputs to the model relating to subsequent CV event risk following an incident event.

Table 91: Model Parameters Pertaining to Prognosis Following Cardiovascular Event

Event	Variable Name (in the Model)	Model Value (95% CI)	Ref
RR of Stroke Following Incident MI			
Year ≤ 1	rrStroke_Yr1PostMI	3.1 (2 to 4.5) [a]	Witt, 2005[153]
1 < Year ≤ 4	rrStroke_SubYrPostMI	1.6 (0.9 to 2.8)[a]	
RR of Stroke Following Incident Stroke			
Year 1	rrRecurrentStroke_Yr1PostStroke	15.4 (12.1 to 19)[a]	Burn, 1994[155]
Year 2	rrRecurrentStroke_Yr2PostStroke	8.5 (5.6 to 11.8)[a]	
Year 3	rrRecurrentStroke_Yr3PostStroke	6.7 (3.9 to 10.7)[a]	
Year 4	rrRecurrentStroke_Yr4PostStroke	4.5 (2.1 to 8.6)[a]	
Yearly Probability of MI After Incident MI			
Year ≤ 1: males	pRecurrentMI_Yr1PostMI_Male	0.056 (0.055 to 0.057)	Smolina, 2012[147]
Year ≤ 1: females	pRecurrentMI_Yr1PostMI_Female	0.072 (0.071 to 0.074)	
1 < Year ≤ 5: males	pRecurrentMI_SubYrPostMI_Male	0.0187 (0.0183, 0.0187)	Converted 4-year probability to yearly probability from Smolina, 2012[147]
1 < Year ≤ 5: females	pRecurrentMI_SubYrPostMI_Female	0.021 (0.020 to 0.021)	
RR of MI Following Incident Stroke			
Year ≤ 5	rrMI_PostStroke_Yr5	1.51 (1.12 to 2.01)[b]	Ducrocq, 2013[154]

CI = confidence interval; MI = myocardial infarction; RR = relative risk.
[a] Measure reported in the publication as standardized morbidity ratios.
[b] Measure reported in the publication as a hazard ratio.

In summary, treatment affects final CV outcomes through its effects on AHI and blood pressure. Alternative assumptions were examined in the sensitivity analyses. For instance, in alignment with the observations of several long-term cohort studies investigating CV risks in untreated OSA, treated OSA, and controls without OSA, it was assumed that, in patients perfectly adherent to PAP-based therapy, the risks of MI, stroke, and incident hypertension

would return to general population levels.[146,156] As no data were present for the other interventions, a similar assumption was made for those adherent to other therapies.

Motor Vehicle Accidents

The annual probability of MVAs in the general population was based on the findings from the Ontario Road Safety Annual Report (2012).[157] MVAs were stratified by the following classes of accidents: property damage without injury, personal injury, or death (Table 92). Because the proportion of OSA in the general population is relatively small, these rates were assumed to apply to a general population without OSA.

Current research has suggested that both OSA severity and EDS lack a clear relationship to road traffic accidents, and are unreliable predictors of collision risk.[158,159] Rather, the majority of data on MVAs come from before-and-after studies, in which the rates of MVAs before treatment are compared with the rates of MVA after treatment. The clinical review identified a meta-analysis of such studies by Antonopoulos et al.[47] based on 1,221 patients, in which the odds of an MVA in patients on CPAP therapy are 80% less than in the pre-treatment period (OR: 0.21; 95% CI, 0.12 to 0.35). This was assumed to be the increased risk of MVA in untreated patients.[47] The MVA rate in OSA patients adherent to treatment was assumed to be comparable to that in the general population, while those non-adherent to treatment would have half the increased risk of MVA. Table 92 summarizes the model parameters pertaining to MVA.

Patients left disabled following a severe stroke event (12.3%) were assumed to no longer be at risk of a MVA. The base-case analysis assumed all patients could drive, with a sensitivity analysis conducted assuming no patients drive, whereby the risk of MVA was removed from the model.

Table 92: Model Parameters Pertaining to MVA Outcomes

Event	Variable Name (in the Model)	Model Value (95% CI)	Ref
General			
Probability that OSA patient drives	pDriver	1	Assumption
Average age that patients stops driving	sAgeStopDriving	80	Assumption
Relative risk pertaining to OSA			
RR for MVA, for untreated OSA	rrMVA_UntreatedOSA	3.59 (2.86 to 4.54)	Tregear, 2010[160]
RR for MVA, treated OSA		1	Assumption
Distribution of MVAs			
Property damage only, male	distMVA_PDO_Male	0.74 (0.7 to 0.78)	Ontario Road Safety Annual Report, 2012[157]
Personal injury, male	distMVA_PI_Male	0.26 (0.23 to 0.28)	
Fatal, male	distMVA_Fatal_Male	No distribution assigned[a]	
Property damage only, female	distMVA_PDO_Female	0.71 (0.66 to 0.76)	
Personal injury, female	distMVA_PI_Female	0.29 (0.26 to 0.32)	
Fatal, female	distMVA_Fatal_Female	No distribution assigned[a]	

CI = confidence interval; MVA = motor vehicle accident; OSA = obstructive sleep apnea.
[a] Distributions must sum to 1. As such, the value for fatal MVA is based on the subtracting distribution for property damage and personal injury from 1.

Treatment Effect

For non-surgical interventions, treatment effects (reported as mean reduction in AHI and blood pressure) were taken directly from the clinical review and incorporated into the economic model to determine the post-treatment AHI and blood pressure values. This was subsequently taken to calculate event risks. AHI was selected as the clinical outcome in which to model long-term health consequences given the considerable research on the predictive validity

of this objective measure of disease severity (**Appendix 15**). Although an NMA was available for the outcome of AHI that compared no treatment, PAP therapy, oral appliances, and lifestyle modification,[161] it was not selected, as the clinical review had found meta-regression and subgroup analyses that suggested that treatment effect on AHI reduction is a function of the baseline disease severity. A meta-analysis that provided naive estimates without incorporating indirect evidence was instead selected, given that it reported treatment effects by baseline disease severity for PAP therapy and oral appliances.[55] In comparing the estimates from the NMA[161] to the meta-analysis,[55] the NMA treatment effect estimates fell within the 95% CI of the meta-analysis estimates for patients with severe OSA. As the inclusion of lifestyle will be conducted as a scenario analysis for obese patients with mild-to-moderate OSA, the treatment effects were taken from meta-analyses of trials that evaluated this patient population specifically.[5,76]

As discussed previously, surgery differs in how the AHI outcomes are incorporated as, conventionally, studies have reported this outcome categorically based on the achieved post-surgical results. The meta-analysis by Zaghi et al.[60] reported treatment response based on patients' baseline AHI value. Treatment response was incorporated into the economic model as follows: patients classified as cured were mapped as a non-OSA population, responders were mapped to an untreated or mild OSA population, and surgical failure was mapped to baseline disease severity. The effect of surgery on blood pressure, a continuous variable, was incorporated into the model in a similar fashion as the other strategies.[162] However, given suggestions from clinical experts that these studies on surgery may be biased by recruiting patients with more severe OSA and other factors that would favour a more likely successful outcome, a sensitivity analysis was conducted exploring smaller treatment effects by setting it to the lower bounds of the 95% CI.

Given that no data were available on the effect of EPAP and positional therapy in reducing blood pressure, an exploratory analysis was conducted that assumed a least conservative (i.e., optimistic) scenario whereby the effect on blood pressure would equal the highest non-surgical treatment effect observed (i.e., PAP therapy).

Table 93: Treatment Effect Measures for Patients Remaining on Treatment and Who Are Perfectly Adherent — Base Case and Exploratory Scenario

<table>
<tr><th>Analysis</th><th>Interventions</th><th>Mean Reduction in AHI, vs. Inactive Control (95% CI)</th><th>Mean Reduction in SBP, vs. Inactive Control (95% CI)</th></tr>
<tr><td>Base-case analysis</td><td>PAP-based therapy[55,63]</td><td><table><tr><th></th><th colspan="3">Baseline disease severity (AHI)</th></tr><tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr><tr><td>Mean reduction in AHI</td><td>2.4 (–3.67 to –1.13)</td><td>–13.67 (−16.13 to −11.2)</td><td>–33.04 (–39.75, −26.34)</td></tr></table></td><td>–2.5 (–1.5 to –3.5)</td></tr>
<tr><td></td><td>MAD[55,63]</td><td><table><tr><th></th><th colspan="3">Baseline disease severity (AHI)</th></tr><tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr><tr><td>Mean reduction in AHI</td><td>–7.79 (−16.38 to 0.79)</td><td>–10.72 (−14.59 to −6.85)</td><td>–7.95 (−15.94 to 0.05)</td></tr></table></td><td>–2.1 (–0.8 to –3.4)</td></tr>
<tr><td></td><td>Surgery[60,162]</td><td><table><tr><th>Treatment response</th><th colspan="4">Probability (based on baseline AHI)</th></tr><tr><td></td><td>< 30</td><td>30 < AHI < 60</td><td>60 < AHI < 90</td><td>AHI > 90</td></tr><tr><td>Cure (post-surgical AHI < 5)</td><td>0.557</td><td>0.458</td><td>0.28</td><td>0.195</td></tr><tr><td>Success (post-surgical AHI < 15 and 50% reduction in baseline AHI)</td><td>0.836</td><td>0.88</td><td>0.727</td><td>0.707</td></tr></table></td><td>–3.5 (–19 to 11)[a]</td></tr>
<tr><td>Scenario analysis</td><td>Weight loss[5,76]</td><td><table><tr><th></th><th colspan="3">Baseline disease severity (AHI)</th></tr><tr><td></td><td>Mild</td><td>Moderate</td><td>Severe</td></tr><tr><td>Mean reduction in AHI</td><td>–1.99 (–5.58 to 1.61)</td><td>–9.08 (−12.87 to –5.30)</td><td>–4.91 (−21.97 to 12.15)</td></tr></table></td><td>–0.6 (–8.4 to 7.2)</td></tr>
</table>

Table 93: Treatment Effect Measures for Patients Remaining on Treatment and Who Are Perfectly Adherent — Base Case and Exploratory Scenario

Analysis	Interventions	Mean Reduction in AHI, vs. Inactive Control (95% CI)	Mean Reduction in SBP, vs. Inactive Control (95% CI)
Exploratory analysis	EPAP[68]	–14.78 (–10.45, –19.12)	**No data available** Estimate: –2.5 (–1.5 to –3.5)
	Positional therapy[163]	–4.6	**No data available** Estimate: –2.5 (–1.5 to –3.5)

AHI = Apnea–Hypopnea Index; CI = confidence interval; EPAP = expiratory PAP; MAD = mandibular advancement device; PAP = positive airway pressure; SBP = systolic blood pressure.
Note: Severity of OSA is defined as: mild (5 ≤ AHI < 15), moderate (15 ≤ AHI < 30) and severe (AHI ≥ 30).
[a] Assume this estimate applies only to patients who are at least considered "treatment success."

In cases where different studies were combined, the baseline clinical characteristics were compared across studies to ensure similarity in patient population (**Appendix 20**). Some differences were revealed across studies. For instance, Balk et al.[5] reported on the effect of a weight-reduction program in which the inclusion criteria specified for obese patients with mild forms of OSA (AHI: 5 to 15). As a result, weight reduction was conducted as a separate analysis with only mild-to-moderate OSA explored. Similarly, studies on surgical interventions tended to recruit patients with more severe forms of the condition as observed by the baseline AHI value. Given that the study population may differ, sensitivity analysis on the treatment effect estimates were conducted in which lower effectiveness was applied for surgery.

Discontinuation and Adherence (Specific to Non-Surgical Interventions)

It is difficult to compare the relative adherence and discontinuation rates of PAP therapy, OA, and/or lifestyle intervention because of differences in the enrolled study population. The majority of studies on PAP therapies were of patients with moderate-to-severe OSA, whereas studies on OA and lifestyle modification considered milder disease severities.[123]

Discontinuation

With respect to discontinuation, the clinical review observed that studies that directly compared CPAP against OA found no significant difference between the two types of intervention in terms of discontinuation. The literature further suggested that patterns of discontinuation are related to disease severity, given patients' perceptions regarding the balance between benefits and side effects.[5,164] As mentioned in the clinical review, the single systematic review that evaluated adherence found that higher baseline AHI was associated with greater treatment continuation with respect to CPAP devices.[5] Given these observations, discontinuation rates were assumed to be a function of disease severity rather than treatment. For patients with moderate-to-severe OSA, discontinuation rates were taken from CPAP studies whereas, for patients with mild OSA, the discontinuation rates were taken from OA studies.

The clinical review identified one systematic review with four studies on the rates of CPAP continuation, of which McArdle et al.[165] was considered the largest study with complete and appropriate documentation. Compared with the other studies, McArdle et al. had no obvious selection or ascertainment biases. The discontinuation rate, up to four years, for this cohort of Scottish patients with moderate-to-severe OSA (i.e., median age of 50) was incorporated into the model. Discontinuation after four years of treatment was extrapolated through one of two assumptions: i) complete discontinuation, or ii) constant adherence. An additional sensitivity analysis was undertaken using the discontinuation rates calculated by Guest et al.[125] that pooled discontinuation rates from several large observational studies. In this study, 74% of patients continued using their device during the first year of treatment and, thereafter, a 3.8% exponential rate of decline per annum was applied.

For mild OSA, discontinuation rates were obtained from a long-term study by Marklund et al.[166] in which 450 consecutively recruited patients treated with MAD were followed for an average of 5.4 years. In this study, 72.2% of patients continued treatment in the first year and, by the fifth year, 52.4% of patients remained on treatment. In sensitivity analyses, the discontinuation rates from two other studies with a smaller sample size were considered: Walker-Engstrom et al.,[167] who reported lower rates of discontinuation contrasted by the higher drop-off rates from Izci et al.[168]

As noted, it was modelled that patients who discontinued treatment would return to the levels of CV, stroke, and MVA risks that were associated with no treatment. In addition to the non–treatment-specific discontinuation rates reported above, it was further assumed 10% of patients (4.5% to 32.4%) would initially refuse CPAP and not fill their prescription.[130]

Adherence

Definitions of (perfect) adherence vary by intervention and are provided in Table 94. Partial adherence captures those patients who remained on treatment but who do not meet the criteria for perfect adherence.

The rates of adherence reported were based on several short-term non-comparative studies. As the studies on adherence come from observational studies of less than a year in duration, the proportion of patients adherent to treatment was applied in the first year and assumed to remain consistent thereafter.

There is a paucity of literature on adherence and its impact on treatment effect. A simplifying assumption was required to model the relationship between adherence and event risks: perfectly adherent patients were assumed to experience the full treatment effect, while those who were partially adherent would receive half the effect. In addition, sensitivity analyses were conducted that varied the magnitude of risk reduced from 0 (i.e., partially adherent users have risks similar to those who have discontinued) to 1 (i.e., partially adherent users have treatment effects similar to perfectly adherent users).

Table 94: Definition of Perfect Adherence

	Perfect Adherence Definition in Study	Study Duration	Adherence Rate	Ref
PAP therapy[a]	> 4 hours per night	Median: 4 years (IQR: 2.7 to 4.4)	64%	Barbé, 2012[169]
MAD	> half of each night for > 4 nights/week	1 year	92%	Dieltjens, 2013[170]
Lifestyle modification	Ability to follow regimen	12 weeks	86%	Dobrosielski, 2015[171]
Position therapy	≥ 4 h per night and ≥ 5 days of usage per week	12 weeks	89%	Benoist, 2016[78]

IQR = interquartile range; MAD = mandibular advancement device; PAP = positive airway pressure.
[a] Given that no literature was identified on the adherence rates for EPAP, the same rates from PAP therapy were applied.

Rate of Relapse (Specific to Surgical Interventions)

Although some of the soft-tissue procedures historically used for OSA provide only temporary relief, most studies on orthognathic surgery report a maintenance of symptom improvement.[162,172] One of the longest studies, with a mean follow-up period of 6.6 years, reported no significant change in the AHI score between the short-term (mean AHI: 9.1 ± 7.9) and long-term time intervals (10.9 ± 15.0; $P > 0.05$) among 16 patients studied.[162] As such, for the base case, it was assumed that improvements in outcomes remained stable over time.

A sensitivity analysis was conducted given that a few smaller observational studies have reported on patient relapse. For instance, in a small study (n = 6) in which all patients were initially classified as surgical successful, one patient reported significant relapse with AHI of 43, while two other patients had their AHI > 5 at the eight-year follow-up.[173] Given the paucity of literature describing the worsening of symptoms, a clinical expert involved in this review was consulted. It was suggested that, in total, 8% of patients may have worsening of symptoms over their lifetime. Given that the rates of relapse from cure to partial success and from partial success to failure are unknown, a simplifying assumption was made that would be biased against the surgery strategy: the relapse of OSA symptoms was assumed to occur immediately in the first cycle.

In summary, transition probabilities in this model are dependent on age, sex, OSA severity, therapy adherence, and/or disease history (i.e., MI, stroke).

8. Utilities

The health effects of OSA and the impacts of alternative treatments were expressed in terms of QALYs. Baseline Canadian age-specific utility values from a general population, based on the EuroQol 5-Dimensions 3-Levels questionnaire (EQ-5D-3L), were taken from Johnson et al.[174] To capture the impact of moderate-to-severe OSA, general population utilities were adjusted by a factor of 0.854 to reflect the lowered QoL associated with this disease.[127] No reduction in utility was assumed for patients with mild OSA.

In terms of the health conditions associated with OSA, a patient's age-specific baseline utility values were decreased by a factor of 4.7% for hypertension, 10.8% for mild stroke, 35.8% for MI, and 65.7% for severe stroke (Table 95).[175-177] The literature further suggests that patients with a history of MI and stroke have a lowered QoL. As such, post-stroke and post-MI were associated with a reduction of baseline utility by a factor of 17.7% and 15.0%, respectively. Non-fatal MVA was handled differently as it was specifically applied one time, to the relevant cycle period, by subtracting the patients' utility value in that health state by the utility decrement associated with the accident, stratified based on the severity of the vehicular crash.

For joint health states, such as comorbid conditions (e.g., OSA and hypertension), the minimum approach was used to estimate the joint utility value in the base-case analysis. The minimum approach [Ui,j = Min(Ui, Uj)] predicts the value of a joint health state based on selecting the lowest utility value among each individual health state. A structural sensitivity analysis was further conducted using a multiplicative approach (Ui,j = Ui × Uj), which involved multiplying the health state for each relevant condition to determine the joint utility value.

Table 95: EQ-5D Utility Values

Description	Mean	Distribution	References
Moderate-to-severe OSA (multiplicative factor)[a]	0.854	Beta (α: 43.56; β: 7.44)	Calculated based on Mar, 2003[127a] Pietzsch, 2015[128]
Health condition utility weights (multiplicative)[a]			
Essential hypertension	0.953	Beta (α: 6751.29; β: 333.71)	Calculated based on Sullivan, 2006[176a]
Mild-to-moderate stroke	0.892	Beta (α: 31.16 β: 13.04)	Calculated based on Golicki, 2015[177a]
Severe stroke	0.343	Beta (α: 40.55; β: 109.09)	Calculated based on Golicki, 2015[177a]
MI	0.642	Beta (α: 296.57; β: 62.44)	Calculated based on Little, 2014[175a]
Post-stroke	0.8228	Beta (α: 2539.11; β: 546.89)	Calculated based on Sullivan, 2006[176a]
Post-MI	0.8502	Beta (α: 207.46; β: 36.54)	
MVA utility decrement (additive)			
MVA, full recovery	–0.0146	Beta (α: 3.56; β: 240.44)	Nyman, 2008[178]
MVA, partial recovery	–0.0238	Beta (α: 5.81; β: 238.19)	
MVA, permanent injury	–0.0375	Beta (α: 9.15; β: 234.85)	

Table 95: EQ-5D Utility Values

Description	Mean	Distribution	References
Treatment-specific utility increment (additive; applied in sensitivity analysis. Assumed to be 0 in the base case)[a]			
PAP therapy	0.04	Gamma (0.79, 0.05)	Chakravorty, 2011[179]
MAD	0.02	Gamma (0.41, 0.05)	Quinnell, 2014[180]
Lifestyle modification	0.007	Gamma (0.05, 0.15)	Chakravorty, 2011[179]
Surgery	0.04	Gamma (1, 0.04)	Assumption

EQ-5D = EuroQol 5-Dimensions questionnaire; MAD = mandibular advancement device; MI = myocardial infarction; MVA = motor vehicle accident; PAP = positive airway pressure; OSA = obstructive sleep apnea.
[a] The utility weight was calculated by adjusting the reported study value to the Canadian baseline utility weight, according to the mean age of studied patients.

In the base case, treatment affects utility according to the post-treatment AHI response. Studies have reported small treatment-specific differences in the change in utility scores between the baseline and post-treatment period. These utility increments ranged between 0.04 and 0.007 depending on the intervention.[179,180] A sensitivity analysis was therefore conducted in which, for patients adherent on treatment, utilities were adjusted by an increment associated with their treatment. Given that no studies were found that elicited patients' preferences by EQ-5D following surgical interventions, several assumptions were necessary. In patients with surgical success, utility values would return to general population values; in patients with surgical response, utility weights would be similar to treated OSA by PAP therapy, while in patients with surgical failure, utility weights would remain as the untreated OSA value.

9. Cost Inputs

Costs in the analysis are described in Table 96, Table 97, Table 98, and Table 99. Based on the perspective of the analysis (i.e., public health care payer), only direct medical costs were considered. Whenever possible, the most current Canadian cost estimates were used. If Canadian costs were unavailable, costs would be estimated from the medical literature from comparable health systems. Conversion of currency was conducted using the Bank of Canada currency converter.[181] All cost estimates were adjusted to 2016 Canadian dollars using the health care component of the consumer price index inflation calculator from the Bank of Canada.[182]

Cost in which the resource had equal utilization across all strategies were omitted from the analysis.

Device Costs
PAP-Based Therapy

As PAP therapies are equally efficacious, these treatments differ primarily on costs. A weighted cost of PAP-based therapy was calculated. For APAP devices, the positive pressure levels applied to the patient change throughout sleep. It is less resource intensive as a titration sleep study is not required because the device automatically adjusts pressures in response to the measured physiological signals. In contrast, CPAP machines require manual titrations, with the majority of patients undergoing a split night in-lab polysomnogram in which sleep apnea is first diagnosed and then a titration test is performed to determine the optimal airway pressures during a single night. In such cases, the cost of titration can be omitted. However, treatment pressure is not always obtained on the first night and, in certain circumstances, a separate titration study may be required on a different day. It was assumed that 10% of patients on CPAP would require an additional titration study to determine their optimal positive pressure levels. In both cases, the device life was assumed to be seven years.

The annual cost of PAP therapy was determined through a micro-costing approach. It captured fixed costs such as the PAP machine alongside the cost of any required refills. Based on the device monographs, it was estimated that yearly replacements would include a new mask, tubing, head gear, and filters.[183] Alternative refill requirements were further explored.[183] In the base-case analysis, it was assumed that all costs relating to PAP therapy would be covered. Sensitivity analyses were conducted based on a different funding model for the CPAP device (**Appendix 17**).

Table 96: Price of PAP-Based Therapy

	Details (Unit Price)	Cost, $	Reference
First-year APAP costs	1 APAP machine ($833), 1 headgear ($118), and 12 filter ($7)	1,039 (Range: 2000)	Individual item costs from Canadian CPAP supply[184]
First-year CPAP costs	1 CPAP machine ($720), 1 headgear ($118), and 12 filter ($7)	927 (Range: 2000)	Individual item costs from Canadian CPAP supply[184]
Costs of refills (in subsequent year)	Estimated typical refills: 1 each of new mask/headgear, tubing, and filter	822	Individual costs from Canadian CPAP supply[184] Resource use based on[183]

APAP = automatic positive airway pressure; CPAP = continuous positive airway pressure.

Nasal EPAP

The cost of nasal EPAP was similarly determined by a micro-costing approach. The cost of a 30-day pack of single-use Provent nasal strips from an online source was $69.99 (or $2.33 daily).[184]

MAD

A macro-costing approach was taken to determine the cost of oral appliances given that the clinical experts involved in this review mentioned that the cost of a customized dental device would entail a package of services that include any required diagnostics tests, the dental appliance itself, and any subsequent visits to make adjustments to the appliance. A 2009 Health Quality Ontario (HQO) report on dental devices estimated that the costs would be approximately $2,000.[38] In the base-case analysis, it was assumed that oral appliances required replacement every two years. Based on clinical experts' opinion, the cost of replacements was assumed to be half of the original costs, given that many of the diagnostic tests required would have been completed.

Lifestyle Management

It was assumed that the costs, from the perspective of the Ministry of Health, for a weight-loss program would primarily entail the cost of visits to a registered dietician whose average hourly fee would be $106.[185] Changes to eating habit and food consumption were assumed to be out-of-pocket expenses by the patient.

The cost of positional therapy would primarily involve the cost of the intervention (retail online price: 189.95 USD[186]) with yearly replacement assumed.

Surgery-Related Costs

The cost of surgery included the costs for pre-surgical workup, hospital stay, and post-surgical assessment. Costs were estimated from a variety of sources and are presented in Table 97. When costs were unavailable, the costs of similar procedures were taken with verification by a clinical expert. A study on consecutive patients receiving orthognatic surgeries reported that, in the first year post-operative assessment period, the most common problem was neurosensory injury involving the inferior alveolar nerve, which was mild in 32% of cases, and severe in only 3% of those affected.[187] The most serious complication was severe bleeding (> 12%). As the post-surgical complications were relatively minor and resolve with time, the cost of managing complications were omitted from this model.

Table 97: Non-Physician Costs Pertaining to Surgery (2016 Values)

	Details (if needed)	Cost, $	Quantity	Reference
Pre-Surgical Workup				
X-ray	Billing code: X006 "mandible X-ray — 3 views (unilateral or bilateral)"	32	1	Ontario Schedule of Benefits[188]
Blood tests		8	1	Ontario Schedule of Laboratory Fees[189]
CT scan[a]	Billing code: X400 "CT head — w/out IV contrast"	43	1	Ontario Schedule of Benefits[188]
Dental cast	Specific to MMA only	1,032	1	Assumption, clinical expert (900 USD, exchange rate: 1 USD = 1.29 CAD)
Hospital Stay (Incl. Nursing, Diagnostic Imaging, Pharmacy, Labs, and Overhead Costs)				
MMA	*NOTE: Average length of hospital stay was 1.5 days*	8,073		Ontario Case Costing Initiative[190]
GTA	Assumed captured in MMA costs above			
Post-surgical assessment (to confirm surgery success)				
Polysomnography		468	1	Ontario Schedule of Benefits[188]

CT = computed tomography; GTA = genial tubercle advancement; MMA = maxillomandibular advancement.
[a] The cost of CT reflects solely the cost of physician interpretation and not the cost of the technical component. A sensitivity analysis was conducted with a higher cost associated with CT.[191]

Physician Fees

Because all patients enter the model diagnosed with OSA, the cost of consultation pertaining to diagnosis was not captured in the model. Pertinent consultation costs that differed across treatment were included, such as visits to the dentist and surgeon for oral appliance and surgery, respectively. Follow-up visits were further captured except in the case of follow-up dental visits, as these are already captured in the cost of the oral appliance itself. Physician costs were obtained from the Ontario Schedule of Benefits for Physician Services[188] and are presented in Table 98.

Table 98: Physician Labour Costs

	Details (If Needed)	Interventions (Related to…)	Cost, $	Quantity	Reference
Consultation Costs					
Dentist		Oral appliances	175	1 per device	HQO[38]
One-hour consult with dietician		Weight loss	135	1 per year	Dietitians of Canada[185]
Pre-surgical consultation		Surgery	91	1 per procedure	Ontario Schedule of Benefits[188]
Follow-up visits					
Respirologists: (except oral appliances and surgery)		PAP therapy Lifestyle modification No treatment	80	1 per year	Ontario Schedule of Benefits[188]
Respirologists: for oral appliances		Oral appliance	80	1 every 5 years	

Table 98: Physician Labour Costs

	Details (If Needed)	Interventions (Related to…)	Cost, $	Quantity	Reference
Surgeon's post-surgery follow-up (before discharge)		Surgery	59	1 per procedure	
Surgical follow-up visit	Quantity: 1/week in first 4 weeks; one during months 1-6; one follow-up re. PSG	Surgery	31	6 per procedure	
Labour Costs Specific to Surgery (Incl. Anesthesiologist and Surgical Assistant)					
Mandibular osteotomies for prognathism, sagittal split	Billing code: Orthognathic surgery #R379 "Le Fort I advancement in one segment" Incl. 15 units of anesthesia and 6 units of surgical assistant	Surgery	1,229	1	Ontario Schedule of Benefits[188]
Le Fort I advancement	Billing code: Orthognathic surgery #R518 "mandibular osteotomies for prognathism, sagittal split" Incl. 20 units of anesthesia and 10 units of surgical assistant		1,224	1	
Genioplasty	Used the price of genioplasty as a proxy as per assumption from the clinical expert. Incl. 10 units of anesthesia and 6 units of surgical assistant		607	1	
Total labour cost of the day of surgery (MMA with genioplasty)					1,229 + 1,224+607 = 3,060
Total labour cost of the day of surgery (MMA without genioplasty)					1,229.49 + 1,224.4 = 2,453

MMA = maxillomandibular advancement; PSG = polysomnography.

Health State Costs

Table 99 presents the cost estimates for the clinical events used in this analysis. The initial cost of hypertension, MI, and stroke and the subsequent year cost for ongoing management were obtained from several Canadian sources.[148,157]

As the analysis is conducted from the perspective of the public payer (i.e., Ministry of Health), only medical costs arising from an MVA would be relevant to capture. These costs were obtained from a publication by the Ontario Ministry of Transportation.[157] In the publication, the direct costs of both non-fatal and fatal MVAs were reported and, to map these costs to the stratified categories for MVA (i.e., property damage, personal injury, and fatal), it was assumed that accidents relating to property damage would not lead to any medical costs, whereas the costs from accidents leading to personal injury would reflect non-fatal MVA cost.

Table 99: Cost Estimates for Clinical Events

	Cost,[a] $	Distribution	References
Initial			
Non-fatal MI	7,760	Gamma (1, 7760)	Anis, 2006[148]
Fatal MI	6,289	Gamma (1, 6289)	
Non-fatal mild-to-moderate stroke	13,327	Gamma (1, 13327)	
Non-fatal severe stroke	73,911	Gamma (1, 73911)	
Fatal stroke	6,168	Gamma (1, 6168)	
Subsequent/ongoing			
Hypertension	429	Gamma (1, 429)	Anis, 2006[148]
MI	1068	Gamma (1, 1068)	
Mild-to-moderate stroke	7148	Gamma (1, 7148)	
Severe stroke	67,903	Gamma (1, 67903)	
Motor vehicle accident (one time)			
Non-fatal, personal injury	2113	Gamma (1, 2113)	Voden, 1994[157]
Fatal	8713	Gamma (1,8713)	

MI = myocardial infarction.
[a] Costs are reported in the year of the study's report but converted to 2016 values by the consumer price index.[182]

10. Statistical Analysis and Sensitivity Analysis

The ICUR was calculated according to convention and, in most cases, the sequential incremental cost-effectiveness ratio (ICER) was presented, unless otherwise specified. Strategies that were dominated (where there is another strategy that has lower expected costs and higher expected QALYs) or "extendedly dominated" (where at least one possible combination of two treatment strategies exists, which would be less costly and result in higher QALYs) were ruled out.

Sensitivity analyses were conducted to evaluate the degree to which the uncertainty in cost and effectiveness parameters affected the models' findings. The base-case findings for the economic evaluations reflect the probabilistic results based on 5,000 Monte Carlo simulations of the parameters' distributions. For the simulation, probability distributions related to natural history, hazard ratios, resource utilization (costs), and utilities were incorporated into the analysis, adopting standard methods for defining parameter uncertainty. Treatment effect was characterized by normal or beta distributions, transition probabilities and relative risks were characterized by beta and lognormal distributions, utility was characterized by gamma or beta distribution, and costs were characterized by gamma distributions. The probabilistic results characterize the extent to which parameter uncertainty affects the cost-effectiveness of the model. Results of the probabilistic analysis will be presented on a cost-effectiveness acceptability

curve (CEAC), whereby interventions on the efficiency frontier will be highlighted. This graph presents the probability that each treatment is optimal given different values of willingness-to-pay for an additional QALY gained.

Sensitivity and scenario analyses were conducted to characterize the impact of different model assumptions and evaluate structural uncertainty. These include:

- Alternative assumption on mortality: In the process of validation, the model's predicted mortality incidence was found to better align to the observed literature when it was assumed that, despite treatment adherence, patients would have an increased risk of mortality if they remained disease severe (i.e., relative risk of death for severe OSA, irrespective of treatment = 1.601). An alternative assumption was tested in which patients' adherent to treatment would have their mortality risks return to baseline levels.
- Relative risk of mortality following CVE: In the base-case model, it was assumed that patients with a history of CVD would have an increased risk of mortality. However, other economic models on OSA do not make this assumption. Rather, mortality rates would be the same for those with or without a prior CVE. This assumption was tested in the economic analysis.
- Effects of surgery on blood pressure: Clinical experts involved in this review have suggested that the treatment estimates for surgery on blood pressure reduction may be an overestimate given that the clinical trial on which this estimate was based recruited patients with a greater disease severity. The mean blood pressure reduction attained by PAP therapy and MAD were both substituted.
- Effects of surgery on AHI: Similarly, the clinical experts noted a similar concern for the outcome, AHI, given that a selective population may have been recruited in surgical trials, potentially biasing in favour of surgery. The lower bounds of the 95% CI for all surgical outcomes for AHI were simultaneously applied to the model to test when lowered rates were tested.
- Relapse following surgery*:* The base-case model assumed surgical outcomes were permanent. However, a few small observational studies have suggested that symptoms of OSA may return over time. Give that the rate of relapse was unknown, the clinical expert consulted in this review provided an estimate of 8%. As the rate was uncertain. the scenario most likely to bias against surgery would be to assume that the relapse occurred within the first year post-surgery.
- Excluding the impact of MVA: The base case assumes all patients drive and are at risk of vehicular accidents until the age of 80. In a scenario in which patients are non-drivers, the risk of MVAs is removed, along with the costs and utilities associated with MVA.
- Adherence rate*:* Scenarios tested on adherence rate included the following: all patients on treatment were assumed to be perfectly adherent (i.e., rate of adherence of 100%), testing the 95% CI of intervention-specific adherence rates in multi-way sensitivity analyses, and testing a lower rate that has been reported in literature (adherence rates = 17%).[31] Device lifespan: Different lifespans for PAP therapy and oral appliances were varied across a plausible range.
- Cost of computed tomography (CT): The full cost of CT to the public player was difficult to determine, as it consists of both the fee billed by physician for the interpretation of the scan and also the operational cost of the CT machine. The base case captures only the publicly reimbursed rate of physician billing and reflects a partial cost of CT. A sensitivity analysis was conducted in which the highest reported cost ($625) from a US laboratory[191] was taken as a possible proxy of the full public payer costs for CT imaging.

Interpretation of the economic findings was based on setting a willingness-to-pay threshold of $50,000 per QALY. Sensitivity analyses were conducted to explore situations in which the results would change; i.e., the order in which the treatment strategies were considered cost-effective differed or when the order remained consistent but the AHI cut-off score differed by more than its clinically meaningful difference when compared with the base-case analysis (**Appendix 15**).

When possible, subgroup analyses were conducted to address whether there was any heterogeneity that could affect the cost-effectiveness results. The clinical review found evidence on some of the pre-specified subgroups of interest on the outcomes of AHI and blood pressure for some of the interventions of interest but not all. As such, in the economic analysis, the subgroup analyses were conducted based on the assumption that subgroups had identical treatment effects but differed by baseline event risks arising from the Framingham risk equation. Subgroups that could be explored in the model included:

- Sex: male vs. female
- Age: 30 vs. 70 years
- Patients who are hypertensive
- Patients who are current smokers
- Patients with diabetes.

11. Model Validation

The model structure and data inputs were presented to four Canadian clinical experts in the areas of sleep medicine: respirology, dentistry, and maxillofacial surgery to ensure that the model, parameters, and assumptions reflect clinical practice and the available body of literature (face validity). Internal validity was assessed by ensuring the mathematical calculations were performed correctly and were consistent with the model specification. Logical inconsistencies were assessed by evaluating them under hypothetical and extreme conditions. The model also underwent external peer review.

External validation was further explored by comparing the model predictions to actual outcomes reported in three existing observational cohorts.[134,135,141] Multiple validations were performed that crisscrossed different outcomes (i.e., all-cause and CV mortality), interventions (i.e., no treatment vs. treated) and patient populations.

12. Model Assumptions

The base-case economic analysis was conducted under the assumptions shown in Table 100.

Table 100: Assumptions Used to Populate the Economic Models

Assumption	Strategy in Which Applicable	Sensitivity Analysis Description
Patients modelled represent a cohort of adult patients who are representative of the Canadian population (e.g., 76.5% male, aged 55 years).	All	-Sex proportion varied from 100% males to 0% males -Age varied in the model (30 and 70 years)
In terms of the surgical procedures, it was modelled that 90% of patients would be receiving MMA in which 20% would be performed in adjunct with GTA. The remaining 10% of procedures were GTA.	All	None (the cost of surgery and treatment effects represents a pooled estimate)
Patients diagnosed with hypertension will be treated with medication, targeting the return to baseline blood pressure levels.	All	None
All patients drive and discontinue this activity at the age of 80, except in patients following an incidence of severe stroke who are assumed unable to drive.	All	Changed the model to reflect non-drivers only
Patients who are perfectly adherent to treatment will have risk of MVAs similar to the general population	Non-surgical interventions	None
Treatment effects on AHI, based on naive treatment	All treatment	Treatment effect estimates from

Table 100: Assumptions Used to Populate the Economic Models

Assumption	Strategy in Which Applicable	Sensitivity Analysis Description
comparison against "no treatment," reflect the likely "true" comparative treatment effects.	interventions	an existing NMA were applied for all non-surgical interventions
Rates of discontinuation were based on disease severity. Long-term studies on CPAP provided the discontinuation rates for severe OSA patients, while studies on OA provided the discontinuation rates for moderate OSA patients.	Non-surgical interventions	None
After the fourth year of treatment, no patients will discontinue their treatment (i.e., LOCF analysis)	Non-surgical intervention	Assume all patients drop out after 4 years of treatment
Surgical outcomes achieved in the first year post-surgery were assumed to be permanent.	Surgery	Assume 8% of patients will experience relapse and become symptomatic after the first year of surgery
For joint health states, a minimum utility approach was taken to determine the appropriate utility value to apply to that health state.	All	Apply a multiplicative approach to utility determination
Treatment would affect the utility weight depending on the post-treatment disease severity.	All	Apply a treatment-specific utility increments to the model
81% of patients receiving PAP therapy would be prescribed APAP. The remainder would be prescribed CPAP. In addition, for patients on CPAP, 90% of patients would have undergone split night polysomnography.	PAP therapy	None
All devices and regular replacements were assumed to be covered by the Ministry of Health. Yearly replacements for PAP-based treatments included a new mask, tubing, head gear, and filter.	PAP therapy	Different reimbursement structures explored
The device life span for PAP machines was 7 years, while for mandibular advancement devices, it would be 2 years.	PAP therapy, MAD	Lifespan for PAP therapy varied from 5 to 10 years; lifespan for oral appliances varied from 2 to 10 years
For oral appliances, it was assumed that the cost of replacement would be half of the original costs.	MAD	Replacement of oral appliance is the same as the first-time costs
Changes to eating habits and food consumption were assumed to be out-of-pocket expenses by the patient.	Weight Loss	None

AHI = Apnea–Hypopnea Index; APAP = automatic PAP; CPAP = continuous PAP; GTA = genial tubercle advancement; LOCF = last observation carried forward; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; MVA = motor vehicle accident; PAP = positive airway pressure; RR = relative risk.

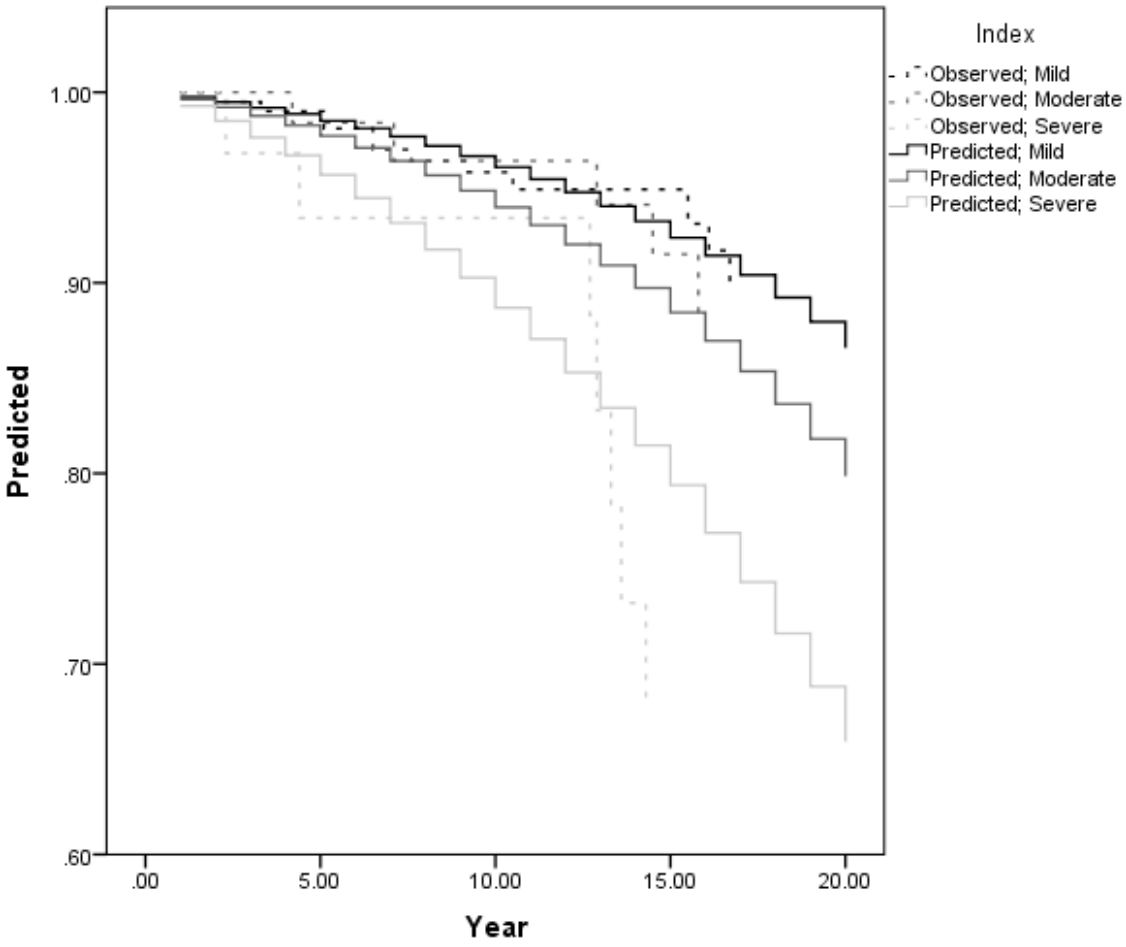
1.1.1. Model Results

1. Model Validation

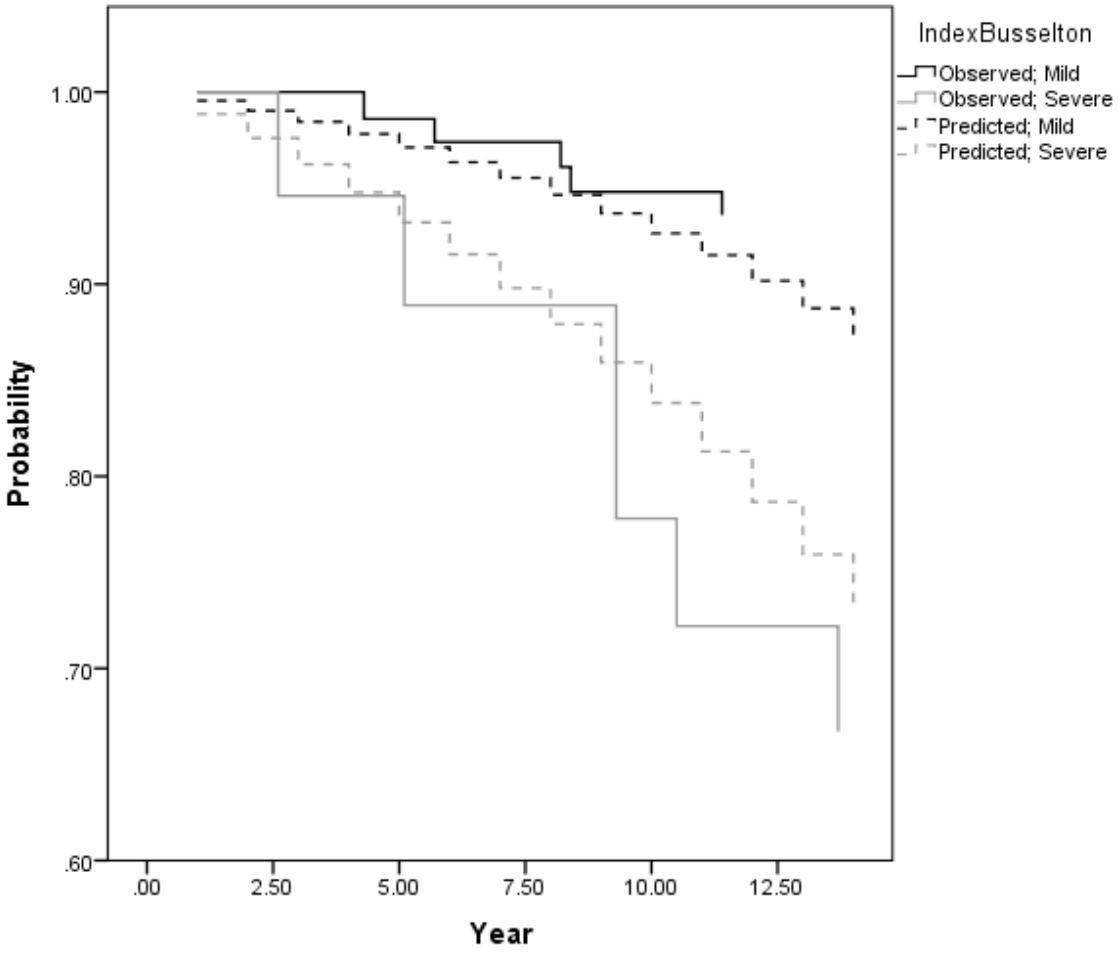
Our model predicted a mortality rate of 14.1% and 42.1% at 10 and 20 years, respectively, under the base case for untreated non-smoker patients with severe OSA, and a mortality rate of 17.6% and 49.3% for patients who are smokers. Figure 3 presents the survival curves at the end of the study follow-up. When the model predictions were

compared with the findings from published clinical trials, our model was found to underestimate mortality for untreated severe OSA in both the Wisconsin Sleep Cohort Study (WSCS)[134] and Busselton study[135] but otherwise, for the other disease severities, the model predictions and study's observations were closely aligned (Figure 2).

Figure 2: Comparison of Model's Predicted and Cohort Studies' Reported Survival Curves.



(A) Wisconsin Sleep Cohort Study[134] (B) Busselton Study[135]



Specifically, the WSCS comes from a considerably different patient population compared with SHHS, upon which the model's CV parameters are based. SHHS recruited an older, geographically and racially diverse sample from a number of "parent" CV cohort studies, whereas WSCS represents a more homogenous population from a common sampled pool of employed individuals. Table 101 reports the incidence rate (per 100 person-years) and proportion of all-cause mortality and CV mortality reported in WSCS and predicted by our model. The incidence rate predicted by the model was slightly higher for all-cause mortality across all disease severities but remained within the reported 95% CI. Given that the estimate was also higher in patients without OSA, this would suggest that there are inherent differences between the general Canadian population (on which the model is based) and the patient population that was studied in the WSCS. The outcome of CV mortality was more aligned between the observed and predicted value.

The model was further validated by comparing the model predictions to a study by Martinez-Garcia et al.[141] of elderly, severe OSA patients, which was conducted in Spain. They reported that 34.1% and 16.1% of patients who were untreated and treated by CPAP died over a mean follow-up period of 69 months. Our model led to similar predicted values. For patients on CPAP, the proportion would depend on adherence as values range from 24.2% (normal adherence) to 20.6% (perfect adherence), with clinical experts suggesting that better adherence is observed in Spanish studies, which would be indicative that the lower estimate is more likely accurate.

Table 101: Comparison of Model's Prediction and Wisconsin Sleep Cohort Study Observation on All-Cause and Cardiovascular Mortality

Parameter	WSCS Study	Reported Results	Model Prediction
All-cause mortality	*WSCS*[136,192,193] 1,522 men and women Severe: proportion males, 78%; age, 50, 19% smokers; tot-C, 212; HDL, 39; SBP, 135 Moderate: proportion males, 72%; age, 50; 15% smokers; tot-C, 211; HDL, 42; SBP, 135 Mild: proportion males, 65%; age, 50; 16% smokers; tot-C, 213; HDL, 44; SBP, 130 None: proportion males, 55%; age, 48; 19% smokers; tot-C, 202; HDL, 49; SBP, 120 Mean observation: 13.8 years Total of 20,963 person-years	**Rate per 100 person-years (95% CI)** Severe AHI: 1.46 (0.75 to 2.54) Moderate AHI: 0.54 (0.20 to 1.18) Mild AHI: 0.55 (0.32 to 0.90) None: 0.29 (0.21 to 0.38) **Proportion: %** Severe AHI: 19.1 Moderate AHI: 7.3 Mild AHI: 7.3 None: 4	**Rate per 100 person-years (95% CI)** Severe AHI: 1.68 Moderate AHI: 0.82 Mild AHI: 0.66 None: 0.51 **Proportion: %** Severe AHI: 18.62 Moderate: 10.40 Mild: 8.52 None: 6.77
Cardiovascular mortality		**Rate per 100 person-years (95% CI)** Severe AHI: 0.61 (0.20 to 1.41) Moderate AHI: 0.18 (0.02 to 0.65) Mild AHI: 0.21 (0.08 to 0.45) None: 0.07 (0.04 to 1.30) **Proportion: %** Severe AHI: 7.9 Moderate AHI: 2.4 Mild AHI: 2.7 None: 1	**Rate per 100 person-years (95% CI)** Severe: 0.59 Moderate: 0.13 Mild: 0.11 None: 0.062 **Proportion: %** Severe: 7.58 Moderate: 1.75 Mild: 1.51 None: 0.85
Incidence of Mortality	Martinez-Garcia, 2012[141] Untreated severe: proportion males, 71.7%; age, 71.9, AHI, 58.6; 47% smokers; tot-C, NR; HDL, NR; SBP, NR Treated severe: proportion males, 62.2%; age, 70.1; AHI, 52.2; 41% smokers; tot-C, NR; HDL, NR; SBP, NR	**Proportion: %** Untreated severe: 34.1% Treated severe: 16.1%	**Proportion: %** Untreated severe: 34.47% Treated severe: 24.2% (normal adherence) 20.57% (perfect adherence)

Table 101: Comparison of Model's Prediction and Wisconsin Sleep Cohort Study Observation on All-Cause and Cardiovascular Mortality

Parameter	WSCS Study	Reported Results	Model Prediction
	Median follow-up: 69 months (49 to 87 months)		

AHI = Apnea–Hypopnea Index; HDL = high-density lipoprotein; NR = not reported; SBP = systolic blood pressure; tot-C = total cholesterol; WSCS = Wisconsin Sleep Cohort Study.

2. Base Case

The model was run, varying baseline AHI values between 5 and 60. The incremental costs, QALYs, and ICUR over a lifetime are presented in Table 102 across select AHI values to highlight how cost-effectiveness of interventions for OSA vary by baseline disease severities.

Table 102: Probabilistic Results of Base-Case Scenario Over Cohort's lifetime (5000 simulations)

Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYS	ICUR, Compared With "No Treatment" ($/QALY)	ICUR, Sequential ($/QALY)
Baseline: Mild OSA (AHI = 5)						
No treatment	11,598	10.911	-reference-			
PAP therapy	*18,137*	*10.947*	*6,539*	*0.036*	*182,261*	*Ext. Dom*
MAD	18,974	10.953	7,375	0.042	175,543	175,543
MMA ± GTA	*23,757*	*10.953*	*4,783*	*0.000*	*289,949*	*Dominated*
Baseline: Moderate OSA (AHI = 15)						
No treatment	11,644	9.552	-reference-			
PAP therapy	18,152	10.360	6,508	0.808	8,058	8,058
MAD	19,015	10.453	862	0.093	8,183	9,276
MMA ± GTA	*23,672*	*10.340*	*4,657*	*–0.113*	*15,262*	*Dominated*
Baseline: Severe OSA (AHI = 30)						
No treatment	8,433	8.917	-reference-			
PAP therapy	18,086	10.218	9,653	1.301	7,420	7,420
MAD	*19,057*	*9.383*	*971*	*–0.835*	*22,811*	*Dominated*
MMA ± GTA	*23,249*	*10.120*	*5,164*	*–0.097*	*12,312*	*Dominated*
Baseline: Severe OSA (AHI = 60)						
No treatment	8,382	8.908	-reference-			
MAD	*16,388*	*8.881*	*8,006*	*–0.027*	*Dominated*	*Dominated*
PAP therapy	*16,866*	*9.101*	*8,485*	*0.193*	*43,899*	*Ext. Dom*
MMA ± GTA	23,042	9.764	14,661	0.856	17,125	17,125

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; ICUR = incremental cost-utility ratio; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; QALY = quality-adjusted life-year; PAP = positive airway pressure

In general, the treatment strategies were associated with higher expected costs compared with the no-treatment strategy. The higher costs were due to both the costs related to treatment itself but also the costs of long-term maintenance (i.e., post-MI, post-stroke, and hypertension) as the life expectancies tended to be longer for patients on treatment (Table 103). There was partial cost offset given the lower rates of MVAs among patients receiving treatment for OSA (Table 103). Across all disease severities, surgery was associated with the highest expected costs while no treatment was contrarily associated with the lowest expected costs.

The expected QALYs were lower with increasing disease severity across all strategies studied due to increased mortality and morbidity associated with more severe forms of OSA. The magnitude to which QALY changed varied by baseline AHI value.

Table 103: Disaggregate Clinical Outcomes for the Base Case (Deterministic)

	Average number of events per patient over their lifetime			LYG
	MVA	MI	Stroke	
Baseline: Mild OSA (AHI = 5)				
No treatment	1.998	0.214	0.083	26.12
PAP therapy	1.277	0.211	0.080	26.20
MAD	1.121	0.211	0.080	26.21
MMA ± GTA	1.028	0.209	0.074	25.47
Baseline: Moderate OSA (AHI = 15)				
No treatment	1.962	0.202	0.077	25.01
PAP therapy	1.261	0.205	0.078	25.69
MAD	1.107	0.206	0.078	25.77
MMA ± GTA	1.003	0.203	0.072	24.97
Baseline: Severe OSA (AHI = 30)				
No treatment	1.800	0.189	0.116	21.25
PAP therapy	1.082	0.201	0.092	24.50
MAD	0.904	0.194	0.085	24.05
MMA ± GTA	1.032	0.200	0.076	24.41
Baseline: Severe OSA (AHI = 60)				
No treatment	1.800	0.189	0.116	21.25
PAP therapy	1.054	0.190	0.097	22.91
MAD	0.869	0.185	0.112	21.41
MMA ± GTA	1.242	0.197	0.082	23.61

AHI = Apnea–Hypopnea Index; GTA = genial tubercle advancement; LYG = life-year gained; MAD = mandibular advancement device; MI = myocardial infarction; MMA = maxillomandibular advancement; MVA = motor vehicle accidence; PAP = positive airway pressure.

Table 104: Disaggregate Costs ($) for the Base Case (Deterministic)

	Device-Specific Costs	Disease-Related Cost (e.g., Professional Visits)	Cardiovascular Event Costs	MVA Event Costs	Long-Term Costs
Baseline: Mild OSA (AHI = 5)					
No treatment	0	1,779	3,323	1,911	17,306
PAP therapy	12,942	2,092	3,246	1,131	16,875
MAD	10,863	3,814	3,239	993	16,834
MMA ± GTA	11,799	805	3,163	911	17,568

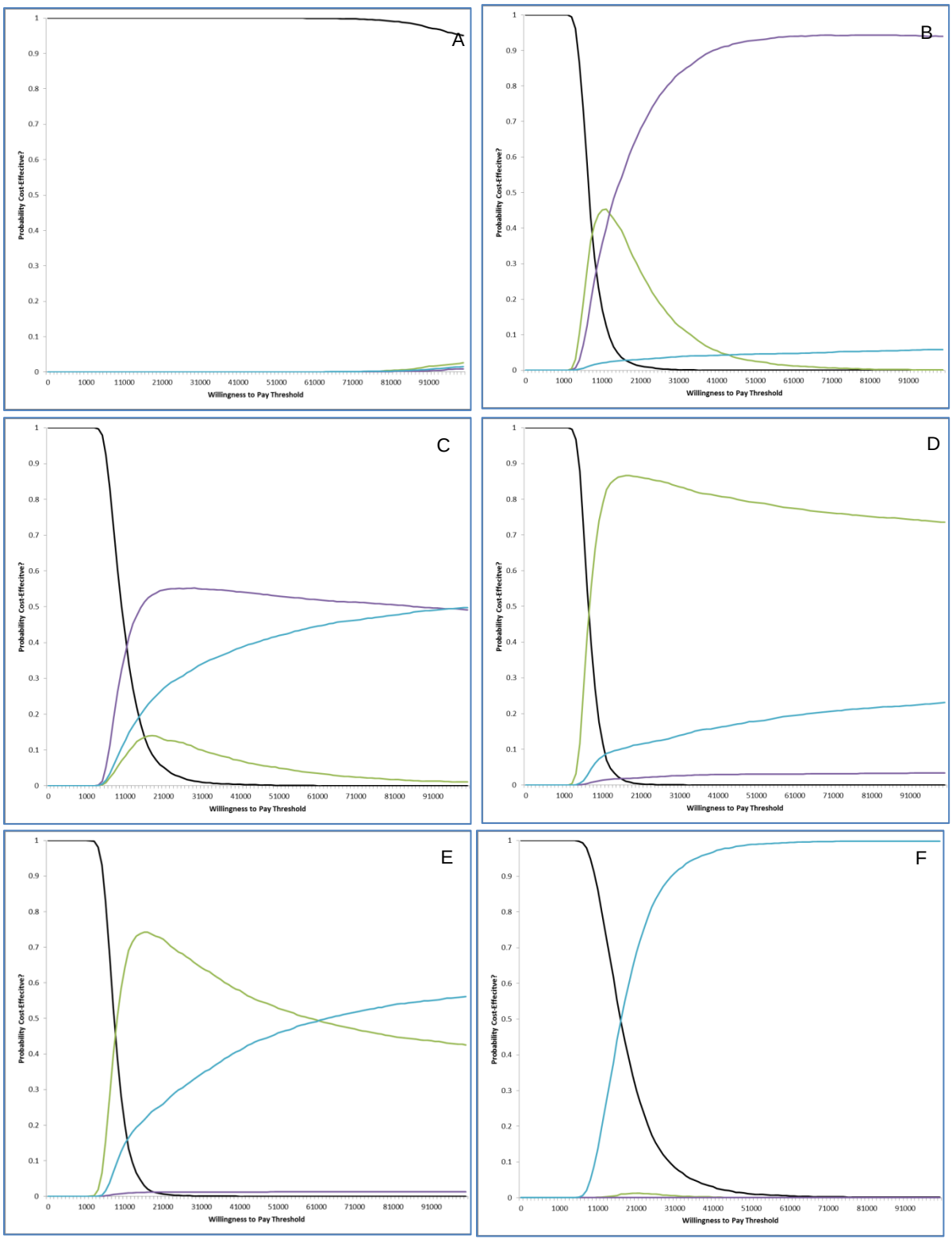
Table 104: Disaggregate Costs ($) for the Base Case (Deterministic)

	Device-Specific Costs	Disease-Related Cost (e.g., Professional Visits)	Cardiovascular Event Costs	MVA Event Costs	Long-Term Costs
Baseline: Moderate OSA (AHI = 15)					
No treatment	0	1,696	3,140	1,875	17,218
PAP therapy	12,942	2,051	3,160	1,117	16,912
MAD	10,863	3,778	3,164	981	16,805
MMA ± GTA	11,799	769	3,089	888	17,532
Baseline: Severe OSA (AHI = 30)					
No treatment	0	1,464	2,754	1,713	12,979
PAP therapy	15,303	1,956	3,023	958	15,347
MAD	12,083	3,905	2,928	801	15,789
MMA ± GTA	11,799	918	3,018	914	17,085
Baseline: Severe OSA (AHI = 60)					
No treatment	0	1,464	2,754	1,713	12,979
PAP therapy	13,963	1,829	2,824	934	14,551
MAD	10,619	3,403	2,688	771	12,922
MMA ± GTA	11,799	1,185	2,956	1,100	16,406

AHI = Apnea–Hypopnea Index; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; MVA = motor vehicle accident; OSA = obstructive sleep apnea; PAP = positive airway pressure.

At a willingness-to-pay threshold of $50,000/QALY, no treatment was the most likely cost-effective strategy in patients with mild OSA (probability ranged from 1.000 to 0.999). For moderate OSA, a cut-off was observed as MAD was the most likely cost-effective strategy at the lower AHI range (15 ≤ AHI ≤ 25), but switched to MMA with or without GTA, at the higher AHI range of moderate OSA (26 < AHI < 30). A cut-off was similarly observed for severe OSA, with PAP therapy emerging as the most likely cost-effective strategy up to a baseline AHI value of 32 and switched to MMA with or without GTA at subsequent higher AHI values (Figure 3). It is important to note that interpretation of these thresholds must be tempered by the fact that is partly an artifact emerging from the model structure as, while treatment effect was modelled as a continuous outcome, natural history of the disease was modelled categorically.

Figure 3: The Evolution of the CEAC Across Different Baseline AHI Severity



(A) AHI = 5; (B) AHI = 15; (C) AHI = 25; (D) AHI = 30; (E) AHI = 32; (F) AHI = 40. Black line = no treatment; green line = PAP; purple line = MAD; blue line = surgery

Scenario Omitting PAP Therapy

As the patient perspectives and experiences review highlights, there are certain circumstances (e.g., Canadian forces, individuals unstably housed, patients with physical or sensory impairments or patients with disabilities) whereby patients may not be suitable candidates for PAP therapy. By removing PAP therapy as a possible treatment option, this scenario was found to differ from the base-case findings specifically in patients with severe OSA. The ICER for MMA with or without GTA reduced (e.g., sequential ICER for surgery in patients with a baseline AHI value of 30 = $12,371 per QALY) (Table 105). As such, at a willingness-to-pay threshold of $50,000/QALY, the analysis demonstrated that MMA with or without GTA was the most likely cost-effective strategy for patients with baseline AHI values greater or equal to 26 (figure not shown).

Table 105: Probabilistic Results of Scenario That Excludes PAP Therapy (5,000 Simulations)

Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYs	ICUR, sequential ($/QALY)
Baseline: Mild OSA (AHI = 5)					
No treatment	11,547	10.911	-reference-		
MAD	18,926	10.953	7,379	0.042	175,553
MMA ± GTA	*23,633*	*10.953*	*4,706*	*0.000*	*Dominated*
Baseline: Moderate OSA (AHI = 15)					
No treatment	11,663	9.543	-reference-		
MAD	19,038	10.450	7,375	0.907	8,134
MMA ± GTA	*23,708*	*10.338*	*4,670*	*-0.112*	*Dominated*
Baseline: Severe OSA (AHI = 30)					
No treatment	8,328	8.906	-reference-		
MAD	*19,029*	*9.369*	*10,701*	*0.463*	*Ext. Dom*
MMA ± GTA	23,273	10.114	14,945	1.208	12,371

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; QALY = quality-adjusted life-year; PAP = positive airway pressure.

Scenario Omitting Surgical Interventions

Similarly, not all OSA patients may be clinically eligible for surgery, or there may be settings in Canada in which surgery is not available. By removing MMA with or without GTA as a possible treatment option, the findings were similar to the previous analysis with the exception that, for the baseline AHI values in which surgery was considered the mostly likely cost-effective, this was replaced by PAP therapy (Table 106). Therefore, at a willingness-to-pay threshold of $50,000/QALY, PAP therapy emerged as the most likely cost-effective intervention for patients with a baseline AHI greater or equal to 26 (figure not shown).

Table 106: Probabilistic Results of Scenario That Excludes Surgical Interventions (5,000 Simulations)

Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYs	ICUR, sequential ($/QALY)
Baseline: Mild OSA (AHI = 5)					
No treatment	11,673	10.910	-reference-		
MAD	18,173	10.946	6,500	0.036	180,397
PAP therapy	19,029	10.952	856	0.006	137,696
Baseline: Moderate OSA (AHI = 15)					
No treatment	11,732	9.541	-reference-		

Table 106: Probabilistic Results of Scenario That Excludes Surgical Interventions (5,000 Simulations)

Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYs	ICUR, sequential ($/QALY)
PAP therapy	18,217	10.353	6,485	0.812	7,984
MAD	19,120	10,446	903	0.093	9,680
Baseline: Severe OSA (AHI = 30)					
No treatment	8,458	8.910	-reference-		
PAP therapy	18,206	10.215	9,749	1.305	7,470
MAD	*19,163*	*9.376*	*957*	*-0.839*	*Dominated*

AHI = Apnea–Hypopnea Index; MAD = mandibular advancement device; OSA = obstructive sleep apnea; QALY = quality-adjusted life-year; PAP = positive airway pressure.

Different Reimbursement Coverage

There is considerable variation in terms of reimbursement coverage across jurisdictions. For instance, in most publicly funded provincial programs, oral appliances are not covered but represent a patient out-of-pocket expense or are reimbursed by a private third-party insurer. Despite this, by removing the costs of oral appliances and dental consults, the overall findings remained consistent with the exception of mild OSA. The expected costs for MAD reduced across all disease severities as the costs of dental-related expenses shifted from the public payer to the private payers. MAD became the least expensive of the treatments and, in the case of patients with mild OSA, MAD emerged as the dominant strategy (i.e., less costly, more effective) compared with all other strategies that were studied (Table 107). At a willingness-to-pay threshold of $50,000/QALY, MAD was the most likely cost-effective strategy for mild-to-moderate OSA (probability = 0.9974 for AHI 10 and 0.6486 for AHI 25) (figure not shown).

In the patient perspective and experience review and the implementation review, both noted that a barrier to treatment is the funding structure. In particular, our clinical experts have suggested that patients' willingness to be on treatment is influenced by the reimbursement structure. As such, a sensitivity analysis was conducted that also applied the lower bounds of the 95% CI of the MAD adherence rates. The model's findings were found to remain robust to changes in this parameter as MAD remained the most likely cost-effectiveness strategy for mild-to-moderate OSA (Table 107).

Table 107: Probabilistic Results Assuming Oral Appliances Are Not Reimbursed (i.e., Represent Out-of-Pocket Expenses)

Adherence Scenario	Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYs	ICUR, sequential ($/QALY)
Base-case adherence	Baseline: Mild OSA (AHI = 5)					
	MAD	10,748	10.954	-reference-		
	No Treatment	*11,580*	*10.912*	*832*	*−0.042*	*Dominated*
	PAP therapy	*18,102*	*10.948*	*7,354*	*−0.006*	*Dominated*
	MMA ± GTA	23,749	10.954	13,001	0.000	$1.4x10^9$
	Baseline: Moderate OSA (AHI = 15)					
	MAD	10,852	10.458	-reference-		
	No Treatment	*11,654*	*9.563*	*802*	*−0.895*	*Dominated*
	PAP therapy	*18,118*	*10.366*	*7,266*	*−0.092*	*Dominated*
	MMA ± GTA	*23,678*	*10.346*	*5,561*	*−0.020*	*Dominated*

Table 107: Probabilistic Results Assuming Oral Appliances Are Not Reimbursed (i.e., Represent Out-of-Pocket Expenses)

Adherence Scenario	Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYs	ICUR, sequential ($/QALY)
	Baseline: Severe OSA (AHI = 30)					
	No treatment	8,400	8.923	-reference-		
	MAD	9,877	9.384	1,477	0.462	3,199
	PAP therapy	18,103	10.221	8,226	0.837	9,830
	MMA ± GTA	*23,356*	*10.125*	*5,253*	*−0.096*	*Dominated*
	Baseline: Severe OSA (AHI = 60)					
	MAD	7,689	8.884			
	No Treatment	*8,329*	*8.910*	*640*	*0.026*	*Ext. Dom*
	PAP therapy	*16,825*	*9.108*	*9,135*	*0.224*	*Ext. Dom*
	MMA ± GTA	22,960	9.770	15,271	0.886	17,235
Lower adherence for MAD	Baseline: Mild OSA (AHI = 5)					
	MAD	10,800	10.953	-reference-		
	No treatment	*11,608*	*10.912*	*808*	*−0.041*	*Dominated*
	PAP therapy	*18,107*	*10.948*	*7,307*	*−0.005*	*Dominated*
	MMA ± GTA	23,681	10.954	12,881	0.001	10,781,667
	Baseline: Mild OSA (AHI = 15)					
	MAD	10,901	10.449	-reference-		
	No treatment	*11,684*	*9.555*	*783*	*−0.894*	*Dominated*
	PAP therapy	*18,145*	*10.359*	*7,243*	*−0.090*	*Dominated*
	MMA ± GTA	*23,700*	*10.340*	*5,555*	*−0.019*	*Dominated*
	Baseline: Severe OSA (AHI = 30)					
	No treatment	8,461	8.910	-reference-		
	MAD	10,016	9.375	1,555	0.465	3,344
	PAP therapy	18,121	10.212	8,105	0.838	9,676
	MMA ± GTA	*23,405*	*10.120*	*5,284*	*−0.092*	*Dominated*
	Baseline: Severe OSA (AHI = 60)					
	MAD	7,860	8.889	-reference-		
	No treatment	*8,482*	*8.917*	*622*	*0.028*	*Ext. Dom*
	PAP therapy	*17,028*	*9.112*	*9,168*	*0.223*	*Ext Dom.*
	MMA ± GTA	23,181	9.772	15,322	0.883	17,354

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; QALY = quality-adjusted life-year; PAP = positive airway pressure.

Similarly, it has been suggested that the cost of PAP devices can vary. The prices used in the reference case were more similar to the Ontario Assistive Devices coverage program (i.e., in Ontario, the total cost is $1,075, of which the Ministry of Health pays $860 and the remainder represents out-of-pocket costs;[194] first-year costs in the model were $1,039 and $927 for APAP and CPAP devices, respectively). Clinical experts involved in this review suggested that the first-year costs of PAP machines vary widely and may be as high as $2,000 in other jurisdictions in Canada. Probabilistic results based on a higher first-year acquisition price for PAP therapy are presented in Table 108. This scenario resulted in higher expected costs for the PAP therapy strategy. Although the ICUR associated with PAP

therapy increased to $8,891 per QALY in patients with baseline severe OSA (AHI = 30), the overall economic findings remained consistent.

Table 108: Probabilistic Results Assuming the First-Year Price of PAP Therapy Is C$2,000

Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYs	ICUR, Sequential ($/QALY)
Baseline: Mild OSA (AHI = 5)					
No Treatment	11,590	10.914	-reference-		
MAD	18,963	10.956	7,373	0.042	175,707
PAP therapy	*19,776*	*10.950*	*813*	*–0.006*	*Dominated*
MMA ± GTA	23,677	10.956	4,714	0.001	8,237,240
Baseline: Moderate OSA (AHI = 15)					
No Treatment	11,607	9.540	-reference-		
MAD	18,987	10.448	7,380	0.909	8,122
PAP therapy	19,808	10.355	822	–0.094	Dominated
MMA ± GTA	23,710	10.335	4,723	–0.114	Dominated
Baseline: Severe OSA (AHI = 30)					
No Treatment	8,471	8.927	-reference-		
MAD	*19,094*	*9.386*	*10,624*	*0.459*	*Ext. Dom*
PAP therapy	19,999	10.224	11,528	1.297	8,891
MMA ± GTA	*23,468*	*10.129*	*3,469*	*–0.095*	*Dominated*
Baseline: Severe OSA (AHI = 60)					
No Treatment	8,277	8.911	-reference-		
MAD	*16,265*	*8.885*	*7,988*	*–0.026*	*Dominated*
PAP therapy	*18,533*	*9.106*	*10,255*	*0.194*	*Ext. Dom*
MMA ± GTA	22,832	9.771	14,554	0.860	16,932

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; QALY = quality-adjusted life-year; PAP = positive airway pressure

2. Sensitivity Analysis

There are a number of uncertainties about several of the modelling assumptions. Selected results of the sensitivity analysis are shown in Table 109. The majority of the sensitivity analyses had minimal impact on the base-case ICUR or on the interpretation of the cost-effectiveness results, except in patients with moderate baseline disease severity (AHI = 25). Additional sensitivity analysis that had minimal impact on the model are presented in **Appendix 21** and include the time horizon (if greater than seven years), variation in adherence rates values, lower treatment effect for surgery, surgical relapse, the type of PAP intervention prescribed (i.e., APAP or CPAP), the average lifespan of devices and higher CT costs.

Selected parameters to which the model was sensitive and their results are presented here:

> *Discount rate:* The reference case assumed a discount rate of 5% as per existing Canadian guidelines.[132] With a lowered discount rate, surgery became a more attractive strategy for patients with moderate-to-severe OSA. This trend can be explained because of the fact that the MMA with or without GTA strategy is associated with high upfront treatment costs relating to the one-time surgical procedure, whereas the treatment cost of non-surgical strategies accumulates in the model over time. As such, in circumstances of no discounting, the cost difference between the non-surgical and surgical strategies reduced as future costs were weighed equivalent to present costs. The CEAC suggested that the probability in which MMA with or

without GTA would be the most likely cost-effective strategy increases as the discount rates decreased. From a willingness-to-pay threshold of $50,000/QALY, MMA with or without GTA was the most likely cost-effective intervention for patients with baseline AHI values greater or equal to 22 when discounting was set to 0 (figure not shown).

AHI Estimates from NMA: The clinical review identified one NMA of non-surgical interventions for OSA that reported on the outcome of AHI.[161] A sensitivity analysis was conducted using the treatment effect estimates reported in that study and incorporating it into the model. Specifically, this study reported an AHI reduction of –25.27 (95% CI, –28.52 to –22.03) and –15.2 (95% CI, –19.5 to –10.91) for PAP therapy and MAD, respectively. Using this NMA assumes that the reduction in AHI by treatment would be consistent across disease severities. In particular, the model was unstable with greater parameter uncertainty toward the higher end of moderate OSA (22 < AHI < 30) as, at a willingness-to-pay threshold of $50,000/QALY, the probability in which any strategy emerged as the most likely cost-effective did not exceed 60%. The model conclusion varied from the base case for patients with moderate and severe OSA. At a willingness-to-pay threshold of $50,000/QALY, the following interventions emerged as the most likely cost-effective: MAD (15 ≤ AHI < 25); CPAP (25 ≤ AHI < 27); MAD (27 ≤ AHI < 31); MMA with or without GTA (AHI ≥ 31) (figure not shown). As noted, caution is required with respect to these cut-offs, given that: i) the cut-off emerges from the model structure with natural history modelled categorically; ii) the competing low probabilities associated with each strategy are in the moderate severity range.

Rate of Discontinuation: There was uncertainty about the long-term rates of treatment discontinuation as the majority of the longitudinal studies had a follow-up period of four to five years. The base case was based on the last-outcome-carried-forward approach given that the patient perspectives and experience review reported that the first six months were the most critical in determining whether patients continued on their treatment. However, when complete discontinuation was assumed after the last observed period, the model was found to overall favour surgery, given that the effects of non-surgical treatment terminated after the last follow-up period. This was found to have an impact on moderate-to-severe OSA, as the ICUR for MMA with or without GTA changed to $41,798 and $19,103/QALY in patients with a baseline AHI of 15 and 30, respectively. The CEAC suggests that, at a willingness-to-pay threshold of $50,000/QALY, MMA with or without GTA was the most likely cost-effective strategy for all patients with moderate-to-severe OSA (i.e., baseline AHI ≥ 15) (figure not shown).

In addition, there was uncertainty regarding the rates of discontinuation, given that the proportion of patients with mild-to-moderate OSA who discontinued after the first year of non-surgical treatment has been reported to range from 88%[167] to 18%.[168] The model's findings remained mostly robust at the upper and lower bounds of the 95% CI for the discontinuation rates. The sole exception that was observed was under the analysis based on the lower discontinuation rate for moderate OSA in which the cost-effectiveness of treatment was sensitive (i.e., first-year discontinuation rates for non-surgical treatment = 88%; second-year discontinuation rates = 100%). The ICUR of MMA with or without GTA reduced to $17,758/QALY for patients with baseline AHI value of 15 and, similarly, surgery emerged as the most likely cost-effective strategy in patients with moderate-to-severe OSA (figure not shown).

Refusal to fill PAP therapy prescription: The base case assumed 10% of patients would not fill their prescription for a PAP device and their disease progression would be modelled similarly to those who had discontinued treatment (e.g., cost of PAP therapy is not applied to this proportion of patients who refuse to fill their prescription).[130] The model was found to be robust to this structural assumption when it was removed (i.e., no patient would refuse filling their PAP prescription; and, rather, all patients would fill their device prescription). In varying the value of this parameter across its reported range (4.5% to 32.4%), the higher refusal rate for PAP therapy was found to affect the patient subgroup with severe OSA. The expected QALYs associated with PAP therapy decreased and, although its ICUR remained mostly unchanged at $7,537/QALY for patients with baseline AHI value of 30, the sequential ICUR for surgery became more favourable at $34,271/QALY given the larger QALY difference between these two strategies. Consequently,

at a willingness-to-pay threshold of $50,000/QALY, MMA with or without GTA was the most cost-effective strategy for patients with a baseline AHI greater or equal to 26.

Adherence rate: Modelling adherence is a structural component of the model. In removing this aspect from the model (i.e., by assuming all patients would be perfectly adherent to their non-surgical treatment), the model was found to be sensitive specifically to the subgroup of patients with severe OSA. In particular, this structural assumption was found to affect the cut-off in which PAP therapy was no longer considered the most likely cost-effective intervention as it shifted from the base case reported AHI value of 33 to an AHI value of 48 (figure not shown).

Relationship between adherence and treatment effect: Given the assumption made regarding the treatment response of partially adherent patients (i.e, partially adherent patients would experience half the treatment effects), two extreme scenarios were tested: i) partially adherent patients would have the same treatment effect as perfectly adherent patients and ii) partially adherent patient would have no treatment response (i.e., event risks would return to values similar to those who have discontinued treatment). The model was sensitive to both assumptions.

Under the first assumption whereby partially adherent patients would have complete treatment benefit (i.e., similar to those fully adherent to treatment), the findings differed from the base case in that PAP therapy emerged as the most likely cost-effective intervention at the higher end of moderate OSA. As such, at a willingness-to-pay of $50,000/QALY, PAP therapy was the most likely cost-effective strategy for patients with a baseline AHI value between 26 and 47.

Under the second assumption, whereby partially adherent patients would have no treatment benefit, PAP therapy no longer appeared cost-effective for severe OSA. Rather, MMA with or without GTA emerged as the most likely cost-effective strategy for patients with a baseline AHI value greater or equal to 26.

Multiplicative approach to utility calculation: For joint health states, the base-case model was based upon a minimum approach to estimate the utility value. An alternative is the multiplicative approach, which places lower weights when multiple comorbidities are present. Specific to this model, it would result in lower utility weights for hypertensive patients that experience a clinical outcome. When the multiplicative approach was instead applied to estimate the value of joint health states, the expected utilities were lowered in all cases but with the greatest reduction observed in the no-treatment strategy compared with the active intervention strategies. Furthermore, as the incidence of developing hypertension was lower in patients undergoing surgery, the ICUR for surgery improved to $13,052, $13,928, and $16,058/QALY for patients with baseline AHI values of 15, 30, and 60, respectively. Across moderate-to-severe OSA, MMA with or without GTA was found to be the most likely cost-effective strategy at a willingness-to-pay threshold of $50,000/QALY (figure not shown).

Treatment-specific utility increment: The model was found to be unstable when treatment-specific utility increments were incorporated into the model for those adherent to non-surgical treatment or those who had undergone a surgical procedure. The CEAC results suggest that the probability in which a particular strategy would be considered the most likely cost-effective at a willingness-to-pay threshold of $50,000/QALY was often less than 50% with multiple strategies competing. It is perhaps important to note that this analysis should be considered exploratory and would be suitable only if there is evidence suggesting differential treatment-specific QoL benefit.

Variation in the reimbursement of PAP-related equipment: The model was found to be sensitive to the replacement schedule for PAP-related equipment and accessories. In applying the Medicare yearly max replacement schedule (i.e., four masks, four tubes, filters, and two headgears),[183] the yearly cost of refills increased from $822 to $2,686. This resulted in a rise in the expected cost of PAP therapy that was higher than a strategy of MMA with or without GTA. The base-case findings differed as, under this analysis, MMA with or without GTA emerged as the most likely cost-effective treatment for patients with moderate-to-severe

OSA, at a willingness-to-pay threshold of $50,000. At a baseline AHI value of 30, the ICUR for MMA with or without GTA was $12,335/QALY and the ICUR for PAP therapy was $101,085/QALY.

Similarly, in some jurisdictions, only the generator unit of the PAP device is reimbursed while the remaining equipment is paid out of pocket by patients.[2] A separate analysis was conducted to explore this scenario where the reimbursed cost of PAP therapy comprised only the generator unit. The expected costs of the PAP strategy reduced across all disease severities. The economic findings were found to be sensitive to the reimbursement price for PAP therapy, as the attractiveness of PAP therapy increased to a greater range of baseline OSA severities. In particular, the main difference compared with the base-case findings was that, at a willingness-to-pay threshold of $50,000/QALY, PAP therapy emerged as the most likely cost-effective strategy in patients with mild (i.e., 5 ≤ AHI < 15) and for a wider AHI range of severe OSA (30 ≤ AHI < 46).

Cost of MAD replacement: The base-case model assumed that the price of subsequent oral appliances replacements would be half its first-time cost, based on clinical experts' opinion. This was considered suitable as many of the diagnostic procedures are not required for replacement devices. However, if the cost of replacement devices was assumed to be the same as its first-time cost, MAD was no longer present on the efficiency frontier in patients with moderate OSA as the expected costs for the MAD strategy increased and, rather, PAP therapy replaced MAD as being the most likely cost-effective intervention for moderate OSA.

Table 109: Overview of Sensitivity Analysis Across Select Baseline Disease Severities (Probability in Which Intervention Is Cost-Effective at a Willingness-to-Pay Threshold of $50,000/QALY)

Sensitivity Analysis	Mild, AHI = 5 ICUR ($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
Base case	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 175,543 (0) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,058 (0.03) 9,276 (0.93) Dominated (0.05)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,420 (0.79) Dominated (0.03) Dominated (0.17)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 17,125 (0.99)
Discount rate, 0%	No Treatment MMA ± GTA PAP therapy MAD	-ref- (0.90) 110,878 (0.10) Dominated (0.00) Dominated (0.00)	No Treatment MMA ± GTA PAP therapy MAD	-ref- (0) Ext. Dom (0.27) Dominated (0.00) 7,276 (0.73)	No Treatment MMA ± GTA PAP therapy MAD	-ref- (0) 6,584 (0.47) 33,117 (0.50) Dominated (0.03)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.00) Dominated (0) Ext. Dom (0.00) 8,585 (1.00)
Discount rate, 3%	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 154,525 (0) 4,316,789 (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) Ext. Dom (0.02) 7,872 (0.89) Dominated (0.10)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,179 (0.70) Dominated (0.03) Dominated (0.26)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.00) Dominated (0) Ext. Dom (0.00) 13,197 (1.00)
AHI estimates from NMA	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Dominated (0) 172,025 (0.00) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,954 (0.03) 9,712 (0.93) Dominated (0.04)	No Treatment **PAP therapy** **MAD** MMA ± GTA	-ref- (0) **9,535 (0.13)** **Dominated (0.51)** 28,630 (0.36)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.01) Dominated (0.00) Dominated (0) 17,095 (0.99)
Complete Discontinuation after last observed period	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) 167,265 (0.00) 232,813 (0) 609,737 (0)	No Treatment PAP therapy **MAD** **MMA ± GTA**	-ref- (0.00) 8,001 (0.04) **14,402 (0.40)** **41,798 (0.56)**	No Treatment **PAP therapy** MAD **MMA ± GTA**	-ref- (0) **7,582 (0.08)** Dominated (0.00) **19,103 (0.92)**	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.01) Ext. Dom (0) Dominated (0) 16,899 (0.99)
Discontinuation for mild-to-moderate OSA, Izci et al.[168] reported rates (higher values)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) 188,918 (0.00) Ext. Dom (0) 312,789 (0.00)	No Treatment PAP therapy **MAD** **MMA ± GTA**	-ref- (0.00) 8,645 (0.03) **Ext. Dom* (0.01)** **17,758 (0.96)**	Not impacted			
Discontinuation for mild-to-moderate OSA, Walker et al.[167] (lower values)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 168,939 (0.00) Dominated (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) Ext. Dom (0.02) 7,849 (0.98) Dominated (0.00)	Not impacted			
Refusal to fill CPAP prescription higher, 32.4%	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 175,372 (0.00) 23,179,015 (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,026 (0.00) 8,421 (0.95) Dominated (0.05)	No Treatment **PAP therapy** MAD **MMA ± GTA**	-ref- (0) **7,537 (0.36)** Dominated (0.04) **34,271 (0.59)**	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.01) Ext. Dom (0.00) Dominated (0) 17,154 (0.99)

Table 109: Overview of Sensitivity Analysis Across Select Baseline Disease Severities (Probability in Which Intervention Is Cost-Effective at a Willingness-to-Pay Threshold of $50,000/QALY)

Sensitivity Analysis	Mild, AHI = 5 ICUR ($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
Refusal to fill CPAP prescription lower, 4.5%	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 175,107 (0) 16,399,477 (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,104 (0.19) 11,130 (0.76) Dominated (0.04)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,461 (0.86) Dominated (0.02) Dominated (0.12)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.02) Dominated (0) Ext. Dom (0.00) 17,108 (0.98)
No refusal to fill CPAP prescription	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 174,672 (0) 71,573,702 (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,071 (0.57) 63,566 (0.40) Dominated (0.03)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0) Ext. Dom (0.01) 7,516 (0.90) Dominated (0.09)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 17,092 (0.99)
Perfect adherence, for all treatment strategies	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) 155,365 (0.00) 559,444 (0) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 7,788 (0.06) 11,904 (0.90) Dominated (0.04)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 6,890 (0.92) Dominated (0.04) Dominated (0.04)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.01) 17,313 (0.97)
Treatment response of partially adherent patients equals treatment response of those who have discontinued	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1) Ext. Dom (0) 192,216 (0.00) 1,182,055 (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) Ext. Dom (0) 8,979 (0.84) Dominated (0.16)	No Treatment **PAP therapy** MAD **MMA ± GTA**	-ref- (0) **10,166 (0.14)** Dominated (0.03) **18,118 (0.83)**	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Dominated (0.00) 16,919 (0.99)
Treatment response of partially adherent patients equals treatment response of perfectly adherent patients	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 141,785 (0.00) Dominated (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,775 (0.03) 10,899 (0.93) Dominated (0.03)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 6,896 (0.90) Dominated (0.05) Dominated (0.05)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.01) 17,135 (0.98)
Utility calculation for joint health states, multiplicative approach	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) 157,982 (0.00) 126,360 (0.00) 3,322,371 (0.00)	No Treatment PAP therapy **MAD** **MMA ± GTA**	-ref- (0.00) Ext. Dom (0.01) **Ext. Dom (0.04)** **13,052 (0.95)**	No Treatment **PAP therapy** MAD **MMA ± GTA**	-ref- (0) **10,374 (0.06)** Dominated (0.00) **13,928 (0.94)**	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 16,078 (0.99)
Treatment-specific utility increments	**No Treatment** PAP therapy	**-ref- (0.09)** 21,659 (0.35)	No Treatment **PAP therapy** **MAD**	-ref- (0) **6,024 (0.34)** **Dominated**	No Treatment PAP therapy MAD	-ref- (0) 6,057 (0.57) Dominated (0.03)	No Treatment MAD PAP therapy	-ref- (0.00) Ext. Dom (0.03) Ext. Dom (0.09)

Table 109: Overview of Sensitivity Analysis Across Select Baseline Disease Severities (Probability in Which Intervention Is Cost-Effective at a Willingness-to-Pay Threshold of $50,000/QALY)

Sensitivity Analysis	Mild, AHI = 5 ICUR ($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
	MAD **MMA ± GTA**	Dominated (0.15) **34,873 (0.41)**	**MMA ± GTA**	**(0.29)** **44,443 (0.38)**	MMA ± GTA	221,712 (0.40)	MMA ± GTA	12,304 (0.88)
Alternative refill strategy for PAP therapy (yearly cost = $2,686)	No Treatment MAD MMA ± GTA PAP therapy	-ref- (1.00) 175,881 (0) 45,391,043 (0.00) Dominated (0)	No Treatment MAD MMA ± GTA PAP therapy	-ref- (0) 8,202 (0.96) Dominated (0.04) Dominated (0)	No Treatment MAD **MMA ± GTA** **PAP therapy**	-ref- (0.00) Ext. Dom (0.04) **12,335 (0.64)** **101,085 (0.32)**	No Treatment MAD MMA ± GTA PAP therapy	-ref- (0.02) Dominated (0) 17,101 (0.98) Dominated (0)
Only PAP generator is reimbursed	**No treatment** **PAP therapy** MAD MMA ± GTA	**-ref- (0.19)** **20,102 (0.81)** 1,176,949 (0) 4,456,111 (0.00)	**No treatment** **PAP therapy** MAD MMA ± GTA	**-ref- (0)** **832 (0.82)** 71,754 (0.16) Dominated (0.02)	No treatment PAP therapy MAD MMA ± GTA	-ref- (0) 2,207 (0.92) Dominated (0.01) Dominated (0.07)	No treatment PAP therapy MAD MMA ± GTA	-ref- (0.01) 10,212 (0.02) Dominated (0) 18,963 (0.97)
Cost of replacement MAD same as the first-time cost	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) 181,215 (0.00) Ext. Dom (0) 815,876 (0.00)	No Treatment **PAP therapy** **MAD** MMA ± GTA	-ref- (0.00) **8,090 (0.55)** **56,830 (0.31)** Dominated (0.14)	No Treatment PAP therapy MMA ± GTA MAD	-ref- (0) 7,498 (0.81) Dominated (0.17) Dominated (0.01)	No treatment PAP therapy MAD MMA ± GTA	-ref- (0.01) Ext. Dom (0.00) Dominated (0) 16,994 (0.99)

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; QALY = quality-adjusted life-year; PAP = positive airway pressure.
Note: Bolded results represent those that deviate significantly from the base-case in terms of interpretation if assuming a cost-effectiveness threshold of $50,000/QALY.

3. Subgroup Analysis

The results of the subgroup analysis are presented in Table 110 with a detailed explanation found below. It is important to note that the clinical review did not identify any differences in the effect of treatment on mean AHI and blood pressure reduction by these subgroups. The cost-effectiveness is rather affected by differences in baseline event risks by these subgroups.

Sex: The clinical review did not identify differences in treatment estimates by sex. Differences exist between males and females given that the baseline event risks are sex-specific. Despite these differences, the cost-effectiveness results remained consistent between sexes. The overall economic findings remained largely unchanged, although the ICUR for MMA with or without GTA was found to be generally lower in the female subgroup, as their longer longevity resulted in greater clinical benefits accrued that surgery, a permanent treatment, offered to their condition. At a willingness-to-pay threshold of $50,000/QALY, the set of interventions most likely to be cost-effective according to increasing levels of disease severity was the same as the base case.

Age: To determine whether the cost-effectiveness results varied according to age, two subgroups were explored: a starting age of 30 and 70 years. Similarly, age had an impact on the baseline rate of clinical events, as patients have lower incidence at an earlier age but the lifetime risks are higher. With a younger age, surgery became a more attractive intervention given the permanence of the effects of surgery and the lack of concern relating to discontinuation and adherence. Regardless, the overall cost-effectiveness findings remained robust regardless of the age cohort.

Smokers: In the base case, it was assumed that all patients were non-smokers. In contrast, if all patients were current smokers, this would affect the risks of CV events predicted by the Framingham risk equations. It was observed that the model results remained robust even when modelling a cohort of patients who were current smokers.

Diabetes: Likewise, another parameter that is predefined in the Framingham risk equation is patients' diabetes status. In the base case, it was assumed that all patients did not have diabetes and a scenario analysis was conducted in which the risk equations were revised to reflect patients with diabetes. Although this would increase the overall baseline risk of CV events, the model results were found to remain robust, as the set of treatments most likely to be cost-effective across different OSA severities remained the same at a willingness-to-pay threshold of $50,000/QALY.

Hypertensive: In the base case, the proportion of OSA patients with hypertension was defined according to general Canadian prevalence rates (male: 33%; female: 33.6%).[145] In the model, those who were hypertensive would incur higher costs, arising from the need for additional medications. In addition, hypertension increases the risk of CVEs and their associated costs and QoL impact. A scenario was tested in which all patients had hypertension at baseline. The model's results remained robust with no changes to the set of treatments that would most likely be considered cost-effective across different OSA severities at a willingness-to-pay threshold of $50,000/QALY.

Table 110: Incremental Cost-Utility Results of Subgroups

		Mild, AHI = 5 ICUR($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
Sex	Male	No Treatment PAP therapy MAD MMA ± GTA	-ref- Ext. Dom 162,076 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 8,061 10,005 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 7,323 Dominated Dominated	No Treatment MAD PAP therapy MMA ± GTA	-ref- Dominated Ext. Dom 7,845
	Female	No Treatment PAP therapy MAD MMA ± GTA	-ref- Ext. Dom Ext. Dom 191,921	No Treatment PAP therapy MAD MMA ± GTA	-ref- 8,049 8,703 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 7,769 Dominated Dominated	No Treatment MAD PAP therapy MMA ± GTA	-ref- Dominated Ext. Dom 16,558
Age (years)	30	No Treatment PAP therapy MAD MMA ± GTA	-ref- 97,568 Dominated 86,737	No Treatment PAP therapy MAD MMA ± GTA	-ref- Ext. Dom 6,768 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 7,078 Dominated Dominated	No Treatment MAD PAP therapy MMA ± GTA	-ref- Dominated Ext. Dom 14,694
	70	No Treatment PAP therapy MAD MMA ± GTA	-ref- Ext. Dom 259,820 406,612	No Treatment PAP therapy MAD MMA ± GTA	-ref- 8,525 14,405 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 6,972 Dominated Dominated	No Treatment MAD PAP therapy MMA ± GTA	-ref- Dominated Ext. Dom 18,492
Smokers		No Treatment PAP therapy MAD MMA ± GTA	-ref- Ext. Dom 149,475 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 8,486 10,176 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 8,143 Dominated Dominated	No Treatment MAD PAP therapy MMA ± GTA	-ref- Dominated Ext. Dom 22,358
Diabetic		No Treatment PAP therapy MAD MMA ± GTA	-ref- Ext. Dom 151,484 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 8,393 9,776 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 8,226 Dominated Dominated	No Treatment MAD PAP therapy MMA ± GTA	-ref- Dominated Ext. Dom 24,650
Hypertensives		No Treatment PAP therapy MAD MMA ± GTA	-ref- Ext. Dom 275,075 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 10,330 10,847 Dominated	No Treatment PAP therapy MAD MMA ± GTA	-ref- 9,947 Dominated Dominated	No Treatment MAD PAP therapy MMA ± GTA	-ref- Dominated Ext. Dom 20,884

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; ICUR = incremental cost-utility ratio; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; QALY = quality-adjusted life-year; PAP = positive airway pressure.

4. Scenario Analyses

Excluding MVA: The reference case assumed all patients were drivers and, thus, would be at risk of an MVA. In the situation where no patients drive, this would remove the impact of OSA on MVAs. The model was found to be robust to this scenario as the results followed a similar pattern to the base case, with the intervention most likely to be cost-effective a function of baseline disease severity. The AHI cut-off thresholds in which an intervention that was considered most likely cost-effective switched to another remained consistent. Across a willingness-to-pay threshold of $50,000/QALY, the set of strategies most likely to be cost-effective were [AHI < 15] no treatment; [15 ≤ AHI < 26] MAD; [26 ≤ AHI < 30] MMA with or without GTA; [30 ≤ AHI < 33] PAP therapy and [AHI ≥ 32] surgery.

Table 111: Incremental Cost-Utility Results Under the Assumption That Patients Do Not Drive

	Mild, AHI = 5 ICUR ($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
No Drivers	No Treatment	-ref-	No Treatment	-ref-	No Treatment	-ref-	No Treatment	-ref-
	PAP therapy	344,932	PAP therapy	8,006	PAP therapy	7,416	MAD	Ext. Dom
	MAD	555,222	MAD	10,042	MAD	Dominated	PAP therapy	Ext. Dom
	MMA ± GTA	Dominated	MMA ± GTA	Dominated	MMA ± GTA	Dominated	MMA ± GTA	16,631

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; ICUR = incremental cost-utility ratio; MAD = mandibular advancement device; MMA = maxillomandibular advancement; PAP = positive airway pressure; QALY = quality-adjusted life-year.

Overweight or obese patients: As noted, weight loss is a suitable intervention in patients who are overweight or obese. A scenario analysis that compared the base-case strategies to weight loss was conducted. Using treatment effect estimates from studies that recruited overweight or obese patients,[5,63,76] the model findings were found to differ from the base case mainly with respect to mild OSA. For patients with a baseline AHI value of 5 to 15, weight loss was the most likely cost-effective strategy at a willingness-to-pay threshold of $50,000/QALY with an ICUR between $19,058/QALY and $727/QALY (Table 112).

Table 112: Probabilistic Results in Overweight or Obese Patients Suitable for Weight-Loss Interventions

Intervention	Expected Costs, $	Expected QALYs	Incremental Cost, $	Incremental QALYs	ICUR, sequential ($/QALY)
Baseline: Mild OSA (AHI = 5)					
No treatment	11,625	10.910	-reference-		
Weight loss	12,222	10.942	597	0.031	19,058
PAP therapy	*18,132*	*10.946*	*5,910*	*0.004*	*Ext. Dom*
MAD	18,988	10.952	6,766	0.010	647,830
MMA ± GTA	23,659	10.953	4,671	0.001	8,707,585
Baseline: Moderate OSA (AHI = 15)					
No treatment	11,749	9.550	-reference-		
Weight loss	12,394	10.437	645	0.887	727
PAP therapy	*18,261*	*10.358*	*5,867*	*-0.080*	*Dominated*
MAD	19,128	10.450	6,734	0.013	524,649
MMA ± GTA	*23,881*	*10.338*	*4,753*	*-0.113*	*Dominated*

AHI = Apnea–Hypopnea Index; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; ICUR = incremental cost-utility ratio; MAD = mandibular advancement device; MMA = maxillomandibular advancement; QALY = quality-adjusted life-year; PAP = positive airway pressure.

5. Exploratory Analysis

Given that no information on the effects of EPAP or positional therapy on blood pressure were found in the clinical review, an exploratory analysis was conducted to evaluate the potential cost-effectiveness of these interventions while making assumptions on its potential treatment effect with respect to blood pressure reduction. Two different assumptions were explored, the more conservative being that blood pressure reduction would be similar to that which was observed for MAD (mean change in SBP = 2.1), and the less conservative assuming that the effectiveness of EPAP and positional therapy on blood pressure would be the same as PAP therapy (mean change in SBP = 3.5).

Regardless of which assumption was taken to approximate treatment effect on blood pressure, the model results remained robust, as the set of interventions most likely to be cost-effective at a willingness-to-pay threshold of $50,000/QALY remained the same as the base-case scenario when EPAP or positional therapy were included in the analysis (Table 113). The overall cost-effectiveness conclusions therefore remained the same.

Table 113: Probabilistic Exploratory Analysis to Evaluate the Potential Cost-Effectiveness of EPAP and Positional Therapy

Scenario		Mild, AHI = 10 ICUR ($/QALY)		Moderate, AHI = 25 ICUR ($/QALY)		Severe, AHI = 40 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
EPAP	SBP ~ MAD	No Treatment PAP therapy EPAP MAD MMA ± GTA	-ref- Ext. Dom Ext. Dom 175,281 15,206,081	No Treatment PAP therapy EPAP MAD MMA ± GTA	-ref- Ext. Dom 7,894 44,385 Dominated	No Treatment PAP therapy MAD EPAP MMA ± GTA	-ref- 7,410 Dominated Dominated Dominated	No Treatment EPAP MAD PAP therapy MMA ± GTA	-ref- Dominated Dominated Ext. Dom 17,033
	SBP ~ PAP	No Treatment PAP therapy EPAP MAD MMA ± GTA	-ref- Ext. Dom Ext. Dom 118,104 $1.3x10^8$	No Treatment PAP therapy EPAP MAD MMA ± GTA	-ref- Ext. Dom 7,854 80,301 Dominated	No Treatment PAP therapy MAD EPAP MMA ± GTA	-ref- 7,480 Dominated Dominated Dominated	No Treatment ePAP MAD PAP therapy MMA ± GTA	-ref- Dominated Dominated Ext. Dom 17,109
Positional Therapy	SBP ~ MAD	No Treatment Pos therapy PAP therapy MAD MMA ± GTA	-ref- Dominated Ext. Dom 175,933 79,958,614	No Treatment Pos therapy PAP therapy MAD MMA ± GTA	-ref- 2,664 Ext. Dom 14,462 Dominated	No Treatment Pos therapy PAP therapy MAD MMA ± GTA	-ref- 6,010 8,356 Dominated Dominated	No Treatment Pos therapy MAD PAP therapy MMA ± GTA	-ref- Ext. Dom Dominated Ext. Dom 17,110
	SBP ~ PAP	No Treatment Pos therapy PAP therapy MAD MMA ± GTA	-ref- Dominated Ext. Dom 176,569 Dominated	No Treatment Pos therapy PAP therapy MAD MMA ± GTA	-ref- 2,500 Ext. Dom 14,915 Dominated	No Treatment Pos therapy PAP therapy MAD MMA ± GTA	-ref- 5,917 8,520 Dominated Dominated	No Treatment Pos therapy MAD PAP therapy MMA ± GTA	-ref- Ext. Dom Dominated Ext. Dom 17,036

AHI = Apnea–Hypopnea Index; CEAC = cost-effectiveness acceptability curve; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; ICUR = incremental cost-utility ratio; MAD = mandibular advancement device; MMA = maxilomandibular advancement; QALY = quality-adjusted life-year; PAP = positive airway pressure; SBP = systolic blood pressure.

Summary of Economic Evaluation Results

The economic evaluation presented here is, to our knowledge, the first cost-effectiveness study published to compare all relevant treatment options in Canada and to reflect the implications for long-term costs and QALYs by stratifying baseline OSA severity. We modelled each treatment strategy individually and did not look into a treatment sequence.

The base-case analysis suggested that the cost-effectiveness of treatments for OSA is dependent on the patient's disease severity, as measured by AHI. For mild OSA, the model suggested that no treatment was the most likely cost-effective strategy up to a willingness-to-pay of $175,543/QALY, as the treatments were either extendedly dominated or were associated with a high ICUR value. For moderate OSA, MAD was the most likely cost-effective strategy at the lower range (15 ≤ AHI ≤ 25), and switched to MMA with or without GTA if the baseline AHI value was greater than 25. Likewise, for severe OSA, PAP-based therapy emerged as the most likely cost-effective strategy at the lower rate AHI of 32 and switched to MMA with or without GTA with subsequently higher AHI values (Figure 3). It is important to note that the thresholds must be interpreted with caution, as they are an artifact of the model structure: treatment effect was modelled as a continuous outcome, while natural history of OSA was modelled categorically based on the available literature.

In the economic model, gains in QALYs are achieved with treatment because of their impact in reducing AHI and blood pressure, which had subsequent morbidity and mortality impacts. The absolute gains in QALYs followed a unimodal distribution and were a function of disease severity. Those with mild or extremely severe OSA (AHI~60) had lower gains in QALYs, whereas the largest gains were observed in patients whose baseline severity reduced from severe (AHI ≥ 30) or moderate (15 < AHI < 30) to mild-to-moderate OSA (AHI < 30) or mild OSA (AHI < 15), respectively. Incremental costs were largely driven by the costs of treatment and long-term maintenance costs, given the longer life expectancies of patients on treatment.

Extensive sensitivity and scenario analyses were conducted to test the assumptions and parameters informing the economic model and to explore the heterogeneity in the reimbursement structures across Canadian jurisdictions. In most circumstances, the model conclusions remained robust. It is interesting to note that, when oral appliances were assumed to be out-of-pocket expenses, this strategy appeared on the efficiency frontier for the lower condition severity (i.e., mild OSA), as the expected cost for MAD was less than the no-treatment strategy. At a willingness-to-pay threshold of $50,000/QALY, MAD would be considered the most likely cost-effective intervention from mild-to-moderate OSA as the treatment costs are shifted to patients. Sensitivity analyses further highlighted that the model was most sensitive to parameters relating to discontinuation and adherence, especially in the context of PAP therapy. The findings presented here are aligned to a poster that was presented at the Society for Medical Decision Making and that compared CPAP, oral appliance, and surgery (i.e., uvulopalatopharyngoplasty and MMA) in Canadian patients with OSA. The authors similarly noted that the cost-effectiveness of treatment for OSA is critically dependent on the adherence with CPAP.[195] Their model was further sensitive to the effectiveness of oral appliance treatment and the cost of uvulopalatopharyngoplasty surgery, although direct comparison of their model to ours is difficult, given the limited reporting in their current presentation format. Our model was further sensitive to the reimbursement of PAP-related equipment and/or accessories and the cost of replacements for MAD. Although subgroup analyses were conducted, the model's findings were found to not differ by subgroup. This may be partly explained by the fact that differences between subgroups were driven solely by their differences in baseline event risks and not by differences in treatment outcomes.

Patient Perspectives and Experiences Review

This section addressed Research Question 3: What are the experiences and perspectives of adult patients, their family members, and their caregivers regarding PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA?

Methods

A systematic review and thematic synthesis of the literature relevant to the research question on patient experiences and perspectives was conducted. The protocol was written a priori and followed throughout the review process. The methods reflect the intention to synthesize results of published studies to address the research question and policy question and yield results that may be useful to decision-makers.

Literature Search Strategy

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[41]

Patient experiences information was identified by searching the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; Embase (1974–) via Ovid; PsycINFO (1967–) via Ovid; CINAHL (1981–) via EBSCO; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH terms, and keywords. The main search concepts were sleep apnea, sleep-disordered breathing, and terms related to patient experiences, perspectives, beliefs, and values. No methodological filters were applied to limit retrieval by study design. Retrieval was limited to documents published since January 1, 2006. Results were limited to English- or French-language publications. Conference abstracts were excluded from the search results. The detailed strategy can be found in **Appendix 1**.

The search was completed on March 3, 2016. Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the *Grey Matters* checklist[42] (https://www.cadth.ca/grey-matters), which includes the websites of clinical trial registries, regulatory agencies, Health Technology Assessment agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials.

Selection Criteria

Eligible reports were those published in English or French of any design that explored or assessed perspectives of adults being treated for OSA, or waiting for treatment for OSA, as well as the perspectives of their partners or other non-clinical caregivers. To be eligible, studies had to explore or assess participants' own perspectives directly. Studies that provided information collected only indirectly — e.g., clinician perspective — were excluded. The following types of publications were excluded: theses and dissertations, data presented in abstract form only, book chapters, editorials, and letters to the editor. Selection criteria are presented in Table 114, characterized following the PICOS elements.

Table 114: Eligibility Criteria

Population	• Adults (i.e., aged ≥ 18 years),[a] diagnosed with any severity of OSA (either treatment-naive or previously treated), as measured objectively by PSG or portable monitoring (Type I to Type IV sleep monitors)[b] • Partners, family members, and non-clinical caregivers of adults with OSA

Intervention	• PAP devices, as follows:
	  ○ APAP
	  ○ BiPAP
	  ○ CPAP
	• EPAP
	• Oral appliances, as follows:
	  ○ MAD[c]
	  ○ Tongue-retaining device
	• Surgical interventions, as follows:[d]
	  ○ GTA
	  ○ MMA
	• Lifestyle modifications,[e] as follows:
	  ○ Exercise program
	  ○ Diet or weight-loss program
	  ○ Positional therapy
	• Combination therapy (i.e., combinations of 2 or more interventions in scope)
	• Inactive treatments (e.g., pre-treatment, supportive care)
	• Waiting list
	• No treatment

Comparator	• Not applicable
Outcomes	• Perspectives and experiences regarding treatments, including such issues as perspectives and beliefs about interventions; experiences waiting for treatment, with shared decision-making regarding treatment; experiences complying or not complying with treatment; reasons for complying and not complying with treatment; and other issues of importance to patients that emerge in the analysis.[f]

Study Design	• Descriptive studies:
	  ○ Qualitative studies
	  ○ Surveys
	  ○ Mixed methods studies
	• SRs of descriptive studies

APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; CPAP = continuous positive airway pressure; EPAP = expiratory positive airway pressure; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; PAP = positive airway pressure; PSG = polysomnography; SR = systematic review.

[a] Studies that included participants aged < 18 years were included if > 80% were adults aged ≥ 18 years or if data for participants aged ≥ 18 years were presented separately.

[b] Studies that did not identify criteria for diagnosing OSA were included. Studies that included non-OSA were included if > 80% were diagnosed with any severity of OSA or if data for participants with OSA were presented separately.

[c] Personalized MADs only were included, and not any over-the-counter, non-personalized devices.

[d] GTA and MMA surgeries are most frequently performed to treat OSA compared with other surgical procedures. In addition, bariatric surgery is out of scope as it is conceived more as a surgical procedure conducted primarily to produce weight loss, but not to treat OSA. [Major Roch Messier, Canadian Armed Forces, Valcartier Regional Dental Specialty Center, Valcartier, QC, expert opinion: 2016 Jun]. Note that the literature search was conducted prior to the decision to exclude other surgical procedures for OSA.

[e] Lifestyle interventions including clinician-directed or -prescribed programs were considered as interventions.

[f] Outcomes of relevance to this research question emerged from the data reported within included study reports. This preliminary list of outcomes is provided to outline issues that were expected to emerge at the outset of this review; however, the final set of outcomes emerged after iterative and careful readings of the data, as reflected in the Results section.

Screening and Selection of Studies

Two reviewers (SG and TR) independently screened the titles and abstracts of all citations retrieved from the literature search, and excluded reports that clearly do not meet the eligibility criteria. The full texts of all potentially relevant reports were ordered for detailed review. Two reviewers (SG and TR) independently reviewed the full-text articles based on the detailed eligibility criteria. Any disagreements among reviewers were resolved through discussion.

Article Sampling

As opposed to quantitative synthesis, which aims for exhaustive sampling, in qualitative and mixed methods synthesis, the principle of saturation drives sampling decisions. In this review, we applied the concept of "conceptual saturation" to developing our sample of included studies. Conceptual saturation refers to the stage when analysis of further evidence provides little in terms of further themes, insights, perspectives, or information.[196] In qualitative syntheses, it is not always necessary to include every eligible study in the analysis, if the results of the synthesis are not substantially changed, or enriched, with the analysis of further study reports that contain the same concept.

To develop our sample of included articles for analysis, based on the list of eligible full-text articles, we used a purposeful sampling strategy that applied the technique of maximum variation until conceptual saturation was reached.[196] The maximum variation sampling strategy helped ensure that a range of articles representing diverse experiences with all relevant interventions for OSA were included. Articles were first sampled to ensure that each OSA intervention was represented. Further sampling was done to ensure a range of experiences, if and when possible, as all experiences were not represented (e.g., limited experiences regarding surgery were found). For example, within subsets of articles for each included OSA intervention, we included studies that described the experiences of diverse patients, caregivers, or family members in varied contexts, by sampling articles based on their description of experiences by factors that, based on the clinical literature, appear to influence treatment experience. We included such factors as participants' sex and age; rural, remote, or urban settings; OSA severity; duration of treatment; prior experience with treatment; access to treatment; and comorbidities. If no literature was found regarding certain experiences (e.g., experiences of female surgical patients), this was noted as a limitation.

All eligible SRs were included and analyzed, and the maximum variation sampling technique was then applied within a subset of articles relevant to each OSA intervention. To assist with sampling decisions, the full text of each eligible primary study was reviewed and emergent concepts (e.g., benefits to self and bed partner, adherence, comfort, information, and access) were extracted along with data to describe the participant population (e.g., age, sex, OSA severity, prior experience with treatment). See "Coding (Stage 1)" for a description of how emergent concepts were identified. Further, at this stage a preliminary assessment of "information richness" was made, guided by initial impressions of study methodology, reporting quality, and relevance to the research question. Each eligible article was then classified as "good," "moderate," or "poor." A good study provided rich data, often collected through interviews or focus groups; detailed information regarding study methods; and represented a diversity of participant perspectives. For example, the study by Henry et al.[197] was considered good as it provided depth and breadth of the patient experience with many supportive quotes. A moderate study lacked details regarding study methods or study participants (e.g., representativeness of the sample population was uncertain) or provided a limited scope of the patient experience (e.g., investigator-driven questionnaire on one aspect of treatment such as comfort). For example, the study by Nolan et al.[198] was considered moderate as it lacked rich data, while the study by Rodgers et al.[199] lacked details about the study participants. A poor study provided thin data; for example, one question to participants regarding their overall satisfaction with their treatment, and limited detail regarding study methods. Typically, poor studies provided only one or two sentences on the patient experience, such as the included study by Goodday et al., which stated, "Eight patients reported a favorable change after MMA surgery. However, all nine patients considered the surgery a worthwhile experience, and eight would recommend the surgery to others." Within intervention categories, studies classified as "good" were analyzed first, followed by studies that were classified as "moderate" and then "poor."

Sampling of articles related to a particular emergent concept, related to each OSA intervention, ceased when conceptual saturation was reached or if there were no more relevant articles for inclusion. When we suspected

saturation had been reached, we reviewed two additional articles to confirm saturation. If saturation was confirmed, no further sampling occurred. If saturation was not confirmed, further articles were sampled and analyzed until reviewers agreed that saturation had been reached.

Data Extraction Strategy

From each eligible article, descriptive data were extracted by one reviewer (either SG or TR) into an a priori developed standardized electronic form (see **Appendix 24**). Descriptive data included such items as first author, article title, study objectives, participant characteristics, and study design.[200] The extracted data were verified by the other reviewer (either SG or TR). Discrepancies were resolved through discussion or referral to a third party if necessary (LW).

Further, result statements from all included (i.e., sampled) articles relevant to the research question were captured for analysis, or coded, using NVivo qualitative data analysis software (QSR International Pty Ltd. Version 11, 2015).[201] (For further detail, refer to the Thematic Analysis section.) Result statements are typically presented within the "results" section of a report, and are characterized as data-driven and integrated findings based in participant experiences. Before being coded, each result statement was assessed to ensure it was differentiated from raw data, methods, external data, and researchers' own conclusions and implications.[202] The latter were not coded. Only results presented within the main report, but not the abstract, were coded. Data from figures were not used unless data points were explicitly labelled.

Quality Assessment Strategy

One reviewer (either SG or TR) independently assessed the quality of each included study using standardized criteria, depending on the study design. The other reviewer (either SG or TR) verified the assessments. Disagreements were resolved by discussion or referral to a third party (LW). Qualitative studies were assessed using criteria outlined in the Critical Appraisal Skills Programme (CASP) checklist (**Appendix 25**).[203] Likewise, survey studies were assessed using standardized criteria commonly applied to assess the validity and reliability of this approach (**Appendix 26**).[204,205] Systematic reviews were assessed using the *JBI Critical Appraisal Checklist for Systematic Reviews and Research Syntheses* (**Appendix 27**).[206]

The results of the quality assessment process are reported narratively and summarized in a table to highlight the strengths and limitations of each study. Quality assessment was not used as a basis for excluding any studies deemed to be of low quality, although by nature of qualitative data analysis, information-rich and higher-quality studies tend to receive more attention in the analysis as they provide more information relevant to the research and policy questions.

Data Analysis Strategy

Descriptive Analysis

A descriptive analysis of study and patient characteristics was conducted, with the goal of characterizing the set of included studies in terms of important study and patient characteristics (e.g., PICOS, sample size). This involved the calculation of frequencies for relevant categories across studies, summarizing study and patient characteristics in tables as presented in **Appendix 32** and **Appendix 33**, respectively, and developing an accompanying narrative summary.

Thematic Analysis

We conducted a thematic analysis comprising three stages: coding, developing descriptive themes, and developing analytic themes. The analysis was conducted using QSR International's NVivo 11 Software.[201]

Coding (Stage 1)

The results section of the sampled studies was coded line by line for meaning and content. Coding began with an a priori "start list" of codes developed based on the research questions and emerging concepts from the one included systematic review;[207] for example, perceived benefits and concerns, adherence, ineligibility, and access. As coding

progressed, other codes not on the start list were added inductively to capture unexpected content. As new codes emerged, all data were recoded to search for further instances of that code. Codes were assigned to results data from all studies regardless of their design in a consistent manner of inductive and iterative coding. Quantitative data were coded in the same manner as the qualitative data, in an approach of qualifying the quantitative data.[208]

Through a staged coding process, two researchers (SG and TR) coded the first five "good," or information-rich, studies from an alphabetical list of all eligible studies. They independently assigned codes to concepts, ideas, and categories to the results reported within each study report. The two researchers (SG and TR) then compared and discussed their code assignments for the selected studies. This discussion allowed us to organize and reflect upon a wide range of interpretations across the body of research and refine the emerging coding template. Following this discussion, another set of three articles were coded independently, with reviewers subsequently meeting to compare and discuss coding assignments, and refine the coding template accordingly. Another three articles were coded until alignment was reached. After coding was found to align, it proceeded with one researcher as the primary coder, and the other researcher verifying the coding until saturation was reached. At this point, the text assigned to each code was read to assess consistency in interpretation and application, and to determine whether any additional levels of coding were needed.

Descriptive Themes (Stage 2)

In the second stage of the analysis, the codes developed in the prior stage were organized into related areas to construct "descriptive" themes. In this process, two reviewers (SG and TR) independently assessed similarities and differences between codes. New codes were created during this process in order to capture the meaning of groups of initial codes.

Reviewers assessed whether emergent themes were transferable across different study contexts. When they were found to be not transferable, they discussed whether the differences were a result of methods or sample characteristics. By seeking out differences in this way, the range of perspectives held by people became apparent, and subgroups were identified; for example, age, sex, or experience with OSA interventions.[202]

Once descriptive themes were identified, a draft summary of the results across the studies organized by each theme was written by one reviewer (SG or TR) and subsequently reviewed by a second reviewer (SG or TR). A group discussion took place to review and discuss the emergent themes. The final version was agreed upon by all review team members[202] and represents a synthesis that remains close to the original results of the included studies, with minimal interpretation.

Analytic Themes (Stage 3)

During the final stage, the "data-driven" descriptive themes from the prior stage were analyzed through the theoretical structure provided by the policy question to develop "theory-driven" analytic themes in response to the policy question. In this stage, two reviewers (SG and TR) used the descriptive themes to independently infer an answer to the question about the optimal use of treatments for OSA. After each reviewer made these inferences independently, the two reviewers reviewed their results. A group discussion including all team members (SG, TR, and LW) was held to discuss the analytic themes in the context of the policy issue. This cyclical process of theme development resulting from group discussions continued until a set of themes emerged that is inclusive of all of the initial descriptive themes and answers the policy question.[202] As in the prior stage, throughout this process, reviewers ensured attention was paid to the transferability of results across different contexts, as a way to determine whether some results might apply only to certain subgroups. Throughout all stages of the analysis, regular meetings between members of the research team took place to discuss emerging results, and analytic ideas. Explicit notes were kept using the memo and annotation features in NVivo to record decisions made regarding coding and theme development, to help demonstrate rigour in the analysis.

Results

A total of 2,400 citations were identified from the initial electronic database, alerts, and search updates. Of those, 2,102 were deemed ineligible and the full text of the remaining 298 citations was retrieved for eligibility screening.

Ninety-three were identified as eligible. Thirty-two studies were ultimately included in the thematic synthesis, following the outlined sampling procedure.

The study selection processes are presented in a PRISMA flow diagram (**Appendix 28**). A list of included studies is provided in **Appendix 29**, a list of the remaining eligible studies is provided in **Appendix 30**, and a list of excluded studies is provided in **Appendix 31**.

Descriptive Analysis

Study Characteristics

Of the 32 included studies, one systematic review[207] was identified, and the remaining 31 included studies were primary studies. Eleven were qualitative descriptions that used interviews as the method of data collection,[209-219] one was a qualitative content analysis of a website,[220] three were grounded theory studies[199,221,222] that also used interviews as the method of data collection, seven were survey studies that used questionnaires to collect data,[89,98,112,223-226] three were randomized controlled trials with questionnaire components,[198,227,228] one was a retrospective chart review,[229] three used a mixed methods approach,[197,230,231] and there was one cross-sectional study[232] and one cohort study,[233] both of which used questionnaires. It should be noted that some of the qualitative description studies used grounded theory techniques, but stopped analysis before a theory was created.

Thirteen papers (40%) were about CPAP.[197,207,210,212,213,216,217,219-221,224,230,231] Three studies were about PAP devices in general,[199,214,229] while one study was on APAP.[198] There were five studies on OAs, all regarding mandibular advancement devices.[223,225-228] There was one study that included participants using CPAP or OA.[209] Regarding surgery for OSA, there were four studies that looked at MMA.[89,98,232,233] For lifestyle modifications, there was one study each on physical activity,[215] diet,[218] and tennis ball technique.[112] Two studies[211,222] with untreated patients were also included.

The sample size across the 31 primary studies ranged from nine participants[214] to 296 participants.[229] The systematic review[207] included 22 papers. Fifteen studies included the perspectives of bed partners,[197,207,209,211,213,216,217,222-226,228,230,232] although in three of these studies,[209,213,230] patients reported on the views of their partners.

Nine countries were represented by the included studies: four studies were from Canada,[209,228,232,233] nine from the United States,[197,199,212,214,216,224,227,229,231] eight from Sweden,[211,213,215,218,219,222,225,230] four from the United Kingdom,[89,220,223,226] two studies from both Australia[112,217] and New Zealand,[207,210] and one study each from France,[98] Ireland[198] and Taiwan.[221] For the systematic review,[207] New Zealand was considered the country of origin because it is the country of the first author; however, studies from the following countries are included: Australia, Canada, China, France, Germany, Italy, Scotland, Sweden, and the United States.

All studies were published between 2006 and 2016. Two studies were published in 2006,[198,223] one study was published in 2007,[211] one study was published in 2008,[220] three studies were published in 2009,[112,226,228] one study was published in 2010,[229] one study was published in 2011,[217] six studies were published in 2012,[213,215,219,222,224,225] six studies were published in 2013,[98,197,209,212,230,231] seven studies were published in 2014,[89,199,207,210,218,221,227] one study was published in 2015,[214] and three studies were published in 2016.[216,232,233]

The characteristics of the included studies are summarized in **Appendix 32**.

Participant Characteristics

Regarding patient characteristics, in 13 studies, the average age of participants was 50 to 59 years.[112,198,199,211,216-219,223,225,226,229,230] A range of ages (but no average) was given in three studies,[207,221,222] and age was not reported in three studies.[213,214,220] In eight studies, the average (or median) age of participants was 40 to 49 years.[89,98,197,212,224,227,228,232] In three studies, the average age of participants was 60 to 69 years.[209,215,231] In one study, the average age of participants was 30 to 39 years.[233] in one study,[210] the average ages of participants varied by ethnicity (i.e., Māori patients averaged 39.3 years, Pacific Peoples averaged 43.5 years, and New Zealand Europeans averaged 58.1 years).

As a whole, the female patient and male caregiver experiences were underrepresented in the studies. In all but three of the studies,[212,213,222] male participants comprised greater than 50% of participants. It may be that the findings do not provide the full range of experiences for these persons. Ethnicity was not reported in most of the studies, but in the seven studies[197,199,210,212,217,224,231] where it was reported, greater than 70% of participants were described as "white," "Caucasian," or "European." One study[216] simply reported that the majority of participants were white, but did not provide exact proportions.

Participants in the included studies had varying degrees of OSA severity. More than half of participants at baseline had moderate OSA in four of the studies.[216,218,223,225] In 11 studies, more than half of patients at baseline had severe OSA.[98,198,209,211-213,221,224,227,230,233] For five studies, OSA severity ranged from mild to severe.[197,207,219,222,226] Of these, AHI ranged from 8 to 135 for one study,[197] and 19 to 72 for another study.[222] Two studies[207,219] reported severity as "moderate-to-severe," and one study reported severity as "mild-to-moderate"[226] with no further detail provided. Ten studies did not report the severity of OSA.[89,112,199,210,214,215,217,228,231,232]

Patients had a range of experience with the OSA interventions (excluding surgery, which was a case of having had or not having surgery, although surgical patients may have tried previous interventions). Participants were experienced (i.e., not treatment-naive) with at least one intervention in 27 studies.[89,98,197-199,207,209,210,212-221,224-226,228-233] Participants were treatment-naive in two studies.[211,227] The views of only non-users (i.e., the views of spouses and not patients) were captured in one study.[222] In two studies,[112,223] it was uncertain whether participants were treatment-naive, or if they were regular users of the studied intervention.

For those who did report on the user's experience with treatment, the length of use varied. Specifically, the duration of treatment or follow-up was reported in 20 studies.[89,98,112,197,198,209,210,212,213,215,219,223-227,229,230,232,233]

- CPAP: two weeks[217] to 10 years[219]
- OA: three weeks[227] to 8.3 years[209]
- Surgery follow-up: four weeks[232] to 21 months[233]
- Positional therapy (tennis ball technique): 2.5 years[112]
- Lifestyle modification: 12 months.[215]

The characteristics of the included study participants are summarized in **Appendix 33**.

Quality Assessment

Overall, the quality of the included studies was moderate. Some studies had more quality concerns than others, yet the body of literature adds the perspectives and experiences of patients and their partners about treatment for OSA. The choice of study design (e.g., survey, qualitative description) and data collection tools (e.g., questionnaire, interview, focus group) greatly influenced the amount of information and range of experiences reported. It also prescribed how each study should be assessed for quality. For this reason, a portion of the summary of the quality assessment is grouped by study design, although some statements can be made for the studies as a collective group.

The maximum variation approach to article sampling for this review aimed to include a range of perspectives relating to the research question; however, the reviewers were limited to the studies identified and eligible based on the inclusion criteria. Thus, while trying to sample studies that presented the views of both males and females about OSA therapy, as a whole, it was determined that female patients and male caregivers were underrepresented in these studies.

Additionally, race was reported for eight studies[197,199,210,212,216,217,224,231] while the remainder did not report on these characteristics. Of those studies that did report on race or ethnicity, the majority of participants were white. As illustrated by these examples, patient demographic information was not well reported by the studies as a whole. As well, CPAP was the most common (40% of papers) intervention studied and fewer papers were available to describe experiences with other OSA interventions.

Qualitative Studies

As a collective, the quality of the qualitative studies was good. All studies clearly reported study objectives and research questions, which were well suited to qualitative inquiry. As well, all of the qualitative studies used some measure to enhance credibility. Many of the studies used verbatim quotes as a means of demonstrating that the findings were rooted in the patient perspective.[197,199,209-213,215-219,222,230] The study by Hu[221] also used quotes, but it was difficult to determine whether these were reported verbatim for each participant, or were summative across participants. Two of the studies also used member checking to further ensure credibility.[210,217] Measures to enhance dependability (e.g., peer review, researcher triangulation, audit trail) were reported by nine studies.[211,213,215,217-219,221,222,230] The study that included Māori participants described methods as being culturally appropriate, including conducting focus groups at appropriate locations and following culturally appropriate formats.[210]

Two of the studies[213,230] explicitly stated that they used maximum variation sampling to ensure that a range of perspectives had been captured. It was uncertain whether the remaining studies used a purposeful sampling strategy. Twelve of the studies reported that they sampled until saturation.[209,211,213-219,221,222,230] It was uncertain in the remaining studies how sample size was determined. Two of the studies[212,214] offered monetary compensation for participation in the study and it may have motivated certain persons to participate. Sampling strategy, typically how eligible patients were identified and recruited, was not well reported for two studies[210,211] and the potential for channelling bias by physician recruitment was identified in two other studies (e.g., physicians may have been inclined to recruit certain patients for the study).[197,215]

Survey Studies

As a group, the survey studies were of moderate quality. A general criticism of survey studies was that based on the study design, survey studies may not capture the full range of patient experiences. For example, one of the studies[231] primed patients to negatively reflect on their experience with CPAP, and questions did not allow any positive experiences to be described. Furthermore, with the exception of the study by Butterfield et al.,[232] the studies regarding MMA[89,98,233] were primarily questionnaires about how patients perceived their appearance after surgery, thereby not allowing participants to describe any other expected or unexpected outcomes. Two of these studies[98,232] used previously validated questionnaires. The questionnaire used by Goodday[233] had face validity (yes or no questions); however, the validity of the questionnaire by Islam[89] is uncertain. This provided a limited perspective on the experience of the MMA patient for the purposes of this review. For two of the other studies, it was uncertain whether the questionnaires used to collect data were sufficiently validated.[223,226]

Another main criticism for some of these studies is that limited demographic information was provided for the participants, and in 12 studies, it is uncertain how representative these patients are of the population from which they were sampled.[89,98,198,223-228,232-234] Sampling strategy was not well reported for nine of the studies.[89,98,198,223-227,232] In addition, a few of the studies[112,231] used postal surveys, and participants without postal addresses or those with low literacy skills may not have been able to complete the questionnaire, lending these studies to selection bias. An a priori sample size calculation was provided by two of the studies.[227,228]

Systematic Review

The systematic review[207] was well done. The authors clearly reported their objectives and justification for their review. An adequate number and choice of databases was used for the literature search; however, a main criticism of these methods was that no repeatable search strategy was reported (although search concepts were presented). The search strategy for this current review identified 10 eligible studies[235-244] that were included in the systematic review by Ward. These 10 studies were not analyzed for the purposes of this review. The stages of synthesis were reported; however, it was uncertain how many researchers took part in data synthesis. It is not clear how coding was approached, and the authors did not use a qualitative software program for the analysis; they used Microsoft Excel. This is not a critical flaw; however, it does pose a limitation in that the researchers would have an added burden of synthesizing information in a platform poorly suited to this type of inquiry. The authors justified the use of the critical appraisal tools used and two researchers took part in this phase, and findings of the critical appraisal were clearly reported.

The quality assessment of the included studies is summarized in **Appendix 34**.

Thematic Analysis

The following sections explore the results of the thematic analysis. Following the initial phases of coding, data were organized into descriptive themes. In the next phase, the descriptive themes were analyzed through consideration of the research and policy questions to identify “analytic themes.” Analytic themes represent the essence of data in direct relation to the research and policy question. For this report, the analytic themes represent the meaning of those experiences and perspectives of OSA patients and their caregivers about interventions that have an impact on their optimal use. Two analytic themes emerged from the data. Figure 4 represents the emergent analytic structure, including analytic themes and their descriptive themes. Table 115 represents the emergent categories, their relationship to the descriptive themes and which ones have results related to each of the categories. In the following section, a descriptive summary of the data in terms of the analytic themes is presented, using results from the descriptive categories as supporting evidence.

Figure 4: Analytic Themes and Related Categories

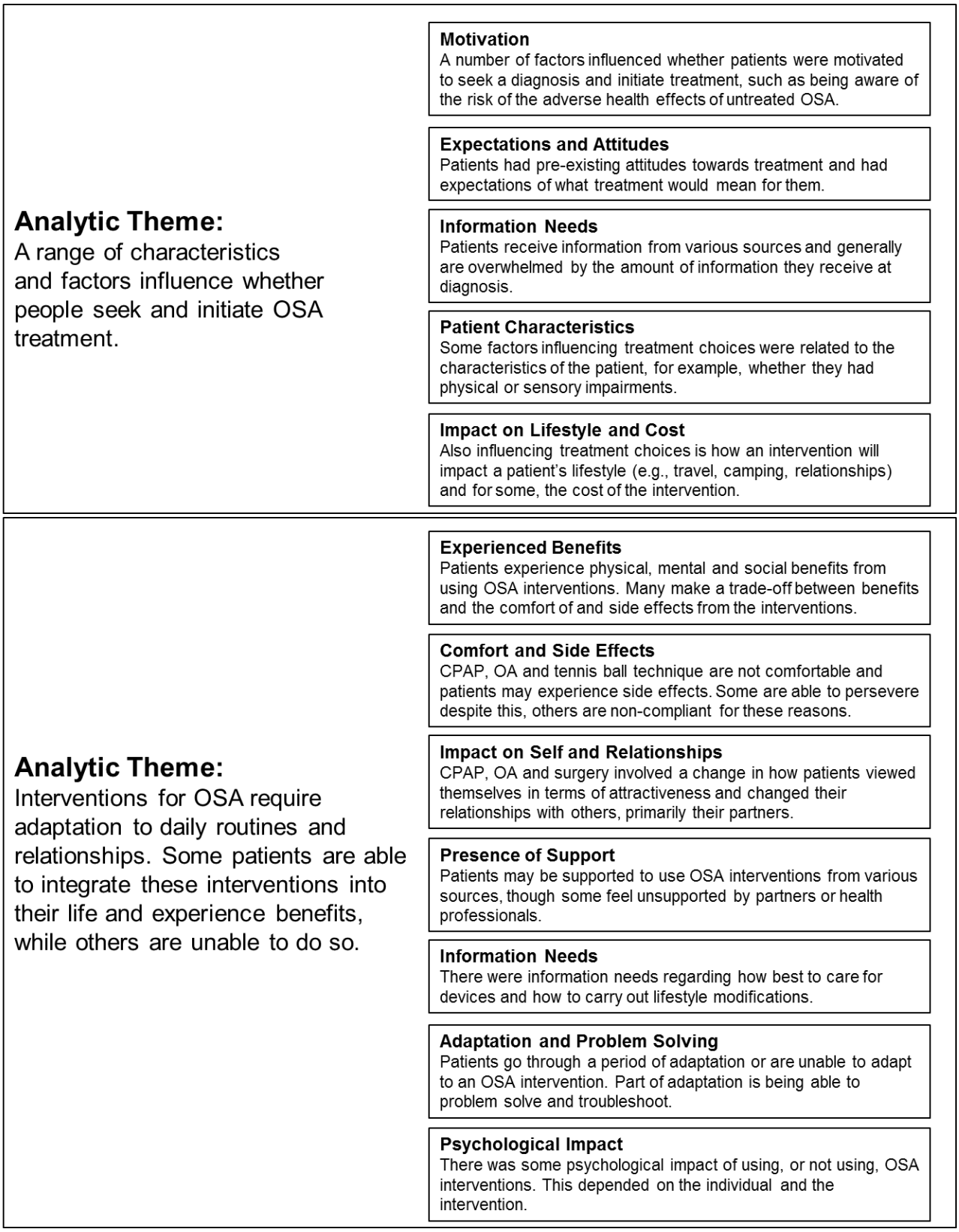


Table 115: Emergent Data Categories, Descriptive Themes, and Analytic Themes

Analytic Themes	Descriptive Themes	Categories	Interventions Included in Category	Exemplary Quotes
A range of characteristics and factors influence whether people seek and initiate OSA treatment.	Motivation	Risk awareness	Pre-treatment	"I've not noticed myself that I'm snoring, but people have told me so. I've not been aware of having so many breathing interruptions. I thought I was close to death!"[230]
		Disease chronicity	Pre-treatment, CPAP	"I felt like it was a double-edged sword. I felt relief that we were finally going to get something done, but sad that I would have to wear this for the rest of my days."[210]
		Fear	Pre-treatment	I'm nervous about having so many apneas and they say it's not supposed to be good for the brain. It frightens me."[222]
		Partner distress	Pre-treatment	[Spouse] "Sometimes I *feel* he's not breathing, so I have to nudge him to wake him up. When it got bad, I was pregnant with our 7th child, and I thought, 'OH MY GOD, he's just going to die on me!'…"[197]
		Sense of self	CPAP, diet	"I stepped on the scale and said no that is not me…"[218]
	Expectations and Attitudes	Pre-existing beliefs about treatment	CPAP	"I think it sounds very demanding to learn to live with a CPAP machine; a lot of demands to cope with. On the other hand, I don't want to take the risk of a stroke, or heart attack, so I have to handle it."[211]
		Anticipated benefits	OA, CPAP, physical activity, untreated, diet	"Because there is the benefit to [the bed partner], at least you're not snoring, so you're not disrupting their sleep. Or you're not stopping breathing for 20 seconds, up to a minute, and they're wondering if you're going to gasp and get going again."[209]
		Doubt of ability to comply with physical activity	Physical activity	NA: no direct participant quotes were provided to support this theme.
		Negative perception of treatment	CPAP, tennis ball technique	"[Referring to OSA] just another way for the medical establishment to make money."[199]

Table 115: Emergent Data Categories, Descriptive Themes, and Analytic Themes

Analytic Themes	Descriptive Themes	Categories	Interventions Included in Category	Exemplary Quotes
	Information Needs	Information Needs	PAP, untreated, CPAP	"I think it was just a lot of information at the time and it kind of went right past me, if you know what I mean. It was not the right time… I didn't take it on board."[210]
	Patient Characteristics	Demographics (disabilities, age, relationship status)	CPAP, untreated, OA	"I have a shoulder I can't really go up with much. That makes it hard for me to … get the straps off and set right to put it on my head…"[214]
	Impact on Lifestyle	Physical environment and travel	CPAP and OA, physical activity	"I have travelled 8 to 10 times internationally each year with my [model] machine for the past 5 years. I had never considered it big and heavy until I saw some more modern CPAP units earlier this year."[220]
		Challenges to lifestyle change	Physical activity, diet, CPAP	"I feel like an alcoholic ... I use the food to lower anxiety, you know."[218]
	Cost	Cost	CPAP and OA, PAP, diet	""There was no guarantee that the extended health would cover [the CPAP]. But I was willing to, because it was more effective."[209]
Interventions for OSA require adaptation to daily routines and relationships. Some patients are able to integrate these interventions into their lives and experience benefits, while others are unable to do so.	Experienced Benefits	Experienced benefits (physical, mental and psychological, social)	CPAP, CPAP, OA, surgery	"I couldn't believe what a difference in how I felt — I've never had such a good night's sleep. I slept!..."[197]
	Side Effects	Side effects	CPAP, OA, surgery, physical activity	"I've been using the CPAP mask for — I think it's about a year, but I'm not positive. I can't stand the thing. I find that it blows all up in around my eyes throughout the night and find my range of motion from my neck is — I'm often stiff in my neck because it holds — makes it so stiff. I do use it."[209]
		Claustrophobia	CPAP	"[With CPAP] I had tremendous panic attacks. Well, they found out in a hurry, because they put it on here and I just — it was horrid. Like, I just ripped it off and I just was panicking and, like, it was awful."[209]

Table 115: Emergent Data Categories, Descriptive Themes, and Analytic Themes

Analytic Themes	Descriptive Themes	Categories	Interventions Included in Category	Exemplary Quotes
	Comfort of Intervention	Discomfort	OA, CPAP, tennis ball technique	"Sometimes it's just so uncomfortable to put that mask on at night and I wake up in the morning with a big mark on my face. Not that the mark bothers me, but it hurts. It's like sleeping, you know, with something pressing into your face all night. It's not worth it."[216]
		Difficulty with CPAP	CPAP	"If you get up [during the night], you don't want to put it back on. I don't want to wake myself up trying to get that thing threaded through there."[216]
		Difficulty with OA	OA	"…after a while, they break down…Either the wire on the top breaks or it becomes undone on the back or the plastic just deteriorates…"[209]
		Difficulty with TBT	Tennis ball technique	"The tennis ball moved around."[112]
	Impact on Self and Relationships	Perceived attractiveness	Surgery, CPAP, OA	"I didn't want anybody to see me...you know, I looked really stupid; I looked like a Martian."[217] "And so, like, I don't know anybody who is in a new relationship who would stick one of those things [the CPAP] to their face, you know. It's just not too appealing. But the oral appliance is not a big deal…Don't even know it's there."[209]
		Relationships	CPAP, surgery, OA	"… I mean, how do you say 'good night' with a big mask over your face and things like that, it's … so, it's a little sad …"[219]

Table 115: Emergent Data Categories, Descriptive Themes, and Analytic Themes

Analytic Themes	Descriptive Themes	Categories	Interventions Included in Category	Exemplary Quotes
		Partner experience	Untreated, CPAP, OA	"The benefits to me have not been as great as I might have hoped, but my wife loves that mask."[210]
	Presence of Support	Partner support	Untreated, physical activity, CPAP	"For the first couple of weeks I'd help her put it on, and make sure everything was OK, and set the machine."[216]
		Health care professional support	Untreated, physical activity, CPAP	"That I got the possibility to talk to that CPAP nurse made us feel very secure, people you can talk to and tell how you feel. That is what's so important."[213]
		Peer support	CPAP	"Have somebody who's been through it and has used CPAP for a while come in to talk to somebody for 10 or 15 minutes that's about to start the process… can assure somebody that you do get used to it."[210]
		Insufficient support	CPAP, PAP	"So I feel I was in kind of a limbo. And if I should have taken any more responsibility for visiting a sleep doctor or revisiting my doctor, I didn't know that, and my doctors weren't telling me that — unlike any other aspects of health care. Like, when I saw [other specialists], my PCP made sure I knew who they were, that they were good, that I went … she'd get follow-up reports…None of that happened with sleep apnea."[199]
	Information Needs	Information needs	CPAP and OA, diet	"[Speaking about treatment] I didn't know there were any options."[199]
	Adaptation and Problem-Solving	Perseverance and intervention as habit or routine	CPAP, OA, physical activity, diet	"If you're not wearing it all the time, certainly the first night that you put it in, your teeth are sore in the morning. And I find I don't sleep as well, I'm a bit restless that first night, just because…it's a bit uncomfortable if you have to adjust to it being in place."[209]

Table 115: Emergent Data Categories, Descriptive Themes, and Analytic Themes

Analytic Themes	Descriptive Themes	Categories	Interventions Included in Category	Exemplary Quotes
		Time	CPAP, physical activity, diet	"I'm having trouble keeping regularity ... skipping lunch now and then ... I'm hungry in the mornings, eat a little too much then because it's so very good."[218]
		Motivation for physical activity	Physical activity	NA: no direct participant quotes were provided to support this theme.
		Cost	CPAP, OA	"…after a while, they break down…Either the wire on the top breaks or it becomes undone on the back or the plastic just deteriorates…"[209]
	Psychological Impact	Anxiety	Untreated, CPAP, surgery	"I don't go to bed before 12, and sometimes even 1 o'clock. I wait until I'm dead tired. I'm afraid of going to bed and I think this is a good way to cope with my situation."[211]
		Confidence	Physical activity, diet, CPAP	"If I could do it last time, it should be just as easy this time."[218]
		Embarrassment	CPAP and OA	"If there's a tangi [funeral] I'll take it with me. I don't care who's watching. At least I'll wake up feeling good."[210]
		Fear	CPAP	"It was scary at first; it felt like one wouldn't get any air."[219]
		Guilty	Untreated, CPAP	NA
		Helplessness	Diet	"... I use to say, if most people ate as I do, no one could be fat ... surely on certain occasions I want a little chocolate ... everybody wants that, I guess ... but not in those amounts, causing me to weigh as much as I do."[218]

Table 115: Emergent Data Categories, Descriptive Themes, and Analytic Themes

Analytic Themes	Descriptive Themes	Categories	Interventions Included in Category	Exemplary Quotes
		Shame	Untreated, CPAP	"In the beginning, I had the full mask and it was very disconcerting, not only physically but emotionally. I don't know that anyone else experienced this, but I really felt ashamed. I was mad at myself for being in this position and I had to build up time on the machine."[216]

CPAP = continuous positive airway pressure; NA = not applicable; OA = oral appliance; OSA = obstructive sleep apnea; PAP = positive airway pressure; PCP = personal care physician.

Analytic Theme: A range of characteristics and factors influence whether people seek and initiate OSA treatment.

This first theme captures results that describe the range of characteristics and factors that influence patient experience with OSA interventions, including patient demographics, and expectations and attitudes toward treatment. As described below, experiences with certain interventions may vary based on characteristics of patients. Additionally, the process of becoming diagnosed with OSA can be incredibly overwhelming for some patients. Persons with OSA might not be aware of what options are available to them, or that they even have a choice. All interventions are seen as an inconvenience for patients, at least at the beginning, and patients describe a period of adaptation to find an intervention that works for them. The following section explores the findings related to this first analytic theme.

Motivation

Risk Awareness

Both patients and partners would downplay or be in denial about the seriousness of OSA,[197,199,217] which often delayed treatment.[199]

Similarly, many participants did recognize that being obese was related to their OSA.[197,215] However, some also did not recognize, or were in denial about, the severity of their weight and the risks with being obese.[197,215,218] This denial, about obesity and OSA, can prevent people from seeing their physicians and seeking treatment. In one study, from the time when patients first recognized a problem, to when they first sought medical help, men averaged five and a half years and women averaged a four-year delay.[197]

As one female participant stated,

> *I think I just kind of preferred to live in my imaginary world. It takes a lot for me to go to a doctor. I knew something was wrong; I just chose not to do anything about it. I kept saying, "I can fix this myself; I don't need a doctor, I don't need to bill this to my insurance." It was hard — I didn't want to admit I was snoring as loud as I was, and that I couldn't fix this on my own. I also didn't want to be told that I had completely lied to myself about my weight for the last 10 years. I'm so good at lying to myself — "you don't have a sleeping problem; you just have three kids and you're tired."*[197]

Patients seemed to weigh the risks of untreated OSA with the inconvenience of treatment to make a personal decision to pursue treatment, as illustrated by this quote, "…well, once I'm aware of a condition and I know that there are options or there are no options, and I weighed it up and I take the road that's the best avenue for you, you know it's a considered option…"[217]

Disease Chronicity

Several studies reported a sense of awareness that patients had about their condition; this was a realization that OSA is a chronic disease, and that treatment may occur over a lifetime. Some patients were uncertain whether OSA was curable, and whether to approach it as a burden or handicap.[221] Some were uncertain whether they would have to wear CPAP for the rest of their lives.[210,221]

Once patients realized that they might have to undergo lifelong treatment, some patients expressed a deep desire to find a cure or for doctors to be able "to just go in and fix it."[197] As one man commented about CPAP, "If there were anything that could be done to be free of that machine, I'd do it right now, regardless of cost. I can't imagine being 75 years old, and still stuck on this machine."[197] Lifelong treatment can be intimidating, and this was expressed by two patients in one study: "Did I need to wear CPAP equipment to sleep for a lifetime? If I accepted CPAP therapy, would my sleeping problems be cured? The physician said that suspension of treatment would cause ventricular hypertrophy due to sleep apnea. This seemed intimidating. At the end of my life, I was afraid that if I had a stroke, I would become a burden to others. This was concerning."[221]

Fear

Before treatment, patients expressed feelings of fear related to OSA.[211,216,218,230] Patients were afraid of dying in their sleep,[211,224] as well as the adverse outcomes of apneas, particularly for patients who had had previous CV problems and feared more events.[211] Partners often made patients feel anxious about their condition or felt fear for their partners.[211,216,222] One partner stated, "It's probably more this, future problems with his heart or a stroke or something. I'm worried about such things! His driving the car and what is currently happening; I'm scared for that, really scared."[222] Some partners became afraid of the patient when they had violent mood swings or aggressive behaviour due to OSA.[222]

For some patients, this fear of adverse outcomes and the fear that something serious could happen motivated patients to get tested.[211,218,230] One participant explained the motivation for testing like this: "I mean, surely if it is a diagnosis — this counts for you, you have got two years left to live if you do not do something drastically now — you would react quite seriously to that. At least I would."[218]

Patients learning about oxygen desaturations and the anxiety this may cause felt the need for quick and effective treatment.[211] One patient stated, "I thought, 'Am I going to die because of this?' I'm afraid that I won't wake up again when I go to bed at night. If my breathing doesn't start again after an apnea, I suppose I'm going to die."[211]

Partner Distress

Prior to receiving interventions for OSA, partners of patients were distressed by their partners' lack of energy,[197] their own disrupted sleep,[216] interference with their own daily activities,[216] and by witnessing their partner stop breathing during sleep.[197,211,216] As one partner described, "It was sometimes hard for me to go to sleep because of the way he was breathing, and if he would stop breathing, then I would have to wake him up sometimes because I didn't think he was gonna ever breathe."[216] Patients also recognized their partners' distress; as one commented, "It was my wife who woke me up, and I think that she thought that it was much worse than it was. She got really scared when she heard that I wasn't breathing."[211]

Sense of Self

Sense of self was related to how patients viewed themselves in general with relation to OSA and treatment, specifically to CPAP and weight loss. A related code of this was Perceived Attractiveness (see second analytic theme), which specifically relates to how attractive patients viewed themselves as being.

With regard to weight loss, some patients had a hard time reconciling their image with their current weight.[197,218] As one patient said, "I stepped on the scale and said 'no, that is not me' ... it did not correspond to me. That was kind of what made it tilt and then all there is to do is change it ... no, I could not identify with the numbers."[218] This discordant sense of self was motivation for behaviour change.[218] Another participant remarked that their recent weight gain had contributed to the problem of their OSA: "I'm new at being heavy. It's a new thing for me. And I don't drink coffee

during the day. If I'm sleepy at work, I drink Coke. I drink five or six cans of Coke a day. That's a lot of calories. So the problem kind of feeds on itself."[197]

For patients with difficulty complying with CPAP, self-image and how they thought others viewed them was a major reason for not using CPAP.[217] A patient's self-efficacy was related to CPAP use and influenced a patient's decision to use CPAP based on how they viewed their health and the barriers to use.[217]

Expectations and Attitudes

Pre-Existing Beliefs About CPAP

The findings of the systematic review were that the pre-existing belief that patients had about CPAP shaped their subsequent experience with CPAP.[207] Beliefs that CPAP would improve health, improve relationships, and reduce symptoms of OSA were reinforced when patients experienced benefits; however, those with mild OSA were increasingly likely to have poor experiences with CPAP, such as unresolved excessive sleepiness, which led to a perception that CPAP was a failed cure.[207]

This finding was confirmed by primary studies, which similarly found that persons viewed CPAP as a way to resolve the negative effects of OSA and formed their attitudes about CPAP.[211] The perception that CPAP could relieve symptoms of OSA motivated patients to seek diagnosis and treatment.[217] Hearing laypeople or professionals talk about CPAP in a positive or negative way helped shape their attitudes toward treatment.[211] Although there was a hope that CPAP would improve their lives, there was also a belief that CPAP could be restrictive and demanding.[211]

These findings all relate to beliefs patients had about CPAP, and how pre-existing beliefs shaped a user's experience with CPAP. Beliefs about other treatments, such as OAs or surgery, are uncertain and were not identified in the literature review.

Anticipated Benefits

Anticipated benefits refer to instances where patients or partners were expecting positive outcomes of using OSA interventions. In general, persons using an OSA treatment expected to experience a reduction in apneas,[209] improved sleep,[209,215,230] prevention of heart disease and strokes,[209,230] reduced fatigue,[209] improved social life,[215] improved mental health,[215] reduced snoring,[209] reduced mortality,[230] and benefits for their partners.[209]

Anticipating these positive outcomes motivated some patients to use CPAP. Patients viewed CPAP as positive when they thought it could rid them of all negative aspects of having OSA.[211] As one participant stated, "I was so tired last autumn that I fell asleep standing at work! When I was told I had this sleep apnea and that I would be getting the CPAP, it was, like, aah, a great relief. Feeling so bad really motivated me a lot to participate."[230] Another stated, "I had so many apneas that I was afraid; yes, I wanted to spare the heart."[230]

Patients were also motivated to use CPAP and OAs in order to improve the sleep of their bed partners, primarily due to the reduction of their own apneas and snoring.[209] One participant stated, "Because there is the benefit to [the bed partner], at least you're not snoring, so you're not disrupting their sleep. Or you're not stopping breathing for 20 seconds, up to a minute, and they're wondering if you're going to gasp and get going again."[209]

Regarding physical activity, some people wished to be more active, and felt that engaging in physical activity would improve their general health, social life (as some activities can be social), sleep, and mental well-being, and enhance their self-image, as well as reduce pain.[215] An initial weight loss was seen as motivating physical activity.[215] However, some patients and partners felt that sufficient weight loss would resolve snoring and OSA symptoms.[197] As one participant stated, "I look at it as kind of temporary, you know? Keep losing the weight, and maybe that will help. Dr. R thinks it's a lifetime deal, but I hope it's not. I do know I snore less when I've lost weight."[197] This was echoed by a bed partner, who said, "Ideally she'll be able to recondition her body so that it's not necessary for her to have to do this [use a CPAP machine]. But I don't know what kind of outcome is expected. Ideally, she could get back to normal."[197] Regarding healthy eating, if participants could anticipate positive outcomes, then they were more likely to view themselves as able to change their behaviour.[218]

Participants using CPAP, OAs, and physical activity reported an anticipated improvement in overall physical health and mental well-being. Those engaged in physical activity also anticipate an improvement in their social life and their self-image. If persons modifying their diet reported they were able to anticipate positive outcomes, they are more likely to view themselves as capable of changing their behaviour. However, it is uncertain what benefits people anticipate before undergoing surgery or when using positional therapies, as these experiences were not identified in the literature.

Doubt About Ability to Comply with Physical Activity

Persons trying to lose weight by being physically active were often doubtful about their ability to be successful.[215] They may have anticipated positive outcomes and knew that it was good for them, but were uncertain whether they could achieve them, as some reported having been unsuccessful in losing weight before.[215]

Negative Perception of Treatment

Some studies reported participants who had a negative perception of OSA treatments. Regarding OSA and CPAP, one study reported that some participants were skeptical that OSA was a real diagnosis.[199] Specifically, one participant thought that OSA was "just another way for the medical establishment to make money" and this was primarily due to CPAP being sold in commercial storefronts; he was uncertain whether OSA was real and needed treatment.[199]

Some participants describe being anxious about CPAP treatment.[217,230] One patient described their feelings of anxiety this way: "I was quite anxious about whether I could do it all by myself — putting the mask together. I think about it now and it's so bloody simple, but at the time it just seemed like too much to take in. What if I didn't get right? How would I travel?..."[217] Others did not use CPAP, because of either a lack of motivation to start using it or a lack of motivation to continue using CPAP, because they did not perceive a benefit from the treatment.[207,216,217]

Participants in one study stated that the shifting bite associated with OAs was a concern for them, and something they would consider when choosing an intervention, however, they would not necessarily choose CPAP instead.[209] It was also perceived that OAs could cause gum disease and cavities, and in some cases, OA users were told this by their dentist, but some of this speculation was based on the user's experience.[209]

One study reported negative expectations with positional therapy. In this study, participants reported their perception that the tennis ball technique would cause back problems.[112]

In summary, persons with OSA perceive negative outcomes of CPAP, OAs, and tennis ball technique. Anticipating negative outcomes is something that a patient may consider but might not necessarily push them toward another intervention, as demonstrated by the views on OAs and CPAP. Whether persons with OSA anticipate negative outcomes from surgery or lifestyle interventions remains uncertain because of a lack of research on this topic.

Information Needs

The process of being diagnosed with OSA and the initial treatment phases can be an overwhelming time for patients. Some patients need initial information regarding OSA as their knowledge of the condition was limited or non-existent.[199] Patients report needing information for both themselves and their partners,[211] but that the amount of information received at initial points of care can be overwhelming.[210,211] Some mentioned that the timing of information made it difficult to process,[210,211,217] and that information should be delivered in steps[211] or in a format that is conducive to learning.[217] With regard to information delivery, some patients were dissatisfied with how their physician delivered the information, particularly related to their communication style.[217]

However, some reported that they did not receive enough education or training related to OSA and CPAP.[211,213] As one participant said, "The only information I've got is that I will receive a CPAP machine. I want more information about my apneas and sleep disturbances, but I think the information should be broken up and delivered in a couple of steps so you get time to think about it and understand it. It's impossible to understand all the information in one go."[211] Another commented, "I thought it was a very advanced machine; I couldn't guess how it would work when I

saw these tubes."[213] Partners also felt insecure, frustrated, and unable to help patients if they had not been a part of the initiation of treatment and therefore lacked knowledge about treatment.[213]

Patients sought information about OSA and CPAP from a variety of places. These included:

- The Internet[210,211,217,221]
- Ear, nose, and throat physician[221]
- Family and friends[210,211,221]
- Media, books, and magazines[221]
- CPAP professionals, including salespeople.[221]

One study found that sources of information varied by race; Māori and Pacific Islanders sought information about OSA and CPAP from family and friends, while New Zealand Europeans sought information from the Internet.[210] Māori participants appreciated when information about OSA and CPAP was delivered in a culturally appropriate manner, which in turn furthered their understanding of the condition and treatment.[210]

Regarding information-seeking on CPAP, one patient said, "Well, there wasn't a lot of personal stuff in there, like people that have actually used machines. So when I was on the 'Net, I was just basically looking at people's experiences with the machines and their own journeys with it, and stuff like that."[217]

Information about OSA and CPAP was also misunderstood, incomplete, or difficult to understand.[211,213,221] Participants also commented that information found on the internet was not always helpful, as it was not tailored to their individual circumstance, and that they wanted to ask questions of persons with professional knowledge.[211,221]

This section relates to information needs on OSA in general and specific information needs related to CPAP prior to initiation with treatment. Any evidence on the information patients wished they had before surgery, or before using OAs or lifestyle interventions, remains uncertain because of a lack of research on this topic.

Patient Characteristics

Patients With Disabilities

One study[214] explored how PAP devices failed to meet the needs of patients with physical or sensory impairments. These patients had a range of conditions, including decreased mobility (e.g., rheumatoid arthritis, osteoarthritis); amputation; diabetic neuropathy; impaired depth perception; Parkinson disease; weakness (e.g., stroke, carpal tunnel syndrome). These patients expressed difficulties they had while using PAP devices, and provided suggestions for change. A few patients recommended modifying the headgear, changing the mechanism for connecting the tubing, and minimizing the number of attachments or adjustments needed. Patients also recommended changes in the location of their machine's control buttons for people with limited mobility or visual impairment. These suggestions included having larger knobs for people with arthritis, placing the controls or displays in the front of the machine, or making them feel different so they were more accessible at bedtime: "I have to turn the light on to find it…Actually, if it wasn't on top, [and instead] was on the front, I'd probably be able to [find it]…But I've been trying to memorize where it is so I can get it by feel." A few participants described ways in which the filter could be designed better. For example, the size of the filter could be increased to reduce the demand for fine motor control, as described by the following patient: "The filter is so small and you have to pinch it on both sides just right. It would be a little bit easier if it was a little bit bigger and easier to get to because it's always in the back and on the bottom and in a corner type…"[214] It is not known whether these difficulties reduced adherence or led to the discontinuation of CPAP.

Literature was not available on the experience of people with disabilities with interventions other than CPAP.

Older Veterans and Patient Age

One study[231] specifically focused on the challenges older (≥ 60 years) veterans have with CPAP. Similar to the study on patients with disabilities, older veterans had difficulties with putting on the mask, adjusting straps, turning dials, pushing buttons, disconnecting tubing, and removing the water chamber.[231] The participants in two other studies had

an average age of ≥ 60 years.[209,215] These studies were regarding physical activity,[215] and both CPAP and OAs.[209] It is uncertain how the age of the patient may have influenced their experience with these interventions.

Additionally, participants in the surgical studies[89,98,232,233] tended to be younger (i.e., with average ages between 38.6[233] and 45.9[232] years) than participants in the other studies. It's uncertain how this may affect their experience with surgery. There were no other clear trends regarding the age of participants.

Relationship Status

A patient's life stage, specifically related to relationship status, in some cases will influence their treatment needs and choices. Relationship status was a complex factor that affected many aspects of OSA treatment; thus, it is presented here as an issue when considering treatment, but will also be discussed in the Thematic Analysis section, as it relates to the adoption of OSA interventions. More than half of participants were married or had a bed-sharing partner in 13 studies.[197,209,211-216,219,222,224,225,230] In the remaining studies, marital status was not reported.[89,98,112,198,199,207,210,217,218,221,223,226-228,231-233]

It should be acknowledged that in some cases, having a partner is a catalyst for getting a person tested for OSA. Partners often had a role in diagnosis or recognizing that their partner had a problem and needed treatment.[197,221] It is also important to acknowledge the emotional strain that OSA can put on a relationship. Partners and patients often expressed feelings of tension, frustration, anger, and emotional pressure that resulted from both having poor-quality sleep.[197,211,216,222] Persons living alone described difficulty in initiating new relationships because of their OSA.[211]

Patients did consider their bed partners and their relationship before being treated for OSA, and this was related primarily to being aware of the disturbance that snoring caused,[197,209,216] but also when it came to choosing a device.[209] Before treatment, some patients and partners slept in separate rooms, in an attempt to mitigate the partner's lack of sleep due to the patient's apneas.[197] However, some couples felt that there was a stigma with respect to sleeping in separate rooms, because of a partner with OSA, and that bed-sharing was a way to maintain normalcy.[197] Participants with untreated OSA described decreased desire for sexual intimacy and decreased sexual activity.[197,211,222] Partners also described feeling less like part of a couple, and more like a caregiver for their untreated spouse.[197,222]

When considering which intervention to use, people may consider how the intervention might affect their sexual relationships.[209,217] This is seen in some participants preferring OAs over CPAP, due to their discreetness; as one participant said, "And so, like, I don't know anybody who is in a new relationship who would stick one of those things [the CPAP] to their face, you know. It's just not too appealing. But the oral appliance is not a big deal…Don't even know it's there."[209]

Impact on Lifestyle

The following section explores some of the considerations a patient may have before undergoing treatment or during treatment initiation.

Physical Environment and Travel

Activities, such as frequent travel, may hinder the use of some interventions. The need for electricity when using CPAP was mentioned by several studies.[209,216,219,220,231] For some, this meant that they could not take CPAP camping or hiking,[209] and for others it was a problem with respect to power outages,[219] or when travelling internationally.[220] Participants mentioned the need for proper electrical outlets[219] or adaptors.[220] For others, CPAP use was difficult because they were unstably housed.[231]

Travelling with CPAP, specifically on planes, was generally regarded as difficult.[209,216] Users preferred CPAP machines that were compact and could travel easily.[209] One user stated they would like to have a CPAP that can be used on a plane.[209] Another CPAP user commented that when staying in hotels he did not need his humidifier, and suggested tips for travelling with CPAP, including using hard containers to store it, bringing along electrical tape to fix leaks, and always taking CPAP as carry-on.[220] One partner recalled the patient's worries about travelling with CPAP,

stating, “He had to make a trip out of town and he said, ‘I’m not carrying that on the plane and being worried about whether I leave it somewhere. I’m not doing that.’”[216]

In contrast to CPAP, fewer worries about travel were expressed regarding OAs. Patients using OAs mentioned the need for a hot water supply.[209] Some participants suggested alternatives to hot water, such as warming the OA in their armpit.[209] The relatively smaller size of OAs compared with CPAP, and the fact that appliances do not require electricity, may appeal to some people with OSA.

There were limited findings for this category regarding lifestyle modifications. The physical environment — more specifically, the weather and place — hindered some patients from engaging in physical activity.[215]

Challenges to Lifestyle Modifications

Interventions for OSA were seen as a change in lifestyle, especially as it related to prescribed diet and exercise for weight loss. However, several studies reported challenges to these lifestyle changes. For exercise, some patients reported psychological distress as a barrier, as well as making excuses not to exercise.[215] Previous negative experiences gaining weight after successful weight loss, or difficulty in currently losing weight, were barriers for patients.[215,218]

Regarding food and diet changes, patients reported complex relationships with food that prevented them from changing their lifestyle.[218] Some used food to cope with feelings of anxiety, as a personal reward, as a substitute for tobacco, or to obtain oral satisfaction.[218] As one patient stated, “I feel like an alcoholic… I use the food to lower anxiety, you know.”[218] Others simply found regulating their food to be challenging, and expressed a wish for a simple way of calculating their energy balance: “It would be easiest if you, in a very simple way, could measure energy in and energy out.”[218] However, some found it easier to implement diet changes when healthy food was readily accessible, easy to prepare, and enjoyed by the whole family.[218]

Cost

Cost was a factor in selecting a treatment. Patients perceived both OA and CPAP as expensive.[209] Some participants indicated that their choice would be influenced by which treatment was covered by their extended health insurance. Others said that they were willing to pay whatever it costs for the treatment, provided that the treatment is highly effective: “We don’t have extended care. So — but as far as health, we would be certainly willing to pay for anything that would help.”[209] In a choice between an OA or a CPAP, the importance of effectiveness was shown in a participant’s comment that he would be willing to pay the cost of the CPAP because he perceived it to be more effective than the OA.[209] The cost factor emerged as a strong additional deterrent in those who had initial difficulties with CPAP issues.[217]

If patients were informed about the features of various CPAP devices — for example, those who had sought information on the Internet or by talking to other CPAP users — then they were aware of types of machines available, as well as different features of each.[199] Some were willing to pay out of pocket when the desired CPAP equipment cost more than their insurance would cover.[199]

For some patient groups, even the partial costs of CPAP would be a barrier when considering starting treatment and long-term use. In one study, a Māori focus group, which included only government-funded patients, discussed financial barriers to long-term treatment in the context of having to replace a device if broken or stolen. Māori patients also reported difficulties arranging transport to appointments.[210] Interviews with Taiwanese patients with partial government funding also revealed the cost of CPAP to be a burden.[221] In this study, costs were reported as between US$1,050 and $2,800. Several patients described the price as expensive and unaffordable. “The CPAP machine was too expensive. The government reimbursed me US$691. I hoped that the government would grant more money, because the price burdened me.”[221]

Cost was also a factor for patients considering or attempting lifestyle changes. In one study, healthy food alternatives were considered too expensive. Some healthy food “...may contain odd ingredients as well but not too much ... it will be too expensive ... I cannot afford to pay just any price.”[218]

No information was identified on the cost related to surgery.

Analytic Theme: Interventions for OSA require adaptation to daily routines and relationships. Some patients are able to integrate these interventions into their life and experience benefits, while others are unable to do so.

This theme captures results that describe how people learn to adapt to their OSA interventions, or not, and some reasons that compel people to adapt, or cause them to be unable to do so. For example, physical comfort was an important factor to patients, regardless of which intervention was used. Some persons may not find a device that works for them, for whatever reason, and thus choose to have surgery. Additionally, this theme explores experienced benefits and side effects from using OSA interventions. Patients express a trade-off between side effects or physical comfort and experienced benefits. For some, the benefits of using OSA interventions outweighed the discomfort; however, for others, this was not the case.

Other findings were related to how patients viewed themselves in light of OSA and treatment. Part of this was a descriptive theme we called “perceived attractiveness” with CPAP use and after surgery. The majority of patients found their appearance acceptable or satisfactory after surgery, and in some cases, patients found their post-operative appearance to be an improvement. A small number found their post-surgery appearance to be worse, and regretted having the surgery. Related in part to a sense of self, there were a few relevant psychological outcomes related to treatment. For some, these outcomes were positive, like reduced anxiety by using CPAP. However, for others, there were feelings of guilt and shame related to using OSA interventions. The following section explores the findings related to the second analytic theme.

Experienced Benefits

Physical, mental, and social benefits with treatment were frequently mentioned by the included studies. These experienced benefits supported some users to continue treatment and motivated them to overcome problems, adjust to the challenges of treatment, and generally persevere even when treatment was perceived as inconvenient, uncomfortable, or embarrassing.[219]

Patients described the positive outcomes of using CPAP therapy, and some patients recommended focusing on the positive outcomes of therapy to make the CPAP mask easier to accept.[212] For some, the outcomes from using CPAP are profound; as one man stated, “The first day I got that machine, and woke up that morning, it was the clearest day of my life. I’d never seen the world like that.”[197] Another stated, “I love putting it on every night. I feel night and day differently. My quality of sleep has improved, and my mood and energy during the days. Now in the mornings, it’s so much easier to get up.”[216] These patients — those experiencing substantial benefits — develop a feeling of confidence and dependency on CPAP.[221] With increased alertness, patients were able to return to activities that they had not been able to do while untreated.[219]

However, patients were often said to develop a “love-hate” relationships with their machines.[197] Some people reported persistent sleepiness in spite of what they described as good adherence to the prescribed therapy. They reported that they had tried to use the equipment provided and followed directions yet, despite their best efforts, did not feel better after initiation of PAP therapy.[199] People who adapted to CPAP experienced the benefits of returned good health, such as the following:

Physical benefits

- Improved energy levels[207,210,216,219,221]
- Improved breathing[221]
- Reduced tiredness[207,216]
- Reduced other symptoms (e.g., nocturia[219] and snoring[221])
- Better sleep[197,207,209,213,216,219,221,230]

Mental and psychological benefits

- Better quality of life[216,219]
- Sense of well-being[219]
- Waking up and feeling refreshed, alert and vibrant[197,209,210,213,216,219,221]
- Daytime alertness[219,245]
- Revitalized memory[221]
- Improved mood[209,216,219,221,225,228,232]
- Confidence while driving[217,221]
- Better ability to manage stress[219]
- Feeling more relaxed[219]

Social

- Less inconvenience to family and others[221,230]
- Social contacts were made easier: "like being welcome to stay overnight"[219]
- Decreased inconvenience to others (i.e., less snoring[221])
- Improved relations with spouses:[209,216,219,221,225,230] "my wife is willing to sleep with me"[221]
- Bed partner's sleep improved[209,216]
- improved work performance[221]

People using OAs also experienced benefits from the device. In one survey study, almost half of patients (49%) experienced great benefit from using the device, while a smaller proportion experienced moderate benefit (37%) and fewer still experienced no benefit at all (14%).[226] Some of the benefits users of OAs experience included:

Physical benefits

- Improved energy levels[223,225]
- Reduced tiredness[225,228]
- Better sleep[228]
- Improved physical strength[225]
- Fewer morning headaches[228]
- Improved snoring[223,228]
- Improved breathing[228]
- Sexual health[228]

Mental and psychological benefits

- Sense of well-being and joyfulness[225]
- Concentration[223,225]
- Increased mental energy[225]
- Less irritability[228]
- Improved mood[225,228]
- Satisfaction with improved health[228]

Social benefits

- reduced effort with regards to social interactions[225]
- Less inconvenience to family and others[228]
- Improved relations with spouses[225]

People who underwent MMA surgery reported being satisfied after the surgery.[98,232,233] One study[232] reported 95.5% (n = 21) of patients were satisfied with how MMA managed their OSA symptoms (including quality of sleep; daytime and sexual functioning; physical, mental, and emotional health). For another study,[98] 100% (n = 15) of participants were satisfied or very satisfied with surgery (all experienced an improved quality of life). Of the nine patients completing both a pre- and post-surgery questionnaire for one study,[233] all reported surgery as a worthwhile experience, although eight reported a favourable change after surgery; no further explanation was provided for this difference, although one patient from this study continued to use CPAP after surgery. Surgical patients experienced less daytime sleepiness and less sleepiness while driving.[233] After surgery, some patients were able to engage in activities they had previously avoided because of their OSA.[232] Patients also reported feeling less annoyed and less likely to become angry after having undergone surgery.[232] In general, patients considered the surgery a worthwhile experience, and most would recommend the surgery to others.[233] Some of the benefits highlighted by the surgery studies included:

Physical benefits

- Reduced tiredness[232]
- Better sleep[232]
- Reduced snoring[233]
- Improved physical activity[232]
- Improved sexual health[232]

Mental and psychological benefits

- Daytime alertness[232,233]
- Revitalized memory[232]
- Improved concentration[98,232]
- Improved decision-making[232]
- Improved mood[232]
- Better ability to manage stress[232]
- Better quality of life[98]
- Reduced stress and worry[232]

Social

- Improved work performance[232]
- Improved interpersonal relationships[232]
- Less activity avoidance[232]

There was some overlap in the benefits experienced by users of CPAP and OAs and for surgical patients. Users of CPAP and OAs, as well as those who underwent surgery, experienced reduced snoring, reduced tiredness, better sleep, and improved mental health. Improved relationships were also reported by CPAP, OA, and surgery studies. CPAP studies and surgery studies both reported improved work performance. An increased confidence while driving was reported by CPAP users.

Side Effects

For this review, the findings regarding side effects do not represent an exhaustive list of side effects experienced by patients on any intervention; rather, this review focused on what patient or partners found important about side effects with regard to their perspectives on treatment. Side effects of different interventions were considered when patients were choosing between interventions.

Several side effects were seen with using OAs. In one study, excess salivation was the most commonly reported side effect, followed by intra-oral soreness, jaw discomfort, and difficulty sleeping due to the device, and difficulty breathing was the least common side effect.[223] For a small subset of these patients experiencing each side effect, the side effects were severe enough to prevent them from using their device.[223] Pain associated with OAs was prevalent when first using the device, but not reported when users had grown accustomed to it.[209]

Participants who underwent surgery did not report a change in speech quality, and some reported that their teeth alignment was improved, although there was no improvement in chewing ability.[232] Post-operative pain was reported as tolerable, and was not accompanied by increased headache frequency.[232]

Regarding physical activity, some participants experienced pain or heart sensations while being active, which was a deterrent for being physically active.[215] Some participants chose activities that were less painful as a means of mitigating this.[215]

The findings of the SR[207] found that studies regarding CPAP were often negatively framed and that patients often reported side effects from a list of pre-determined outcomes prepared by the investigators, rather than allowing patients to discuss their own experiences. Patients who regarded CPAP negatively were primed to have more severe and more frequent side effects, and that these side effects were more likely to hinder their CPAP use.[207] Side effects were reported as a reason for discontinuing CPAP use, although it was noted that patients made trade-offs between the discomfort and side effects experienced with CPAP and the benefits they received from its use, and the exhaustion resulting from untreated OSA.[207] Patients who perceived the side effects and discomfort of CPAP to be greater reduced their use of CPAP.[207] Side effects were thought of as something a patient tolerates or struggles with, in order to receive the benefits of using CPAP.[207]

Claustrophobia When Using CPAP

Several studies reported patients feeling claustrophobia when using CPAP[209,217,229,231] and that it could be a barrier to CPAP use. Patients reported feeling panicked[209] or hungry for air[219,229] while using CPAP. One study reported that veterans with post-traumatic stress disorder (PTSD) were more likely to report claustrophobia than veterans without PTSD.[229]

Side effects experienced by participants varied by intervention. For CPAP, OA, and physical activity, some side effects were a deterrent to being compliant with the intervention.

Comfort of Intervention

Studies on CPAP, OAs, and the tennis ball technique were identified, although it should be noted that the theme Comfort of Intervention encompassed codes on difficulties with the interventions. These themes were not evident for lifestyle modifications or for surgical patients.

Many patients experience discomfort while using interventions for OSA, and comfort with the intervention can change over time. For example, patients using OAs stated that the longer they used the device, the more comfortable they felt with it.[209,228] For people using an OA, minimal pain was reported when the device was first used or when it was used infrequently. “If you’re not wearing it all the time, certainly the first night that you put it in, your teeth are sore in the morning. And I find I don’t sleep as well, I’m a bit restless that first night, just because…it’s a bit uncomfortable if you have to adjust to it being in place.”[209] This was supported by findings from another study, which found that 25% of patients felt comfortable using an OA within a week, with 69% of patients were comfortable within a month.[223] However, for some patients, discomfort with the appliances may stop them from using them. This is evidenced by the previously referenced study, in that the remaining 31% of patients stopped using an OA because they felt unable to

wear it; follow-up for this study was three months after being provided with the device.[223] Patients using the tennis ball technique also stopped using it because it was too uncomfortable — specifically, backache, shoulder ache, skin irritation, and the feeling that the tennis ball would create back problems.[112]

CPAP was also described as being uncomfortable to use.[207,209,216,219,221] Using a CPAP device limited patients' ability to sleep on their side or stomach and limited their nighttime mobility.[209,213,221] Patients also complained of air blowing in their faces,[209,221] air leaking out of their machine,[219] and waking up with a stiff neck.[209]

Difficulty With CPAP

Related to the physical discomfort of CPAP, another issue affecting patient experience could be characterized as difficulty with the device. Using CPAP is often seen as a hassle, frustration, and inconvenience, and this can frame a patient's experience with the machine. Because of these difficulties with CPAP, patients expressed that it was difficult to persist and stay motivated to use CPAP.[239]

Some participants experienced frustration and inconvenience related to the functioning of the equipment. Specifically, patients report that the CPAP is noisy, either because of the machine itself or air escaping or moisture in the tube. Patients are also concerned that the noise is disturbing to bed partners,[197,209] and some partners did comment on the noise of the machine.[213] People mentioned that it is frustrating to have to adjust mask straps, especially if people wake up because of ill-fitting straps and masks.[207,216,221]

Technical problems with the CPAP device were perceived as hard to manage, and if any part of the CPAP breaks, it can be inconvenient or costly to repair. This situation is expressed as frustration because it is expensive to fix or replace parts and it can be difficult to get the right size.[207] Part of the frustration relates to the importance of being able to update equipment, to opt for a better-fitting mask, as equipment wears out or as technology changes.[210,239] Inconvenience and frustration were also mentioned in the context of getting insurance to pay for the best-fitting mask.[197] Dissatisfaction was noted among patients who could not get their insurance to pay for a machine with a better-fitting mask or straps.[197] One study[198] had CPAP-experienced users trial APAP devices, with 14 patients (52%) preferring APAP at the end of the study; the authors speculated that the patients may have been biased to CPAP because in studies with CPAP-naive patients, patients find APAP easier to use.

Maintenance and cleaning of CPAP can also be challenging.[197,207,209,221,239] As one participant commented, "There is a lot of small, fussy stuff associated with the CPAP machine. Filling the reservoir and washing it, which I don't do every night, but fairly often. It's a chore like flossing; I mean, you know, various other things."[209] Several studies mentioned that buying filtered water was also seen as annoying.[197,209] People expressed a desire for support or explanations of procedures for cleaning and maintaining of CPAP equipment.[221] They complained about the "unavailability" of medical professionals to provide explanations, purposes, and precautions when using CPAP.[221]

Despite these difficulties, which some describe as a torment or an imposition,[207] some people could see using CPAP as a trade-off: "it works, but it's difficult."[239] Some described a process to get over the difficulties,[221] although some expressed a fear of "flunking" therapy.[207] Once these patients feel the benefits of their treatment, they people report feeling dependent on their CPAP machine.[207,221] They felt the need to use CPAP and believed it was worth the trouble and difficulties in order to avoid the return of symptoms.[219] For these people, there was satisfaction enough to use the CPAP nearly every night, and some accepted it from the onset.[219]

Difficulty With Oral Appliance

As with CPAP, users of OA expressed difficulties with the device. OA users were disappointed in the durability of the device and the frequency with which the device needed to be repaired or replaced.[209] The expense and inconvenience of doing repairs or getting replacement devices was also difficult, as one patient explained: "Well, they break down, you know; after a while, they break down in the, you know — either the wire on the top breaks, or it becomes undone on the back or the plastic just deteriorates and, you know, chunks off."[209]

Patients described some minor inconvenience associated with cleaning the OA, which was perceived as a nuisance. Patients were also uncertain about the best way to clean the device and which cleaning products were best.[209]

Difficulty With Tennis Ball Technique

One study reported specific difficulties with the tennis ball technique. Patients felt that the tennis ball moved around too much, that it caused backache, and that it was ineffective on a soft mattress, and some patients felt the treatment was not relevant to them because they did not sleep on their back.[112]

Perceived Attractiveness

Perceived Attractiveness refers to how a patient feels about their appearance while using CPAP, OAs, or after surgery.

Regarding a patient's view of their aesthetics after surgery, most patients seem to consider their appearance acceptable or satisfactory.[89,98,232] In some cases, patients may even consider their post-operative appearance to be an improvement. One study found that 11 out of 15 patients found an improvement in their appearance post-surgery, related to the nose, upper lip, and lower lip;[98] this is similar to another study, in which 14 patients (54%) also found an improvement in their appearance.[89] Some patients may not notice a difference in appearance, or feel as if their preoperative appearance is just as attractive as their post-operative appearance.[89,98]

However, some patients may feel worse about their appearance post-surgery, which for some, may mean they regret having the surgery. In one study (n = 15), one patient reported a worse appearance, particularly a worse appearance of their nose and upper lip.[98] In this study, five patients also reported a change in their teeth, with two patients reporting their dental situation to be worse and three reporting an improvement.[98] One patient who had experienced an improvement in their teeth had orthodontic preparation; however, the rest of the patients who reported an improvement or worse appearance did not have orthodontic preparation.[98] In another study, eight patients (31%) of patients felt their post-surgery appearance was worse.[89] Of these eight patients, one regretted having the surgery.[89]

In contrast with the outcomes from surgery, where most participants felt as or more attractive post-surgery, many participants reported feeling unattractive with CPAP[197,207,209,216,217] and reported feeling the need to keep their CPAP use a secret.[209] Some even felt that their partners might feel differently toward them or view them differently because of their CPAP use.[199,216] Patients who were dating, and considering progressing to a more intimate relationship, had concerns about telling their partners about their PAP machine.[199] This was expressed as having to "break the news" to a new partner.[199] Patients with longer-term relationships still felt less attractive to their partners, but describe more support from their partners.[199]

There was a certain stigma to using a medical device to aid in sleep,[207,216] and using the device was something people described as identifying them as ill.[207] Patients also commented on a swollen face and marks on their face from using CPAP, which caused embarrassment and revealed to others that they used CPAP.[219] Patients were unable to lessen these marks without compromising the effectiveness of CPAP.[219] One woman felt so strongly about her appearance with CPAP that she commented,

> *I don't like it — it's got these straps that go here and here, kind of like "Hannibal Lecter." It looks really funny. I don't know if it's a personality issue or what, but women aren't supposed to be like that; we're supposed to be dainty when we sleep. So I'll go to sleep at night without it, but then wake up and put it on… Let's face it, that thing is ugly, and putting that big, goofy thing on in front of my husband… those first few nights I would make sure he was asleep first. Then, in the morning, I'll take it off when his alarm goes off. I've even asked him, "what's better, me snoring or you waking up and seeing your wife with this horrible contraption wrapped around her face?"*

Partners also recognized that patients were sensitive to their appearance while wearing CPAP.[207] One partner commented, "My husband was very uncomfortable wearing that mask when he went to bed. He kind of hid because it was, you know, not attractive. It's an apparatus and it was just a very uncomfortable feeling for him."[216]

In the one study that included people who had experience with both CPAP and OA, some people reported preferring OAs as a more discreet and more attractive option, which lessened the feeling of embarrassment and ugliness around bed partners.[209]

Sexual and Intimate Relationships

Some participants found that CPAP enabled them to resume bed-sharing with their partners and improved relationships, whereas for others, the negative impact of CPAP on their intimate and sexual relationships, due to shame or interference of the machine, was a barrier to use.[216] Some users of CPAP describe the machine as a hindrance to physical intimacy,[197,219] and as being "unsexy."[197] As one participant described, "…It's had an impact on our relationship; you've got a frickin' snorkel thing across your marriage bed, and you create a windstorm from the exhaust. That's why it's not so fun. It makes cuddling difficult. If you're snuggling someone, then you're blowing wind on the back of their head, like you're in a hurricane."[197] Another commented, "…I mean, how do you say 'good night' with a big mask over your face and things like that, it's… so, it's a little sad…"[219] However, although partners may recognize that the patient finds themselves less attractive while wearing CPAP, not all were deterred by this. As one partner stated, "I think somehow in his mind he thinks that this machine interferes to some extent with intimacy. And it's like, you know what, it's a convenient mask to take off."[216]

Regarding relationships after surgery, one study found that the majority of patients reported an improvement in their relationship with their significant other.[232] In this same study, about a third of participants (37%) reported an improvement in their desire for sexual intimacy.[232] Another study found that one-fifth of patients slept in separate bedrooms from their partners even after surgery.[225]

Both people who used CPAP and those who underwent surgery saw improvements in their relationships with bed partners, although users of CPAP also found that the device hindered their intimate relationships.

Partner Experience

The spouses perceived it as important to be a support for their partner and adjusted their lives accordingly.[222] Some patients also perceived this as an opportunity to become closer to each other and do activities together, despite the fact that these were steered by the partner's symptoms. "I have made a real effort to get him out for a walk. I enjoy fresh air and getting some exercise; we just can walk round the block with the dog or something."[222] The spouses felt responsible for helping their partner to find a solution to their nightly sleep problems. For example, they knew from their own experience that if their partner lay on her/his side, then the problems lessened.[222]

Often, partners experienced personal and social distress prior to CPAP initiation, and were motivated to help the patient adapt.[207] For example, married users problem-solved and incorporated CPAP into their lives quicker than unmarried users.[207] Conversely, negative or absent partner support led to poorer experiences with treatment,[207] with male spouses reported in one study to be less involved with their partners' CPAP treatment than female spouses.[207] For some partners, the positive attitude of the patient toward CPAP was a reason to be less involved in their care.[213] As one partner said, "He's so positive about it himself, so he doesn't need any support from me. He's so positive about it and wants to use it. He feels such a difference."[213] Additionally, some partners used to hearing the patients snore became concerned by the patient's lack of snoring in the early days after initiation with CPAP.[216] As one partner said, "It was really scary because I didn't hear him. I didn't hear him snore. And that was frightening."[216] However, these partners still reported an improvement in their own sleep.[216]

Spouses and bed partners are affected by OSA treatment, in particular the use of CPAP. Many spouses appreciate the change that CPAP makes to their lives; for one man: "…The benefits to me have not been as great as I might have hoped, but my wife loves that mask."[210]

Other positive experiences reported by OSA patient's partners are:

- Better sleep quality since the patient started CPAP therapy[216]
- Less sleepiness during the day[223]
- Less snoring by the OSA patient using CPAP[223] or OA[226]
- Improved mood[223]

- Fewer breathing pauses by the OSA patient[223]
- Being able to sleep with their spouse in the same bed again with CPAP[197]
- Seeing the positive changes in their spouse's health, attitude, mood, and demeanor[197]
- Adjusting to the loudness of the CPAP machine, and finding it to be tolerable, if not relaxing. One wife explained, "It's like a white noise machine. It was great. It was like the first night that I actually realized how much I wasn't sleeping. I didn't have to roll over and kick anybody."[216]

Some negative experiences are:

- Having to change or adjust their sleeping arrangements[213]
- Finding the noise of the machine disruptive[213]
- The OSA patient waking up to adjust the mask was disruptive to the partner's sleep[213]
- Inability to engage in conversation when the patient is wearing the mask[213]

Presence of Support

This theme describes whether patients received support regarding their interventions for OSA and if they did, where this support came from. In this review, patients received support from a number of sources, including their partners, health care professionals, and other users of CPAP. However, it should also be noted that some patients perceived insufficient support for adequately managing their condition or their intervention.

Partner Support

The importance of support and encouragement during treatment for OSA was reported in the literature. Patients talked about support from both their spouse and health care professionals.

Support from spouses often began before the start of treatment. Patients felt "protected" by their partner.[211] In the case of physical activity, the support of friends, family, and co-workers was important.[215] They reported that partners encouraged patients to get help[197] for their sleep issues and to make appointments,[197] and simply recognized that the person needed support and reassurance.[197] Regarding CPAP use, one spouse explained, "I had to reassure him quite often that, you know what, it makes no difference [what he looks like with the mask on] as long as you have a good night's sleep, you can breathe and you don't feel exhausted in the day, you know? At the end of the day, that's really all that matters."[216]

Especially in the first few weeks, spouses played an essential role in supporting their partners' CPAP in a practical way by setting up the machine, maintaining it, helping adjust the mask, and telling the patient to put the mask back on if it came off during the night.[216] Some partners described taking charge of the practical aspects of CPAP; they aided in facilitating the use of the machine by maintaining it, troubleshooting, and supervising the patient.[213] One patient explained, "I'm very fortunate to have a lovely wife who has taken charge of the machine and makes sure that I use it. She makes sure that there's water in it and she's very attentive to it, so it makes it easy for me to just go along with it."[216]

Spouses supported patients emotionally by encouraging their partners to use CPAP and reassuring them that their appearance with the mask on is unimportant. Some couples tried to find the humour in the situation[213,224] and opportunities to laugh together, while partners emphasized listening to the patient.[213] Partners tried a range of things to encourage CPAP use, such as changing something at home or work to encourage CPAP use; telling the patient that they were happy they were using CPAP; talking about using CPAP or asking the patient outright to use CPAP; giving the patient space and demonstrating patience; trying to use logic or reasoning; showcasing others who were using CPAP; discussing patients' responsibility to their family; giving praise and encouragement for use.[224]

Some partners perceived that the patient would be less adherent to therapy if they felt ashamed by using CPAP.[213] Also, giving reminders and encouragement motivated patients to persist with CPAP.[216,224] As previously mentioned, married users problem-solved and incorporated CPAP into their lives quicker than unmarried users.[207] Adaptation to CPAP may need to be accomplished as a couple, not by any one individual in the relationship. In one study,[224]

perceived collaborative spousal support at three months was correlated with increased CPAP adherence; negative spousal involvement, positive spousal involvement, and one-sided spousal involvement were not associated with CPAP adherence.

Partners may also motivate patients to comply with therapy in less positive ways. Some partners would try to scare patients about the consequences of not using CPAP, became silent and withdrawn to encourage use, and others manipulated patients by stating that the patient did not care about them if they weren't using CPAP.[224] Others, however, verbally abused patients into using their CPAP machines or delivered ultimatums, such as the threat of separate bedrooms, to encourage adherence.[213]

Partners' involvement in managing CPAP ranged from encouraging the patient to take control and full responsibility for using and maintaining the CPAP to taking over the care and maintenance of the machine and by offering reminders to use or adjust the CPAP, and helping to explain the situation to friends and family.[213,224] The nature of the advice and comments from partners ranged from gentle remarks and reminders, to "nagging" or "telling him off" for not using the CPAP.[213]

The presence of a supportive partner was important to the use of CPAP and engaging in physical activity. It is uncertain how partners may or may not support OSA patients in their use of OAs or regarding the decision to undergo surgery due to the lack of literature.

Health Care Professional Support

Support from health care professionals was also mentioned as important in helping to adjust to CPAP treatment[211] and attempts to be more physically active with OSA.[215] Because of a lack of literature, it was uncertain what role health care professional support had in enabling patients to adjust to OA use or regarding surgery.

People wanted to improve their awareness of OSA, and support in acceptance of their condition and therapy and hope that they would get relief from the symptoms of OSA.[211]

Patients identified the importance of having early interaction with a health care professional following initiation of CPAP.[216] Given that questions or concerns are likely to arise during the first night or weeks of using CPAP, patients suggested having access to a 24-hour hotline and follow-up phone calls from a health care professional during this early time. Patients expressed a desire for professional support and reassurance at night. "If somebody is struggling or has a question or is frustrated or upset, they'd be able to call in and be able to talk to someone. Like a CPAP hotline. So you can ask questions or somebody can just walk you through it and tell you, 'It'll be all right. It's hard at first, but eventually you get used to it and it will help you in the long run.' It's different when the techs are at your house telling you that, but then when you're there, at night, and you're doing it, it's a different feeling."[216]

Patients also discussed that early feedback regarding patients' CPAP usage could be valuable to new users. As one patient described, "That I got the possibility to talk to that CPAP nurse made us feel very secure; people you can talk to and tell how you feel. That is what's so important."[213]

In the case of physical exercise, patients stressed the importance of a welcoming and tolerant atmosphere of feeling accepted and fitting in during exercise sessions and visits to medical appointments.[215] Acceptance from health care staff and supportive environmental conditions[215] were also important factors in supporting exercise programs. Some patients reported that they were physically active or not as a consequence of direct advice from a health care provider.[215]

Peer Support

Peer support was not identified in the articles regarding lifestyle modification, OAs, or surgery. These findings speak to peer support for OSA in general and for the use of CPAP. Patients reported the value of communicating with others with OSA to get support and information about their condition and treatment. Peers shared insights about adjusting to CPAP therapy.[212] However, for some, the OSA diagnosis was hidden as much as possible from other people, and there was a reluctance to share with others that they had OSA. One man had to share sleeping accommodations on work trips, and would not use his CPAP, but rather sleep upright to avoid apneas.[199] However, a

few participants took the opportunity to share with others that they had OSA and the benefits of treatment, in hopes of educating others and helping others seek treatment.[199] Patients who had friends with OSA reported less delay in obtaining a diagnosis and treatment. After disclosure of their OSA diagnosis, some patients learned of friends and co-workers who also had OSA. One man stated as his motivation for taking part in the study, "I would really like to be part of something that might prevent other people from going through what I have and am dealing with."[199]

Comments from peers were positive and supportive.[210,212] For example, one person shared their experience with CPAP: "It is not scary as it seems…once you start using the machine, you feel better."[212] Some practical aspects that patients share are:

- How to get used to CPAP (for example, one suggestion was "to put the mask on before even going to bed at the beginning, to get used to it and to focus thinking on the positive outcomes that would make it easier to accept the mask"[212])
- Different types of CPAP devices and components[220]
- How do deal with discomfort, specifically backache[220]
- Sleep position.[220]

The peer support could be in person and, in one case, was described as a role model.[210] The use of a role model was felt to be a positive step in terms of helping patients with the acceptance of treatment, as well as the practicalities of using CPAP. One Māori woman made use of peer support and reports: "I used the resources; I had a person that's been on this machine for 16 years, so she weaned me into what I'm supposed to do."[212] Others appreciated that the role model was someone who had adjusted to CPAP. Some patients in turn saw themselves as role models for others in their social networks.[212]

Some patients found peer support online. Similar to in person, people who turned to the Internet for information and support reported that they "found a supportive community online and it was helpful to be able to interact with others who understood their situations and who could provide, from their own experience, what the participants described as useful suggestions for dealing with the challenges of therapy."[199]

Insufficient Support

Conversely, lack of support from a health care provider may affect adherence with CPAP.[216,221] Some patients reported that they had "tried" to adhere to their treatment; however, poor communication among providers, and a perceived lack of involvement in care and follow-up, created significant barriers to a patient's adherence and success with therapy.[199] As one patient described, "Initially, there was no medical staff to clearly explain details or provide consultation about how I should operate CPAP equipment. There was no medical staff to explain information concerning CPAP therapy to me. I found most CPAP therapy information from hearsay, the World Wide Web, newspapers, friends, or salespersons."[221] As one patient described, "Mostly when I had problems, I asked my salesman, but he was unprofessional, and did not provide me specific information or precautions for CPAP therapy."[221] Patients face challenges in adjusting to the use of the PAP; sometimes it was basic information related to problem-solving.[199]

Patients described several examples of when they feel insufficiently supported:

- Learning cleaning and maintenance procedures of CPAP equipment[199,221]
- Learning explanations, purposes and precautions when using CPAP[221]
- The risks and dangers of not using CPAP therapy[221]
- The desire to be treated as an individual[199]
- A lack of follow-up from their health care provider[199]
- Lack of knowledge of when to call their health care provider[199]
- Lack of communication between the sleep specialists and the primary care physician[199]

- Lack of assistance from family members or caregiver in maintaining and setting up PAP devices.[214]

A lack of support from health care providers contributed to feelings of distress and uncertainty for some patients. One person reported, “No medical staff taught me how to clean, maintain, or use it during CPAP therapy. I used my own methods to take care of the CPAP machine. I did not know if my servicing techniques were correct or not?”[221] Another mentioned, “When the machine malfunctioned, I worried about how I could get it serviced.”[221] Patients described the feeling of having been “turned over” to the equipment provider.[199] This provider delivered the machine, provided only minimal instruction on how to use it, and then, as two participants specifically stated, “left as if to say ‘Bye, and have a good life’.”[199] Patients were unclear about follow-up. “…If I should have taken any more responsibility for visiting a sleep doctor or revisiting my doctor, I didn't know that and my doctors weren't telling me that…”[199]

Participants spoke about insufficient support with regard to their OSA in general and lack of follow-up with health care professionals, and with regard to CPAP use. Because of a lack of literature on the topic, it is uncertain whether OA users, or those undergoing surgery or lifestyle modifications, feel insufficiently supported.

Information Needs

Participants of one study suggested more initial support when first starting CPAP, especially as patients are likely to have questions in the first days and weeks of using CPAP. One participant stated, “I would make sure that they had good instructions on how to adjust those masks and little different things you can do to them. Just to make the transition a little bit easier. ’Cause I know it was real difficult for me the first night ’cause it was the first time I had ever put on one of those full masks. I had a tough time getting the straps all right and situated.”[216] This included ensuring that partners were involved in receiving information, and discussing the benefits that both partners and patients experience when CPAP is used.[213,216] One partner commented, “She got all information by herself; I knew much less than she knew, so I wasn’t much of a support and help when it didn’t work and she got insecure.”[213] Other suggestions for getting patients to use CPAP more effectively included access to a 24-hour hotline, early interaction with health care practitioners, hands-on demonstrations of the equipment, and receiving feedback about their CPAP use.[216] Participants also had a lack of knowledge about their PAP machine, as a fifth of participants in one study did not know the manufacturer of their machine, the model, or the pressure settings.[199]

There was some uncertainty regarding how to best care for CPAP machines, including the best ways to clean them and what cleaning products should be used.[209,221] Participants in one study tried to seek information related to CPAP usage, choosing a mask, cleaning, troubleshooting, servicing, repair and maintenance, but found this difficult.[221] OA users also expressed uncertainty over how best to clean the appliance, including which cleaning products were most suitable.[209]

Regarding lifestyle changes, participants were uncertain about nutritional knowledge for weight loss.[218] Participants reported uncertainty regarding nutrition, portion size, cooking skills, and shopping for healthy foods.[218] Some participants wanted more practical support to be able to better implement healthy eating practices.[218]

Those using CPAP and OA and changing their diet expressed a lack of practical knowledge about the intervention. There was some overlap in these information needs, such as a need for information about cleaning CPAP and OAs. However, CPAP users also needed more information regarding how best to use the device.

Adaptation and Problem-Solving
Perseverance and Intervention as Routine or Habit

CPAP and OA users and people making lifestyle changes report a need to adjust and adapt to the new routine or treatment to overcome difficulties and initial discomfort as described above. People identified this as an adjustment period, with the experience improving after they got used to the device. For some, this was a matter of weighing the benefits of using CPAP to persevere through any difficulties they might experience.[216,217]

A process of adaptation and adjustment was described by people using CPAP, and their partners. Both patient and spouse recognized the adaptation process and gained a deeper understanding of the OSA, and the need for CPAP treatment and its positive effects, as well as an acceptance of its side effects.[217] Some patients are able to integrate

CPAP into their lives and it becomes an established routine.[213] This sense of a period of adaptation, from the initiation of CPAP and integration into a patient's life, was explored by the systematic review by Ward.[207] The authors found that the less time had passed from the initiation of CPAP, the more dissatisfied patients were with treatment; however, the majority of patients (90% to 99%) who persevered with therapy beyond six months were satisfied with treatment.[207] As reported by a study included in the SR, after six months of CPAP treatment, patients and their spouses noticed that they had adapted to the CPAP device and were experiencing benefits: "I don't need to tell him to use the CPAP as before, because he's so aware of the positive effects."[237] Problem-solving and adaptation over time were reported as essential to mastering the device; otherwise, treatment was abandoned.[207] For some, there is a sense of dependence on the machine and they express a feeling of not being able to live without it,[210,221] although it is uncertain how soon after initiation with therapy dependence develops. This was expressed as a positive emotional attachment to their CPAP machines.[210] One participant stated, "You've got to practically love your machine, knowing that it's there to keep you alive."[210]

Integrating CPAP is a complicated routine for some and difficult to establish.[213,219] Patients can have a difficult time adjusting to the pressure of CPAP and creating a routine with CPAP.[219] Patients found it difficult to read in bed while using CPAP, and some would fall asleep while reading and thus not wear their CPAP.[219] Spouses too can find it difficult to integrate it into their routine. As one spouse described, "I help out by boiling water each and every other night; that's one thing I can feel is a bit complicated, if I remember it too late, and the water needs to cool and stuff."[213]

The process of persevering with OAs was not well described in the literature; however, it should be noted that it also may take time before OAs are routine for patients. In one study,[226] only 27% of patients were immediately able to tolerate on OA, while 33% required a few days, 21% needed more than one week, and the remaining patients (8%) needed more than a month. This study reported that patients were willing to wear the Dynamax appliance on a long-term basis.[226]

For people making lifestyle changes, specifically to their diet and exercise, recognizing problems and making adjustments was seen to be important to adapting to the change. Physical activity was mentioned as being routine for some, and that lapses in routine could hinder the ability to be physically active.[215] Creating structure around meals and diet, such as planning regular meal times, was seen as helpful to maintaining a healthy diet.[218]

It took time for both CPAP and OA users to persevere with the device and incorporate it into their daily routines. For those undergoing lifestyle modifications, this was also expressed as a change in routine and the need to establish the intervention as part of their life.

Time

Interventions were described as time-consuming in three studies.[214,215,218] For CPAP, participants spent a great deal of time setting up or maintaining their devices.[214] One patient remarked, "Yeah, [at first] [getting PAP equipment ready for use] took a while. It was about 40 minutes and then I broke it down in about 20 minutes."[214] Similarly, participants also commented that physical activity[215] and healthy eating[218] were time-consuming, and too difficult to become part of their routine.

Motivation for Physical Activity

Problems with CPAP treatment[230] and complying with exercise and physical activity[215] motivated patients to participate in programs to support adherence.[230] The desire to receive more information and knowledge about sleep apnea[230] and seeing positive results of their effort[218] was a motivational factor for many patients.[230] In other cases,[215] some patients articulated a lack of personal motivation for exercising, but an admission that incentive to exercise was important.[215]

People expressed various incentives to participate in their recommended exercise:

- Exercise had few side effects, and there was more reason than just OSA to exercise[215]
- People had positive expectations of engaging in physical activity[215]

- Exercise had become an established habit for some people[215]
- For some informants, there was ambivalence between positive and negative outcomes of physical activity[215]
- Choosing an activity that participants find enjoyable, interesting, and safe[215]
- That the activity should have an achievable goal[215]
- To some patients, "challenging yourself would make it easier to be physically active," whereas others mentioned the "importance of a welcoming and tolerant atmosphere of feeling accepted."[215]

In addition, experiencing benefits from CPAP use also motivated some individuals to become more physically active, likely due to an increase in energy. As one Māori male commented, "In turn, it's giving me a bit more energy, which I… I'm in the gym, losing weight… I've changed my diet."[210]

For some people, their dog was perceived as a facilitator for physical activity as it was easier to take a walk with the dog than alone.[215]

Cost

Even after initiation of treatment, patients may find the cost of maintaining their devices to be challenging. The features and durability of a device (CPAP or OA) can vary. Patients were sometimes disappointed in the durability of the OA and the frequency with which it needed to be repaired or replaced. In one study, patients' estimates of the life of an OA ranged from 1.5 to three years. Patients were disappointed by the poor durability and subsequent expense and inconvenience of doing repairs or getting replacement OAs.[209]

Additionally, in one study,[220] a patient experiencing relief from CPAP as well as significant weight loss expressed a desire to schedule another sleep study, but struggled to justify the cost. "I've been using a CPAP for eight years now and recently have lost 81 lbs... Is it possible I don't even need a CPAP anymore? What would symptoms be of too high a pressure (or not needing CPAP but using it anyway)? I know I probably need to schedule another sleep study but don't have the money right now to do so — will as soon as possible!"[220]

Psychological Impact

In the same vein as experienced benefits, patients had an array of psychological impacts related to treatment. The following section explores the described psychological impact, both positive and negative, that patients experienced on treatment. In some cases, the manifestation of these feelings before treatment is also explored, as it gives insight into how this might change over time or be pervasive even after treatment initiation.

Anxiety

Before treatment, both patients and partners described feelings of anxiety.[211,222] This anxiety often revolved around apneas and a fear for future health risks, such as CV disease or MVA.[222] A partner's anxiety was motivation for some patients to seek information.[211] Partners were also worried about their own health.[222]

Both CPAP use and surgery reduced anxiety felt by patients. Two participants, from different studies, stated that their CPAP machines reduced anxiety and were their "security blankets."[210,219] Regarding surgery, one study found that patients' anxiety lessened post-surgery.[232] Patients were less anxious about the long-term health consequences of OSA, and were less anxious about sleeping away from home.[232]

Confidence

Confidence enabled both lifestyle modifications and CPAP use. Participants trying to lose weight reported being encouraged if they felt confident in exercising,[215] or had experience with previous success that gave them confidence.[218] The SR found that users of CPAP were able to persevere with therapy if they had confidence using the equipment.[207]

Embarrassment

Before treatment, patients may be embarrassed due to their snoring.[197] Women in particular were embarrassed about snoring and they perceived it to be a less embarrassing condition for a man.[197]

Several studies mentioned patients feeling embarrassed because of CPAP use.[209,210,219] Embarrassment was a factor in choosing which device to use.[209] As previously stated, some patients prefer a discreet intervention, such as an OA rather than CPAP, because they would be less embarrassed to use this around others.[209] Māori patients described feelings of embarrassment due to using CPAP in shared accommodations; however, this embarrassment might be overcome because of the benefits of CPAP use.[210] As one patient said, "If there's a tangi [funeral], I'll take it with me. I don't care who's watching. At least I'll wake up feeling good."[210] Using CPAP left marks on the face, which some patients also found embarrassing.[219]

Fear

Two causes of fear related to CPAP use were reported. In two studies, patients were afraid of the consequences of not using CPAP.[207,224] In one study, partners made the patients feel afraid of not using CPAP.[224] For some, the fear of nonadherence was multilayered, and related to a fear of adverse social outcomes, reduced productivity, risk to relationships, and driving; this fear motivated CPAP use.[207] Other users of CPAP were afraid of the machine and feelings of air hunger. One patient commented, "It was scary at first; it felt like one wouldn't get any air."[219]

Guilt

Before treatment, partners felt guilty about sleeping in a different room although they also wanted an undisturbed night's sleep.[222] The SR found that some patients felt guilty for not using CPAP.[207]

Helplessness

Feelings of helplessness were reported by one study, and some participants stated they felt helpless when it came to controlling obesity through diet.[218]

Shame

Before treatment, persons with OSA felt shame about falling asleep in front of others, or about their loud snoring, and would avoid activities (such as travel or visiting friends) because of this.[211] Patients also perceived that their families felt ashamed of their snoring.[211] Women felt particularly ashamed, as they felt this was related to gender; as one woman said, "It's very difficult for a woman to be a snorer. It doesn't sound nice! It has, and will always be, related to men. It's clearly an annoying problem."[211]

Regarding CPAP, users had feelings of shame related to using the machine.[197,213,216] Shame was related to their appearance while using the machine[197,213] and for needing to use CPAP.[216] These feelings of shame may be initial barriers to CPAP, and as one patient put it, "In the beginning, I had the full mask and it was very disconcerting, not only physically but emotionally. I don't know that anyone else experienced this, but I really felt ashamed. I was mad at myself for being in this position and I had to build up time on the machine."[216] This included being reluctant to talk about their CPAP use with their partner and friends, as described by one participant: "We do get visitors, but they haven't seen the device, because they're not in our bedroom, and we haven't told anyone."[213] Partners feared that if the patient felt ashamed, this would negatively impact adherence with CPAP.[213]

Summary of Patient Perspectives and Experiences Results

This review aimed to address the question of what the experiences and perspectives of adult patients and their caregivers are regarding treatment for OSA. Thirty-two studies were included in the thematic synthesis, from which two analytic themes were derived.

First, patient characteristics and the surrounding context in which treatment is offered will affect treatment choices, including the decision on whether or not to pursue treatment. Patients are influenced by the information they have on therapy, any disability the patient may have, whether they receive support for complying with the intervention, and

their current life situation. Before even starting treatment, patients may have perceptions and attitudes regarding treatment. There were some people who knew others with OSA and who had experience with treatment, mainly CPAP, and thus had pre-existing expectations. Some of these attitudes were positive, and there was hope that interventions could relieve the symptoms of OSA, but there were others who considered the interventions to be invasive and burdensome. This will also factor into whether a person considers their lifestyle to be conducive to certain therapies. Patients who travel frequently, or enjoy activities such as camping, may find CPAP restrictive and thus prefer something more portable (it's uncertain how they view surgery in comparison). Those who are partnered may find something discreet, such as an oral appliance, preferable to CPAP. Related to Lifestyle Impact, the cost of an intervention can directly relate to what intervention a patient chooses and how a patient is able to navigate their treatment. Cost is contextual, and the cost of devices and reimbursement practices will vary by region, just as the socioeconomic status of patients will vary. A patient's private health insurance may be another factor related to treatment choice. It is important to note that the cost of treatment may be too great a barrier for some, and that others will be willing to pay any price to find an intervention that works.

Interventions for OSA require a period of adaptation (for devices) and lifestyle change, although some patients are non-compliant to therapy for a variety of reasons, each of which is personal and contextual to the individual. All interventions had some degree of discomfort, and this discomfort may change over time as patients become accustomed to the device and there is a recovery time for surgery. For some patients, especially those with mild OSA, these feelings of discomfort were enough of a deterrent for using therapy. For others, the experienced physical, mental, and social benefits of using an intervention for OSA were motivation to continue treatment, and there were numerous benefits. Patients using devices and patients post-surgery experienced improved moods and had more energy, in addition to other benefits. However, there were various reasons for using or not using a prescribed therapy, and this will be individualized for each patient. For those using CPAP, the sense of embarrassment and perceived ugliness while using the device might be a reason for nonadherence. Those with supportive partners may be able to persevere and continue with treatment, although not all partnered peoples had supportive spouses. In a very real way, OSA interventions affected patients and their partners, and decisions regarding treatment may be made within the context of their relationship with a consideration of their spouse.

When considering which intervention to use, people may consider how the intervention might affect their sexual relationships.[209,217] This is seen in some participants preferring OAs over CPAP, due to their discreetness; as one participant said, "And so, like, I don't know anybody who is in a new relationship who would stick one of those things [the CPAP] to their face, you know. It's just not too appealing. But the oral appliance is not a big deal…Don't even know it's there."[209]

Regardless of what patients choose to do, they must be supported by their health care providers and their partners and family. Receiving the right information, whether it be information about treatment choices or how to care for the devices they choose to use, is an important component of supporting patients with OSA, as well as their caregivers. This was related to whether patients felt supported, and if so, where they received that support. Patients identified the importance of having early interaction with a health care professional following initiation of CPAP, and also expressed a desire for professional support and reassurance at night. One finding was that patients had to persevere with treatment and that for those who could tolerate treatment, the intervention had to become part of their routine. Partners found this, too: that the intervention also became a matter of routine, with some partners helping patients with their CPAP machines, or with lifestyle changes.

It became evident that sleep influences many aspects of a patient's life and that the patient experiences regarding treatment were multifaceted, drawing on the individual experience but also the influence of OSA on the partner. Patients would benefit from a choice of intervention, and choice of device within each intervention category. This would help to address concerns regarding adherence with OSA interventions and whether patients are maximizing the benefits of treatment. The findings of the implementation review offer a practical lens of the challenges and supports to how programs for OSA interventions may be realized in clinical practice.

Ethics Analysis

This section addressed Research Question 4: What ethical issues are raised by providing PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications to treat OSA in adults? How should these issues be addressed?

Background

Ethics is the inquiry into the goodness or rightness in life; it examines questions about what we owe to each other and what it means to be a good person. Applied ethics uses ethical or moral theory (ethics and morals are used interchangeably in this analysis) to find answers to these questions for particular topics and contexts. Topics or questions where important values are clearly at stake for individuals or populations are called ethical issues. An ethical issue may also be an ethical dilemma if two competing values are at stake. For example, whether or not to require health care providers to be vaccinated is an ethical issue because it challenges two important values: the value of supporting freedom and independence and the value of patient safety and maximizing public health. It is also an ethical dilemma because it is not possible to live up to both values in their entirety at once. The goal of an applied ethics inquiry is to balance values and arrive at a resolution for the question at hand.

Ethics analysis is used in this report to evaluate new technologies for ethical issues and dilemmas. HTA is the evaluation of new technologies or new applications of existing technology to determine whether they should be implemented (and sometimes publicly funded) within a health care system. HTA is fundamentally value-laden and proceeds with the following implicit values:

- The technology should achieve the goal it is set out to achieve
- The technology should achieve that goal without creating more harm than good
- The financial requirement to adopt and implement the technology should not be disproportionate to its benefit
- Adopting the technology should not pose serious threats to human integrity and dignity.

In addition, there are two broad normative questions that are relevant to most HTAs:

1. Should the technology be endorsed or made widely available?
2. If yes, how should the technology be made available?

This HTA pertains to interventions that may resolve or prevent symptoms for patients with OSA. OSA can cause daytime sleepiness, irritability, inability to actively participate in life, and inattentiveness (which can increase the risk of MVAs) as well as long-term health consequences such as stroke, heart failure, and cardiovascular disease.[246] In this HTA, we analyze and summarize the ethical issues for treatment of OSA with symptom-reducing interventions — PAP ventilators (commonly CPAP) and mandibular devices — as well as more curative interventions, such as surgery and lifestyle changes.

Inquiry

There are two broad normative questions to consider regarding interventions for OSA:

3. Which, if any, interventions for OSA should we recommend for usage, and why?
4. How should these interventions be provided to OSA patients?

Both of these questions are matters of systems-level or population-level ethics, which examine questions that will affect a large number of people and in which outcomes and interests are considered in aggregate (organizational ethics, policy ethics, and public health ethics are all domains of systems-level ethics). For systems-level ethics, instead of asking “Does this technology benefit the patient?” and “Does this technology disadvantage vulnerable individuals?”, we ask, “Does this technology create overall benefit for the population?” and “Does this technology

disadvantage marginalized groups?" Questions of individual autonomy are of lesser concern when using this approach; however, if a technology were to present broad challenges to individual choice within a relevant population, this would be reason to consider seriously whether it would be ethically justifiable to endorse or implement the technology universally.

The determination that a technology should not be implemented may be made for several reasons:

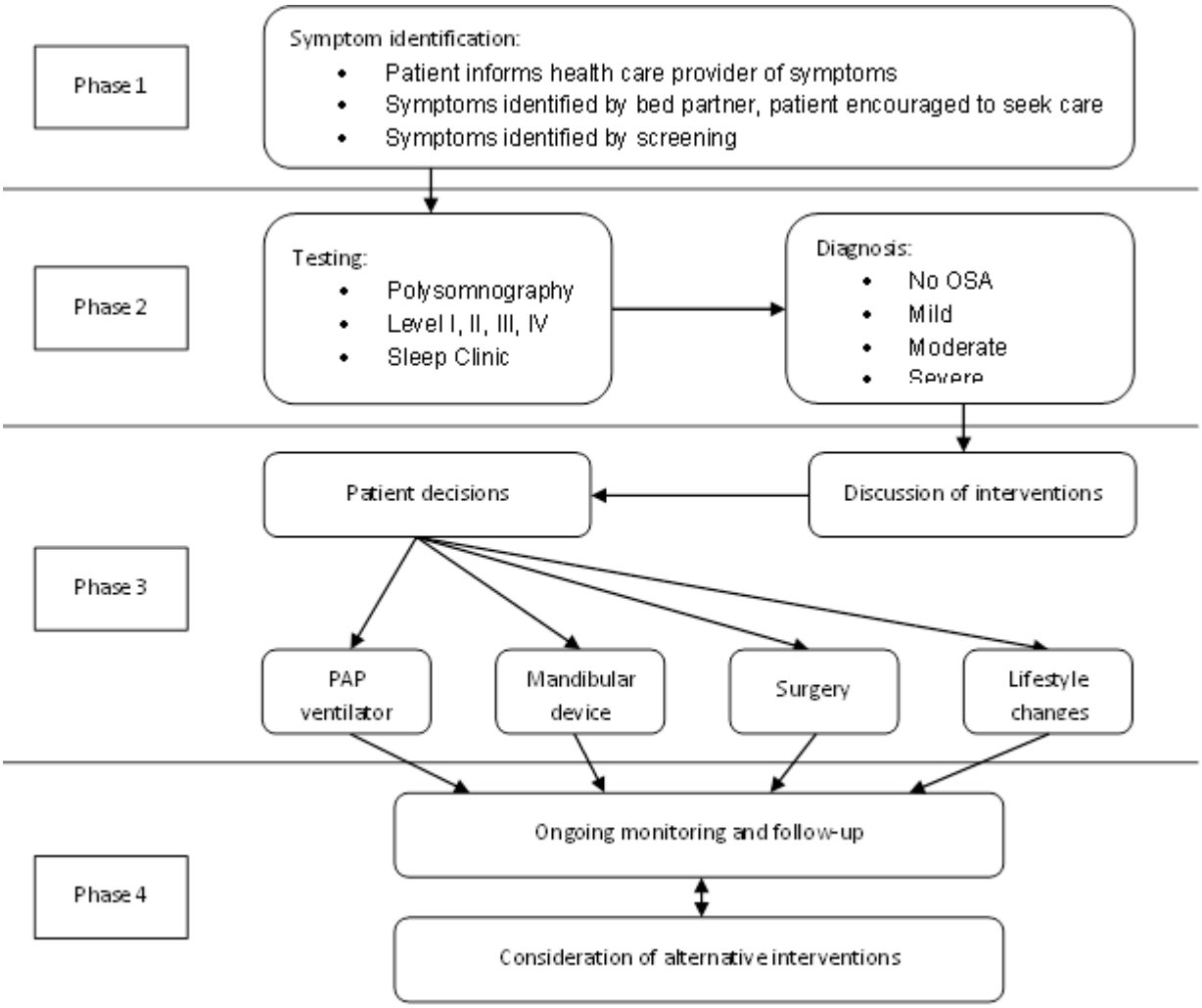
- The technology offers little to no evidence of benefit at the population level.
- The technology does offer benefit at the population level, but the degree of benefit is disproportionate to the cost.
- The technology presents significant issues for respect for populations affected by the technology, and these issues cannot be mitigated by careful implementation. Such issues include systematic affronts to dignity, autonomy, and personhood and the oppression of particular groups, especially those who are already vulnerable or who may become vulnerable as a result of the technology.

If the answer to the first question is "yes, the technology should be implemented" or at least not "no," the second question about how the technology should be implemented should be considered.

The development of a response to this question requires consideration of the nature of the technology from the individual perspective, invoking an individualist or bedside ethics approach (sometimes referred to as clinical ethics). Closer attention must be paid to considerations of respect, benefit, autonomy, dignity, and fairness from the individual perspective to uncover how the technology could be implemented and delivered in a way that lives up to key values or principles. If the analysis determines that the technology cannot be implemented in a way that sufficiently lives up to core values, it may cause the first question to be reconsidered.

To consider the ethics dimensions of interventions for OSA, this ethics analysis understands the technology under consideration to be represented by the pathway in Figure 5. This pathway is purposely broad in scope to address the range of interventions available (symptom-reducing to curative) and to underpin the wide array of potential ethical issues associated with those interventions. Consideration of all steps along the pathway (symptom identification, testing, discussion of interventions, intervention use, and follow-up) is important because the anticipated benefits of the technology (i.e., overall improvement of public health) are achieved in the final phase.

Figure 5: Clinical Care Pathway of Diagnosis and Interventions for OSA



OSA = obstructive sleep apnea; PAP = positive airway pressure.

The ethics analysis of interventions for OSA also involves a descriptive question:

- What are the key ethical concerns identified in the literature on interventions for OSA?

This question aims to uncover the arguments and values that others have proposed to be relevant to ethical deliberation about OSA interventions and their use within the pathway (Figure 5). Those arguments and values can then be used to inform the answers to the normative questions posed by this HTA.

Methods

Literature Search Strategy

The literature search was performed by an information specialist, using a search strategy peer-reviewed according to the PRESS checklist — an evidence-based checklist for the peer review of electronic search strategies.[41]

Ethics-related information was identified through targeted literature searches of the following bibliographic databases: MEDLINE (1946–), with in-process records and daily updates, via Ovid; CINAHL (1981–) via EBSCO; and PubMed. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH terms, and keywords. The main search concepts were sleep apnea, sleep-disordered breathing, and key terms for ethics concepts. No methodological filters were applied to limit retrieval by study design. Retrieval was not limited by publication date. Results were limited to English- and French-language publications. The detailed strategy can be found in **Appendix 1**.

The search was completed on March 7, 2016. Regular alerts were established to update the search until the publication of the final report. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching sources identified in the *Grey Matters* checklist[42] (https://www.cadth.ca/grey-matters), which includes the websites of clinical trial registries, regulatory agencies, HTA agencies, clinical guideline repositories, and professional associations. Google and other Internet search engines were used to search for additional Web-based materials.

Selection Criteria

The selection of relevant literature occurred in two stages. In the first stage, the title and abstracts of citations were independently screened for relevance by two reviewers (KD and KB). Articles were categorized as "potentially relevant" or "not relevant" based on the following criterion:

- Explicitly identified an ethical issue related to interventions for OSA for either patients or family members affected by OSA

In the second stage, full-text reports that met the following three criteria were included in the analysis:

- Pertained to OSA in adult populations
- Pertained to the interventions for treatment of OSA
- Suggested ethical issues relating to
    a. Patient decision-making (Autonomy)
    b. Adherence to treatment (Benefit)
    c. Quality of life (Benefit)
    d. Access to diagnosis, interventions, follow-up (Fairness/Equity)
    e. Allocation of resources (Fairness/Equity)
    f. Effect for bed partners (Well-Being of Others)

Screening and Selection of Studies

During the screening process, ethical issues that were identified from articles captured by the literature search that did not meet the strict relevance criterion of explicitly mentioning ethical issues. This second stage reflects the more typical approach of ethics scholars of performing a comprehensive literature review to uncover relevant material, relying in part on reason and judgment. Although a formal SR is an excellent way to gather relevant articles within the scientific literature, ethics issues are often not named explicitly in articles, which can make it challenging to identify good search terms. For example, an article may describe the inequities in access to diagnostic services for OSA without ever being explicit about the clearly ethical dimensions relating to fairness and justice. This can create issues if the selection criterion requires that the article's subject matter be explicitly identified as about or relating to "ethics." In addition, rigour in ethics scholarship comes from accurate contextualization and strong argument, and unlike scientific findings, ethics conclusions do not become more significant as their frequency in the literature increases. Similarly, the lack of material about the ethics dimensions of a particular technology does not mean that there are no

ethical issues raised by the technology. For these reasons, implicitly raised ethical issues identified by the reviewers were used to supplement the SR and achieve a robust ethics analysis by giving them equal weight.

Disagreements between reviewers were resolved by discussion to reach a consensus. The details of each report, including lead author, publication date, journal, potential ethical issues raised, and report conclusions, were summarized in a separate document.

Results

The literature search yielded 1,268 unique citations, none of which passed the first stage of screening, because no articles on OSA treatment were found that explicitly mentioned ethical issues. However, the reviewers selected 142 potentially relevant articles which raised implicit ethical issues. See **Appendix 17: Coverage in Canada (Research Question 2), Appendix 22** for the flow diagram of the literature search and selection process, and **Appendix 23** for the list of potentially relevant studies.

Two reviewers (KD, KB) each reviewed the full text of 20 articles to identify ethical issues implicit in the articles. A list of potential issues was identified and the reviewers discussed the issues raised to ensure that the issues were relevant and had been adequately described. Based on this initial review, one reviewer (KD) examined the remaining 102 articles for additional implicit ethical issues. The results of the clinical, economic, and patient perspective reports were also examined for information relevant to the ethics analysis. Table 116 provides a summary of the ethical issues implicit in the examined articles and that were relevant to the six categories of issues listed in the Methods section.

Table 116: Values and Ethical Issues Raised by Treatments for OSA

Maximizing benefits and minimizing harms to patients This value sits at the core of bioethics and describes duties at every level to fund, organize, and deliver health care services in a way that gives maximal chance of benefit and creates minimal harm. Benefits and harms can be physiological (relating to illness, comfort) and psychosocial (relating to emotional, relational, and psychological well-being). For treatment of OSA, patient adherence to the treatment plan is crucial for the benefits of treatment to materialize. For this reason, factors that lead to increased adherence were extracted for this analysis.		
Physiological	Maximizing quality of life through symptom management[237,247-251]	Boone 2006; Brostrom 2008; Brostrom 2010; Glazer Baron 2012; Johal 2011; Parish 2003
	Minimizing harm of long-term health effects (hypertension and CVD)[237,250]	Brostrom 2008; Johal 2011
	Ongoing support for intervention use from health care providers (lack of adherence due to lack of ongoing support to manage issues)[217,248,252-256]	Brostrom 2010; Archibold 2009; Gauthier 2012; Gotzche 2010; Neuzeret 2016; Shapiro 2010; Shoukry 2011
	Relationship between social arrangements (e.g., marriage or stable relationships) and seeking of treatment and adherence[197,249,256-262]	Cartwright 2008; Aloia 2009; Ashtyani 2003; Baron 2009; Baron 2011; Glazer Baron 2012; Gunbey 2014; Henry 2013; Shapiro 2010
	Harms of CPAP due to technical issues (mask leaks, etc.) and side effects (dry throat; blocked-up nose; claustrophobia)[209,248,256,263]	Brostrom 2010; Almeida 2012; Bollig 2010; Shapiro 2010
	Improved CPAP adherence with surgery[264]	Chandrashekariah 2008

Table 116: Values and Ethical Issues Raised by Treatments for OSA

Psychosocial	Improved CPAP adherence with education (polysomnograph viewing[265]) and support[235,239,246,256,266-271]	Dickerson 2006; Falcone 2014; Aloia 2007; Ayow 2009; Fox 2012; Lettieri 2013; Parthasarathy 2013; Pelletier 2012; Shapiro 2010; Smith 2006; Stepnowski 2007
	Engagement with work or social life[237,248,272]	Brostrom 2008; Brostrom 2010; Reishtein 2006
	Embarrassment due to need for or appearance created by CPAP[209,248]	Brostrom 2010; Almeida 2012
	Fear or stigma of image of being sick[235,237,254,273]	Brostrom 2008; Ayow 2009; Gotzche 2010; Shahrabani 2014
	OSA treatment improves mental health[274,275]	Doghramji 1993; Joseph 2009
	Work of incorporating CPAP into daily life[220]	Moreira 2008
	Economic harms[276]	Jennum 2014
Maximizing benefits and minimizing harms to others This value describes duties to fund, organize, and deliver health care services in a way that takes account of impacts on those who are not the patient but who could be affected nonetheless. In most cases, the focus is on family and loved ones. At a systems level, this includes whether the technology creates harms for specific subpopulations that are not the intended target of the technology. Benefits and harms can be physiological (relating to illness, comfort) and psychosocial (relating to emotional, relational, and psychological well-being).		
Physiological	Improved sleep of bed partner[249,259]	Ashtyani 2003; Glazer Baron 2012
	Risks posed by increased MVA risk associated with OSA[159,277,278]	Olszewski 2013; Rodenstein 2009; Sanna 2013
	Quality of life for bed partner[222,237,249,251,259]	Brostrom 2008; Ashtyani 2003; Glazer Baron 2012; Parish 2003; Stalkrantz 2012
Psychosocial	Economic harms[276,279]	Jennum 2014; Jennum 2011
	Quality of relationship with patient[237,248,272]	Brostrom 2008; Brostrom 2010; Reishtein 2006
Distributing benefits and burdens fairly (equity) This value describes broad social duties to consider matters of justice and to avoid disproportionately benefiting or burdening particular individuals or populations without clear justification.		
Access to appropriate diagnosis (polysomnography and sleep clinics)[273,280-282]		Hirsch Allen 2016; Marchildon 2015; Paine 2007; Shahrabani 2014
Access to equipment (devices, CPAP)[258,283-287]		Fleury 2015; Aloia 2009; Tarasiuk 2012; Hamblin 2014; Simon-Tuval 2009; Tzichinsky 2011
Prevalence of OSA in marginalized populations (lower SES; obesity; substance use; veterans with PTSD)[288-291]		Campbell 2010; Johnson 2015; Williams 2015; Yesavage 2012
Ability of patients to sustain adherence to CPAP due to context[247,262,273,288,292]		Boone 2006; Campbell 2010; Gunbey 2014; Platt 2009; Shahrabani 2014

Table 116: Values and Ethical Issues Raised by Treatments for OSA

Respecting patient autonomy This is a key value in Western society that recognizes individuals' roles in determining their life course. In health care contexts, informed consent is a means of respecting patient autonomy by enabling patients to make an informed decision about their care.	
Good decision-making through informed consent[254,293]	Gotzche 2010; Jalbert 2012
Enabling context sensitive decision-making and flexibility[382]	Shapiro 2010
Decision to end CPAP intervention[247]	Boone 2006
Improved self-efficacy through information sharing and attitude shifts[252,258,266,267]	Aloia 2007; Aloia 2009; Archibold 2009; Lettieri 2013

CPAP = continuous positive airway pressure; CVD = cardiovascular disease; HTA = health technology assessment; MVA = motor vehicle accident; OSA = obstructive sleep apnea; PTSD = post-traumatic stress disorder; QALY = quality-adjusted life-year; SES = socioeconomic status.

Articles obtained from the literature review predominantly examined the question of how best to use various interventions to manage OSA; a small number of studies examined broader systems-level questions (e.g., the economic costs of untreated OSA and the evidence base for making decisions about interventions for OSA). As systems-level questions are appropriate domains to begin our ethics analysis, we added two broad values to the analysis: maximizing benefit and minimizing burdens for populations and stewarding scarce resources (Table 117). These values are relevant to the discussion of the question of whether interventions to address OSA should be provided.

Table 117: Relevant Systems-Level Ethics Considerations (Values)

Maximizing benefits and minimizing burdens for populations This value articulates the importance of actions that confer benefit to the community or population as a whole. In health care, benefits are typically taken to be minimized incidence and prevalence of disease, minimized suffering associated with illness, and a reduction in preventable deaths. In HTA, we examine the extent to which a technology can be beneficial by looking at its clinical effectiveness.	
Accurate screening for risk[294,295]	Adams 2012; Annamalai 2005
Quality of evidence for OSA interventions (surgical)[254]	Gotzche 2010
Stewarding scarce resources This value describes the duties to make wise use of scarce resources, especially if these resources are shared by many. Closely related to values of efficiency, this value places economic decisions within the realm of ethics, with the view that resources should be used to achieve agreed-upon aims, and further, that these aims are achieved within reasonable expenditures. In health care, the aim is typically to minimize suffering and improve health outcomes. To assess whether resources are being used appropriately, economists can support decision-makers by examining how much it costs for the technology to produce a QALY. Although this is not without controversy, it is generally thought that a cost per QALY that is beyond a certain threshold is not an appropriate use of resources.	
Socioeconomic costs of untreated OSA[34,279]	Jennum 2011; Tarasiuk 2013
Improved CPAP adherence with education (polysomnograph viewing[265]) and support[235,239,246,256,266-271]	Dickerson 2006; Falcone 2014; Aloia 2007; Ayow 2009; Fox 2012; Lettieri 2013; Parthasarathy 2013; Pelletier 2012; Shapiro 2010; Smith 2006; Stepnowski 2007

CPAP = continuous positive airway pressure; CVD = cardiovascular disease; HTA = health technology assessment; MVA = motor vehicle accident; OSA = obstructive sleep apnea; PTSD = post-traumatic stress disorder; QALY = quality-adjusted life-year; SES =socioeconomic status.

Analysis

Should Interventions for OSA Be Provided?

Maximizing Benefits and Minimizing Burdens for Populations

Articles obtained from the literature review predominantly examined the question of how best to use various interventions to manage OSA; a small number of studies examined broader systems-level questions (e.g., the economic costs of untreated OSA and the evidence base for making decisions about interventions for OSA). As systems-level questions are appropriate domains to begin our ethics analysis, we added two broad values to the analysis: maximizing benefit and minimizing burdens for populations and stewarding scarce resources (Table 117). These values are relevant to the discussion of the question of whether interventions to address OSA should be provided.

Generally, health care funding is intended to improve the health and well-being of a population; however, the specific intentions and goals of services, as well as effectiveness of interventions, need to be considered when assessing benefit at the population level. For OSA, the general intention of treatment at both the individual and population level is to minimize short-term and long-term effects. Clinical effectiveness data show that CPAP, particularly when compared with inactive controls and pre-treatment measurements, is effective at achieving many significant outcomes, including minimizing perceived sleepiness (as measured by the Epworth Sleepiness Scale [ESS]), improved disease severity, decreased blood pressure, and improved cognitive and psychological functioning (see 3.2.4. Data Analysis and Synthesis). Of note, MADs also show favourable outcomes among many of these domains, when compared with inactive controls and pre-treatment measures. Studies comparing MADs with CPAP find no difference in their respective effectiveness at reducing perceived sleepiness (again, ESS), lowering blood pressure, improving cognitive functioning, and improving quality of life. Studies have shown that CPAP is more effective at reducing disease severity (defined in terms of AHI events).

Limited data are available on the comparative effectiveness of surgical interventions and lifestyle changes (such as diet, exercise, weight loss, and positional therapy). The studies that are available suggest that lifestyle changes can generate improvements in the various dimensions above compared with inactive controls and/or pre-treatment; they do not generally provide as much benefit as CPAP and MADs. Surgical interventions have been shown to improve perceived sleepiness and are best able to create outcomes that could be considered a cure (defined as an AHI < 5). The clinical effectiveness portion of this report should be reviewed for a more detailed summary of the data on these interventions.

Unlike the more curative interventions (surgery and lifestyle changes), the effectiveness of symptom-reducing interventions (CPAP and mandibular devices) is more dependent on adherence by the individual patient. For example, CPAP is a complex and burdensome treatment and adherence (often defined as more than four hours per night, seven nights a week) can vary from 28% to 83%.[256] Adherence can also be an issue for mandibular devices. Ultimately, whether benefit to the population is achieved will depend on the actual use of the intervention within the population. For this reason, overall effectiveness of interventions must be considered under variable conditions, not optimal usage. When considering whether CPAP (or other interventions) should continue to be funded, or be funded differently, factors that appear to increase adherence and their ability to be implemented in an OSA intervention strategy should be considered.

Overall, it appears that all four major intervention categories (PAP, mandibular devices, surgery, and lifestyle changes) have some potential to create benefit for the population. Those that are anticipated to offer the most benefit (likely, CPAP or mandibular devices, depending on disease severity) ought to be offered first, although an openness to the pursuit of other options either alongside, or in combination, should be considered in circumstances where the patient is unlikely or unable to benefit from the more optimal intervention.

Stewarding Scarce Resources

From an ethics perspective, the value of stewarding scarce resources describes duties of decision-makers in our health system to use scarce public resources in a way that provides as much benefit (broadly interpreted) as possible. This usually requires using the treatments that provide the most benefit at the lowest cost. The evaluation of how a resource can most appropriately be spent requires not only knowledge about QALYs for a particular technology, but also knowledge about opportunity costs and relative QALYs for competing technologies and services within the same budget. Because this contextual knowledge cannot be known here, it is difficult to conclude whether interventions for OSA deliver on our values of stewarding scarce resources. However, studies that examine health care costs of individuals with untreated OSA suggest that unmanaged OSA can create significant costs for health systems. Presumably, the costs of treated OSA would be less than those that arise from care for those who do not receive treatment. If this is true, there would still be a need to evaluate the benefit within overall health spending to assess the trade-offs that may be required should additional public funds be diverted to further treatments of OSA.

The economic evaluation for OSA interventions (not including lifestyle changes) shows that based solely on cost, CPAP is the least costly option, followed by mandibular devices, and surgery (see 4.2.2. Model Results). The effectiveness of a given intervention, and therefore cost-effectiveness, may vary depending on the severity of the disorder. For example, mandibular devices are more effective than CPAP for mild OSA but the opposite is true for more severe cases. For severe OSA, surgery may even be considered the most cost-effective option, depending on the willingness-to-pay per QALY. Overall, CPAP is both more effective and less expensive than alternatives for moderate or severe OSA and should be offered as the first-line treatment in the context of stewarding scarce resources. Surgery could be considered for more severe cases, although individual jurisdictions would need to consider this in their specific contexts.

Distributing Benefits and Burdens Fairly (Equity)

Ideally, access to the necessary expertise, services, and devices involved in OSA treatment would be fairly distributed among the affected population regardless of income level, education, or cultural background. As with many health services in Canada, access to OSA treatments is not equally available to all residents. If the current or anticipated system favours access only for those of a particular group (especially a privileged group) *and* that this injustice cannot be rectified, decision-makers would need to think carefully about implementing the program.

Further consideration needs to be given to the consequences of funding for OSA interventions. Studies in other jurisdictions have shown that differences in coverage between interventions (e.g., between a CPAP machine and surgery) can influence patient decisions,[285-287] where patients will choose the less optimal intervention because it is less expensive. This value requires that we address financial barriers to optimal treatment. This does not require that all barriers be removed, but at least that the burdens of these financial considerations not fall disproportionately on those will fewer means.

Respecting Patient Autonomy

When considering the ethics dimensions of whether a particular technology should be offered, we consider whether the technology can be provided in a way that respects patient autonomy, and more broadly, whether it aligns with our fundamental duties to respect people. The value of respecting patient autonomy can be met narrowly, through meaningful informed consent procedures. In any decision-making process in health care, patients should be informed of the clinical risks and benefits of the treatments being offered as well as the practical challenges and burdens that treatments may present. Informed consent processes can ensure that patients understand medical procedures and consent to them. More broadly, we need to consider whether interventions for OSA challenges our duties of respect in other ways (e.g., by further marginalizing vulnerable people, by stigmatizing particular diseases or subgroups within the population). In the case of interventions for OSA, there appear to be no systemic barriers to delivering on these values. On these grounds, the provision of OSA interventions can be ethically justified.

General Implications

Provided that OSA interventions minimize the harms of OSA for the population, that the costs of this testing are proportional to the benefits, and that they do not pose threats to core individual interests or fairness, funding for interventions for OSA can be ethically justified.

How Should Interventions for OSA Be Provided?

For the purposes of this analysis, we will assume that providing interventions for OSA *does* create benefit for populations in the form of improved quality of life and decreased incidences of long-term effects and that these benefits can be obtained with responsible use of public funds. From here, we consider the ethics dimensions of how we might organize the provision of these interventions. We will examine this question with reference to the four phases of the OSA treatment indicated in Figure 5.

Phase 1: Identification of symptoms of possible OSA

Phase 1 of the OSA intervention pathway is initiated when the patient becomes aware that he or she may suffer from OSA. This may emerge from the patient noticing symptoms (e.g., daytime sleepiness, inability to engage in social life), from a bed partner noticing symptoms (e.g., gasping, snoring heavily, or having intermittent periods without breathing during sleep), or through a screening program initiated by a health care provider. In all cases, when the health care provider becomes aware of symptoms, they will refer the patient to testing.

Three key values are relevant to this phase of the pathway: maximizing benefits and minimizing harms to the patient; maximizing benefits and minimizing harms to others (with emphasis on the quality of life and quality of relationships for both patient and bed partner); and distributing benefits and burdens equally.

Maximizing Benefits and Minimizing Harms to Patients

Note that use of the term “patient” refers to the person who has OSA, regardless of his or her actual connection to the health system. Patients suffering from OSA experience difficult day-to-day symptoms (e.g., sleepiness, irritability, inability to spend time with friends and family, difficulty engaging at work, unemployment[197,237,247-251,256-262,272]) and increased risk of serious long-term consequences (e.g., stroke, hypertension, CVD[237,250]), so are subject to harms that could be minimized with effective OSA interventions. From a broad social perspective, individual burdens as well as social costs of this disorder should be considered to see whether interventions (e.g., increased screening, public education) might encourage people to take action to minimize these harms.

Maximizing Benefits and Minimizing Harms to Others

OSA can cause harms and burdens for non-patients as well as patients; therefore, maximizing benefit and minimizing harm to others is also important when considering interventions. Studies have found that bed partners of patients with OSA experience the effects of disrupted sleep[249,259] and can have increased rates of anxiety and depression.[251] In addition, due to the daytime sleepiness of the patient, bed partners are often required to take on more household tasks, including child-rearing and chores.[222] The family may experience economic consequences as a result of the patient’s inability to perform at work, or to work at all.[276,279] Children and other loved ones may be affected by the patient’s lack of energy to engage in relationships; co-workers may be affected if the patient is unable to focus at work, if this leads to errors and absenteeism;[272] and the general public may be at risk if the patient drives vehicles or operates other types of machinery that could harm others in the case of an accident.[159,277,278] Once again, individual burdens as well as social costs of this disorder should be considered to see whether interventions (e.g., increased screening, public education) might encourage people to take action to minimize these harms.

Distributing Benefits and Burdens Fairly (Equity)

One of the unique factors with OSA is that patients are asleep when apnea events occur and cannot witness them firsthand. This creates a difference between individuals with and without a bed partner. For patients with a bed partner, it is often the bed partner who notices snoring, disrupted breathing, and other symptoms and urges the

patient to seek help.[257,258] In contrast, those who sleep alone may notice the consequences of apnea events, but may never become aware of their disrupted breathing. Because those who happen to have bed partners are more likely to receive an OSA diagnosis and treatment in a timely fashion, general efforts to increase awareness among patients who may be at risk for OSA should be considered in the context of fairness to balance out the differing effects of context.

Consideration of the impact on gender is also important from a justice perspective. Women are more likely to have undiagnosed OSA[747] and may not have the same social support as men that encourages them to seek help.[400] The patient experience data (sections 5.2.1 and 5.2.3) suggest that women may be more concerned about perceptions of attractiveness, which may be disrupted by OSA diagnosis and treatment, thus affecting their willingness to seek treatment early or for mild or moderate presentations.

Further, OSA is more prevalent among particular populations, including among those in lower socioeconomic classes, those who use substances, those who are obese, and veterans with PTSD.[288-291] Targeted efforts to increase OSA awareness and access to screening among these populations may be warranted.

Phase 2: Referral to diagnostic testing and/or sleep clinic

During this phase, the patient receives a referral for and undergoes diagnostic testing. There are four levels of diagnostic testing, which vary in comprehensiveness. Level I testing takes place in a sleep clinic under the observation of trained staff, whereas Levels II, III, and IV take place outside a sleep clinic (often in the patient's home) without a sleep technician. Measurements of the sleep cycle from Level I and Level II testing are the most comprehensive, followed by Level III, then Level IV, which only measures one or two variables (typically oxygen saturation and/or air flow [Level I and Level III Sleep Studies for the diagnosis of Sleep Disordered Breathing (SDB) in Adults, The Alberta Health Technologies Decision Process, Alberta Health. July 2013]). Level I testing is the most comprehensive and reliable and is sometimes referred to as the gold standard,[281] but may not be clinically necessary in all cases.

Distributing Benefits and Burdens Fairly (Equity)

There are both private and public sleep clinics in Canada; waitlists are longer in public clinics where cases are triaged according to severity. Private vendors typically offer diagnostic services in addition to testing. The value of distributing benefits and burdens fairly requires that we pay attention to whether and how access to services is distributed across the population.

In the case of OSA, the disorder tends to be more prevalent among people in lower socioeconomic circumstances,[288] for whom access to diagnostic services can be more difficult, especially given that these individuals are less likely to have the means to pay for private services.[273,280-282] Further, sleep clinics tend to be in larger cities, making it more difficult for individuals to easily access diagnostics. In one study, relatively small travel distances (one to two hours) affected a patient's willingness to come in for testing[280] and patients tended to come only when symptoms were more severe. In another, it was observed that patients were required to have a Level I test to qualify for funded equipment, which altered physicians' practices and created a need for some patients to travel large distances to cities with sleep clinics.[281] A major consideration during this phase is the extent to which individuals are able to access the level of diagnostic testing they require. Although differences in access are largely unavoidable, steps should be taken to mitigate situations where services are more easily accessible by those with means and privilege.

Phase 3: Discussion of treatment options and patient decision-making

In phase 3, the patient has received a diagnosis and will next discuss treatment options with a health care provider. For OSA, the four major options for intervention are CPAP use at night, a device that adjusts the mandible, surgery, and lifestyle changes. CPAP has been long considered the gold standard and is often recommended as the first line of treatment.[13] Devices do not affect the condition itself, but create temporary physiological changes that minimize incidence of apnea events, enabling patients to sleep well and thus minimizing short- and long-term effects of OSA.

Surgery and lifestyle changes are intended to create more permanent changes in the patient's physiology, such that they have fewer apnea events.

Respecting Patient Autonomy

Informed consent processes offer a means of respecting patient autonomy by ensuring that patients understand medical interventions and can elect to consent them. It provides patients with the ability to determine what happens to their body and, more broadly, their life course. An informed consent process as part of the discussion about OSA would require that the patient is given complete information about all options for intervention, including the opportunity to decline all interventions if desired. This discussion should include information about the effectiveness of each option as well as the potential challenges, burdens, and limitations. Shared decision-making models that enable patients and health care providers to arrive at a joint decision that takes into account the clinical evidence as well as the patient's values and preferences may be helpful in this regard. Patient involvement in decision-making for OSA interventions is especially important because adherence to the device-based treatments is essential to produce benefits.

Empirical data obtained from the literature on patient experience with OSA interventions suggest that patients do not always feel they are given full information about the options available to them (see 5.2.3. Thematic Analysis). Some patients reported that they were told that CPAP was the only treatment, whereas others indicated that, at least in the case of CPAP, they did not have enough relevant information about the potential challenges and side effects of the intervention. Some researchers have suggested that the default recommendation of CPAP may not be appropriate in all circumstances and that some patients may wish to pursue a potentially less effective option to which they are more likely to adhere. A supportive relationship between the patient and health care provider, where the patient's autonomy is respected, may ultimately serve to build an ongoing partnership that will be of benefit in the next phase of the pathway.

The decision-making period for OSA intervention is a crucial time to assess which option will best serve the particular patient in their context. *Effectiveness alone is not sufficient for decision-making in OSA.* It is neither respectful of patient autonomy nor beneficial for patients to force a particular option on a patient, regardless of the clinical evidence for its effectiveness.

Maximizing Benefits and Minimizing Harms to Patients

This value requires that consideration be given to what options are likely to create the most benefit and the minimal amount of harm to patients. Accordingly, health care providers must arrange their care to maximize the likelihood that patients will use their devices appropriately and consistently. In the case of CPAP and mandibular devices, patient attitudes and behaviours determine whether the device is used consistently enough to generate intended benefits.

This value also requires that health care providers and patients consider how benefit is defined by the patient as well as details of the patient context that may affect the extent to which intended benefit can be created. For example, patients who are homeless, who are deployed in the military, who travel extensively, or who otherwise have decreased access to a consistent sleep environment conducive to CPAP use (e.g., with electricity, with access to cleaning equipment) may reasonably choose another intervention even if CPAP would be most effective in principle.

Distributing Benefits and Burdens Fairly (Equity)

As already discussed in section 6.1.1, health care systems and providers should identify any additional factors that may be creating burdens or barriers for patients. Coverage and costs of devices (including repair and maintenance) should be considered when supporting patients to make a decision about how to treat their OSA. Where possible, considerations of cost should be minimized.

Phase 4: Adherence, support, and follow-up

In this phase, the patient has opted for a treatment and is adjusting to day-to-day use (CPAP and mandibular devices), recovering from surgery, or adjusting to a new lifestyle. During this phase, patients follow up with their

health care provider and may consider adopting an alternative intervention, depending on the effectiveness of the option they initially chose.

Maximizing Benefits and Minimizing Harms to Patients

This phase of the pathway is crucial to creating the benefits of treatment. Studies have shown that the first few weeks of device usage (especially CPAP) reflect long-term usage patterns;[247,255,256,296] more intensive support and education early on can lead to increased adherence over the long run. Long-term adherence for CPAP use is a continual problem and there is no clearly effective approach for improving adherence for all patients. Adherence to CPAP has been shown to be improved when patients have access to high-quality information and support when they start on CPAP,[247,255,256,296] ongoing access to health care providers in person or over the phone,[246,256,267,270] and when they have peer support.[268,271] Collaborative support from bed partners has also been shown to increase CPAP adherence.[249] Other studies have shown that patients who understand the clinical need for treatment of their OSA, either by discussion of long-term outcomes[273] or by observing the severity of their apneas through polysomnography results,[265] may also increase the patients' willingness to endure treatment-related challenges and adhere to use.

Continued access to clinical experts has also been shown to improve adherence to CPAP.[256] If access cannot be facilitated through sleep clinics, consideration may be given to whether other professionals, such as dentists and pharmacists, who may be more accessible than sleep experts, could take on part of this role.[217,253,297]

The obvious need for adherence in order to achieve benefit suggests that processes set up to treat OSA, both by the health system and individual providers, ought to see OSA treatment as an ongoing partnership that continues beyond the provision of an intervention. Continued use is not only important in achieving the broad health goals, but is also necessary for patients to be able to maximize the changes they experience to achieve an improvement in their quality of life.

Maximizing Benefits and Minimizing Harms to Others

Just as a patient's OSA can affect their loved ones negatively, a patient's success with an OSA intervention can affect them positively. Continued support to maximize patient success with OSA interventions has cascading effects on those around them, including bed partners, family members, co-workers, and the general public, all of whom may benefit from a reduction in the symptoms of OSA.

Distributing Benefits and Burdens Fairly (Equity)

Many factors can affect a patient's chances of success with their OSA intervention. Studies on adherence to CPAP have found that patients with supportive bed partners are more likely to have their difficulties resolved quickly.[249] Similarly, patients with supportive bed partners are also more likely to persevere through adjustment challenges.[220]

Patient context can also affect the capacity to adhere to CPAP. For example, patients who travel frequently or who live in unstable circumstances may face greater challenges and have less access to support that would increase their resilience.[247,262,273,288,292]

Ongoing access to health care provider expertise and support could even out these inequities, enabling patients who do not have bed partners or who live in more unstable contexts to have support to address the challenges and difficulties associated with CPAP use.

Policy Implications of Ethics Considerations for OSA Interventions

Providing Interventions for OSA

All four interventions for OSA appear to live up to values of creating benefit and stewarding public resources, as such interventions can improve patient's quality of life, prevent the development of serious health conditions, and minimize costs to the health system (e.g., accrued costs to care for patients with untreated OSA; costs of treating the sequelae from OSA). As such, interventions for OSA discussed here can be ethically justified.

How Should Interventions for OSA Be Provided?

Phase 1: Identification of symptoms of possible OSA

In light of the significant personal and public harms that undiagnosed OSA can cause, supporting the value of benefits to individuals and the population requires giving consideration to further screening protocols and public education. This will enable greater opportunity for treatment benefit and help offset the inequity between patients with and without bed partners.

Phase 2: Referral to diagnostic testing or sleep clinic

Timely and expert diagnosis requires that patients have access to necessary resources. Our duties to distribute benefits and burdens fairly require that we are attentive to the accessibility of these services.

Phase 3: Discussion of treatment options and patient decision-making

The ultimate effectiveness of all interventions for OSA, except surgery, is highly dependent on the patient's context, behaviours, and attitude. A singular approach not only fails to live up to duties of respect to the individual patient, but also increases the likelihood that individuals will not adhere to treatment. Instead, a flexible and shared approach should be used by health care providers to develop treatment plans and may include phased or multifaceted approaches to OSA treatment. Patients also need access to accurate and comprehensive information, provided in a way that is easy to understand and that facilitates informed decision-making.

Phase 4: Adherence, support, and follow-up

To maximize overall benefit, OSA treatment should be provided through an ongoing partnership between health care provider and patient, rather than through discrete events of diagnosis, decision, and intervention. Structuring programs in a way that enables longer-term connection between patients and experts will require additional financial and human resources, but could be created with existing expertise (e.g., through the use of dentists and pharmacists as resources for continued OSA support).

Summary of Relevant Ethical Issues

Whether Universal Treatments for Obstructive Sleep Apnea Should Be Implemented

Interventions for OSA (CPAP, mandibular devices, surgery, lifestyle changes) have been shown to offer benefit to OSA patients and to reduce overall costs and so appear to live up to values of conferring benefit at a population level and stewarding scarce resources. With consistent use, CPAP and mandibular devices can minimize symptoms and long-term consequences of OSA. In contrast, surgery and lifestyle changes have the potential to minimize the severity of OSA or eliminate the condition entirely, depending on the individual.

How Interventions for Obstructive Sleep Apnea Should Be Provided

In light of the significant personal and public harms that undiagnosed OSA can cause, we recommend that consideration be given to further screening protocols and public education. In addition, our duties to distribute benefits and burdens fairly require that we are attentive to the accessibility of testing and diagnostic services. Optimizing interventions for OSA to minimize harmful outcomes on both an individual and a population level is of great benefit, given variability in adherence based on patient behaviours and attitude. To maximize overall benefit, OSA treatment should be provided through an ongoing partnership between health care provider and patient, rather than through discrete events of diagnosis, decision, and intervention.

Contextualizing Questions

The ethical implications of a health technology are often determined by the nature of the local context. The implications of values of fair access and consistency of service within the population, in particular, are determined by

facts about how health care services are arranged and provided. To understand localized impact, decision-makers could consider the following questions:

1. How is access to sleep diagnostic clinics funded in your area? How are the various interventions funded? Are there barriers to access caused by these funding arrangements?
2. Who discusses options for OSA intervention with patients? How are patients' preferences, contexts, and perspectives taken into account? How can you ensure that patients will be able to make an informed decision about how to proceed with OSA management?
3. How are sleep clinics geographically distributed in your area? Which patients would be required to travel the longest distances? How would the burdens of this travel (cost, time off work, childcare) be offset? What impact might these burdens have on accessibility?
4. How do sleep clinics determine support and availability to follow-up with patients actively receiving intervention for CPAP? What supports are in place (individual follow-up, access to clinic appointments, group education, peer support)?
5. What potential is there to address any of the factors identified in questions 1 to 5?

Implementation Issues

This section addressed Research Question 5: What are some of the implementation issues associated with PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle for the treatment of OSA in adults?

Methods

Study Design

A narrative literature review was conducted to identify some of the implementation issues associated with different interventions for the treatment of OSA in adults.

Screening and Selection of Studies

Citations arising from the literature searches conducted to address Research Questions 1 to 4 were screened independently in duplicate for information related to implementation issues at the same time as reviewers of those respective sections screened citations for their sections. Articles addressing any of the following domains, as defined by INTEGRATE-HTA,[298] were considered to be potentially relevant to implementation: setting, provider, geographical issues, epidemiology, socioeconomic issues of individuals and their communities, sociocultural issues, political considerations, legal issues, ethical issues, and funding issues. In addition, two relevant CADTH Rapid Response reports[299,300] were identified and reviewed as well. From each relevant article, the bibliographic details (i.e., authors, year of publication, and country of origin), population and intervention information, and implementation issues identified were captured by one reviewer.

Descriptive Analysis and Synthesis Strategy

Issues identified from relevant studies are organized by OSA intervention (i.e., PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications) and further categorized by the level where the issue arises: individual, team, organization, or system or policy. This information was summarized narratively.

Results

Quantity of Research Available

From the included and excluded studies found through the literature search for Research Questions 1 through 4, 27 articles were identified that included information on potential supports and barriers to implementing the various interventions for the treatment of OSA. Of these, 14 plus one Rapid Response report pertained to PAP devices,[183,236,268,270,300-310] four discussed OAs,[311-314] one article focused on surgery for OSA,[315] no articles focused on lifestyle interventions or EPAP valves, and eight studies plus one Rapid Response report covered either more than one intervention, diagnosis of OSA, or specific populations.[285,299,316-321] Following peer review, an additional two articles were added to further clarify identified implementation issues,[322,323] bringing the final tally of included studies to 29.

Diagnosing OSA

One overarching issue was identified, which pertains to all OSA interventions and affects all levels of the health care system: the issue of getting diagnosed.[306,319,321] If OSA is not diagnosed, it cannot be effectively treated.

Barriers:

One of the biggest barriers to diagnosis, as reported in the literature, is the difficulties encountered by family physicians and their patients and families when trying to confirm a diagnosis of suspected OSA. Lack of access to sleep specialists and specialized sleep labs was recognized as a barrier to the diagnosis and subsequent treatment of OSA.[319] This can be even more of a barrier in Canada for our rural populations[306] and for those living in northern and remote areas far from a specialized sleep lab.[320]

Supports:

The literature suggests that one way to overcome this barrier and improve accessibility to OSA diagnosis is to use home-based portable diagnostic testing devices and treatment titration options when access to sleep labs is limited or difficult.[306,319] These could be used together with telehealth-based support.[321]

A Rapid Response of the evidence on the diagnostic accuracy, clinical effectiveness, cost-effectiveness, and evidence-based guidelines of home-based sleep studies versus lab-based sleep studies for the diagnosis of OSA was undertaken to supplement the information found in the clinical literature for Research Questions 1 to 4. Overall, the summary of abstracts appears to indicate that home-based testing is accurate, feasible, and acceptable to patients.[299] Making home-based devices available to patients who cannot readily access sleep labs and specialists may then help to overcome this barrier to the effective treatment of OSA.

Positive Airway Pressure Devices

Much of the literature on implementation issues for OSA interventions focuses on CPAP devices. Although the effectiveness of these devices depends on their constant use, there are a number of barriers and supports at multiple levels that can affect their use.[236,302-307,310,316,317,317] Estimates of non-adherence with CPAP in the first year of therapy vary from one-third to more than 50% of patients.[183,303,309]

Barriers:

At a health care system and policy level, funding of CPAP devices remains a barrier for patients, particularly for those who already face significant socioeconomic challenges.[285,310] An approach to overcoming this barrier with adequate funding that minimizes patient costs for CPAP therapy has been recommended in the literature.[285,310] Currently, coverage for CPAP devices and therapy varies greatly across Canada.

At the individual patient level, discomfort or problems that result from CPAP use can lead to patients choosing not to continue with CPAP therapy. These are covered in depth in the Patient Experience section of this report. However,

many of these issues may arise from a lack of patient education and training on use of the CPAP device, as there are no generally accepted guidelines for CPAP education for patients.[236]

While not well documented, Indigenous peoples in Canada may have a higher prevalence of OSA than non-Indigenous peoples, and more severe OSA.[318] At the same time, Indigenous peoples may be less likely to seek and receive an OSA diagnosis,[320] and may be less likely to adhere to their CPAP, if prescribed.[318] This could, in part, be explained by an environmental scan that found no strategies, projects, programs, or initiatives targeting sleep apnea in this population.[323]

Supports:

Supports that have been suggested in the literature to overcome these various barriers often target the team or organization level of the health care continuum and their interactions with patients (and their family members). These include close monitoring and retesting,[300,301,306] evaluation for anatomical abnormalities or functional abnormalities that may be increasing nasal resistance and treating these if found,[301] and patient education about the risks of OSA and the benefits of CPAP therapy.[236,305,307,316] These interventions could include structured telehealth and/or teleconsultation and telemonitoring,[270,305,306,321] or an interactive website or audio intervention to support CPAP users.[308,309]

One study found that patients do better with their CPAP therapy if the sleep centre and the health care providers involved in their care are accredited for the treatment of OSA.[316]

Efforts at the manufacturer level have also been recognized as significant to improving CPAP adherence and these include using air humidification to help prevent dry mouth and throat, heated humidification, quieter machines, mask interface and pressure modalities, flexible (C-flex, A-flex) air pressure; using telehealth to detect any CPAP issues; and providing access to technical assistance.[270,321,322]

Oral Appliances

A number of implementation issues are identified in the literature for OAs in the treatment of OSA.

Barriers:

Even once diagnosed with OSA, access to therapy with an OA can be difficult. Physicians may not consider OAs for OSA because they are unfamiliar with them or are unsure how to access them for their patients.[313] Another concern of physicians may be how well OAs work in the treatment of OSA and physicians are uncertain how to evaluate their effectiveness.[313] To be suitable candidates, patients must meet specific anatomical requirements, and have healthy teeth and alveolar ridges.[311,313] Problematic dental fillings or dentures may be contraindications to oral appliance therapy for OSA and dental rehabilitation may be a necessary, and often expensive, first step.[311] In the economic review, the first-year costs of OA were twice that of PAP therapy (based on Ontario costs), making cost another barrier to OA therapy. Even once therapy with an oral appliance has been established, regular re-evaluations to prevent and treat side effects, such as changes to the condyle, are necessary, and access to dental professionals including orthodontists is essential.[311]

Supports:

To address these challenges with implementation of OA therapy for OSA, an organized multidisciplinary approach has been recommended, perhaps in the form of a dental sleep clinic.[314] Respirologists, sleep specialists, dentists, dental surgeons, orthodontists, and other health professionals may be required as part of the multidisciplinary team.

Surgery

Little information from the literature on implementation issues for surgery in the treatment of OSA was found. No studies on implementation issues for OSA surgeries performed by dental specialists (i.e., oral and maxillofacial surgeons) were found, and only one study on OSA surgery performed by non-dental surgeons was identified. The Australian paper identified the issue that many surgeons have little or no exposure to performing surgery for OSA and

that there is little consistency for training of surgical residents in this type of surgery.[315] The paper does indicate that surgery for OSA is a "developing multidisciplinary field."[315]

Lifestyle Interventions

Little information was identified in the clinical literature related to implementation issues with lifestyle interventions for the treatment of OSA. Although one paper recognized weight control and bariatric surgery as possible treatments for OSA, it also acknowledged that weight-loss programs may be likely to fail because of the metabolic changes that can occur with OSA.[317] The same paper also stated the importance of patient education by physicians regarding the contribution of obesity to OSA and to provide advice about maintaining an optimal weight.

Environmental Impact

This section addressed Research Question 6: What are some potential environmental impacts associated with PAP devices, EPAP valves, OAs, surgical interventions, and lifestyle modifications for the treatment of OSA in adults?

Methods

A narrative literature review was conducted to identify some of the environmental considerations associated with different interventions for the treatment of OSA in adults.

Results

One narrative review article[324] was identified regarding the environmental implications associated with obstructive sleep apnea. The objective of this review article was to describe the product comparisons on CPAP units, including automatic PAP units, BiPAP units, and their accessories. The review article briefly examined the environmental considerations of the CPAP unit, including manufacturers adopting green shipping and production methods; for example, promoting building designs and work practices that reduce waste and encourage the use of recycled materials and shipping with less packaging material. The article suggests also creating products that are more energy efficient; for example, adding energy-saving features such as standby, hibernation mode, or automatic shut-off. Moreover, the article recommends creating products to be more recyclable; for example, offering mask replacement plans that replace only components that have worn out, rather than disposing of the entire unit.

Discussion

Overall Findings

For this HTA report, several interventions and outcomes for the treatment of OSA were of interest, although the majority of the included studies focused on CPAP. The clinical review found that across mild-to-severe cases of OSA, while various interventions may have similar and only marginal effects on improving sleepiness, CPAP may have the largest effect on improving OSA severity, given that patients comply with the therapy. More specifically, clinical and economic data suggest that while moderate cases of OSA may benefit most from MADs, severe cases of OSA may benefit most from CPAP. For severe cases of OSA, who are eligible for surgery, MMA with or without GTA demonstrated the largest effect with respect to improving both EDS and OSA severity, while being safe and cost-effective, at a willingness-to-pay threshold of $17,125 per QALY in patients with baseline AHI values of 60. However, it must be highlighted that the findings on MMA with or without GTA were obtained from small, uncontrolled pre-and-post studies of highly selected patients. In fact, some authors[91] proposed that GTA alone may be effective at improving EDS and OSA severity for less severe cases OSA. Therefore, MMA may be appropriate for highly selected populations and not generalizable to all OSA patients. The economic findings remained robust when lower rates of effectiveness on blood pressure and AHI reduction for surgery were explored in sensitivity analyses. Nonetheless, the potentially selective effectiveness of MMA remains an important consideration. From an implementation perspective, because MMA and other surgeries are performed by highly specialized individuals and are usually available only in major centres, some jurisdictions may not have the capacity to publicly fund MMA surgery for OSA and may not have the expertise locally to perform the surgery. In jurisdictions with no access to trained personnel to perform surgery for OSA, no dedicated operating room time, no public funding or associated billing codes, or no referral structure in place, implementing surgery for OSA as a treatment option would be a major undertaking. Making the issue even more complex, oral and maxillofacial surgeons are dental specialists who are trained to perform MMA, whereas OSA surgical training in the medical specialties is limited to intrapharyngeal procedures. (Major Roch Messier, Canadian Armed Forces, Valcartier Regional Dental Specialty Center, Valcartier, QC, expert opinion: 2016 Sept.) Because no studies on implementation issues for OSA surgeries performed by dental specialists (i.e., oral and maxillofacial surgeons) were found, it is uncertain how the jurisdictions would implement MMA surgery for OSA or integrate and fund services for MMA coming from both the dental and medical specialties. Further, physicians may not always know that surgery is a treatment option for OSA and fail to refer patients for MMA, suggesting a need for educating health care professionals. (Lieutenant-Colonel Glenda Ross, Canadian Armed Forces, Dental Unit Detachment, Halifax, NS expert opinion: 2016 Sept.) In addition, little evidence was found about patient perspectives on surgery, other than the findings that patients generally preferred their facial aesthetics post MMA,[89,98,103] making it difficult to understand the patient experience for surgery. There may be barriers to implementing surgery, despite the favourable evidence on its effectiveness and cost-effectiveness in patients with severe OSA.

For patients who find CPAP unacceptable or for whom surgery is not feasible, OAs and lifestyle interventions are viable alternatives,[55,62,63] especially in cases of mild or moderate OSA. For example, patients who travel frequently, engage in activities such as camping, have unreliable access to clean water or electricity, or have physical and sensory impairments may find CPAP challenging to use and may prefer other devices or interventions.[214,231] Those who are partnered may find something discreet, such as an OA, preferable to CPAP. In circumstances, where PAP therapy is not a suitable intervention, MMA with or without GTA would become the most likely cost-effective strategy for patients with baseline AHI ≥ 26, at a willingness-to-pay of $50,000 per QALY.

Men are more likely to be diagnosed with OSA than women.[1] Consequently, the literature identified and included in this report, particularly for the clinical review and patient perspectives and experiences review, included more men than women. However, the patient perspectives and experiences review found that the rates of OSA diagnosis may be lower in women, compared with men, because women are more likely than men to feel shame related to snoring and, therefore, less likely to seek diagnosis.[211] Further, women are more likely than men to encourage their spouses to be diagnosed.[197] There may be other reasons that women are less likely to receive a diagnosis of OSA that were not evident in this review,[325] including a hypothesis that women are underdiagnosed because they do not present

with “classic” symptoms of OSA. These findings suggest that OSA affects women more often than proposed by current diagnosis rates. Because treatment effects may also vary between men and women (e.g., different levels of adherence from varying levels of spousal support[197,221]), the findings focused on men are not necessarily generalizable to women. In fact, in the clinical review, while sex was not significantly associated with the effects of CPAP on blood pressure, male patients experienced greater effects with CPAP on CVEs, compared with female patients. No subgroup analysis by sex on the effects of CPAP or any other intervention on EDS or OSA severity was identified. Therefore, in the economic analysis, an assumption was necessarily made that the treatment effects did not differ by sex; rather, differences between men and women were factored in by differences in baseline event risks. The subsequent subgroup analysis by sex in the economic evaluation found that the order of interventions considered cost-effective remained consistent across disease severity.

Across the different sections of this report, patient adherence with various treatment options for OSA was identified as a crucial component in the success of the non-surgical interventions, which changed over time. For example, in the patient perspectives and experiences review, time from CPAP initiation was an important factor in determining the level of patient satisfaction with those who adhered to CPAP.[207] The SR on patient experiences found that the less time had passed from the initiation of CPAP, the more dissatisfied patients were with treatment; however, the majority of patients (90% to 99%) who persevered with therapy beyond six months were satisfied with CPAP.[207] In the clinical review, one SR[5] reported that the level of discontinuation with CPAP increased with time, from 16% to 32% of patients at year 1 to year 4 of treatment, respectively. There was also evidence that the longer the study duration, the lower the effects of CPAP, MADs, and positional therapy, potentially due to lower continuation over time, although it is also possible that the effects of CPAP and OAs first peak and then taper, causing the level of continuation to first rise and then fall over time. Whichever the direction of causality, these findings provide support for continued follow-up of patients by dentists and physicians. In a recent study (retrieved after analysis),[326] improving clinician communication skills can help support shared decision-making and “motivate patients to try CPAP after the initial visit, and thereafter to improve long-term adherence.”[326] Adherence with MADs, compared with CPAP, was higher, confirming that, for patients who find CPAP unacceptable, OAs are viable alternatives, especially in cases of mild or moderate OSA. Patient adherence was modelled in the economic analysis in terms of both adherence (e.g., the number of hours per night of device use) and continuation (e.g., the proportion of patients using a device at a given time). Results were found to be sensitive to both of these parameters, especially in the context of PAP therapy. Improvements in discontinuation rates resulted in lower ICERs for non-surgical interventions, with the contrary (i.e., higher discontinuation rates) resulting in surgery being more economically attractive (i.e., lower ICER for MMA with or without GTA). Similarly, higher refusal to fill a CPAP prescription resulted in surgery being the most likely cost-effective intervention for severe OSA at a willingness-to-pay threshold of $50,000 per QALY while removal of adherence as a structural feature in the economic model resulted in PAP therapy being cost-effective across a broader range of severe OSA values.

In the implementation issues review, whether the findings from this HTA can be transferred to the intended jurisdictions across Canada remains uncertain. For non-surgical OSA interventions, such as PAP devices and OAs, in which various supports have been suggested by the literature to improve adherence and OSA outcomes, it is uncertain whether every jurisdiction across Canada could implement these strategies and whether they would be successful, if implemented. Specifically, OAs present a unique challenge to jurisdictions because funding of dental procedures often differs from that of medical and surgical treatment (**Appendix 17**). The economic analysis explored this issue through scenario analyses based on the different reimbursement and coverage rates that have been observed across Canada. The findings were relatively robust to the different reimbursement strategies explored. When oral appliances, however, were out-of-pocket expenses, they would be the most likely cost-effective intervention for mild-to-moderate OSA. Both the patient perspectives and experience and the implementation reviews have highlighted that one issue with adherence to treatment is the financial burden from out-of-pocket costs. As such, if higher rates of discontinuation and lower rates of adherence were applied, the economic results were found to return to the base-case results.

Limitations

Although the literature search strategy was comprehensive, the literature searches conducted for the different sections of the report invariably identified more information on CPAP, compared with any other intervention. Further, head-to-head comparisons were not available for all interventions, and some of the observations presented were based on indirect comparisons of effect sizes across studies, with no formal statistical testing being conducted. Here, it is important to differentiate between lack of evidence (i.e., when there is little or no literature) and evidence of absence (i.e., when there is literature on little or no effectiveness). In other words, where there is evidence on CPAP, in the absence of evidence on other interventions, it will be important not to unfairly penalize or favour CPAP, based solely on the evidence available, without considering the uncertainty associated with the other interventions of interest.

The findings in the clinical review were often from pre-and-post studies and vulnerable to bias that is inherent in that study design, such as maturation, and should be interpreted with caution. Specifically, the findings on EPAP and surgery were solely from uncontrolled studies with sample sizes of fewer than 10 patients. Further, the 33 SRs in the overview included primary studies that ranged widely in quality, as well as in study design and study duration, which may have contributed to the large, unexplained heterogeneity sometimes seen in the MA results. However, it was not possible to determine their effects on the study findings.

For this HTA report, several subgroups of patients with OSA were also of interest. The subgroups included various comorbidities, different levels of baseline EDS, OSA severity, or BMI, different levels of therapy adherence and treatment duration, and sex. Limited evidence was found on the subgroups of interest for both the clinical review and patient perspectives and experiences review. For example, in the clinical review, an SR on EPAP[68] included pre-and-post studies, which varied widely in study duration, ranging from one night to 12 months, but did not conduct subgroup analyses on study duration. In addition to the subgroups of interest, no information was found on other populations that may be at elevated risk of OSA and, of particular interest, to certain Canadian jurisdictions, such as Indigenous populations, except for one study on a Māori population identified in the patient perspectives and experiences review.[210] In a study on oral appliances published after our analyses were done, it may be important to note that older people perceived OAs to be ineffective at reducing their OSA.[327] Some reported a lack of confidence in being able to use their OAs and getting the support they need.[327] One survey respondent commented that dental work was needed before the device could be used, which could have implications for possible patient-borne costs of OAs in some juristictions.[327] In the economics review, certain subgroup analyses were conducted. Although it found that the findings remained consistent across subgroups, it is important to note that the model did not take into account potential treatment effect differences by subgroup, as the clinical review did not identify suitable estimates on clinical treatment by subgroup. As a result, subgroup analyses were based on the differences in baseline event risks by subgroup. This may explain why the economic findings were consistent across the subgroups studied, as one of the model's drivers was the treatment effect estimates in which the same values were applied across subgroups.

Considering the large volume of literature currently available, an overview of SRs, MAs, and HTAs was conducted, supplemented by a review of primary studies. Because of resource constraints, the review of primary studies focused on areas in which no published SRs, MAs, or HTAs were found on any given intervention-comparator combination (e.g., positional therapy versus inactive controls on any outcome of interest) and did not encompass all missing outcomes (e.g., PAP devices on snoring). Further, individual studies on any given intervention-comparator-outcome combination, on which published SRs were found and had been included in the report (e.g., CPAP versus inactive controls on CVEs), would be out of scope. For example, a recently published SAVE study,[33] as well as other studies,[328-331] although relevant to the policy and research questions posed for this HTA, would be out of scope, according to the inclusion and exclusion criteria of this report.

For the economic evaluation, the non-surgical treatment effect estimates on blood pressure were based on the findings of an NMA identified in the clinical review.[63] The value of incorporating evidence from NMA is that all available evidence is incorporated, permitting simultaneous consideration of the treatment effects of different interventions against a common comparator. Although an NMA was identified in the clinical review that addressed the second clinical outcomes of interest to the economic model, AHI,[161] naive treatment estimates from individual MA

were used in the base-case analysis. The rationale underlying this decision was related to findings from the clinical review in which the effects of treatment on AHI were found to be dependent on baseline disease severity. Given the selected approach, the validity of the economic findings would be dependent on the assumption that the clinical study populations taken from the individual MA are similar. As noted, this assumption may not hold in the case of surgery, as the studies tend to recruit a highly selective population that is more likely to demonstrate favourable surgical outcomes. Sensitivity analyses considering lowered treatment effects were conducted and the model was found to remain robust to these changes. In a sensitivity analysis whereby the treatment estimates for AHI from the NMA were used (i.e., treatment estimates assumed to be consistent across baseline severity), the economic findings changed as expected. By not factoring differences by subgroups and not conducting a stratified NMA, the current NMA point estimates may have underestimated the likely treatment effect for severe OSA but overestimated them for moderate OSA. An NMA stratified by baseline disease severity would likely provide less biased assessment of relative clinical benefit and, thus, a more valid assessment of cost-effectiveness.

There were limited data on discontinuation and adherence, given the lack of published literature on these outcomes, specific to treatment. As a result, assumptions had to made, given the limited data, in order to incorporate these factors into the economic model. Extensive sensitivity analyses suggest that the model is sensitive to the assumptions used and this represents an area important for future research.

The ethics analysis was developed through a literature search that did not yield any studies of OSA intervention that explicitly identify ethical issues. The values identified in this analysis were drawn from OSA literature that implied the ethical relevance of these values without explicitly mentioning them. The lack of explicit ethics literature on OSA interventions does not mean that this technology does not raise ethical issues. Rather, the lack of explicit ethics discussion is likely due to decisions about which technologies get attention in the literature. Drawing out implied values may bring limitations, as we are primarily relying on the issues that were discussed in the literature. Other relevant values may emerge through other methods including interviews and/or focus groups with health care providers, patients, and their families.

For the patient perspectives and experiences, implementation issues, and environmental factors reviews, the literature searches may not have included all relevant databases. In fact, for implementation issues and environmental factors, citations arising from the literature searches conducted to address Research Questions 1 to 4 were screened for information. This represents a limitation in that not all of the existing literature on implementation issues or environmental factors for OSA may have been identified using this approach. In addition, other methods used to identify implementation issues or environmental factors, such as surveys, focus groups, environmental scans, or a current practice analysis of health care professional, patient, and caregiver beliefs and attitudes about OSA treatments, were not employed. This approach may have resulted in some implementation issues or environmental factors not being identified for both all or specific interventions.

Directions for Future Research

In this HTA, the following areas were identified as being potential gaps or having limited evidence, where future research may be warranted:

- Research on direct, head-to-head comparisons or NMAs of various treatment interventions, including CPAP, OAs, and MMA, on clinical effectiveness and safety
- Research on the impact of various treatment interventions in subgroups of OSA patients who have hypertension or CVD on the primary outcome and OSA severity
- Research on adherence, especially its change with time and relationship with the effectiveness of various treatment interventions, comparative data across treatment interventions, and factors that influence it
- Research on OSA treatment for underrepresented subgroups, including women, Indigenous populations, and work occupation (e.g., military or law enforcers)
- Research on intervention-specific implementation issues and environmental factors, especially in Canadian settings.

In addition, the following areas were identified as being out of scope for this report but important issues for future HTA:

- Although this HTA included several interventions for the treatment of OSA, new devices are increasingly available and will need to be assessed against the currently available treatment options, in terms of their effectiveness, safety, and implementation needs. As the technology available to treat OSA continues to evolve, many of the identified implementation issues may no longer apply, but new issues may also come to light. Further research into how these new devices — such as Bluetooth-enabled PAP devices that can allow patients' use of their CPAP machine to be monitored remotely, affect the implementation of, and adherence with, OSA treatment — will be required. The readiness of the current health care systems to utilize these new devices will be an important aspect of this research.
- The present HTA focused on single strategies for the treatment of OSA and not on a treatment pathway to determine the optimal treatment sequencing. Future research may be of use to explore the effectiveness, safety, economic, and implementation issues relating to a broader treatment pathway.
- While this HTA focused on interventions for the treatment of OSA, the latter is closely linked to, and should be considered in relation to, the diagnosis of OSA. For example, the issue of access to appropriate diagnosis, which may vary by jurisdiction, remains a considerable barrier to effectively implementing OSA treatment for those who require it, when accurate and timely diagnoses would increase the likelihood of effective treatments for patients. Research that addresses OSA diagnosis and that includes patients' perspectives and experiences, the impact of partner and peer support, barriers and supports, and new technologies, such as self-titrating PAP devices and telehealth or telemonitoring options for diagnosis, will be important to the successful treatment of OSA.

Conclusions

Clinical data show that various treatment interventions for OSA were found to significantly improve EDS and OSA severity across trials, with similar effect sizes among interventions for EDS but with CPAP showing the largest effect for OSA severity. Limited evidence was found on other outcomes, such as blood pressure, CVEs, quality of life, MVAs, and mortality. Treatment of patients with moderate-to-severe OSA appears to be a cost-effective use of resources under a willingness-to-pay threshold of $50,000/QALY.

Nevertheless, for any non-surgical therapy, patient adherence was considered key in achieving treatment success and cost-effectiveness. Relevant patient factors were highly individualized and contextual and the factors that influence whether patients seek treatment and how they experience treatment will differ for each individual. It may be that patients who are symptomatic, have a supportive partner, experience resolution of their symptoms when using CPAP or an OA, and experience few or mild side effects may be more likely to be compliant with these interventions. Patients appear to make a trade-off between the discomfort of CPAP and oral appliances, and the perceived benefits of using these devices. If patients find these interventions acceptable, they experience a period of problem-solving and adaptation to integrate these interventions into their lives. Information needs were expressed during the patient experience, from diagnosis and throughout treatment. Support from peers, health care professionals, and bed partners was also important, although some patients did not feel supported in using interventions for OSA.

From an ethics perspective, interventions for OSA have been shown to offer benefit to OSA patients and to reduce overall costs and so appear to live up to the values of conferring benefit at a population level and stewarding scarce resources. In light of the significant personal and public harms that undiagnosed OSA can cause, further consideration of screening protocols and public education is warranted. In addition, our duties to distribute benefits and burdens fairly require that we are attentive to the accessibility of testing and diagnostic services, recognizing any sociocultural factors (gender, ethnicity, socioeconomic class) that may unjustly affect this access. Optimizing interventions for OSA that reflect individuals' individual contexts and abilities appear most likely to maximize adherence, thus leading to benefits at the individual and the population level. OSA treatment should be provided through an ongoing partnership between health care provider and patient, rather than through discrete events of diagnosis, decision, and intervention.

The review of implementation issues further highlighted the difficulties in accessing sleep specialists and laboratories as critical to initiating treatment of OSA, as well as the benefits of multidisciplinary sleep clinics. A single review was found to recommend environmental considerations for CPAP, such as energy-efficient and recyclable products and green shipping. Therefore, for the treatment of OSA, in addition to clinical and cost-effectiveness evidence, patient, provider, supplier, and system readiness for the various interventions will need to be considered.

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Appendix 1: Literature Search Strategy

Original Clinical Database Search for Systematic Reviews, Meta-Analyses, and Health Technology Assessments

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 26, 2016
Alerts:	Monthly search updates until project completion
Study Types:	Health technology assessments; systematic reviews; meta-analyses; network meta-analyses; overviews of reviews; and guidelines
Limits:	Date limit: 2011-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase); Keyword (CDSR and DARE)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
coch	Ovid database code; Cochrane Database of Systematic Reviews
dare	Ovid database code; Database of Abstracts of Reviews of Effects

#	Searches
1	exp sleep apnea syndromes/
2	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kf.
3	(sleep* adj3 disordered adj3 breathing).ti,ab,kf.
4	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kf.
5	((OSA or SAHS) and sleep*).ti,ab,kf.
6	OSAHS.ti,ab,kf.
7	or/1-6
8	7 use pmez
9	exp sleep disordered breathing/
10	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kw.
11	(sleep* adj3 disordered adj3 breathing).ti,ab,kw.
12	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kw.
13	((OSA or SAHS) and sleep*).ti,ab,kw.
14	OSAHS.ti,ab,kw.
15	or/9-14
16	15 use oemezd
17	16 not conference abstract.pt.
18	8 or 17
19	sleep apnea syndromes*.kw.
20	sleep apnea, obstructive*.kw.
21	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kw.
22	(sleep* adj3 disordered adj3 breathing).ti,ab,kw.
23	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kw.
24	((OSA or SAHS) and sleep*).ti,ab,kw.
25	OSAHS.ti,ab,kw.
26	or/19-25
27	26 use coch,dare
28	meta-analysis.pt.
29	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
30	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
31	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
32	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
33	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
34	(handsearch* or hand search*).ti,ab,kf,kw.
35	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
36	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kf,kw.
37	(meta regression* or metaregression*).ti,ab,kf,kw.
38	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw,kf,kw.
39	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
40	(cochrane or (health adj2 technology assessment) or evidence report).jw.
41	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
42	(outcomes research or relative effectiveness).ti,ab,kf,kw.

#	Searches
43	((indirect or indirect treatment or mixed treatment) adj4 comparison*).ti,ab,kf,kw.
44	(network adj3 (meta-analys* or metaanalys*)).ti,ab,kf,kw.
45	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
46	((overview* or review or synthesis or summary or cochrane or analysis) and (reviews or meta-analyses or articles or umbrella)).ti,kf,kw. or umbrella review.ab. or (meta-review or metareview).ti,ab,kf,kw.
47	((overview* or reviews) and (systematic or cochrane)).ti,kf,kw.
48	(reviews adj2 meta).ab.
49	(reviews adj2 (published or quality or included or summar*)).ab.
50	cochrane reviews.ab.
51	(evidence and (reviews or meta-analyses)).ti,kf,kw.
52	or/28-51
53	18 and 52
54	27 or 53
55	(guideline or practice guideline or consensus development conference or consensus development conference, NIH).pt.
56	(guideline* or standards or consensus* or recommendat*).ti.
57	(practice parameter* or position statement* or policy statement* or CPG or CPGs or best practice*).ti.
58	(care adj2 (path or paths or pathway or pathways or map or maps or plan or plans or standard)).ti.
59	((critical or clinical or practice) adj2 (path or paths or pathway or pathways or protocol*)).ti.
60	(algorithm* and (pharmacotherap* or chemotherap* or chemotreatment* or therap* or treatment* or intervention*)).ti.
61	(algorithm* and (screening or examination or test or tested or testing or assessment* or diagnosis or diagnoses or diagnosed or diagnosing)).ti.
62	or/55-61
63	18 and 62
64	54 or 63
65	limit 64 to english language [Limit not valid in CDSR,DARE; records were retained]
66	limit 64 to french [Limit not valid in CDSR,DARE; records were retained]
67	65 or 66
68	limit 67 to yr = "2011 -Current" [Limit not valid in DARE; records were retained]
69	remove duplicates from 68

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.

Patient Experiences and Preferences Database Search

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations PsycINFO **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.

Date of Search:	March 3, 2016
Alerts:	Monthly search updates until project completion
Study Types:	Patient experiences and preferences
Limits:	Date limit: 2006-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.kw	Author keyword (Embase); Keyword (CDSR and DARE)
.kf	Author keyword heading word (MEDLINE)
.mp	Mapped term
.yr	Year
.jw	Journal title word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily
psyb	Ovid database code; PsycINFO 1967 to present
freq = 2	Frequency (must appear at least two times)

#	Searches
1	exp *sleep apnea syndromes/
2	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,kf.
3	(sleep* adj3 disordered adj3 breathing).ti,kf.
4	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,kf.
5	((OSA or SAHS) and sleep*).ti,kf.
6	OSAHS.ti,kf.
7	or/1-6
8	7 use pmez
9	exp *sleep disordered breathing/
10	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,kw.
11	(sleep* adj3 disordered adj3 breathing).ti,kw.
12	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or

#	Searches
	apnoeic-hypopnoeic)).ti,kw.
13	((OSA or SAHS) and sleep*).ti,kw.
14	OSAHS.ti,kw.
15	or/9-14
16	15 use oemezd
17	*sleep apnea/
18	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti.
19	(sleep* adj3 disordered adj3 breathing).ti.
20	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti.
21	((OSA or SAHS) and sleep*).ti.
22	OSAHS.ti.
23	or/17-22
24	23 use psyb
25	8 or 16 or 24
26	exp patient acceptance of health care/ or caregivers/
27	26 use pmez,psyb
28	exp patient attitude/ or patient preference/ or patient participation/ or patient satisfaction/ or patient decision making/ or caregiver/ or relative/ or caregiver burden/ or caregiver support/
29	28 use oemezd
30	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers or personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) and (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ti.
31	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab,kf.
32	((patient or patients or proband* or individuals or survivor* or family or families or familial or kindred* or relative or relatives or care giver* or caregiver* or carer or carers) adj7 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or

#	Searches
33	willingness or convenience or convenient or challenges or concern or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq = 2 ((personal or spous* or partner or partners or couples or users or participant* or people or child* or teenager* or adolescent* or youth or girls or boys or adults or elderly or females or males or women* or men or men's or mother* or father* or parents or parent or parental or maternal or paternal) adj2 (preference* or preferred or input or experience or experiences or value or values or perspective* or perception* or perceive or perceived or expectation* or choice* or choose* or choosing or "day-to-day" or lives or participat* or acceptance or acceptability or acceptable or accept or accepted or adheren* or adhere or nonadheren* or complian* or noncomplian* or willingness or convenience or convenient or challenges or concerns or limitations or quality of life or satisfaction or satisfied or dissatisfaction or dissatisfied or burden or attitude* or knowledge or belief* or opinion* or understanding or lessons or reaction* or motivation* or motivated or intention* or involvement or engag* or consult* or interact* or dialog* or conversation* or decision* or decide* or deciding or empower* or survey* or focus group* or interview* or questionnaire* or Likert or qualitative or theme* or thematic or barrier* or facilitator*)).ab. /freq = 2
34	(patient adj (reported or centered* or centred* or focused)).ti,ab,kf.
35	(treatment* adj2 (satisf* or refus*)).ti,ab,kf.
36	(lived experience* or shared decision making).ti,ab,kf.
37	or/27,29-36
38	25 and 37
39	limit 38 to yr = "2006 -Current"
40	39 not conference abstract.pt.
41	limit 40 to english language
42	limit 40 to french
43	41 or 42
44	remove duplicates from 43

OTHER DATABASES	
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.

Ethics Implications Database Search

OVERVIEW	
Interface:	Ovid
Databases:	MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Duplicates between databases were removed in Ovid.
Date of Search:	March 7, 2016

Alerts:	Monthly search updates until project completion
Study Types:	Ethics/Legal/Social
Limits:	Date limit: none Language limit: English- and French-language

SYNTAX GUIDE

/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj	Requires words are adjacent to each other (in any order)
.ti	Title
.ab	Abstract
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word
.fs	Floating subheading

#	Searches
1	exp Ethics/
2	exp Privacy/
3	exp Sociology/
4	exp Jurisprudence/
5	exp Psychology, Social/
6	"Legislation & Jurisprudence".fs.
7	ethics.fs.
8	exp Geography, Medical/
9	exp Environmental Pollution/
10	Medically Underserved Area/
11	(waste* or pollution or polluting or contamination or contaminated).ti,ab,kf.
12	((Healthcare or Health Care or nonclinical or Community Based) adj (Deliver* or Distribution* or System*)).ti,ab,kf.
13	(geographic adj (region* or area*)).ti,ab,kf.
14	(remote or urban or rural).ti,ab,kf.
15	(ethic or ethics or ethical or moral* or bioethic*).ti,ab,hw,kf.
16	(legal* or liabilit* or litigation* or constitutional or justice or law or laws or jurisprudence or complicit*).ti,ab,hw,kf.
17	(lawsuit* or lawyer* or lawmaker*).ti,ab,kf.
18	human right*.ti,ab,kf.
19	civil right*.ti,ab,kf.
20	(prejudice* or stigma or stigmas or stigmatization or stigmatize or stigmatise or stigmatisation or inequalit* or fairness).ti,ab,kf.
21	((care or treatment) adj2 (duty or obligat*)).ti,ab,kf.
22	(social* adj (responsibl* or obligat*)).ti,ab,kf.
23	(communitarian* or beneficence or nonmaleficence or non-maleficence or accountability).ti,ab,kf.
24	harm.ti,ab,kf.
25	(privacy or private or confidential*).ti,ab,hw,kf.

#	Searches
26	((informed or presumed) adj2 (consent or choice or decision making)).ti,ab,kf.
27	autonomy.ti,ab,hw,kf.
28	transparency.ti,ab,kf.
29	or/1-28
30	exp *sleep apnea syndromes/
31	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,kf.
32	(sleep* adj3 disordered adj3 breathing).ti,kf.
33	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,kf.
34	((OSA or SAHS) and sleep*).ti,kf.
35	OSAHS.ti,kf.
36	or/30-35
37	29 and 36
38	limit 37 to english language
39	limit 37 to french
40	38 or 39
41	remove duplicates from 40

OTHER DATABASES		
PubMed	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	
CINAHL	Searched to capture records not indexed in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used, including the addition of CINAHL headings.	

Grey Literature for Systematic Reviews, Meta-Analyses, Health Technology Assessments, Patients Experiences and Preferences, and Ethics

Dates for Search:	March 9 to 16, 2016; additional searching on March 30 to April 1, 2016
Keywords:	Sleep apnea, obstructive sleep apnea, sleep disordered breathing
Limits:	Publication years: HTA/SR/MA – 2011-present; Patient experiences and preferences – 2006-present; Ethics – no date limit

Relevant websites from the following sections of the CADTH grey literature checklist, “Grey matters: a practical tool for searching health-related grey literature” (https://www.cadth.ca/grey-matters), will be searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals.

Supplemental Clinical Database Search for Primary Studies

OVERVIEW	
Interface:	Ovid
Databases:	Embase MEDLINE Epub Ahead of Print MEDLINE Daily and MEDLINE MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 13, 2016
Alerts:	Monthly search updates until project completion
Study Types:	Not limited by study design
Limits:	Date limit: 2006-present Language limit: English- and French-language Conference abstracts: excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Requires words are adjacent to each other within a specified range (in any order)
.ti	Title
.ab	Abstract
.pt	Publication type
.kw	Author keyword (Embase)
.kf	Author keyword heading word (MEDLINE)
.yr	Year
ppez	Ovid database code; MEDLINE Epub Ahead of Print, In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

#	Searches
1	exp sleep apnea syndromes/
2	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kf.
3	(sleep* adj3 disordered adj3 breathing).ti,ab,kf.
4	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kf.
5	((OSA or SAHS) and sleep*).ti,ab,kf.
6	OSAHS.ti,ab,kf.
7	or/1-6

#	Searches
8	(Expiratory positive airway pressure or EPAP).ti,ab,kf.
9	(tongue adj2 (retain* or reposition* or stabiliz* or stabilis* or advancement or retention)).ti,ab,kf.
10	oral appliance*.ti,ab,kf.
11	mandibular advancement/
12	((mandibular or mandible) adj2 (advancement or advancing or protruding or reposition*)).ti,ab,kw.
13	((genial tubercle or genioglossus) adj2 advanc*).ti,ab,kf.
14	Orthognathic surgery/
15	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 advanc*).ti,ab,kf.
16	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 osteotom*).ti,ab,kf.
17	Supine position/
18	Prone position/
19	exp Posture/
20	exp Patient positioning/
21	((supine or prone or sleep* or patient*) adj2 position*).ti,ab,kf.
22	(positional therapy or posture).ti,ab,kf.
23	or/8-22
24	7 and 23
25	Continuous positive airway pressure/
26	(continuous positive airway pressure or CPAP).ti,ab,kf.
27	Airway pressure release ventilation.ti,ab,kf.
28	(nCPAP or APAP or BiPAP).ti,ab,kf.
29	((bilevel or bi-level or biphasic or bi-phasic or automatic or autotitrating or auto-titrating or autoadjusting or auto-adjusting or nasal) adj3 (positive airway pressure or CPAP or PAP)).ti,ab,kf.
30	(positive airway pressure or PAP or C-PAP).ti,ab,kf.
31	or/25-30
32	exp Life style/
33	exp Weight loss/
34	exp Exercise/
35	exp Diet/
36	(weight adj2 (loss or reduc* or decreas*)).ti,ab,kf.
37	(lifestyle or life style or exercise or diet).ti,ab,kf.
38	or/32-37
39	7 and 31 and 38
40	24 or 39
41	7 and ((combin* or adjunct*) adj2 (therapies or therapy)).ti,ab,kf.
42	40 or 41
43	limit 42 to english language
44	limit 42 to french
45	43 or 44
46	45 use ppez
47	exp sleep disordered breathing/
48	((sleep* or nocturnal) adj2 (apnea* or apnoea*)).ti,ab,kw.
49	(sleep* adj3 disordered adj3 breathing).ti,ab,kw.
50	((sleep* or nocturnal) adj2 (hypopnea* or hypopnoea* or hypo-apnea* or hypo-apnoea* or apneic-hypopneic or apnoeic-hypopnoeic)).ti,ab,kw.
51	((OSA or SAHS) and sleep*).ti,ab,kw.
52	OSAHS.ti,ab,kw.
53	or/47-52
54	Expiratory positive airway pressure/

#	Searches
55	(Expiratory positive airway pressure or EPAP).ti,ab,kw.
56	tongue retaining device/ or tongue repositioning device/ or tongue stabilizing device/ or tongue stabilising device/ or oral appliances/
57	(tongue adj2 (retain* or reposition* or stabiliz* or stabilis* or advancement or retention)).ti,ab,kw.
58	oral appliance*.ti,ab,kw.
59	mandibular reconstruction/
60	((mandibular or mandible) adj2 (advancement or advancing or protruding or reposition*)).ti,ab,kw.
61	genial tubercle advancement/ or genioglossus advancement/
62	((genial tubercle or genioglossus) adj2 advanc*).ti,ab,kw.
63	exp orthognathic surgery/
64	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 advanc*).ti,ab,kw.
65	((maxillomandibular or maxillo-mandibular or bimaxillary) adj2 osteotom*).ti,ab,kw.
66	maxillomandibular advancement/ or maxillo-mandibular advancement/ or bimaxillary advancement/
67	exp body position/
68	body posture/
69	supine position/
70	patient positioning/
71	((supine or prone or sleep* or patient*) adj2 position*).ti,ab,kw.
72	(positional therapy or posture).ti,ab,kw.
73	or/54-72
74	53 and 73
75	(continuous positive airway pressure or CPAP).ti,ab,kw.
76	Airway pressure release ventilation.ti,ab,kw.
77	(nCPAP or APAP or BiPAP).ti,ab,kw.
78	((bilevel or bi-level or biphasic or bi-phasic or automatic or autotitrating or auto-titrating or autoadjusting or auto-adjusting or nasal) adj3 (positive airway pressure or CPAP or PAP)).ti,ab,kw.
79	(positive airway pressure or PAP or C-PAP).ti,ab,kw.
80	or/75-79
81	lifestyle/
82	exp weight reduction/
83	exp exercise/
84	exp diet/
85	(weight adj2 (loss or reduc* or decreas*)).ti,ab,kw.
86	(lifestyle or life style or exercise or diet).ti,ab,kw.
87	or/81-86
88	53 and 80 and 87
89	74 or 88
90	53 and ((combin* or adjunct*) adj2 (therapy or therapies)).ti,ab,kw.
91	89 or 90
92	91 not conference abstract.pt.
93	limit 92 to english language
94	limit 92 to french
95	93 or 94
96	95 use oemezd
97	46 or 96
98	limit 97 to yr = "2006 -Current"
99	remove duplicates from 98

OTHER DATABASES		
PubMed	Searched to capture records not found in MEDLINE. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	
Cochrane Central Register of Controlled Trials	Searched via Ovid. Same MeSH, keywords and limits used as per MEDLINE search, with appropriate syntax used.	

Grey Literature for Primary Studies

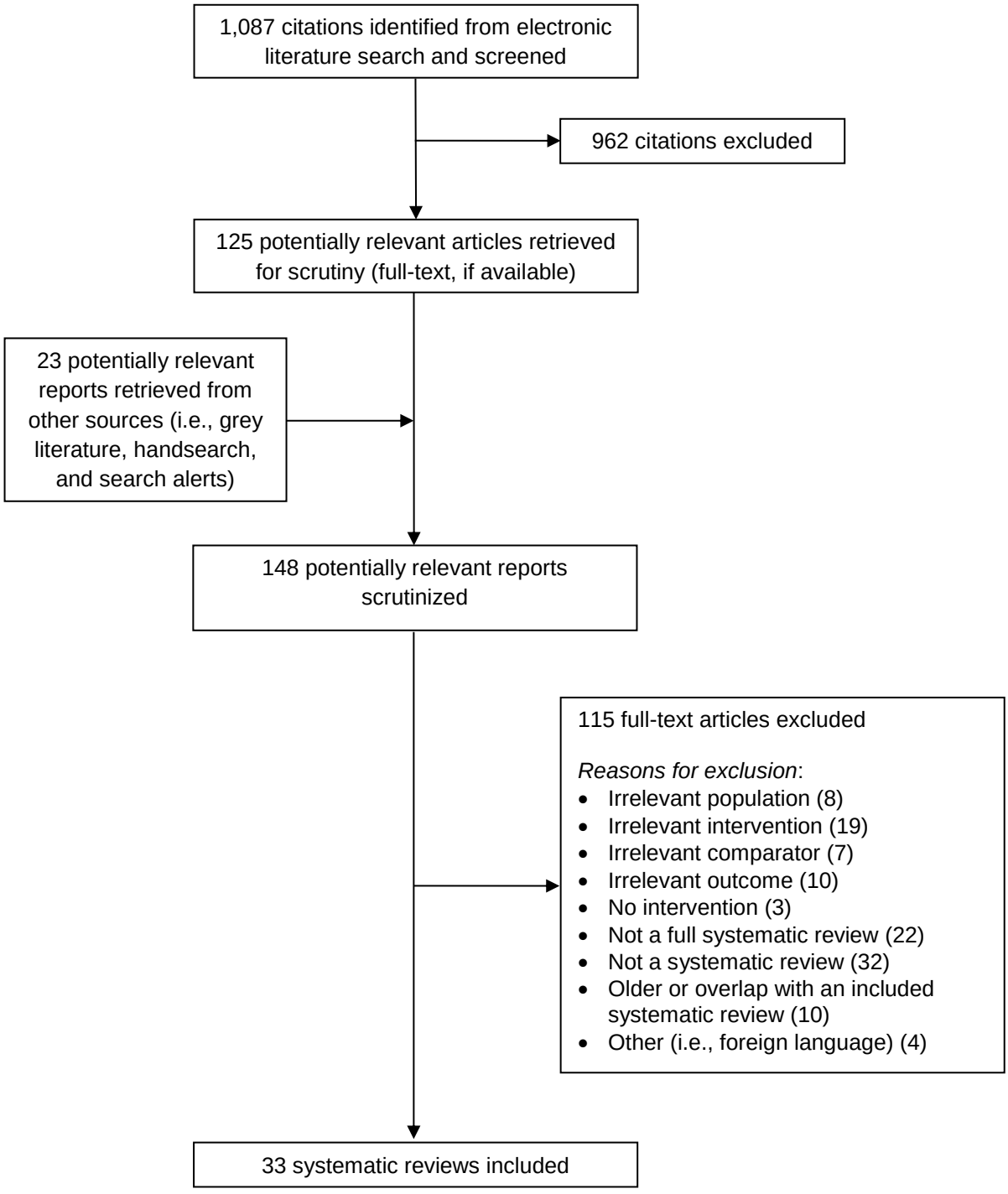
Dates for Search:	May 27, 2016
Keywords:	Sleep apnea, obstructive sleep apnea, sleep disordered breathing
Limits:	Publication years: Clinical trials – 2006-present

Relevant websites from the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters), have previously been searched, using the methods described in the main health technology assessment protocol.[40] An additional search of clinical trial registries was undertaken to retrieve study data from completed trials.

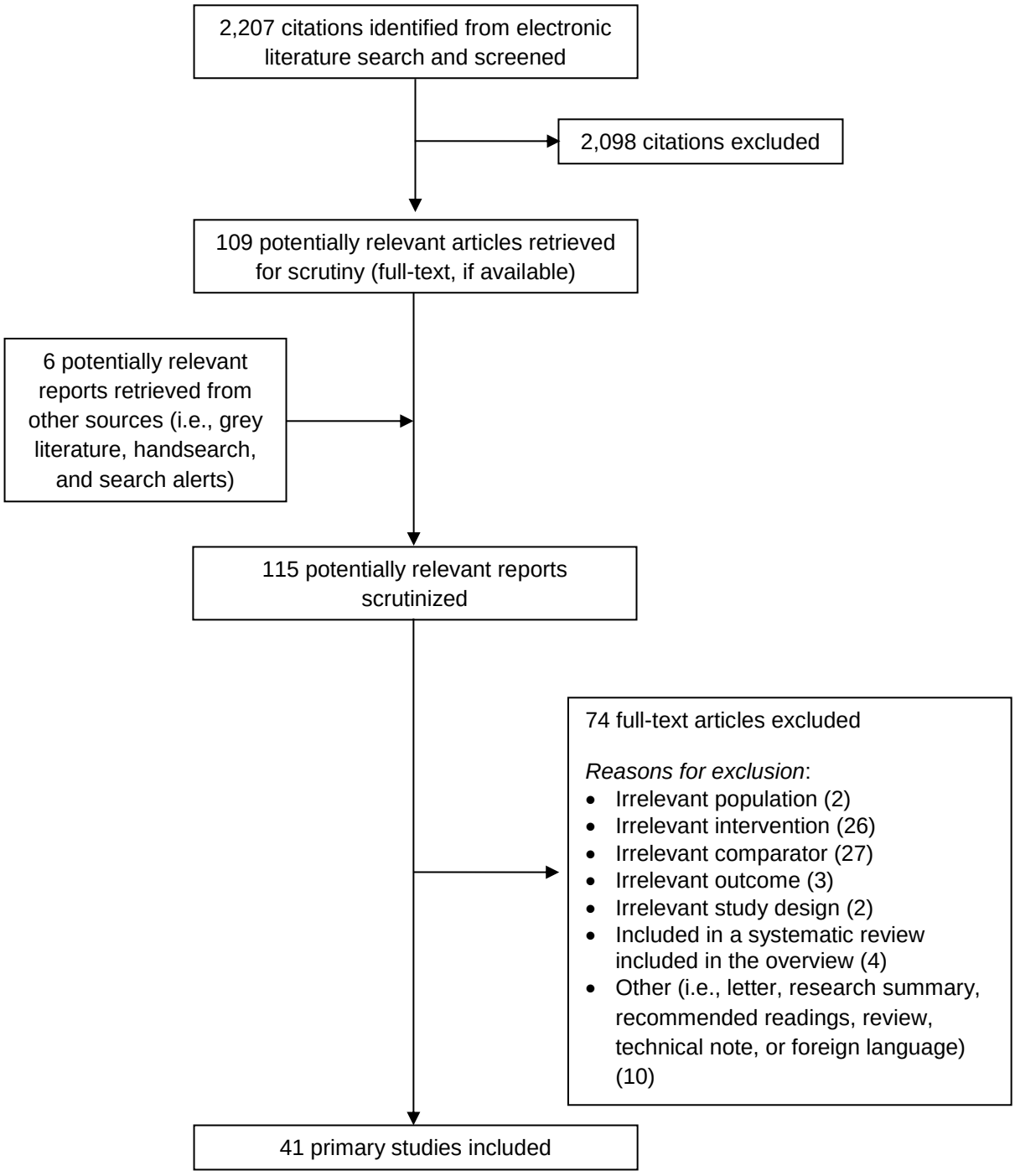
Clinicaltrials.gov
http://clinicaltrials.gov
Search -- Studies with results | sleep apnea* OR sleep apnoea* OR sleep disordered breathing

Appendix 2: STUDY SELECTION FLOWCHART (Research Question 1)

Overview of Reviews



Review of Primary Studies



Appendix 3: List of Included Studies (Research Question 1)

Overview of Reviews

1. Aiello KD. Effect of exercise training on sleep apnea: a systematic review and meta-analysis. Respir Med. 2016;116:85-92.
2. Bartolucci ML, Bortolotti F, Raffaelli E, D'Anto V, Michelotti A, Alessandri BG. The effectiveness of different mandibular advancement amounts in OSA patients: a systematic review and meta-regression analysis. Sleep Breath. 2016 Sep;20(3):911-9.
3. Fu Y, Xia Y, Yi H, Xu H, Guan J, Yin S. Meta-analysis of all-cause and cardiovascular mortality in obstructive sleep apnea with or without continuous positive airway pressure treatment. Sleep Breath. 2016 Aug 8. Epub ahead of print.
4. Guo J, Sun Y, Xue LJ, Huang ZY, Wang YS, Zhang L, et al. Effect of CPAP therapy on cardiovascular events and mortality in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath. 2016 Sep;20(3):965-74.
5. Gupta MA, Simpson FC, Lyons DC. The effect of treating obstructive sleep apnea with positive airway pressure on depression and other subjective symptoms: a systematic review and meta-analysis. Sleep Med Rev. 2015 Aug 3;28:51-64.
6. Iftikhar IH, Bittencourt L, Youngstedt SD, Ayas N, Cistulli PA, Schwab R, et al. Comparative efficacy of CPAP, MADs, exercise-training and dietary weight loss for sleep apnea: a network meta-analysis. Sleep Med. 2016 Jun 28. Epub ahead of print.
7. Kim Y, Koo YS, Lee HY, Lee SY. Can continuous positive airway pressure reduce the risk of stroke in obstructive sleep apnea patients? A systematic review and meta-analysis. PLoS One. 2016;11(1):e0146317.
8. Liu L, Cao Q, Guo Z, Dai Q. Continuous positive airway pressure in patients with obstructive sleep apnea and resistant hypertension: a meta-analysis of randomized controlled trials. J Clin Hypertens (Greenwich). 2016 Feb;18(2):153-8.
9. Serra-Torres S, Bellot-Arcis C, Montiel-Company JM, Marco-Algarra J, Almerich-Silla JM. Effectiveness of mandibular advancement appliances in treating obstructive sleep apnea syndrome: a systematic review. Laryngoscope. 2016 Feb;126(2):507-14.
10. Sharples LD, Clutterbuck-James AL, Glover MJ, Bennett MS, Chadwick R, Pittman MA, et al. Meta-analysis of randomised controlled trials of oral mandibular advancement devices and continuous positive airway pressure for obstructive sleep apnoea-hypopnoea. Sleep Med Rev. 2016;27:108-24.
11. Song SA, Chang ET, Certal V, Del Do M, Zaghi S, Liu SY, et al. Genial tubercle advancement and genioplasty for obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2016 Aug 22. Epub ahead of print.
12. Zaghi S, Holty JE, Certal V, Abdullatif J, Guilleminault C, Powell NB, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea: a meta-analysis. JAMA Otolaryngol Head Neck Surg. 2016 Jan 1;142(1):58-66.
13. Ashrafian H, Toma T, Rowland SP, Harling L, Tan A, Efthimiou E, et al. Bariatric surgery or non-surgical weight loss for obstructive sleep apnoea? A systematic review and comparison of meta-analyses. Obes Surg. 2015 Jul;25(7):1239-50.
14. Bratton DJ, Gaisl T, Schlatzer C, Kohler M. Comparison of the effects of continuous positive airway pressure and mandibular advancement devices on sleepiness in patients with obstructive sleep apnoea: a network meta-analysis. Lancet Respir Med. 2015 Nov;3(11):869-78.
15. Bratton DJ, Gaisl T, Wons AM, Kohler M. CPAP vs mandibular advancement devices and blood pressure in patients with obstructive sleep apnea: a systematic review and meta-analysis. JAMA. 2015 Dec 1;314(21):2280-93.

16. Feng Y, Zhang Z, Dong ZZ. Effects of continuous positive airway pressure therapy on glycaemic control, insulin sensitivity and body mass index in patients with obstructive sleep apnoea and type 2 diabetes: a systematic review and meta-analysis. NPJ Prim Care Respir Med. 2015;25.
17. Hu X, Fan J, Chen S, Yin Y, Zrenner B. The role of continuous positive airway pressure in blood pressure control for patients with obstructive sleep apnea and hypertension: a meta-analysis of randomized controlled trials. J Clin Hypertens (Greenwich). 2015 Mar;17(3):215-22.
18. Pan YY, Deng Y, Xu X, Liu YP, Liu HG. Effects of continuous positive airway pressure on cognitive deficits in middle-aged patients with obstructive sleep apnea syndrome: a meta-analysis of randomized controlled trials. Chin Med J. 2015 Sep 5;128(17):2365-73.
19. Qureshi WT, Nasir UB, Alqalyoobi S, O'Neal WT, Mawri S, Sabbagh S, et al. Meta-analysis of continuous positive airway pressure as a therapy of atrial fibrillation in obstructive sleep apnea. Am J Cardiol. 2015 Dec 1;116(11):1767-73.
20. Riaz M, Certal V, Nigam G, Abdullatif J, Zaghi S, Kushida CA, et al. Nasal expiratory positive airway pressure devices (Provent) for OSA: a systematic review and meta-analysis. Sleep Disord. 2015;2015:734798.
21. Wang J, Yu W, Gao M, Zhang F, Li Q, Gu C, et al. Continuous positive airway pressure treatment reduces cardiovascular death and non-fatal cardiovascular events in patients with obstructive sleep apnea: a meta-analysis of 11 studies. Int J Cardiol. 2015 Jul 15;191:128-31.
22. Wang T, Huang W, Zong H, Zhang Y. The efficacy of continuous positive airway pressure therapy on nocturia in patients with obstructive sleep apnea: a systematic review and meta-analysis. Int Neurourol J. 2015 Sep;19(3):178-84.
23. Zhu Y, Long H, Jian F, Lin J, Zhu J, Gao M, et al. The effectiveness of oral appliances for obstructive sleep apnea syndrome: a meta-analysis. J Dent. 2015 Oct 17;43(12):1394-402.
24. Fava C, Dorigoni S, Dalle VF, Danese E, Montagnana M, Guidi GC, et al. Effect of CPAP on blood pressure in patients with OSA/hypopnea a systematic review and meta-analysis. Chest. 2014 Apr;145(4):762-71.
25. Ha SC, Hirai HW, Tsoi KK. Comparison of positional therapy versus continuous positive airway pressure in patients with positional obstructive sleep apnea: a meta-analysis of randomized trials. Sleep Med Rev. 2014 Feb;18(1):19-24.
26. Mitchell LJ, Davidson ZE, Bonham M, O'Driscoll DM, Hamilton GS, Truby H. Weight loss from lifestyle interventions and severity of sleep apnoea: a systematic review and meta-analysis. Sleep Med. 2014 Oct;15(10):1173-83.
27. Okuno K, Sato K, Arisaka T, Hosohama K, Gotoh M, Taga H, et al. The effect of oral appliances that advanced the mandible forward and limited mouth opening in patients with obstructive sleep apnea: a systematic review and meta-analysis of randomised controlled trials. J Oral Rehabil. 2014 Jul;41(7):542-54.
28. Povitz M, Bolo CE, Heitman SJ, Tsai WH, Wang J, James MT. Effect of treatment of obstructive sleep apnea on depressive symptoms: systematic review and meta-analysis. PLoS Med. 2014 Nov;11(11):e1001762.
29. Araghi MH, Chen YF, Jagielski A, Choudhury S, Banerjee D, Hussain S, et al. Effectiveness of lifestyle interventions on obstructive sleep apnea (OSA): systematic review and meta-analysis. Sleep. 2013 Oct;36(10):1553-62.
30. Li W, Xiao L, Hu J. The comparison of CPAP and oral appliances in treatment of patients with OSA: a systematic review and meta-analysis. Respir Care. 2013 Jul;58(7):1184-95.
31. Thomasouli MA, Brady EM, Davies MJ, Hall AP, Khunti K, Morris DH, et al. The impact of diet and lifestyle management strategies for obstructive sleep apnoea in adults: a systematic review and meta-analysis of randomised controlled trials. Sleep Breath. 2013 Sep;17(3):925-35.
32. Antonopoulos CN, Sergentanis TN, Daskalopoulou SS, Petridou ET. Nasal continuous positive airway pressure (nCPAP) treatment for obstructive sleep apnea, road traffic accidents and driving simulator performance: a meta-analysis. Sleep Med Rev. 2011 Oct;15(5):301-10.

33. Balk EM, Moorthy D, Obadan NO, Patel K, Ip S, Chung M, et al. Diagnosis and treatment of obstructive sleep apnea in adults. Rockville (MD): Agency for Healthcare Research and Quality (US); 2011 Jul. (AHRQ comparative effectiveness reviews).

Review of Primary Studies

1. Benoist LB, Verhagen M, Torensma B, van Maanen JP, de Vries N. Positional therapy in patients with residual positional obstructive sleep apnea after upper airway surgery. Sleep Breath. 2016 Aug 17. Epub ahead of print.
2. Levendowski D, Cunnington D, Swieca J, Westbrook P. User compliance and behavioral adaptation associated with supine avoidance therapy. Behav Sleep Med. 2016 May 9;1-11.
3. Passeri LA, Choi JG, Kaban LB, Lahey ET III. Morbidity and mortality rates after maxillomandibular advancement for treatment of obstructive sleep apnea. J Oral Maxillofac Surg. 2016 Apr 21. Epub ahead of print.
4. Scarlata S, Rossi B, I, Santangelo S, Giannunzio G, Pedone C, Antonelli Inc. Short-term effects of a vibrotactile neck-based treatment device for positional obstructive sleep apnea: preliminary data on tolerability and efficacy. J Thorac Dis. 2016 Jul;8(7):1820-4.
5. Afrashi A, Ucar ZZ. Effect of prone positioning in mild to moderate obstructive sleep apnea syndrome. Sleep Breath. 2015 Sep;19(3):1027-34.
6. Bidarian-Moniri A, Nilsson M, Attia J, Ejnell H. Mattress and pillow for prone positioning for treatment of obstructive sleep apnoea. Acta Otolaryngol (Stockh). 2015 Mar;135(3):271-6.
7. Bidarian-Moniri A, Nilsson M, Rasmusson L, Attia J, Ejnell H. The effect of the prone sleeping position on obstructive sleep apnoea. Acta Otolaryngol (Stockh). 2015 Jan;135(1):79-84.
8. Chen WC, Lee LA, Chen NH, Fang TJ, Huang CG, Cheng WN, et al. Treatment of snoring with positional therapy in patients with positional obstructive sleep apnea syndrome. Sci Rep. 2015;5:18188.
9. de Vries GE, Hoekema A, Doff MH, Kerstjens HA, Meijer PM, van der Hoeven JH, et al. Usage of positional therapy in adults with obstructive sleep apnea. J Clin Sleep Med. 2015 Feb 15;11(2):131-7.
10. Dieltjens M, Vroegop AV, Verbruggen AE, Wouters K, Willemen M, De Backer WA, et al. A promising concept of combination therapy for positional obstructive sleep apnea. Sleep Breath. 2015 May;19(2):637-44.
11. Eijsvogel MM, Ubbink R, Dekker J, Oppersma E, de Jongh FH, van der Palen J, et al. Sleep position trainer versus tennis ball technique in positional obstructive sleep apnea syndrome. J Clin Sleep Med. 2015 Feb 15;11(2):139-47.
12. Islam S, Aleem F, Ormiston IW. Subjective assessment of facial aesthetics after maxillofacial orthognathic surgery for obstructive sleep apnoea. Br J Oral Maxillofac Surg. 2015 Mar;53(3):235-8.
13. Jackson M, Collins A, Berlowitz D, Howard M, O'Donoghue F, Barnes M. Efficacy of sleep position modification to treat positional obstructive sleep apnea. Sleep Med. 2015 Apr;16(4):545-52.
14. Kuscu O, Suslu AE, Ozer S, Gunaydin RO, Ogretmenoglu O, Onerci M. Sole effect of genioglossus advancement on apnea hypopnea index of patients with obstructive sleep apnea. Acta Otolaryngol (Stockh). 2015 Aug;135(8):835-9.
15. Roplekar R, Dixon H, Young P, Harries M. The use of a tongue stabilising device: an audit study of patient compliance, and effect on sleep quality. Otorhinolaryngologist. 2015;8(2):115-9.
16. Chirinos JA, Gurubhagavatula I, Teff K, Rader DJ, Wadden TA, Townsend R, et al. CPAP, weight loss, or both for obstructive sleep apnea. N Engl J Med. 2014 Jun 12;370(24):2265-75.
17. Garreau E, Wojcik T, Bouscaillou J, Ferri J, Raoul G. Comparative effectiveness of maxillomandibular advancement surgery versus mandibular advancement device for patients with moderate or severe obstructive sleep area. Orthod Fr. 2014 Jun;85(2):163-73.
18. Islam S, Uwadiae N, Ormiston IW. Orthognathic surgery in the management of obstructive sleep apnoea: experience from maxillofacial surgery unit in the United Kingdom. Br J Oral Maxillofac Surg. 2014 Jul;52(6):496-500.
19. Levendowski DJ, Seagraves S, Popovic D, Westbrook PR. Assessment of a neck-based treatment and monitoring device for positional obstructive sleep apnea. J Clin Sleep Med. 2014 Aug 15;10(8):863-71.

20. van Maanen JP, de Vries N. Long-term effectiveness and compliance of positional therapy with the sleep position trainer in the treatment of positional obstructive sleep apnea syndrome. Sleep. 2014 Jul;37(7):1209-15.
21. Cohen-Levy J, Petelle B, Vieille E, Dumitrache M, Fleury B. Changes in facial profile after maxillomandibular advancement surgery for obstructive sleep apnea syndrome. Int Orthod. 2013 Mar;11(1):71-92.
22. van Maanen JP, Meester KA, Dun LN, Koutsourelakis I, Witte BI, Laman DM, et al. The sleep position trainer: a new treatment for positional obstructive sleep apnoea. Sleep Breath. 2013 May;17(2):771-9.
23. Ackel-D'Elia C, da Silva AC, Silva RS, Truksinas E, Sousa BS, Tufik S, et al. Effects of exercise training associated with continuous positive airway pressure treatment in patients with obstructive sleep apnea syndrome. Sleep Breath. 2012 Sep;16(3):723-35.
24. Dort L, Remmers J. A combination appliance for obstructive sleep apnea: the effectiveness of mandibular advancement and tongue retention. J Clin Sleep Med. 2012 Jun 15;8(3):265-9.
25. Heinzer RC, Pellaton C, Rey V, Rossetti AO, Lecciso G, Haba-Rubio J, et al. Positional therapy for obstructive sleep apnea: an objective measurement of patients' usage and efficacy at home. Sleep Med. 2012 Apr;13(4):425-8.
26. Liu SR, Yi HL, Guan J, Chen B, Wu HM, Yin SK. Changes in facial appearance after maxillomandibular advancement for severe obstructive sleep apnoea hypopnoea syndrome in Chinese patients: a subjective and objective evaluation. Int J Oral Maxillofac Surg. 2012 Sep;41(9):1112-9.
27. van Maanen JP, Richard W, van Kesteren ER, Ravesloot MJ, Laman DM, Hilgevoord AA, et al. Evaluation of a new simple treatment for positional sleep apnoea patients. J Sleep Res. 2012 Jun;21(3):322-9.
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29. El-Solh AA, Moitheennazima B, Akinnusi ME, Churder PM, Lafornara AM. Combined oral appliance and positive airway pressure therapy for obstructive sleep apnea: a pilot study. Sleep Breath. 2011 May;15(2):203-8.
30. Johansson K, Hemmingsson E, Harlid R, Trolle LY, Granath F, Rossner S, et al. Longer term effects of very low energy diet on obstructive sleep apnoea in cohort derived from randomised controlled trial: prospective observational follow-up study. Br Med J. 2011;342:d3017.
31. Kim SJ, Choi J, Park YH, Hong JH, Park D, Lee SH, et al. Positional therapy for the reduction of obstructive sleep apnea. Sleep Biol Rhythms. 2011;9(3):150-6.
32. Sutherland K, Deane SA, Chan AS, Schwab RJ, Ng AT, Darendeliler MA, et al. Comparative effects of two oral appliances on upper airway structure in obstructive sleep apnea. Sleep. 2011 Apr;34(4):469-77.
33. Fujii H, Miyamoto M, Miyamoto T, Muto T. Weight-loss approach during routine follow-up is effective for obstructive sleep apnea hypopnea syndrome subjects receiving nasal continuous positive airway pressure treatment. Ind Health. 2010;48(4):511-6.
34. McDoniel SO, Hammond RS. A comprehensive treatment program for obese adults diagnosed with obstructive sleep apnea: a pilot study. Top Clin Nutr. 2010;25(2):172-9.
35. Bignold JJ, Deans-Costi G, Goldsworthy MR, Robertson CA, McEvoy D, Catcheside PG, et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. J Clin Sleep Med. 2009 Oct 15;5(5):428-30.
36. Lazard DS, Blumen M, Levy P, Chauvin P, Fragny D, Buchet I, et al. The tongue-retaining device: efficacy and side effects in obstructive sleep apnea syndrome. J Clin Sleep Med. 2009 Oct 15;5(5):431-8.
37. Bruno CB, Mauro P, Silvia B, Enrico S. Modified genioplasty and bimaxillary advancement for treating obstructive sleep apnea syndrome. J Oral Maxillofac Surg. 2008 Sep;66(9):1971-4.
38. Dort L, Brant R. A randomized, controlled, crossover study of a noncustomized tongue retaining device for sleep disordered breathing. Sleep Breath. 2008 Nov;12(4):369-73.
39. Loord H, Hultcrantz E. Positioner--a method for preventing sleep apnea. Acta Otolaryngol (Stockh). 2007 Aug;127(8):861-8.

40. Santos Junior JF, Abrahao M, Gregorio LC, Zonato AI, Gumieiro EH. Genioplasty for genioglossus muscle advancement in patients with obstructive sleep apnea-hypopnea syndrome and mandibular retrognathia. Rev Bras Otorrinolaringol (Engl Ed). 2007 Jul;73(4):480-6.
41. Oksenberg A, Silverberg D, Offenbach D, Arons E. Positional therapy for obstructive sleep apnea patients: a 6-month follow-up study. Laryngoscope. 2006;116(11):1995-2000.

Appendix 4: List of Excluded Studies (Research Question 1)

Overview of Reviews

Study Reference	Reasons for Exclusion
Abdullatif J, Certal V, Zaghi S, Song SA, Chang ET, Gillespie MB, et al. Maxillary expansion and maxillomandibular expansion for adult OSA: a systematic review and meta-analysis. J Craniomaxillofac Surg. 2016 May;44(5):574-8.	Irrelevant intervention (i.e., maxillary and maxillomandibular expansion)
Ayers CM, Lohia S, Nguyen SA, Gillespie MB. The effect of upper airway surgery on continuous positive airway pressure levels and adherence: a systematic review and meta-analysis. ORL J Otorhinolaryngol Relat Spec. 2016 Apr 7;78(3):119-25.	Irrelevant intervention (i.e., nasal valve repair, palate RFA, turbinate reduction, septoplasty, pillar implants, tonsillectomy, and UPPP)
Camacho M, Dunn B, Torre C, Sasaki J, Gonzales R, Liu SY, et al. Supraglottoplasty for laryngomalacia with obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2016 May;126(5):1246-55.	Irrelevant population (i.e., children) and intervention (i.e., supraglottoplasty)
Camacho M, Li D, Kawai M, Zaghi S, Teixeira J, Senchak AJ, et al. Tonsillectomy for adult obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2016 Mar 22.	Irrelevant intervention (i.e., tonsillectomy)
Camacho M, Song SA, Tolisano AM. Oral pressure therapy (winx) for obstructive sleep apnea: a meta-analysis updating the systematic review. Sleep Breath. 2016 Sep;20(3):1011-2.	Irrelevant intervention (i.e., oral pressure therapy)
Camacho M, Zaghi S, Piccin O, Certal V. Expansion sphincter pharyngoplasty for obstructive sleep apnea: an update to the recent meta-analysis. Eur Arch Otorhinolaryngol. 2016 Sep;273(9):2857-8.	Updates to an excluded SR (i.e., Pang 2015[332]) for irrelevant population (i.e., children)
Chowdhuri S, Quan SF, Almeida F, Ayappa I, Batool-Anwar S, Budhiraja R, et al. An official American Thoracic Society research statement: impact of mild obstructive sleep apnea in adults. Am J Respir Crit Care Med. 2016 May 1;193(9):e37-e54.	Not an SR (i.e., a research statement)
Dos Santos Canellas JV, Barros HL, Medeiros PJ, Ritto FG. Sleep-disordered breathing following mandibular setback: a systematic review of the literature. Sleep Breath. 2016 Mar;20(1):387-94.	Irrelevant population (i.e., mandibular setback patients with or without OSA)
Fatureto-Borges F, Lorenzi-Filho G, Drager LF. Effectiveness of continuous positive airway pressure in lowering blood pressure in patients with obstructive sleep apnea: a critical review of the literature. Integr Blood Press Control. 2016;9:43-7.	Not an SR (i.e., a narrative review)
Feldstein CA. Blood pressure effects of CPAP in nonresistant and resistant hypertension associated with OSA: a systematic review of randomized clinical trials. Clin Exp Hypertens. 2016 May 9;1-10.	Not a full SR (i.e., no QA) and complete overlap with an included SR with QA (i.e., Bratton 2015[63])
Heidsieck DS, de Ruiter MH, de Lange J. Management of obstructive sleep apnea in edentulous patients: an overview of the literature. Sleep Breath. 2016 Mar;20(1):395-404.	Not a full SR (i.e., no synthesis and no QA)
Imran TF, Ghazipura M, Liu S, Hossain T, Ashtyani H, Kim B, et al. Effect of continuous positive airway pressure treatment on pulmonary artery pressure in patients with isolated obstructive sleep apnea: a meta-analysis. Heart Fail Rev. 2016 Mar 21.	Irrelevant outcome (i.e., pulmonary artery pressure)
King S, Cuellar N. Obstructive sleep apnea as an independent stroke risk factor: a review of the evidence, stroke prevention	Irrelevant population (CPAP effectiveness on OSA patients with stroke)

Study Reference	Reasons for Exclusion
guidelines, and implications for neuroscience nursing practice. J Neurosci Nurs. 2016 Jun;48(3):133-42.	
Myles H, Myles N, Antic NA, Adams R, Chandratilleke M, Liu D, et al. Obstructive sleep apnea and schizophrenia: a systematic review to inform clinical practice. Schizophr Res. 2016 Jan;170(1):222-5.	Not an SR (i.e., a narrative review)
Nigam G, Pathak C, Riaz M. Effectiveness of oral pressure therapy in obstructive sleep apnea: a systematic analysis. Sleep Breath. 2016 May;20(2):663-71.	Irrelevant intervention (i.e., negative pressure therapy)
Rosário HD, Oliveira GM, Freires IA, de Souza MF, Paranhos LR. Efficiency of bimaxillary advancement surgery in increasing the volume of the upper airways: a systematic review of observational studies and meta-analysis. Eur Arch Otorhinolaryngol. 2016 Mar 30.	Irrelevant outcome (i.e., upper airway volume)
Rotenberg BW, Murariu D, Pang KP. Trends in CPAP adherence over twenty years of data collection: a flattened curve. J Otolaryngol Head Neck Surg. 2016;45(1):43.	Not a full SR (i.e., no comprehensive search strategy and no QA)
Rotenberg BW, Vicini C, Pang EB, Pang KP. Reconsidering first-line treatment for obstructive sleep apnea: a systematic review of the literature. J Otolaryngol Head Neck Surg. 2016;45:23.	Not a full SR (i.e., no comprehensive search strategy, no synthesis, and no QA) and significant overlap with an included SR with QA (i.e., Sharples 2016[59])
Song SA, Wei JM, Buttram J, Tolisano AM, Chang ET, Liu SY, et al. Hyoid surgery alone for obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2016 Jan 23.	Irrelevant intervention (i.e., hyoid surgery)
Steinke E, Palm JP, Fridlund B, Brostrom A. Determinants of sexual dysfunction and interventions for patients with obstructive sleep apnoea: a systematic review. Int J Clin Pract. 2016 Jan;70(1):5-19.	Irrelevant outcome (i.e., sexual dysfunction)
Torre C, Camacho M, Liu SY, Huon LK, Capasso R. Epiglottis collapse in adult obstructive sleep apnea: a systematic review. Laryngoscope. 2016 Feb;126(2):515-23.	No intervention (i.e., association study)
Volner K, Dunn B, Chang ET, Song SA, Liu SY, Brietzke SE, et al. Transpalatal advancement pharyngoplasty for obstructive sleep apnea: a systematic review and meta-analysis. Eur Arch Otorhinolaryngol. 2016 Jun 11.	Irrelevant intervention (i.e., pharyngoplasty)
Zhou J, Camacho M, Tang X, Kushida CA. A review of neurocognitive function and obstructive sleep apnea with or without daytime sleepiness. Sleep Med. 2016 Mar 2.	Not a full SR (i.e., no synthesis and no QA) and some overlap with an included SR with QA (i.e., Pan 2015[66])
Al-Hussaini A, Berry S. An evidence-based approach to the management of snoring in adults. Clin Otolaryngol. 2015 Apr;40(2):79-85.	Not an SR (i.e., a narrative review)
Baba RY, Mohan A, Metta VV, Mador MJ. Temperature controlled radiofrequency ablation at different sites for treatment of obstructive sleep apnea syndrome: a systematic review and meta-analysis. Sleep Breath. 2015 Sep;19(3):891-910.	Irrelevant intervention (i.e., temperature-controlled RFA)
Bostanci A, Turhan M. A systematic review of tongue base suspension techniques as an isolated procedure or combined with uvulopalatopharyngoplasty in obstructive sleep apnea. Eur Arch Otorhinolaryngol. 2015 Oct 27.	Not a full SR (i.e., no comprehensive search strategy)
Bury SB, Singh A. The role of nasal treatments in snoring and	Not an SR (i.e., a narrative review)

Study Reference	Reasons for Exclusion
obstructive sleep apnoea. Curr Opin Otolaryngology Head Neck Surg. 2015;23(1):39-46.	
Camacho M, Certal V, Abdullatif J, Zaghi S, Ruoff CM, Capasso R, et al. Myofunctional therapy to treat obstructive sleep apnea: a systematic review and meta-analysis. Sleep. 2015 May;38(5):669-75.	Irrelevant intervention (i.e., myofunctional therapy)
Camacho M, Teixeira J, Abdullatif J, Acevedo JL, Certal V, Capasso R, et al. Maxillomandibular advancement and tracheostomy for morbidly obese obstructive sleep apnea: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2015 Apr;152(4):619-30.	Older than, and complete overlap with, an included SR (i.e., Zaghi 2016[60])
Camacho M, Riaz M, Capasso R, Ruoff CM, Guilleminault C, Kushida CA, et al. The effect of nasal surgery on continuous positive airway pressure device use and therapeutic treatment pressures: a systematic review and meta-analysis. Sleep. 2015;38(2):279-86.	Irrelevant intervention (i.e., inclusion of nasal surgery)
de Godoy LBM, Palombini LO, Guilleminaulth C, Poyares D, Tufik S, Togeiro SM. Treatment of upper airway resistance syndrome in adults: where do we stand? Sleep Science. 2015;8(1):42-8.	Not a full SR (i.e., no synthesis and no QA)
Fernández-Ferrer L, Montiel-Company JM, Pinho T, Almerich-Silla JM, Bellot-Arcís C. Effects of mandibular setback surgery on upper airway dimensions and their influence on obstructive sleep apnoea - a systematic review. J Craniomaxillofac Surg. 2015 Mar;43(2):248-53.	Irrelevant intervention (i.e., mandibular setback surgery)
Gupta MA, Simpson FC. Obstructive sleep apnea and psychiatric disorders: a systematic review. J Clin Sleep Med. 2015 Feb 15;11(2):165-75.	No intervention (i.e., association study)
Van Haesendonck G, Dieltjens M, Kastoer C, Shivalkar B. Cardiovascular benefits of oral appliance therapy in obstructive sleep apnea: a systematic review. Journal of Dental Sleep Medicine 2015;2(1):9-14.	Not a full SR (i.e., no QA) and significant overlap with included and larger SRs with QA (i.e., Bratton 2015[62,63])
Heck T, Zolezzi M. Obstructive sleep apnea: management considerations in psychiatric patients. Neuropsychiatr Dis Treat. 2015;11:2691-8.	Not an SR (i.e., a narrative review)
Iftikhar IH, Hoyos CM, Phillips CL, Magalang UJ. Meta-analyses of the association of sleep apnea with insulin resistance, and the effects of CPAP on HOMA-IR, adiponectin, and visceral adipose fat. J Clin Sleep Med. 2015 Apr;11(4):475-85.	Irrelevant outcome for the population (i.e., insulin markers in non-diabetic patients)
Ishii L, Roxbury C, Godoy A, Ishman S, Ishii M. Does nasal surgery improve OSA in patients with nasal obstruction and OSA? A meta-analysis. Otolaryngol Head Neck Surg. 2015 Sep;153(3):326-33.	Irrelevant intervention (i.e., nasal surgery)
Knudsen TB, Laulund AS, Ingerslev J, Homoe P, Pinholt EM. Improved Apnea–Hypopnea Index and lowest oxygen saturation after maxillomandibular advancement with or without counterclockwise rotation in patients with obstructive sleep apnea: a meta-analysis. J Oral Maxillofac Surg. 2015 Apr;73(4):719-26.	Not a full SR (i.e., no QA) and older than, and significant overlap with, an included SR with QA (i.e., Zaghi 2016[60])
Kumar AR, Guilleminault C, Certal V, Li D, Capasso R, Camacho M. Nasopharyngeal airway stenting devices for obstructive sleep apnoea: a systematic review and meta-analysis. J Laryngol Otol.	Irrelevant intervention (i.e., nasal trumpets and nasopharyngeal obturators)

Study Reference	Reasons for Exclusion
2015 Jan;129(1):2-10.	
Maspero C, Giannini L, Galbiati G, Rosso G, Farronato G. Obstructive sleep apnea syndrome: a literature review. Minerva Stomatol. 2015 Apr;64(2):97-109.	Not an SR (i.e., a narrative review)
Murphey AW, Kandl JA, Nguyen SA, Weber AC, Gillespie MB. The effect of glossectomy for obstructive sleep apnea: a systematic review and meta-analysis. Otolaryngol Head Neck Surg. 2015 Sep;153(3):334-42.	Irrelevant intervention (i.e., glossectomy)
Nagappa M, Mokhlesi B, Wong J, Wong DT, Kaw R, Chung F. The effects of continuous positive airway pressure on postoperative outcomes in obstructive sleep apnea patients undergoing surgery: a systematic review and meta-analysis. Anesth Analg. 2015 May;120(5):1013-23.	Irrelevant population (i.e., OSA patients after any surgery)
Nakamura S, Asai K, Kubota Y, Murai K, Takano H, Tsukada YT, et al. Impact of sleep-disordered breathing and efficacy of positive airway pressure on mortality in patients with chronic heart failure and sleep-disordered breathing: a meta-analysis. Clin Res Cardiol. 2015 Mar;104(3):208-16.	Irrelevant population (i.e., heart failure patients with sleep-disordered breathing)
Pang KP, Pang EB, Win MT, Pang KA, Woodson BT. Expansion sphincter pharyngoplasty for the treatment of OSA: a systemic review and meta-analysis. Eur Arch Otorhinolaryngol. 2015 Nov 5.	Irrelevant population (i.e., children)
Shukla A, Aizer A, Holmes D, Fowler S, Park DS, Bernstein S, et al. Effect of obstructive sleep apnea treatment on atrial fibrillation recurrence: a meta-analysis. JACC: Clinical Electrophysiology. 2015;1(1-2):41-51.	Complete overlap with an included SR (i.e., Qureshi 2015[67])
Smith DF, Cohen AP, Ishman SL. Surgical management of OSA in adults. Chest. 2015 Jun;147(6):1681-90.	Not an SR (i.e., a narrative review)
Wons AM, Kohler M. Established vascular effects of continuous positive airway pressure therapy in patients with obstructive sleep apnoea-an update. J Thorac Dis. 2015;7(5):912-9.	Not an SR (i.e., a narrative review)
Woods CE, Usher K, Maguire GP. Obstructive sleep apnoea in adult indigenous populations in high-income countries: an integrative review. Sleep Breath. 2015 Mar;19(1):45-53.	Not an SR (i.e., a narrative review)
Wu H, Yuan X, Zhan X, Li L, Wei Y. A review of EPAP nasal device therapy for obstructive sleep apnea syndrome. SleepBreath. 2015;19(3):769-74.	Not an SR (i.e., a narrative review)
Aggarwal S, Nadeem R, Loomba RS, Nida M, Vieira D. The effects of continuous positive airways pressure therapy on cardiovascular end points in patients with sleep-disordered breathing and heart failure: a meta-analysis of randomized controlled trials. Clin Cardiol. 2014 Jan;37(1):57-65.	Irrelevant population (i.e., heart failure patients with sleep-breathing disorders)
Andrade RG, Piccin VS, Nascimento JA, Viana FM, Genta PR, Lorenzi-Filho G. Impact of the type of mask on the effectiveness of and adherence to continuous positive airway pressure treatment for obstructive sleep apnea. J Bras Pneumol. 2014 Nov;40(6):658-68.	Not an SR (i.e., a narrative review)
Bakker JP, Edwards BA, Gautam SP, Montesi SB, Durán-Cantolla J, Aizpuru Barandiarán F, et al. Blood pressure improvement with continuous positive airway pressure is independent of obstructive sleep apnea severity. J Clin Sleep Med. 2014 Apr 15;10(4):365-9.	Older than, and significant overlap with, an included SR (i.e., Bratton 2015[63])

Study Reference	Reasons for Exclusion
Birkbak J, Clark AJ, Rod NH. The effect of sleep disordered breathing on the outcome of stroke and transient ischemic attack: a systematic review. J Clin Sleep Med. 2014 Jan 15;10(1):103-8.	No intervention (i.e., association study)
Bratton DJ, Stradling JR, Barbe F, Kohler M. Effect of CPAP on blood pressure in patients with minimally symptomatic obstructive sleep apnoea: a meta-analysis using individual patient data from four randomised controlled trials. Thorax. 2014 Dec;69(12):1128-35.	Older than, and complete overlap with, an included SR (i.e., Bratton 2015[63])
Camacho M, Certal V, Brietzke SE, Holty JE, Guilleminault C, Capasso R. Tracheostomy as treatment for adult obstructive sleep apnea: a systematic review and meta-analysis. Laryngoscope. 2014 Mar;124(3):803-11.	Irrelevant intervention (i.e., tracheostomy)
Chai-Coetzer CL, Pathinathan A, Smith BJ. Continuous positive airway pressure delivery interfaces for obstructive sleep apnoea. Cochrane DatabaseSyst Rev. 2006;(4):CD005308. Assessed as up-to-date: 2011 Jan 14.	Irrelevant comparator (i.e., CPAP interfaces)
Chen L, Pei JH, Chen HM. Effects of continuous positive airway pressure treatment on glycaemic control and insulin sensitivity in patients with obstructive sleep apnoea and type 2 diabetes: a meta-analysis. Arch Med Sci. 2014 Aug 29;10(4):637-42.	Older than, and complete overlap with, an included SR (i.e., Feng 2015[64])
Gaddam S, Gunukula SK, Mador MJ. Post-operative outcomes in adult obstructive sleep apnea patients undergoing non-upper airway surgery: a systematic review and meta-analysis. Sleep Breath. 2014 Sep;18(3):615-33.	Irrelevant intervention (i.e., non-upper airway surgery)
Gallegos L, Dharia T, Gadegbeku AB. Effect of continuous positive airway pressure on type 2 diabetes mellitus and glucose metabolism. Hosp Pract (Minneap). 2014 Apr;42(2):31-7.	Not an SR (i.e., a narrative review)
de Lourdes Rabelo Guimaraes M, Loureiro CA, Rabelo Guimaraes G, Alves Ferreira C. Oral appliances to prevent occupational accidents involving obstrutive sleep apnea syndrome patients - a systematic review and meta-analysis. Orthod. Sci. Pract. 2014; 7(25):111-7.	Older than, and significant overlap with, an included SR (i.e., Sharples 2016[59])
Handler E, Hamans E, Goldberg AN, Mickelson S. Tongue suspension: an evidence-based review and comparison to hypopharyngeal surgery for OSA. Laryngoscope. 2014 Jan;124(1):329-36.	Irrelevant intervention (i.e., tongue suspension)
Iftikhar IH, Kline CE, Youngstedt SD. Effects of exercise training on sleep apnea: a meta-analysis. Lung. 2014 Feb;192(1):175-84.	Not a full SR (i.e., no QA) and significant overlap with an included SR with QA (i.e., Araghi 2013[76])
Iftikhar IH, Valentine CW, Bittencourt LR, Cohen DL, Fedson AC, Gislason T, et al. Effects of continuous positive airway pressure on blood pressure in patients with resistant hypertension and obstructive sleep apnea: a meta-analysis. J Hypertens. 2014 Dec;32(12):2341-50.	Not a full SR (i.e., no QA) and older than, and significant overlap with, an included SR with QA (i.e., Liu 2016[57])
Kotecha BT, Hall AC. Role of surgery in adult obstructive sleep apnoea. Sleep Med Rev. 2014;18(5):405-13.	Not an SR (i.e., a narrative review)
Li L, Wang ZW, Li J, Ge X, Guo LZ, Wang Y, et al. Efficacy of catheter ablation of atrial fibrillation in patients with obstructive sleep apnoea with and without continuous positive airway pressure	Irrelevant comparator (i.e., OSA with CPAP versus non-OSA)

Study Reference	Reasons for Exclusion
treatment: a meta-analysis of observational studies. Europace. 2014 Sep;16(9):1309-14.	
Lowe ASW, Ebrahim IO, Wiliams AJ. The effect of lifestyle interventions on obstructive sleep apnoea and the metabolic syndrome: a systematic review. J Sleep Disor: Treat Care. 2014;3:3.	Not a full SR (i.e., no QA) and some overlap with an included SR with QA (i.e., Balk 2011[5])
Pepin JL, Timsit JF, Tamisier R, Levy P. Is CPAP effective in reducing blood pressure in minimally symptomatic obstructive sleep apnoea? Thorax. 2014;69(12):1068-70.	Not an SR (i.e., an editorial)
Rabelo Guimaraes ML, Hermont AP. Sleep apnea and occupational accidents: are oral appliances the solution? Indian J Occup Environ Med. 2014 May;18(2):39-47.	Not an SR (i.e., a narrative review)
Schein AS, Kerkhoff AC, Coronel CC, Plentz RD, Sbruzzi G. Continuous positive airway pressure reduces blood pressure in patients with obstructive sleep apnea; a systematic review and meta-analysis with 1000 patients. J Hypertens. 2014 Sep;32(9):1762-73.	Older than, or significant overlap with, included SRs (i.e., Bratton 2015[63] and Fava 2014[10])
Sharples L, Glover M, Clutterbuck-James A, Bennett M, Jordan J, Chadwick R, et al. Clinical effectiveness and cost-effectiveness results from the randomised controlled Trial of Oral Mandibular Advancement Devices for Obstructive sleep apnoea-hypopnoea (TOMADO) and long-term economic analysis of oral devices and continuous positive airway pressure. Health Technol Assess. 2014 Oct;18(67):1-296.	Older than, and complete overlap with, an included SR (i.e., Sharples 2015[59])
Srijithesh PR, Aghoram R, Goel A, Dhanya J. Positional therapy for obstructive sleep apnoea (protocol). Cochrane Database Syst Rev. 2014;(2): CD010990.	Not an SR (i.e., a protocol)
Sun X, Luo J, Xiao Y. Continuous positive airway pressure is associated with a decrease in pulmonary artery pressure in patients with obstructive sleep apnoea: a meta-analysis. Respirology. 2014 Jul;19(5):670-4.	Irrelevant outcome (i.e., pulmonary artery pressure)
Varounis C, Katsi V, Kallikazaros IE, Tousoulis D, Stefanadis C, Parissis J, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: a systematic review and meta-analysis. Int J Cardiol. 2014 Jul 15;175(1):195-8.	Not a full SR (i.e., no QA) and older than, and significant overlap with, an included SR with QA (i.e., Liu 2016[57])
Veer V, Yang WY, Green R, Kotecha B. Long-term safety and efficacy of radiofrequency ablation in the treatment of sleep disordered breathing: a meta-analysis. Eur Arch Otorhinolaryngol. 2014 Nov;271(11):2863-70.	Not a full SR (i.e., no QA) and older than, and significant overlap with, an included SR with QA (i.e., Baba 2015[333])
Virk JS, Nouraei R, Kotecha B. Multilevel radiofrequency ablation to the soft palate and tongue base: tips and pitfalls. Eur Arch Otorhinolaryngol. 2014 Jun;271(6):1809-13.	Not an SR (i.e., a narrative review)
Anandam A, Akinnusi M, Kufel T, Porhomayon J, El-Solh AA. Effects of dietary weight loss on obstructive sleep apnea: a meta-analysis. Sleep Breath. 2013 Mar;17(1):227-34.	Not a full SR (i.e., no QA) and older than, and complete overlap with, an included SR with QA (i.e., Ashrafian 2015[61])
Borel JC, Chaudot C, Bresse C, Clot F, Deschaux C. What are the criteria for selecting a continuous positive airway pressure interface in the treatment of the obstructive sleep apnea syndrome. Medecine du Sommeil. 2013;10(3):116-23.	Not an SR (i.e., a narrative review)

Study Reference	Reasons for Exclusion
Camacho M, Certal V, Capasso R. Comprehensive review of surgeries for obstructive sleep apnea syndrome. Braz J Otorhinolaryngol (Engl Ed). 2013 Nov;79(6):780-8.	Not an SR (i.e., a narrative review)
Choi JH, Kim SN, Cho JH. Efficacy of the Pillar implant in the treatment of snoring and mild-to-moderate obstructive sleep apnea: a meta-analysis. Laryngoscope. 2013 Jan;123(1):269-76.	Irrelevant intervention (i.e., pillar implant)
Chwiesko-Minarowska S, Minarowski L, Kuryliszyn-Moskal A, Chwiesko J, Chyczewska E. Rehabilitation of patients with obstructive sleep apnea syndrome. Int J Rehabil Res. 2013 Dec;36(4):291-7.	Not an SR (i.e., a narrative review)
Hsieh YJ, Liao YF. Effects of maxillomandibular advancement on the upper airway and surrounding structures in patients with obstructive sleep apnoea: a systematic review. Br J Oral Maxillofac Surg. 2013 Dec;51(8):834-40.	Not a full SR (i.e., no comprehensive search strategy) and older than, and significant overlap with, an included SR with QA (i.e., Zaghi 2016[60])
Iftikhar IH, Hays ER, Iverson MA, Magalang UJ, Maas AK. Effect of oral appliances on blood pressure in obstructive sleep apnea: a systematic review and meta-analysis. J Clin Sleep Med. 2013 Feb 1;9(2):165-74.	Not a full SR (i.e., no comprehensive search strategy and no QA) and older than, and significant overlap with, an included SR with QA (i.e., Bratton 2015[63])
Iftikhar IH, Khan MF, Das A, Magalang UJ. Meta-analysis: continuous positive airway pressure improves insulin resistance in patients with sleep apnea without diabetes. Ann Am Thorac Soc. 2013 Apr;10(2):115-20.	Irrelevant outcome for the population (i.e., insulin markers in non-diabetic patients)
Kylstra WA, Aaronson JA, Hofman WF, Schmand BA. Neuropsychological functioning after CPAP treatment in obstructive sleep apnea: a meta-analysis. Sleep Med Rev. 2013 Oct;17(5):341-7.	Older than, and significant overlap with, an included SR (i.e., Pan 2015[66])
Mehta V, Vasu TS, Phillips B, Chung F. Obstructive sleep apnea and oxygen therapy: a systematic review of the literature and meta-analysis. J Clin Sleep Med. 2013 Mar 15;9(3):271-9.	Irrelevant comparator (i.e., CPAP versus O_2 therapy)
Olaithe M, Bucks RS. Executive dysfunction in OSA before and after treatment: a meta-analysis. Sleep . 2013 Sep;36(9):1297-305.	Not a full SR (i.e., no QA) and older than, and some overlap with, an included SR with QA (i.e., Pan 2015[66])
Ramar K, Olson EJ. Management of common sleep disorders. Am Fam Physician. 2013;88(4):231-8.	Not an SR (i.e., a narrative review)
Shah N, Kizer JR, Yaggi HK. Effects of obstructive sleep apnea therapy on cardiovascular disease. Sleep Med Clin. 2013;8(4):453-61.	Not an SR (i.e., a narrative review)
Sun H, Shi J, Li M, Chen X. Impact of continuous positive airway pressure treatment on left ventricular ejection fraction in patients with obstructive sleep apnea: a meta-analysis of randomized controlled trials. PLoS One . 2013;8(5):e62298.	Irrelevant outcome (i.e., left ventricular ejection fraction)
Wang N, Tu XP, Hu K, Xiao JX, Guo Y. Effectiveness of oral appliance versus continuous positive airway pressure in treating patients with mild to moderate obstructive sleep apnea-hypopnea syndrome: a meta-analysis. Chin J Evid Based Med. 2013;13(2):231-5.	Not in English (i.e., in Chinese)
Wozniak DR, Smith I. Beyond CPAP-design and use of complex positive airway pressure devices in the treatment of obstructive sleep apnea. Minerva Pneumol. 2013;52(4):163-81.	Not an SR (i.e., a narrative review)

Study Reference	Reasons for Exclusion
Yang D, Liu Z, Yang H, Luo Q. Effects of continuous positive airway pressure on glycemic control and insulin resistance in patients with obstructive sleep apnea: a meta-analysis. Sleep Breath. 2013 Mar;17(1):33-8.	Irrelevant outcome for the population (i.e., glucose and/or insulin markers in non-diabetic patients)
Hosseini Araghi M, Chen YF, Jagielski A, Mannan Choudhury S, Banerjee D, Thomas NG, et al. Weight-loss intervention through lifestyle modification or pharmacotherapy for obstructive sleep apnoea in adults (protocol). Cochrane Database Syst Rev. 2012;(12):CD010281.	Not an SR (i.e., a protocol)
Crawford MR, Bartlett DJ, Coughlin SR, Phillips CL, Neill AM, Espie CA, et al. The effect of continuous positive airway pressure usage on sleepiness in obstructive sleep apnoea: real effects or expectation of benefit? Thorax. 2012 Oct;67(10):920-4.	Not an SR (i.e., an MA of 3 select studies)
Gao W, Jin Y, Wang Y, Sun M, Chen B, Zhou N, et al. Is automatic CPAP titration as effective as manual CPAP titration in OSAHS patients? A meta-analysis. Sleep Breath. 2012 Jun;16(2):329-40.	Irrelevant comparator (i.e., APAP versus CPAP)
Sleep apnea diagnosis and treatment in adults. Olympia (WA): Washington State Health Care Authority; 2012.	Complete overlap with an included and larger SR (i.e., Balk 2011[5])
Iftikhar IH, Blankfield RP. Effect of continuous positive airway pressure on hemoglobin A(1c) in patients with obstructive sleep apnea: a systematic review and meta-analysis. Lung. 2012 Dec;190(6):605-11.	Not a full SR (i.e., no QA) and older than, and significant overlap with, an included SR with QA (i.e., Feng 2015[64])
Ip S, D'Ambrosio C, Patel K, Obadan N, Kitsios GD, Chung M, et al. Auto-titrating versus fixed continuous positive airway pressure for the treatment of obstructive sleep apnea: a systematic review with meta-analyses. Syst Rev. 2012;1:20.	Irrelevant comparator (i.e., APAP versus CPAP)
Marklund M, Verbraecken J, Randerath W. Non-CPAP therapies in obstructive sleep apnoea: mandibular advancement device therapy. Eur Respir J. 2012;39(5):1241-7.	Not an SR (i.e., a narrative review)
Montesi SB, Edwards BA, Malhotra A, Bakker JP. The effect of continuous positive airway pressure treatment on blood pressure: a systematic review and meta-analysis of randomized controlled trials. J Clin Sleep Med . 2012 Oct 15;8(5):587-96.	Not a full SR (i.e., no comprehensive search strategy and no QA) and older than, and significant overlap with, an included SR with QA (i.e., Bratton 2015[63])
Prinsell JR. Primary and secondary telegnathic maxillomandibular advancement, with or without adjunctive procedures, for obstructive sleep apnea in adults: a literature review and treatment recommendations. J Oral Maxillofac Surg. 2012 Jul;70(7):1659-77.	Not an SR (i.e., a narrative review)
Sommer JU, Maurer JT, Hörmann K, Stuck BA. Randomized controlled trials in the surgical treatment of obstructive sleep apnea. HNO. 2012;60(4):294-9.	Not in English (i.e., German)
Wang SL, Shi DZ, Wang CL. Prognostic effects of obstructive sleep apnea treated with continuous positive airway pressure or upper airway surgery on coronary heart disease: a systematic review. Chin J Evid Based Med. 2012;12(9):1105-9.	Not in English (i.e., Chinese)
Xu T, Li T, Wei D, Feng Y, Xian L, Wu H, et al. Effect of automatic versus fixed continuous positive airway pressure for the treatment of obstructive sleep apnea: an up-to-date meta-analysis. Sleep Breath. 2012 Dec;16(4):1017-26.	Irrelevant comparator (i.e., APAP versus CPAP)

Study Reference	Reasons for Exclusion
Yang D, Liu Z, Yang H. The impact of effective continuous positive airway pressure on homeostasis model assessment insulin resistance in non-diabetic patients with moderate to severe obstructive sleep apnea. Diabetes Metab Res Rev. 2012 Sep;28(6):499-504.	Irrelevant outcome to the population (i.e., insulin resistance in non-diabetic patients)
Ahrens A, McGrath C, Hägg U. A systematic review of the efficacy of oral appliance design in the management of obstructive sleep apnoea. Eur J Orthod. 2011 Jun;33(3):318-24.	Not a full SR (i.e., no synthesis and no QA) and older than, and significant overlap with, an included SR with QA (i.e., Sharples 2016[59])
Bakker JP, Marshall NS. Flexible pressure delivery modification of continuous positive airway pressure for obstructive sleep apnea does not improve compliance with therapy: systematic review and meta-analysis. Chest. 2011 Jun;139(6):1322-30.	Irrelevant comparator (i.e., CPAP versus flexible CPAP)
Hecht L, Mohler R, Meyer G. Effects of CPAP-respiration on markers of glucose metabolism in patients with obstructive sleep apnoea syndrome: a systematic review and meta-analysis. Ger Med Sci. 2011;9:Doc 20.	Irrelevant outcome for the population (i.e., glucose markers in non-diabetic patients)
Li HY, Wang PC, Chen YP, Lee LA, Fang TJ, Lin HC. Critical appraisal and meta-analysis of nasal surgery for obstructive sleep apnea. Am J Rhinol Allergy. 2011 Jan;25(1):45-9.	Irrelevant intervention (i.e., nasal surgery)
Li KK. Maxillomandibular advancement for obstructive sleep apnea. J Oral Maxillofac Surg. 2011 Mar;69(3):687-94.	Not an SR (i.e., a narrative review)
Pirklbauer K, Russmueller G, Stiebellehner L, Nell C, Sinko K, Millesi G, et al. Maxillomandibular advancement for treatment of obstructive sleep apnea syndrome: a systematic review. J Oral Maxillofac Surg. 2011 Jun;69(6):e165-e176.	Not a full SR (i.e., no comprehensive search strategy and no QA) and older than, and significant overlap with, an included SR with QA (i.e., Zaghi 2016[60])
Porhomayon J, El-Solh A, Chhangani S, Nader ND. The management of surgical patients with obstructive sleep apnea. Lung. 2011;189(5):359-67.	Not an SR (i.e., a narrative review)
Ravesloot MJ, de Vries N. 'A good shepherd, but with obstructive sleep apnoea syndrome': traditional uvulectomy case series and literature review. J Laryngol Otol. 2011 Sep;125(9):982-6.	Not an SR (i.e., a narrative review)
Sundar E, Chang J, Smetana GW. Perioperative screening for and management of patients with obstructive sleep apnea. J Clin Outcomes Manage. 2011;18(9):399-411.	Not an SR (i.e., a narrative review)
Xu T, Li TP, Xian LW, Li DQ, Wang YY. Effectiveness of auto-CPAP versus fixed-CPAP for the treatment of obstructive sleep apnea syndrome: a meta-analysis. Chin J Evid Based Med. 2011;11(6):687-92.	Not in English (i.e., in Chinese)

APAP = autotitrating positive airway pressure; CPAP = continuous positive airway pressure; HOMA-IR = homeostatic model assessment insulin resistance; OSA = obstructive sleep apnea; OSAHS = obstructive sleep apnea hypopnea syndrome; QA = quality assessment; RFA = radiofrequency ablation; SR = systematic review; UPPP = uvulopalatopharyngoplasty.

Review of Primary Studies

Study Reference	Reasons for Exclusion
Azbay S, Bostanci A, Aysun Y, Turhan M. The influence of multilevel upper airway surgery on CPAP tolerance in non-responders to obstructive sleep apnea surgery. Eur Arch Otorhinolaryngol. 2016 Sep;273(9):2813-8.	Irrelevant intervention (i.e., septoplasty, TBS, and UPPP)
Bachour P, Bachour A, Kauppi P, Maasilta P, Makitie A, Palotie T. Oral appliance in sleep apnea treatment: respiratory and clinical effects and long-term adherence. Sleep Breath. 2016 May;20(2):805-12.	Irrelevant comparator (i.e., pre-treatment)
Barrera JE, Dion GR. Predicting surgical response using tensiometry in OSA patients after genioglossus advancement with uvulopalatopharyngoplasty. Otolaryngol Head Neck Surg. 2016 Mar;154(3):558-63.	Irrelevant intervention (i.e., inclusion of UPPP)
Butterfield KJ, Marks PL, McLean L, Newton J. Quality of life assessment after maxillomandibular advancement surgery for obstructive sleep apnea. J Oral Maxillofac Surg. 2016 Jan 30.	Irrelevant comparator (i.e., pre-treatment)
Gjerde K, Lehmann S, Berge ME, Johansson AK, Johansson A. Oral appliance treatment in moderate and severe obstructive sleep apnoea patients non-adherent to CPAP. J Oral Rehabil. 2016 Apr;43(4):249-58.	Irrelevant comparator (i.e., pre-treatment)
Goodday RH, Bourque SE, Edwards PB. Objective and subjective outcomes following maxillomandibular advancement surgery for treatment of patients with extremely severe obstructive sleep apnea (Apnea–Hypopnea Index > 100). J Oral Maxillofac Surg. 2016 Mar;74(3):583-9.	Irrelevant comparator (i.e., pre-treatment)
Kostrzewa-Janicka J, Sliwinski P, Wojda M, Rolski D, Mierzwinska-Nastalska E. Mandibular advancement appliance for obstructive sleep apnea treatment. Adv Exp Med Biol. 2016 Jul 29.	No primary study (i.e., a review)
Marklund M. Long-term efficacy of an oral appliance in early treated patients with obstructive sleep apnea. Sleep Breath. 2016 May;20(2):689-94.	Irrelevant comparator (i.e., pre-treatment)
Nerfeldt P, Friberg D. Effectiveness of oral appliances in OSA with respiratory arousals. J Clin Sleep Med. 2016 Jul 1.	Irrelevant comparator (i.e., pre-treatment)
Sakamoto Y, Yanamoto S, Rokutanda S, Naruse T, Imayama N, Hashimoto M, et al. Predictors of obstructive sleep apnoea-hypopnea severity and oral appliance therapy efficacy by using lateral cephalometric analysis. J Oral Rehabil. 2016 May 1.	Irrelevant comparator (i.e., pre-treatment)
Sekizuka H, Osada N, Akashi YJ. Effect of oral appliance therapy on blood pressure in Japanese patients with obstructive sleep apnea. Clin Exp Hypertens. 2016 May 9;1-5.	Irrelevant comparator (i.e., pre-treatment)
Woods CM, Gunawardena I, Chia M, Vowles NJ, Ullah S, Robinson S, et al. Long term quality of life outcomes following treatment for adult obstructive sleep apnoea: comparison of upper airway surgery, continuous positive airway pressure and mandibular advancement splints. Clin Otolaryngol. 2016 Feb 29.	Irrelevant intervention (i.e., UPPP)
Boyd SB, Walters AS, Waite P, Harding SM, Song Y. Long-term effectiveness and safety of maxillomandibular advancement for treatment of obstructive sleep apnea. J Clin Sleep Med. 2015	Irrelevant comparator (i.e., pre-treatment)

Study Reference	Reasons for Exclusion
Jul;11(7):699-708.	
Chen S, Shi S, Xia Y, Zhu M, Zhang C, Xia S, et al. A prospective study of the surgical outcome of simple uvulopalatopharyngoplasty (UPPP), UPPP combined with genioglossus advancement or tongue base advancement for obstructive sleep apnea hypopnea syndrome patients with multilevel obstruction. Clin Exp Otorhinolaryngol. 2015 Jun;8(2):136-41.	Irrelevant intervention (i.e., inclusion of UPPP)
Cilil VR, Sapana Varma NK, Gopinath S, Ajith VV. Efficacy of custom made oral appliance for treatment of obstructive sleep apnea. Contemp Clin Dent. 2015 Jul;6(3):341-7.	Irrelevant comparator (i.e., pre-treatment)
Clifton C, Andry J, Bryk C. CAT of the month. Critically appraised topics. The cardiovascular health benefits of oral appliance therapy for obstructive sleep apnea typically outweigh the risk of tooth movement and malocclusion (UT CAT #2808). Tex Dent J. 2015 Nov;132(11):903.	No primary study (i.e., a research summary)
Gasparini G, Torroni A, Di Nardo F, Pelo S, Foresta E, Boniello R, et al. OSAS surgery and postoperative discomfort: phase I surgery versus phase II surgery. Biomed Res Int. 2015 ;2015:439847.	Irrelevant intervention (i.e., unspecified surgery)
Hein H. Positional therapy for obstructive sleep apnea. Med Welt. 2015;66(3):127-39.	Not in English (i.e., in German)
Iftikhar IH, Donley MA, Al-Jaghbeer M, Monserrate A. Continuous positive airway pressure plus weight loss for obstructive sleep apnea (OSA), association of cancer with OSA, and hypoglossal nerve stimulation for OSA treatment. Am J Respir Crit Care Med. 2015 Apr 1;191(7):845-7.	No primary study (i.e., recommended readings)
Islam S, Taylor CJ, Ormiston IW. The predictive value of obstructive sleep apnoea severity on clinical outcomes following maxillomandibular advancement surgery. Br J Oral Maxillofac Surg. 2015 Mar;53(3):263-7.	Irrelevant comparator (i.e., pre-treatment)
Islam S, Taylor C, Ormiston IW. Effect of preoperative continuous positive airway pressure duration on outcomes after maxillofacial surgery for obstructive sleep apnoea. Br J Oral Maxillofac Surg. 2015 Feb;53(2):183-6.	Irrelevant comparator (i.e., pre-treatment)
Islam S, Taylor CJ, Ormiston IW. Effects of maxillomandibular advancement on systemic blood pressure in patients with obstructive sleep apnoea. Br J Oral Maxillofac Surg. 2015 Jan;53(1):34-8.	Irrelevant comparator (i.e., pre-treatment)
Nerfeldt P, Nilsson BY, Mayor L, Udden J, Rossner S, Friberg D. Weight reduction improves sleep, sleepiness and metabolic status in obese sleep apnoea patients. Obes Res Clin Pract. 2008 Dec;2(4):251-62.	Irrelevant intervention (i.e., weight-reduction program with CPAP or MADs, analyzed together)
Upadhyay R, Dubey A, Kant S, Singh BP. Management of severe obstructive sleep apnea using mandibular advancement devices with auto continuous positive airway pressures. Lung India. 2015 Mar;32(2):158-61.	Irrelevant study design (i.e., a case report)
Wang J, Ma W, Xie Y, Hui P, Zhao L, Wei X, et al. The curative effect analysis of continuous positive airway pressure combined with modified oral appliance in the treatment of severe OSAHS. Lin Chung Er Bi Yan Hou Tou Jing Wai Ke Za Zhi. 2015	Not in English (i.e., in Chinese)

Study Reference	Reasons for Exclusion
Dec;29(23):2044-7.	
Yang D, Zhou HF, Xie Y. Efficacy of uvulopalatopharyngoplasty combined with oral appliance in treatment of obstructive sleep apnea-hypopnea syndrome. Ir J Med Sci. 2015 Jun;184(2):329-34.	Irrelevant intervention (i.e., inclusion of UPPP)
Chen S, Shi S, Xia Y, Liu F, Chen D, Zhu M, et al. Changes in sleep characteristics and airway obstruction in OSAHS patients with multi-level obstruction following simple UPPP, UPPP-GA, or UPPP-TBA: a prospective, single-center, parallel group study. ORL J Otorhinolaryngol Relat Spec. 2014;76(4):179-88.	Irrelevant intervention (i.e., inclusion of UPPP)
Fukuda T, Tsuiki S, Kobayashi M, Nakayama H, Inoue Y. Selection of response criteria affects the success rate of oral appliance treatment for obstructive sleep apnea. Sleep Med. 2014 Mar;15(3):367-70.	Irrelevant comparator (i.e., pre-treatment)
Johansson A, Gjerde K, Lehmann S, Bjorvatn B, Al-azawy K, Gulati S, et al. Oral appliance therapy for sleep apnoea. Tidsskrift for den Norske Legeforening. 2014 May 27 ;134(10):1030-1.	Not in English (i.e., in Norwegian)
Rohrer JW, Eller R, Santillan PG, Barrera JE. Geniotubercle advancement with a uvulopalatal flap and its effect on swallow function in obstructive sleep apnea. Laryngoscope. 2014;125(3):758-61.	Irrelevant intervention (i.e., UPF)
Zakhar A, Wirth C, Farrow E, Tison C, Ferri J, Raoul G. Surgical treatment of obstructive sleep apnea syndrome. Functional assessment. Rev Stomatol Chir Maxillofac Chir Orale. 2014 Apr;115(2):79-83.	Irrelevant intervention (i.e., inclusion of UPPP)
Cillo JE, Dalton PS, Dattilo DJ. Combined elliptical window genioglossus advancement, hyoid bone suspension, and uvulopalatopharyngoplasty decrease apnea hypopnea index and subjective daytime sleepiness in obstructive sleep apnea. J Oral Maxillofac Surg. 2013 Oct;71(10):1729-32.	Irrelevant intervention (i.e., inclusion of HS and UPPP)
Gong X, Zhang J, Zhao Y, Gao X. Long-term therapeutic efficacy of oral appliances in treatment of obstructive sleep apnea-hypopnea syndrome. Angle Orthod. 2013 Jul ;83(4):653-8.	Irrelevant comparator (i.e., pre-treatment)
Kim H, Kim MS, Lee JE, Kim JW, Lee CH, Yoon IY, et al. Treatment outcomes and compliance according to obesity in patients with obstructive sleep apnea. Eur Arch Otorhinolaryngol. 2013 Nov;270(11):2885-90.	Irrelevant intervention (i.e., inclusion of RFA and UPPP)
Boyd SB, Walters AS, Song Y, Wang L. Comparative effectiveness of maxillomandibular advancement and uvulopalatopharyngoplasty for the treatment of moderate to severe obstructive sleep apnea. J Oral Maxillofac Surg . 2013 Apr;71(4):743-51.	Irrelevant intervention (i.e., inclusion of UPPP)
Ravesloot MJ, van Maanen JP, Dun L, de Vries N. The undervalued potential of positional therapy in position-dependent snoring and obstructive sleep apnea-a review of the literature. Sleep Breath. 2013 Mar;17(1):39-49.	No primary study (i.e., a review)
Schutz TC, Cunha TC, Moura-Guimaraes T, Luz GP, Ackel-D'Elia C, Alves ES, et al. Comparison of the effects of continuous positive airway pressure, oral appliance and exercise training in obstructive sleep apnea syndrome. Clinics . 2013;68(8):1168-74.	Found in an SR included in the overview (i.e., Ifthikhar 2016[55])
Seehra J, Winchester LJ. Customised mandibular advancement	No primary study (i.e., a technical note)

Study Reference	Reasons for Exclusion
splint for apnoeic patients undergoing maxillomandibular advancement. Br J Oral Maxillofac Surg. 2013 Apr;51(3):266-7.	
Jalbert F, Lacassagne L, Bessard J, Dekeister C, Paoli JR, Tiberge M. Oral appliances or maxillomandibular advancement osteotomy for severe obstructive sleep apnoea in patients refusing CPAP. Rev Stomatol Chir Maxillofac. 2012 Feb;113(1):19-26.	Irrelevant comparator (i.e., pre-treatment)
Liu SR, Yi HL, Yin SK, Guan J, Chen B, Meng LL, et al. Primary maxillomandibular advancement with concomitant revised uvulopalatopharyngoplasty with uvula preservation for severe obstructive sleep apnea-hypopnea syndrome. J Craniofac Surg. 2012 Nov;23(6):1649-53.	Irrelevant intervention (i.e., inclusion of UPPP)
Mora R, Salzano FA, Mora F, Guastini L. Outcomes of uvulopalatopharyngoplasty with harmonic scalpel after failure of continuous positive airway pressure in sleep apnea syndrome. Acta Otolaryngol (Stockh). 2012 Mar;132(3):299-304.	Irrelevant intervention (i.e., inclusion of HS and UPPP)
Emara TA, Omara TA, Shouman WM. Modified genioglossus advancement and uvulopalatopharyngoplasty in patients with obstructive sleep apnea. Otolaryngol Head Neck Surg. 2011 Nov;145(5):865-71.	Irrelevant intervention (i.e., inclusion of UPPP)
Hamans E. Multicenter study of a novel adjustable tongue-advancement device for obstructive sleep apnea. Otolaryngol Head Neck Surg. 2011 Jun;144(6):1009-10.	No primary study (i.e., a letter to the editor)
Holley AB, Lettieri CJ, Shah AA. Efficacy of an adjustable oral appliance and comparison with continuous positive airway pressure for the treatment of obstructive sleep apnea syndrome. Chest. 2011 Dec;140(6):1511-6.	Irrelevant comparator (i.e., CPAP)
Lam B, Sam K, Lam JC, Lai AY, Lam CL, Ip MS. The efficacy of oral appliances in the treatment of severe obstructive sleep apnea. Sleep Breath. 2011 May;15(2):195-201.	Irrelevant comparator (i.e., pre-treatment)
Nerfeldt P, Nilsson BY, Mayor L, Udden J, Friberg D. A two-year weight reduction program in obese sleep apnea patients. J Clin Sleep Med. 2010 Oct 15;6(5):479-86.	Irrelevant intervention (i.e., weight-reduction program with CPAP or MADs, analyzed together)
Kezirian EJ, Malhotra A, Goldberg AN, White DP. Changes in obstructive sleep apnea severity, biomarkers, and quality of life after multilevel surgery. Laryngoscope. 2010 Jul;120(7):1481-8.	Irrelevant intervention (i.e., inclusion of HS, tonsillectomy, and UPPP)
Permut I, Diaz-Abad M, Chatila W, Crocetti J, Gaughan JP, D'Alonzo GE, et al. Comparison of positional therapy to CPAP in patients with positional obstructive sleep apnea. J Clin Sleep Med. 2010 Jun 15;6(3):238-43.	Found in an SR included in the overview (i.e., Ha 2014[72])
Schaaf WE, Wootten CT, Donnelly LF, Ying J, Shott SR. Findings on MR sleep studies as biomarkers to predict outcome of genioglossus advancement in the treatment of obstructive sleep apnea in children and young adults. AJR Am J Roentgenol. 2010 May;194(5):1204-9.	Irrelevant population (i.e., children)
Tsuiki S, Kobayashi M, Namba K, Oka Y, Komada Y, Kagimura T, et al. Optimal positive airway pressure predicts oral appliance response to sleep apnoea. Eur Respir J. 2010 May ;35(5):1098-105.	Irrelevant comparator (i.e., pre-treatment)
Woodson BT, Steward DL, Mickelson S, Huntley T, Goldberg A.	Irrelevant intervention (i.e., implanted tongue-

Study Reference	Reasons for Exclusion
Multicenter study of a novel adjustable tongue-advancement device for obstructive sleep apnea. Otolaryngol Head Neck Surg. 2010 Oct;143(4):585-90.	advancement device)
Choi JH, Park YH, Hong JH, Kim SJ, Park DS, Miyazaki S, et al. Efficacy study of a vest-type device for positional therapy in position dependent snorers. Sleep Biol Rhythms. 2009;7(3):181-7.	Irrelevant population (i.e., snorers with or without mild OSA)
Deane SA, Cistulli PA, Ng AT, Zeng B, Petocz P, Darendeliler MA. Comparison of mandibular advancement splint and tongue stabilizing device in obstructive sleep apnea: a randomized controlled trial. Sleep. 2009 May;32(5):648-53.	Found in an SR included in the overview (i.e., Balk 2011[5])
Giannasi LC, Almeida FR, Magini M, Costa MS, de Oliveira CS, de Oliveira JC, et al. Systematic assessment of the impact of oral appliance therapy on the temporomandibular joint during treatment of obstructive sleep apnea: long-term evaluation. Sleep Breath. 2009 Nov;13(4):375-81.	Irrelevant comparator (i.e., pre-treatment)
Jayan B, Prasad BNBM, Dhiman RK. Role of oral appliances in the management of sleep disorders. Med J Armed Forces India. 2009;65(2):123-7.	Irrelevant intervention (i.e., mixed OAs, including MADs and TRDs)
Nakamura S, Sato M, Mataki S, Kurosaki N, Hasegawa M. Subjective and objective assessments of short-term adverse effects induced by oral appliance therapy in obstructive sleep apnea: a preliminary study. J Med Dent Sci. 2009 Mar;56(1):37-48.	Irrelevant outcomes (i.e., occlusion changes)
Oksenberg A, Silverberg DS. Avoiding the supine posture during sleep for patients with mild obstructive sleep apnea. Am J Respir Crit Care Med. 2009 Jul 1;180(1):101-2.	No primary study (i.e., a letter to the editor)
Ranieri AL, Jales SM, Formigoni GG, de Aloe FS, Tavares SM, Siqueira JT. Treatment of obstructive sleep apnea syndrome in patients from a teaching hospital in Brazil: is it possible? Sleep Breath. 2009 May;13(2):121-5.	Irrelevant comparator (i.e., pre-treatment)
Abo-Khatwa MM, Osman EZ, Hill PD, Lee BW, Osborne JE. Objective evaluation of tongue base snoring after the use of an oral appliance: a prospective case series. Clin Otolaryngol. 2008 Dec;33(6):592-5.	Irrelevant comparator (i.e., pre-treatment)
Chen H, Lowe AA, Strauss AM, de Almeida FR, Ueda H, Fleetham JA, et al. Dental changes evaluated with a 3D computer-assisted model analysis after long-term tongue retaining device wear in OSA patients. Sleep Breath. 2008 May;12(2):169-78.	Irrelevant study design (i.e., case reports)
Krishnan V, Collop NA, Scherr SC. An evaluation of a titration strategy for prescription of oral appliances for obstructive sleep apnea. Chest. 2008 May;133(5):1135-41.	Irrelevant comparator (i.e., pre-treatment)
Skinner MA, Kingshott RN, Filsell S, Taylor DR. Efficacy of the 'tennis ball technique' versus nCPAP in the management of position-dependent obstructive sleep apnoea syndrome. Respirology. 2008 Sep;13(5):708-15.	Found in an SR included in the overview (i.e., Balk 2011[5])
Sun X, Yi H, Cao Z, Yin S. Reorganization of sleep architecture after surgery for OSAHS. Acta Otolaryngol (Stockh). 2008 Nov;128(11):1242-7.	Irrelevant intervention (i.e., inclusion of HS and UPPP)
Ueda H, Almeida FR, Lowe AA, Ruse ND. Changes in occlusal contact area during oral appliance therapy assessed on study	Irrelevant comparator (i.e., pre-treatment)

Study Reference	Reasons for Exclusion
models. Angle Orthod. 2008 Sep;78(5):866-72.	
Conley RS, Boyd SB. Facial soft tissue changes following maxillomandibular advancement for treatment of obstructive sleep apnea. J Oral Maxillofac Surg. 2007 Jul;65(7):1332-40.	Irrelevant outcomes (i.e., facial soft tissue changes)
Foltan R, Hoffmannova J, Pretl M, Donev F, Vlk M. Genioglossus advancement and hyoid myotomy in treating obstructive sleep apnoea syndrome - a follow-up study. J Craniomaxillofac Surg. 2007 Jun;35(4-5):246-51.	Irrelevant intervention (i.e., inclusion of hyoid monotomy)
Hsu PP, Tan AK, Tan BY, Gan EC, Chan YH, Blair RL, et al. Uvulopalatopharyngoplasty outcome assessment with quantitative computer-assisted videoendoscopic airway analysis. Acta Otolaryngol (Stockh). 2007 Jan;127(1):65-70.	Irrelevant intervention (i.e., UPPP)
Richard W, Kox D, den Herder C, van Tinteren H, de Vries N. One stage multilevel surgery (uvulopalatopharyngoplasty, hyoid suspension, radiofrequent ablation of the tongue base with/without genioglossus advancement), in obstructive sleep apnea syndrome. Eur Arch Otorhinolaryngol. 2007 Apr;264(4):439-44.	Irrelevant intervention (i.e., inclusion of HS, RFA, and UPPP)
Stouder S, Jones L, Brietzke S, Mair EA. Does an oral appliance reduce palatal flutter and tongue base snoring? Otolaryngol Head Neck Surg. 2007 May;136(5):827-31.	Irrelevant comparator (i.e., pre-treatment)
Yin SK, Yi HL, Lu WY, Guan J, Wu HM, Cao ZY. Genioglossus advancement and hyoid suspension plus uvulopalatopharyngoplasty for severe OSAHS. Otolaryngol Head Neck Surg. 2007 Apr;136(4):626-31.	Irrelevant intervention (i.e., inclusion of HS and UPPP)
Almeida FR, Lowe AA, Otsuka R, Fastlicht S, Farbood M, Tsuiki S. Long-term sequellae of oral appliance therapy in obstructive sleep apnea patients: Part 2. Study-model analysis. Am J Orthod Dentofacial Orthop. 2006 Feb;129(2):205-13.	Irrelevant outcomes (i.e., occlusion changes)
Jacobowitz O. Palatal and tongue base surgery for surgical treatment of obstructive sleep apnea: a prospective study. Otolaryngol Head Neck Surg. 2006 Aug;135(2):258-64.	Irrelevant intervention (i.e., inclusion of HS, RFA, and UPPP)
Otsuka R, Ribeiro de Almeida F, Lowe AA, Linden W, Ryan F. The effect of oral appliance therapy on blood pressure in patients with obstructive sleep apnea. Sleep Breath. 2006 Mar;10(1):29-36.	Irrelevant comparator (i.e., pre-treatment)
Sam K, Lam B, Ooi CG, Cooke M, Ip MS. Effect of a non-adjustable oral appliance on upper airway morphology in obstructive sleep apnoea. Respir Med. 2006 May ;100(5):897-902.	Irrelevant comparator (i.e., pre-treatment)

CPAP = continuous positive airway pressure; GA = genioglossus advancement; HS = hyoid suspension; MAD = mandibular adjustment device; OSA = obstructive sleep apnea; RFA = radiofrequency ablation; SR = systematic review; TBA = tongue base advancement; TBS = tongue base suspension; TRD = tongue-retaining device; UPF = uvulopalatal flap; UPPP = uvulopalatopharyngoplasty.

Appendix 5: Quality Assessment Questions (Research Question 1)

ROBIS

1. Domain 1: study eligibility criteria
   - 1.1 Did the review adhere to pre-defined objectives eligibility criteria?
   - 1.2 Were the eligibility criteria appropriate for the review questions?
   - 1.3 Were eligibility criteria unambiguous?
   - 1.4 Were all restrictions in eligibility criteria based on study characteristics appropriate (e.g., date, study design, sample size, study quality, outcomes measured)?
   - 1.5 Were any restrictions in eligibility criteria based on sources of information appropriate (e.g., publication status or format, language, availability of data)?
2. Domain 2: identification and selection of studies
   - 2.1 Did the search include an appropriate range of databases/electronic sources for published and unpublished reports?
   - 2.2 Were methods additional to database searching used to identify relevant methods?
   - 2.3 Were the terms and structure of the search strategy likely to retreive as many eligibility studies as possible?
   - 2.4 Were restrictions based on date, publication format, or language appropriate?
   - 2.5 Were efforts made to minimise error in selection of studies?
3. Domain 3: data collection and study appraisal
   - 3.1 Were efforts made to minimise error in data collection?
   - 3.2 Were sufficient study characteristics available for both review authors and readers to be able to interpret the results?
   - 3.3 Were all relevant study results collected for use in the synthesis?
   - 3.4 Was risk of bias (or methodological quality) formally assessed using appropriate criteria?
   - 3.5 Were efforts made to minimise error in risk of bias assessment?
4. Domain 4: synthesis and findings
   - 4.1 Did the synthesis include all studies that it should?
   - 4.2 Were all pre-defined analyses reported or departures explained?
   - 4.3 Was the synthesis appropriate given the nature and similarity in the research questions, study designs and outcomes across included studies?
   - 4.4 Was between-study variation (heterogeneity) minimal or addressed in the synthesis?
   - 4.5 Were the findings robust, e.g. as demonstrated through funnel plot or sensitivity analyses?
   - 4.6 Were biases in primary studies minimal or addressed in the synsthesis?

AMSTAR

Select criteria:

1. Was the status of publication (i.e., grey literature) used as an inclusion criterion?
2. Was a list of included studies provided?
3. Was a list of excluded studies provided?
4. Was the conflict of interest included?

ISPOR

1. Domain 1: relevance
   - 1.1 Is the population relevant?
   - 1.2 Are any relevant interventions missing?
   - 1.3 Are any relevant outcomes missing?
   - 1.4 Is the context (settings and circumstances) applicable?

2. Domain 2: credibility
    - 2.1 Did the researchers attempt to identify and include all relevant RCTs [randomized controlled trials]?
    - 2.2 Do the trials for the interventions of interest form one connected network of RCTs?
    - 2.3 Is it apparent that poor-quality studies were included, thereby leading to bias?
    - 2.4 Is it likely that bias was induced by selective reporting of outcomes in the studies?
    - 2.5 Are there systematic differences in treatment effect modifiers (i.e., baseline patient or study characteristics that have an impact on the treatment effects) across the different treatment comparisons in the network?
    - 2.6 If yes (i.e., there are such systematic differences in treatment effect modifiers), were these imbalances in effect modifiers across the different treatment comparisons identified before comparing individual study results?
3. Domain 3: analysis
    - 3.1 Were statistical methods used that preserve within study randomization? (No naive comparisons)
    - 3.2 If both direct and indirect comparisons are available for pairwise contrasts (i.e., closed loops), was agreement in treatment effects (i.e., consistency) evaluated or discussed?
    - 3.3 In the presence of consistency between direct and indirect comparisons, were both direct and indirect evidence included in the network meta-analysis?
    - 3.4 With inconsistency or an imbalance in the distribution of treatment effect modifers across the different types comparisons in the network of trials, did the researchers attempt to minimize this bias with the analysis?
    - 3.5 Was a valid rationale provided for the use of random-effects or fixed-effect models?
    - 3.6 If a random-effects model was used, were assumptions about heterogeneity explored or discussed?
    - 3.7 If there are indications of hetergeneity, were subgroup analyses or meta-regression analysis with prespecified covariates performed?
4. Domain 4: reporting quality and transparency
    - 4.1 Is a graphical or tabular representation of the evidence network provided with information on the number of RCTs per direct comparison?
    - 4.2 Are the individual study results reported?
    - 4.3 Are the results of direct comparisons reported separately from results of the indirect comparisons or network meta-analysis?
    - 4.4 Are all pairwise contrasts between interventions as obtained with the network meta-analysis reported along with measures of uncertainty?
    - 4.5 Is a ranking of interventions provided given the reported treatment effects and its uncertainty by outcome?
    - 4.6 Is the effect of important patient characteristics on treatment effects reported?
5. Domain 5: interpretation
    - 5.1 Are the conclusions fair and balanced?
6. Domain 6: conflict of interest
    - 6.1 Were there any potential conflicts of interest?
    - 6.2 If yes, were steps take to address these?

RoBANS

1. Comparability: selection bias due to selection of inappropriate comparison target group
2. Selection of patients: selection bias due to inappropriate intervention or inappropriate selection of exposure group or patient group
3. Confounder: selection bias due to inappropriate confounder confirmation and consideration
4. Exposure measurement: performance bias due to inappropriate intervention or inappropriate exposure measurement
5. Blinding of assessors: confirmation bias due to inappropriate blinding of assessors
6. Outcome assessment: confirmation bias due to inappropriate outcome assessment methods

7. Incomplete outcome data: attrition bias due to inappropriate handling of incomplete data
8. Selective outcome reporting: reporting bias due to selective outcome reporting

Cochrane Risk of Bias

1. Sequence generation: was the allocation sequence adequately generated?
2. Allocation concealment: was the sequence generation adequately concealed before group assignments?
3. Blinding of participants and personnel: was knowledge of the allocated interventions adequately hidden from the participants and personnel after participants were assigned to respective groups?
4. Blinding of outcome assessment: was knowledge of the allocated interventions adequately hidden from the outcome assessors after participants were assigned to respective groups?
5. Incomplete outcome data: were incomplete outcome data adequately addressed?
6. Selective outcome reporting: are reports of the study free of suggestion of selective outcome reporting?
7. Other potential threats to validity: was the study apparently free of other problems that could put it at a risk of bias?

Appendix 6: Characteristics of Included Systematic Reviews (Research Question 1)

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
Aiello 2016[50] US No industry funding	SR/MA of RCTs and observational studies CENTRAL, MEDLINE (searched from 1993 to 2014), Web of Science, and CINAHL QA using Jadad	RCTs (n = 6) and single-arm trials (n = 2) 2000 to 2014	180 patients (sample size range: 8 to 43 patients) Mean age range: 32.2 to 54.4 years 99% male (% range: 89 to 100%) Mild-to-severe OSA (mean AHI range: 3.47 to 42.3 events/hour) Overweight to obese (mean BMI range: 25.9 to 35.5 kg/m^2)	Exercise* versus inactive controls *Including supervised (in 6 studies) and unsupervised (in 2 studies) aerobic exercise (e.g., walking or running on a treadmill), stair climbing, Airdyme machines, stationary bicycles, resistance training, and oropharyngeal exercises	2 to 6 months of study duration Loss to follow-up: NR Adherence level: NR	Primary outcome: • OSA severity (measured by AHI) Secondary outcome: • EDS (measured by ESS)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
Bartolucci 2016[51] Italy Funding: NR	SR/MA of RCTs MEDLINE, Cochrane Database of Systematic Reviews, Google Scholar Beta, ISI Web of Knowledge, Scopus, and LILACS, searched from Jan 1990 to Apr 2015 QA using EPHPP's quality assessment tool, Cochrane Risk of Bias tool, and GRADE	RCTs (n = 13) 2000 to 2010	514 patients (sample size range: 12 to 95 patients) Mean age range: 47.6 to 55.6 years Sex: NR Moderate-to-severe OSA (mean AHI range: 16.2 to 50.4 events/hour) Overweight to obese (mean BMI range: 25.9 to 32.3 kg/m^2)	MADs pre versus post* *The RCTs compared MADs with inactive controls or other interventions (i.e., other types or protrusion amounts of MADs [n = 5], placebo [n = 3], PAPs [n = 2], subjective titration [n = 1], TSDs [n = 1], or UPPP [n = 1]). However, the MA was based on AHI levels pre- and post-MADs.	3 weeks to 1 year of study duration Loss to follow-up: NR Adherence level: NR	• Success rate* *Defined as [(mean AHI at baseline – mean AHI after treatment) / mean AHI at baseline]	None
Fu 2016[52] China Funding from Shanghai Jiao Tong University	SR/MA of cohort studies PubMed and Embase, searched up to Jan 2016	Cohort studies (n = 11) 2005 to 2015	3,112,644 patients (sample size range: 124 to 3,079,514 patients) Mean age range:	CPAP* versus inactive controls** *Based on an average cumulative adherence of ≥ 4 hours/night and 5 times/week	5 years-10.6 years of study duration Loss to follow-up:	• Mortality (all-cause or cardiovascular)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
and Shanghai Shen-Kang Hospital	QA using Newcastle–Ottawa scale		46.8 to 77.8 years 92.8% male (% range: 0% to 100%) OSA severity: NR Comorbidities: NR	**No treatment.	NR Adherence level: NR		
Guo 2016[53] China No funding received	SR/MA of RCTs MEDLINE, EMBASE, Cochrane Controlled Clinical Trials Register, and ClinicalTrials.gov, searched from Jan 2005 to Apr 2015 QA using select risk of bias criteria	RCTs (n = 18) 2006 to 2015	4,146 patients (sample size range: 35 to 1,098 patients) Mean age range: 43 to 71 years 75.1% male (% range: 38% to 88%) Moderate-to-severe OSA (mean AHI range: 24 to 60 events/hour)	CPAP versus inactive controls* *Including no treatment [n = 10], sham CPAP [n = 6], weight loss [n = 1], and O_2 therapy or education on lifestyle and sleep [n = 1]	2 to 60 months of study duration 13.6% of patients lost to follow-up (% range: 2.4% to 24.3% of patients) Adherence level: see outcome	Primary outcomes: • CVEs • Stroke Secondary outcomes: • EDS (measured by ESS) • BP (measured by SBP and DBP) • Mortality (all-cause) • CPAP adherence level	Subgroup analysis on CVEs, stroke, and mortality: • Study duration (i.e., < 12 or ≥ 12 months)

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			Overweight to obese (mean BMI range: 28 to 40 kg/m^2); 22.3% diabetes (% range: 28% to 63%, where reported); 34.7% smoking (% range: 12% to 84%, where reported)				
Gupta 2016[54] Canada No funding received	SR/MA of RCTs and observational studies MEDLINE (searched from 1946), EMBASE (searched from 1947), PsycInfo (searched from 1806), and trial registers QA using Cochrane Risk of Bias tool and GRADE	RCTs (n = 10) and single-arm trials (n = 16) 1988 to 2013	895 patients (sample size range: 7 to 300 patients) Mean age range: 41.1 to 59.3 years 82% male (% range: 38% to 100%)	CPAP versus inactive controls* CPAP versus another intervention** *Including pre versus post [n = 21], oral placebo [n = 5], and sham CPAP [n = 4] **Including OAs [n = 2] and exercise [n = 1]	11 days to 2 years of study duration Loss to follow-up: NR Adherence level: NR	Primary outcomes: • Depression (measured by BDI, BSI-D, CES-D, HADS-D, HAM-D, MADRS, MMPI, POMS-D, or SDS) Secondary outcomes: • EDS (measured by ESS, QSQ, or SSS)	None

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			Mild-to-severe OSA (mean AHI range: 11 to 71.5 events/hour) Overweight to obese (mean BMI range: 27.8 to 38 kg/m^2)			• OSA severity (measured by AHI or RDI) • Anxiety (measured by BSI-A, HADS-A, MMPI-Pt, POMS-T, STAI, or TAS) • QoL (measured by SF-36, GQL, SF-12, WHOQOL, NHP-2, GHQ-28, WHO-5, or FOSQ)	
Iftikhar 2016[55] Brazil, Canada, and US No funding received	SR/MA/NMA of RCTs PubMed, SCOPUS, Web of Science, and CENTRAL, searched from inception to September 2015 QA using Cochrane Risk of Bias tool	RCTs (n = 80) 1985 to 2015	7,882 patients (sample size range: 10 to 725 patients) Mean age range: 39 to 75 years (for intervention groups) or 41 to 76 years (for control groups)	CPAP versus inactive controls (n = 54) MADs versus inactive controls (n = 11) Dietary weight loss versus inactive controls (n = 6) Supervised aerobic	2-144 weeks of study duration Loss to follow-up: NR Adherence level: NR	Primary outcome: • EDS (measured by ESS) • OSA severity (measured by AHI) Secondary outcome: • OSA severity (measured by	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			% male range: 0% to 100% Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) Comorbidities: NR	exercise versus inactive controls (n = 4) CPAP versus MADs (n = 12) CPAP versus supervised aerobic exercise (n = 1) MADs versus supervised aerobic exercise (n = 1) Dietary weight loss versus supervised aerobic exercise (n = 0)		ODI)	
Kim 2016[56] South Korea Funding from Kangwon	SR/MA of RCTs and observational studies MEDLINE (searched from Jan 1976 to Jul 2015), EMBASE	RCT (n = 1), prospective cohort studies (n = 5), and retrospective administrative	60,186 patients (sample size range: 168 to 33,274 patients) Mean age range:	CPAP versus no treatment	48 to 132 months of study duration Loss to	Primary outcomes: • Stroke Secondary outcomes:	Subgroup analysis on hypertension and CVEs: • CPAP

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
National University	(searched from Jan 1985 to Jul 2015), and Cochrane Library (searched from Jan 1987 to Jul 2015) QA using Cochrane Risk of Bias tool (for RCTs) and RoBANS (for observational studies)	database studies (n = 2) 2005 to 2015	50.1 to 71.9 years 74.8% male (% range: 0% to 96%) Mild-to-severe OSA (AHI threshold range: ≥ 5 to ≥ 20 events/hour) Previous CVD (excluded from the RCT and 1 cohort study but included in the other studies)		follow-up: NR Adherence level: see outcome	• CVEs • Mortality (caused by stroke or CVEs) • CPAP adherence level	adherence (i.e., ≥ 4 hours/night)
Liu 2016[57] China No funding received	SR/MA of RCTs MEDLINE, Embase, and Cochrane databases, searched from inception to Mar 2015 QA using Jadad	RCTs (n = 5) 2010 to 2015	446 patients (sample size range: 35 to 194 patients) Mean age range: 56 to 60.5 years 60.8% male (%	CPAP versus inactive controls* *Including no CPAP [n = 4] and sham CPAP [n = 1]	3 to 8 months of study duration Loss to follow-up: NR	Primary outcomes: • BP (measured by 24-hour ambulatory and daytime and nighttime SBP and DBP)	Subgroup analysis on 24-hour ambulatory DBP: • ESS (i.e., < 10 or ≥10) • AHI (i.e., < 30

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	score		range: 40% to 77%) Moderate-to-severe OSA (mean AHI range: 20 to 52.7 events/hour) Overweight to obese (mean BMI range: 29.8 to 34.1 kg/m^2); 100% resistant hypertension		Adherence level: see outcome	Secondary outcomes: • CPAP adherence level	or > 30 events/h) • Baseline SBP/DBP (i.e., < 140/90 or ≥ 140/90 mm Hg) • BMI (i.e., ≤ 32 or > 32 kg/m^2) • CPAP adherence level (i.e., ≤ 5 or > 5 hours/night) • Study duration (i.e., ≤ 3 or > 3 months)
Serra-Torres 2016[58] Spain No funding received	SR of RCTs and observational studies MEDLINE, Scopus, and Cochrane Library, searched from 2004 to 2014 QA using CONSORT criteria	Prospective (n = 21) and retrospective (n = 1) observational studies 2004 to 2014	1,495 patients (sample size range: 10 to 922 patients) Adults (age: NR) Sex: NR	MADs pre versus post	0.5 to 84 months of study duration 222 patients lost to follow-up (range: 0 to	Primary outcomes: • EDS (measured by ESS) • OSA severity (measured by AHI) • Snoring	None

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			Mild-to-severe OSA (mean AHI range: 14 to 45.5 events/hour) Overweight to obese (mean BMI range: 25.9 to 32.3 kg/m^2)		117 patients) Adherence level: NR	Secondary outcomes: • AEs	
Sharples 2016[59] UK Funding from National Institute for Health Research	Updates to 2 existing SRs/MAs of RCTs First SR: 14 databases, searched up to Aug 2012; and MEDLINE, Embase, and Science Citation Index, searched from Mar 2012 to Aug 2013 Second SR: Cochrane Airways Group Specialised Register, searched up to Jun 2005; and MEDLINE, Embase,	RCTs (n = 71) 1996 to 2014	6,757 patients (sample size range: 10 to 1,105 patients) Mean age range: 44 to 59.2 years % male range: 65-100% Mild-to-severe OSA (AHI or DI: NR) Overweight to obese (mean BMI range: 28.3 to	CPAP versus inactive controls* (n = 52) MADs versus inactive controls* (n = 12) CPAP versus MADs (n = 13) *Including usual care, recommendations to lose weight or reduce alcohol consumption, sham devices, oral placebo, or postural devices	2 to 156 weeks of study duration Loss to follow-up: NR Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	Subgroup analysis for CPAP versus controls on ESS and AHI: • Baseline ESS (i.e., normal/mild, moderate, or severe) • Baseline AHI (i.e., mild, moderate, or severe) • Study duration (i.e., 2 to 4, 5 to 12, or

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	and Science Citation Index, searched from Jun 2008 to Aug 2013 QA using Jadad score		35.1 kg/m^2)				> 12 weeks) Subgroup analysis for MADs versus controls on ESS and AHI: • Baseline ESS (i.e., moderate or severe) • Baseline AHI (i.e., mild, moderate, or severe) • Study duration (i.e., ≤ 12 or > 12 weeks) Subgroup analysis for CPAP versus MADs on ESS and AHI: • Baseline ESS

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							(i.e., moderate) • Baseline AHI (i.e., moderate or severe) • Study duration (i.e., ≤ 12 or > 12 weeks)
Song 2016[24] US No funding received	SR/MA of pre-and-post studies MEDLINE, Embase, Cochrane Library, ACP Journal Club, DARE, CCRCT, CMD, HTA, Scopus, Web of Science, and NHSEED, searched up to Nov 2015 QA using NICE QA tool	Pre-and-post studies (n = 9) 1994 to 2015	61 patients (sample size range: 1 to 17 patients) Mean age range: 37.8 to 65.0 years % male range: NR Moderate-to-severe OSA (mean AHI range: 13.0 to 88.2 events/hour)	GP* or GTA pre versus post *Standard GP and modified GP were analyzed separately, when possible	Study duration: NR Loss to follow-up: NR Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	None

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			Comorbidities: NR				
Zaghi 2016[60] US Funding: NR	SR/MA of RCTs and observational studies MEDLINE, Cochrane Library, Scopus, and Web of Science, searched from Jun 2014 to Mar 2015 QA using a quality control questionnaire	RCT (n = 1) and observational studies (n = 44) 1986 to 2014	518 patients Adults (mean age: 45.3 years [from 345 patients]) 83.2% male (from 339 patients) Severe OSA (mean AHI: 57.2 events/hour [from 455 patients]) Obese (mean BMI: 33.8 kg/m^2 [from 82 patients]) 73.5% with prior OSA surgery (e.g., tonsillectomy, nasal surgery, UPPP, septoplasty, turbinate	MMA with or without GTA* pre versus post *Performed on 33.6% of all patients at the time of MMA	2 to 6 months of study duration Loss to follow-up: NR Adherence level: NR	Primary outcome: • OSA severity (measured by AHI or RDI) Secondary outcomes: • EDS (measured by ESS) • Success rate* • Cure rate** *% patients with > 50% reductions in AHI to < 20, < 15, or < 10 events/hour after MMA ** Percentage of patients with reductions in AHI to < 5 events/hour after MMA	Subgroup analysis on AHI, success rate, and cure rate: • Baseline AHI (i.e., < 30, 30 to < 60, 60 to < 90, or ≥ 90 events/hour)

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			reduction, or partial glossectomy (from 268 patients)				
Ashrafian 2015[61] UK Funding: NR	SR/MA of RCTs and observational studies PubMed, Ovid, Embase, and Cochrane Library, searched up to Jul 2013 QA using modified Newcastle–Ottawa scale	RCTs (n = 7) and prospective observational studies (n = 13) 1987 to 2014	825 patients (sample size range: 8 to 139 patients) Age: NR Sex: NR Mild-to-severe OSA (mean AHI range: 10-90 events/hour) Overweight to obese (mean BMI range: 29.8 to 54 kg/m^2)	Non-surgical weight loss* pre versus post *Including diet [n = 12]; diet plus exercise [n = 4]; diet plus exercise plus drugs [n = 2]; exercise [n = 1]; weight-loss advice [n = 1]; diet plus drugs [n = 1]; and diet plus behavioural support [n = 1]	1 to 94.3 months of study duration Loss to follow-up: NR Adherence level: NR	Primary outcome: • OSA severity (measured by AHI)	None
Bratton 2015[62] Switzerland	SR/MA/NMA of RCTs MEDLINE and Cochrane Library,	RCTs (n = 67) 1997 to 2015	6,873 patients (sample size range: 16 to 1,098 patients)	CPAP versus inactive controls* (MA: n = 54) MADs versus inactive	1-157 weeks of study duration	Primary outcome: • EDS (measured by ESS)	Meta-regression analysis for CPAP versus controls on ESS:

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Funding from Swiss National Science Foundation and University of Zurich	searched from inception to May 2015 QA using Cochrane Risk of Bias tool		Mean age range: 40 to 78 years 78% male (% range: 52% to 100%) Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) Overweight to obese (mean BMI range: 25 to 43 kg/m^2); other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension)	controls* (MA: n = 8) CPAP versus MADs (MA: n = 11) *Including sham CPAP, placebo MADs, oral placebo, no treatment, and usual care	Loss to follow-up: NR Adherence level: NR		• Baseline ESS • Baseline AHI • Baseline ODI • Age • CPAP adherence level (hours/night) • Study duration

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
Bratton 2015[63] Switzerland Funding from Swiss National Science Foundation and University of Zurich	SR/MA/NMA of RCTs MEDLINE, Embase, and Cochrane Library, searched from inception to Aug 2015 QA using Cochrane Risk of Bias tool	RCTs (n = 51) 1996 to 2015	4,888 patients (sample size range: 12 to 725 patients) Mean age range: 41 to 71 years 80% male (% range: 40% to 100%) Mild-to-severe OSA (mean AHI range: 13 to 64 events/hour) Overweight to obese (mean BMI range: 26 to 37 kg/m^2); other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder)	CPAP versus inactive controls* (n = 47) MADs versus inactive controls* (n = 6) CPAP versus MADs (n = 4) *Including sham CPAP, placebo MADs, or no treatment	1 to 157 weeks of study duration Loss to follow-up: NR Adherence level: NR	Primary outcomes: • BP (measured by 24-hour ambulatory, morning, daytime ambulatory, nighttime, or office SBP and DBP)	Meta-regression analysis for CPAP versus controls on SBP and DBP: • Baseline AHI • Baseline ODI • Baseline SBP and DBP • CPAP adherence level (hours/night) • Study duration

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
Feng 2015[64] China No funding received	SR/MA of RCTs and prospective observational studies MEDLINE, Embase, and Cochrane Library, searched from inception to Jan 2014 QA using Cochrane Risk of Bias tool	RCTs (n = 2) and prospective observational studies (n = 4) 1994 to 2012	128 patients (sample size range: 9 to 44 patients) Mean age range: 50.7 to 66.1 years % male range: 60% to 100% OSA severity: NR Obese (mean BMI range: 33.6 to 42.7 kg/m^2); 100% diabetes	CPAP pre versus post	1 to 4 months of study duration Loss of follow-up: NR Adherence level: see outcome	Primary outcomes: • A1C Secondary outcomes: • Insulin sensitivity • CPAP adherence level	Subgroup analysis on A1C: • CPAP adherence level (i.e., ≤ 5 or > 5 hours/night)
Hu 2015[65] China and Germany Funding from a research foundation of the Chinese	SR/MA of RCTs MEDLINE, Embase, and CENTRAL, searched up to Jul 2014 QA using Jadad scale	RCTs (n = 7) 2006 to 2014	794 patients (sample size range: 35 to 340 patients) Mean age range: 53.2 to 59.2 years	CPAP versus inactive controls *Including no CPAP [n = 4] and sham CPAP [n = 3]	1 to 6 months of study duration Loss of follow-up: NR	Primary outcomes: • BP (measured by 24-hour ambulatory, daytime, or nighttime SBP and DBP)	Subgroup analysis on SBP and DBP: • Hypertension (i.e., non-resistant or resistant)

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Medical Doctor Association			74% male (% range: 55.8% to 88.6%) Moderate-to-severe OSA (mean AHI range: 28.1 to 58.3 events/hour) Obese (mean BMI range: 30.8 to 35.7 kg/m^2); 100% hypertension (in 3 RCTs) or 100% resistant hypertension (in 4 RCTs)		Adherence level: see outcome	Secondary outcomes: • CPAP adherence level	Meta-regression analysis on SBP and DBP: • Baseline ESS • Baseline AHI • Baseline SBP • Age • Sex • CPAP adherence level (hours/night) • Study duration • BMI
Pan 2015[66] China Funding from National Natural Science Foundation of China	SR/MA of RCTs PubMed, CINAHL, MEDLINE, PsycInfo, Embase, Cochrane Library, CNKI, WanFang, VIP, and CBMdisc, searched from Jun 1971 to Jul	RCTs (n = 13) 1994 to 2012	1,744 patients (sample size range: 16 to 1,098 patients) Adults (mean age: 51.2 years) 68% male (%	CPAP versus inactive controls* *Including sham CPAP [n = 5], oral placebo [n = 5], no treatment [n = 2], and conservative lifestyle modifications [n = 1]	1-24 weeks of study duration Loss to follow-up: NR Adherence	• Cognitive functions (i.e., attention, vigilance, processing speed, working memory, memory, verbal	None

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	2014 QA using Jadad scale		range: 54% to 100%) Mild-to-severe OSA (mean AHI range: 10 to 55.4 events/hour) Overweight to obese (mean BMI range: 27.8 to 37.1 kg/m^2)		level: see outcome	fluency, and visuoconstructive skills) • CPAP adherence level	
Qureshi 2015[67] US and Saudi Arabia Funding: NR	SR/MA of RCTs and prospective cohort studies MEDLINE, Embase, CINAHL, Cochrane databases, EBSCO, and Web of Science, searched from inception to Jun 2015 QA using *Cochrane Handbook for Systematic Reviews*	RCT (n = 1) and prospective cohort studies (n = 7) 2003 to 2013	4,516 patients (sample size range: 56 to 3,000 patients) Mean age range: 50 to 66 years 76.3% male (% range: 73% to 100%) 1,247 patients with OSA (%	CPAP versus no CPAP	Study duration: NR Loss to follow-up: NR Adherence level: NR	• CVEs (i.e., recurrence of AF)	Meta-regression analysis on CVEs: • Hypertension • Diabetes • Age • Sex • BMI

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
	of Interventions		severe OSA range: 10% to 100%) Overweight to obese (mean BMI range: 25 to 35 kg/m^2); 100% AF; hypertension (% range: 24% to 70%); diabetes (% range: 15% to 24%, where reported)				
Riaz 2015[68] US, Portugal, and Argentina No industry funding	SR/MA of RCTs and observational studies PubMed, Scopus, Embase, Google Scholar, Web of Science, CINAHL, and Cochrane Library, searched from inception to Nov 2015 QA using NICE QA	RCTs (n = 3), cohort studies (n = 5), and conference abstracts (n = 10) 2008 to 2015	920 patients (sample size range: 6 to 229 patients) Mean age range: 47.7 to 63.2 years 71.6% male (% range: 62.8% to 79.1%)	EPAP pre versus post	1 night to 12 months of study duration Loss to follow-up: NR Adherence level: NR	Primary outcomes: • EDS (measured by ESS) • OSA severity (measured by AHI or ODI) Secondary outcome: • Snoring	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
	tool		Mild-to-severe OSA (mean AHI range: 14.4 to 43.3 events/hour) Overweight to obese (mean BMI range: 27 to 34.9 kg/m^2)				
Wang 2015[69] China Funding from International Science & Technology Cooperation Program of China and Beijing Municipal Science & Technology Commission	SR/MA of RCTs and observational studies PubMed, MEDLINE, and Embase, searched up to Mar 2015 QA using Downs and Black score	RCTs and observational studies (n = 11) 2005 to 2015	4,620 patients (sample size range: 96 to 1,010 patients) Age: NR Sex: NR Moderate-to-severe OSA (in 5 studies) or unselected OSA (in 6 studies)	CPAP versus no CPAP	Study duration: NR Loss to follow-up: NR Adherence level: NR	Primary outcomes: • Non-fatal CVEs (e.g., MI, stroke, coronary artery bypass surgery, and PTCA) • CV death	Subgroup analysis on CV death: • OSA severity (i.e., moderate-to-severe)

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			Comorbidities: NR				
Wang 2015[70] China Funding: NR	SR/MA of RCTs MEDLINE (searched from1966 to Jul 2015), Embase (searched from 1974 to Jul 2015), and Cochrane Trials Register QA using select risk of bias criteria	RCTs (n = 5) 2001 to 2015	307 patients (sample size range: 30 to 226 patients) Age: NR Sex: NR Moderate-to-severe OSA (mean AHI range: 24 to 51.5 events/hour) 100% nocturia	CPAP pre versus post	1 to 12 months of study duration Loss to follow-up: none Adherence level: NR	Secondary outcomes: • EDS (measured by ESS) • OSA severity (measured by AHI)	None
Zhu 2015[71] China Funding from National Natural Science Foundation of	SR/MA of RCTs and observational studies PubMed, Embase, Web of Science, CENTRAL, and SIGLE, searched from Jan 1980 to Sep	RCTs (n = 16) and cohort study (n = 1) 1997 to 2015	840 patients (sample size range: 15-91 patients) Mean age range: 44.6 to 55.6 years)	OAs* versus inactive controls** *Including MASs and TRDs *Including oral placebo, placebo	1 week to 6 months of study duration Loss to follow-up: NR	Primary outcome: • OSA severity (measured by AHI) Secondary outcome: • EDS (measured	Subgroup analysis on ESS and AHI: • OSA severity (i.e., mild-to-moderate or mild-to-severe)

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
China	2015 QA using Cochrane Risk of Bias tool and GRADE		Sex: NR Moderate-to-severe OSA (mean AHI ± SD: 23.2 ± 8.2 events/hour [for OA group] or 22.6 ± 7.6 events/hour [for control group]) Comorbidities: NR	device, inactive devices, and no treatment	Adherence level: NR	by ESS)	
Fava 2014[10] Italy and Poland No funding received	SR/MA of RCTs MEDLINE, Embase, Web of Science, and Cochrane Library, searched from inception to May 2012 QA using Jadad scale and GRADE	RCTs (n = 29) 1996 to 2012	1,820 patients (sample size range: 12 to 359 patients) Mean age range: 41.3 to 63.5 years 85.3% male (% range: 60.3% to 100%) Mild-to-severe OSA (mean AHI range: 12.9 to 63.8 events/hour)	CPAP versus inactive controls* *Including sham CPAP [n = 14], oral placebo [n = 3], conservative treatment [7], and usual care [n = 5]	2 to 52 weeks of study duration Loss to follow-up: NR Adherence level: see outcome	Primary outcomes: • BP (measured by SBP and DBP) Secondary outcomes: • CPAP adherence level	Subgroup analysis on SBP and DBP: • Baseline ESS (i.e., < 10 or ≥ 10) • Baseline AHI (i.e., ≤ 30 or > 30 events/hour) • Hypertension (i.e., yes or no) • Age (i.e., < 50 or ≥ 50 years)

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			Overweight to obese (mean BMI range: 27.2 to 37 kg/m^2); hypertension (% range: 0% to 100%, where reported)				• CPAP adherence level (i.e., < 4 or ≥ 4 hours/night) • Study duration (i.e., ≤ 9 or > 9 weeks) Meta-regression analysis on SBP: • Baseline AHI (events/hour)
Ha 2014[72] China No funding received	SR/MA of RCTs MEDLINE, Embase, and CINAHL, searched from inception to Sep 2012 QA using Cochrane Risk of Bias tool and quality criteria	RCTs (n = 3) 1999 to 2010	71 patients (sample size range: 13 to 38 patients) Mean age range: 49 to 55.9 years 70% male (% range: 63% to 92%)	CPAP versus positional therapy* *Including backpacks, thoracic anti-spine bands, and the Zzoma positional sleeper	3 nights to 9 weeks of study duration Loss to follow-up: NR Adherence level: NR	Primary outcome: • OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			Mild-to-moderate OSA (mean AHI range: 13 to 22.7 events/hour) Obese (mean BMI range: 30 to 31 kg/m^2)				
Mitchell 2014[73] Australia Funding: NR	SR/MA of RCTs MEDLINE, Embase, Cochrane Library, CINAHL, Web of Science, and Scopus, searched from 1980 to Feb 2012 QA using Cochrane Risk of Bias tool	RCTs (n = 8) 1985 to 2013	618 patients (sample size range: 11 to 264 patients) Age range: 18 to 75 years 66.3% male (% range: 41% to 100%) Moderate-to-severe OSA (AHI: 21.4 to 49 events/hour [in mean range] or 5 to 15 events/hour [in threshold])	Intensive lifestyle interventions for weight loss* versus inactive controls** *Including group sessions and maintenance programs **Including general diet and exercise information and usual diet	8 weeks to 48 months of study duration Loss to follow-up: NR Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			Overweight to obese (BMI range: 25 to 40 kg/m^2)				
Okuno 2014[74] Japan Funding from Japanese Academy of Dental Sleep Medicine	SR/MA of RCTs MEDLINE, CENTRAL, and Japan Medical Abstracts Society database, searched from inception to Apr 2012 QA using Cochrane Risk of Bias tool and GRADE	RCTs (n = 5) 2005 to 2011	395 patients (sample size range: 24 to 111 patients) Adults (mean age range: 45 to 55.6 years) 80.3% male Moderate-to-severe OSA (mean AHI range: 20.9 to 40.3 events/hour [for CPAP group], 20.9 to 39.4 events/hour [for OA group], and 20.1 to 32.6 events/hour [for control group])	OAs versus control appliances (n = 3) CPAP (n = 3) versus OAs	1 to 6 months of study duration 42 patients lost to follow-up Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • QoL (measured by SF-36)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			Comorbidities: NR				
Povitz 2014[75] Canada No funding received	SR/MA of RCTs MEDLINE, Embase, CENTRAL, and PsycINFO, searched from inception to Aug 2014 QA using Cochrane Risk of Bias tool	RCTs (n = 24) 1998 to 2013	1,732 patients (sample size range: 18 to 391 patients) Adults (mean age range: 42 to 78 years) 79% male Mild-to-severe OSA (mean AHI range: 10 to 65.1 events/hour, where reported) Normal-to-obese (mean BMI range: 24.7 to 42.5 kg/m^2)	CPAP versus inactive controls MADs versus inactive controls** *Including sham CPAP [n = 11], oral placebo [n = 4], standard care [n = 5], and sham exercise [n = 1] **Including sham MADs [n = 3], oral placebo [n = 1], and standard care [n = 1]	1 to 24 weeks of study duration Loss to follow-up: NR Adherence level: see outcome	Primary outcomes: • Depression (measured by BDI, BSI, HADS-D, POMS-D, and SF-36 Secondary outcomes: • CPAP or MAD adherence level	Subgroup analysis for CPAP versus inactive controls: • Baseline AHI (i.e., < 30 or ≥ 30 events/hour) • Baseline depression (i.e., yes or no) • CPAP adherence level (i.e., < 4 or ≥ 4 hour/night) • Study duration (i.e., < 4, 4 to 8, or > 8 weeks)

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
Araghi 2013[76] UK No industry funding	SR/MA of RCTs and observational studies MEDLINE (searched from 1948), Embase (searched from 1988), CINAHL (searched from 1983), OpenGrey, OAIster, Zetoc, BioMed Central, NLM Gateway, Cochrane Library, ISRCTN, ClinicalTrials.gov (searched from inception), searched up to Apr 2011 QA using Cochrane Risk of Bias tool (for RCTs) and Cochrane EPOC risk of bias (for before-and-after studies)	RCTs (n = 7) and before-and-after studies (n = 14) 1987 to 2011	893 patients (sample size range: 8 to 264 patients) Adults (mean age range: 42 to 61 years) Sex: NR Mild-to-severe OSA (mean AHI range: 10 to 66.5 events/hour) Overweight to obese (mean BMI range: 26.5 to 54.6 kg/m^2)	Lifestyle modifications* versus inactive controls** or pre versus post, analyzed separately *Defined as a comprehensive program of diet or exercise therapy without treatment with CPAP at intervention start, including very-low-calorie diet [n = 13], exercise [n = 4], or combination [n = 4] **Including no intervention, usual care, and placebo	4 weeks to 24 months of study duration Loss to follow-up: NR Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	Subgroup analysis on AHI: • Baseline AHI (i.e., < 15, 15 to 25, or ≥ 25 events/hour) • Change in BMI (i.e., 0 to 3, 3 to 5, or ≥ 5 kg/m^2) • Study duration (i.e., ≤ 12 or > 12 weeks) Meta-regression analysis on AHI: • Baseline AHI • Weight loss

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
Li 2013[77] China Funding: NR	SR/MA of RCTs PubMed (searched from 1966 to May 2012), Embase (searched from 1984 to May 2012), and CENTRAL (2nd quarter 2012) QA using Cochrane Risk of Bias tool	RCTs (n = 14) 1996 to 2011	638 patients (sample size range: 10 to 114 patients) Mean age range: 44 to 89.3 years 82.3% male (% range: 49.7% to 100%) Mild-to-severe OSA (AHI threshold: ≥5 events/hour) Comorbidities: NR	CPAP versus OAs	6 to 48 weeks of study duration Loss to follow-up: NR Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP (measured by SBP or DBP) • Cognitive functions • Psychological functions • QoL (measured by SF-36) • Treatment usage • Treatment preference • Side effects • Withdrawals	None
Thomasouli 2013[19] UK Funding from Leicester Diabetes	SR/MA of RCTs MEDLINE (searched from 1996), Embase (searched from 1996), CINAHL (from inception), CENTRAL (from inception),	RCTs (n = 12) 1997 to 2012	873 patients (sample size range: 20 to 264 patients) Adults (mean age range: 46.9 to 61.2 years)	CPAP plus diet programs versus diet programs (n = 3) Intensive lifestyle modifications versus usual care with dietary or exercise advice	2 to 24 months of study duration Loss to follow-up: NR	Secondary outcomes: • EDS (measured by ESS) • OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
Centre and Hanning Sleep Laboratory	CDSR (from inception), and DARE (from inception), searched up to Oct 2012 QA using Jadad score		Sex: NR Mild-to-severe OSA (mean AHI range: 9.7 to 56 events/hour) Overweight to obese (mean BMI range: 28.2 to 43.8 kg/m^2)	(n = 6) Breathing and aerobic exercise program versus no treatment (n = 1) Dietary advice program versus hypnotherapy (n = 1) Very-low-calorie diet versus usual diet (n = 1)	Adherence level: NR	• QoL	
Antonopoulos 2011[47] Greece and Canada Funding from National and Kapodistrian University of Athens	SR/MA of all study designs MEDLINE, Embase, Scopus, Google scholar, Ovid, and Cochrane Library, with search time frame NR No QA performed	10 studies of unknown designs 1989 to 2007	1,331 patients (sample size range: 14 to 547 patients) Mean age range: 46 to 57 years % male range: 50% to 100% Moderate-to-severe OSA	CPAP pre versus post	Study duration for real and near-miss accidents: 6 to 36 months Study duration for accident-related events: 7 to	• Real accidents • Near-miss accidents	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			(mean AHI range: 24.8 to 73 events/hour) Overweight to obese (mean BMI range: 29.5 to 39 kg/m^2)		276 days Loss to follow-up: NR Adherence level: NR		
Balk 2011[5] US Funding from AHRQ	SR/MA of RCTs and observational studies (for surgical interventions) MEDLINE (searched from inception to Sep 2010), CENTRAL (3rd quarter 2010), and Cochrane Database of SRs (3rd quarter 2010) QA using AHRQ methods guide	*CPAP versus inactive controls*					
		RCTs (n = 22) 1994 to 2010	1,116 patients Mean age range: 43 to 58 years) % male range: 52% to 100% Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) Overweight to obese (mean BMI range: 27.3 to 43.8 kg/m^2)	CPAP versus inactive controls* *Including placebo [n = 9], no treatment [n = 5], conservative treatment [n = 6], lifestyle modifications [n = 1], and drugs (n = 1])	1 to 12 months of study duration Dropout rate range: 0% to 33% Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP • A1C • Cognitive functions • Psychological functions • QoL (measured by FOSQ, SF-36, NHP, GHQ-28 UMACL, SAHS-related symptoms	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
						questionnaire, and SAQLI)	
		CPAP versus sham CPAP					
		RCTs (n = 24) 1999 to 2010	1,076 patients Mean age range: 46 to 64 years) % male range: 56-100% Moderate-to-severe OSA (mean AHI range: 22 to 68 events/hour) Overweight to obese (mean BMI range: 27.2 to 42.6 kg/m^2)	CPAP versus sham CPAP	1 week to 3 months of study duration Dropout rate range: 0% to 47% Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP • Cognitive functions • QoL (measured by SF-36 and SAQLI)	None
		MADs versus inactive controls					
		RCTs (n = 5) 2000 to 2008	301 patients Mean age range: 47 to 51 years	MADs versus inactive controls* *Including no	1 to 10 weeks of study duration	• EDS (measured by ESS) • OSA severity (measured by	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			% male range: 79% to 81% Moderate-to-severe OSA (mean AHI range: 19 to 34 events/hour) Overweight to obese (mean BMI range: 27.3 to 31.3 kg/m^2); exclusion of patients with heart disease and diabetes	treatment [n = 2], conservative treatment [n = 1], oral placebo [n = 1], and no OA [n = 1]	Dropout rate range: 0% to 14% Adherence level: NR	AHI) • BP (measured by SBP and DBP) • Cognitive functions • QoL (measured by SF-36)	
		MADs versus sham OAs					
		RCTs (n = 5) 1997 to 2008	186 patients Mean age range: 48 to 55 years) % male range: 79% to 83%	MADs versus sham OAs	8 days to 6 weeks of study duration Dropout rate range: 0% to 29%	• EDS (measured by ESS) • OSA severity (measured by AHI or RDI) • BP • Cognitive functions	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			Moderate-to-severe OSA (mean AHI range: 25 to 36 events/hour) Overweight to obese (mean BMI range: 29-32 kg/m^2)		Adherence level: NR	• QoL (measured by FOSQ or SAQLI)	
		MADs versus TRDs					
		RCT (n = 1) 2009	22 patients Mean age: 49 years 73% male Moderate OSA (mean AHI: 27.0 events/hour) Overweight (mean BMI: 29.3 kg/m^2)	MADs versus TRDs	1 week of study duration Dropout rate: 19% Adherence level: NR	• OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
		CPAP versus MADs					
		RCTs (n = 10) 1996 to 2009	384 patients Adults (mean age range: 45 to 57 years) % male range: 61% to 100% Moderate-to-severe OSA (mean AHI range: 18-40 events/hour) Overweight to obese (mean BMI range: 26.7-34.1 kg/m^2)	CPAP versus MADs	6 weeks to 4 months of study duration Dropout rate range: 0% to 24% Adherence level: see outcome	• OSA severity (measured by AHI) • EDS (measured by ESS) • Cognitive functions • QoL • MAD adherence level • Treatment response* *Defined differently by various studies, in terms of per cent reductions in AHI and post-treatment AHI values	Subgroup analysis on treatment response: • Baseline AHI (i.e., ≤ 30 or > 30 events/hour)

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
		CPAP versus positional therapy					
		RCTs (n = 3) 1999 to 2008	47 patients Adults (mean age range: 51 to 56 years) 85% male (from 1 study) Moderate OSA (mean AHI range: 18 to 27 events/hour) Obese (mean BMI range: 30 to 34 kg/m^2)	CPAP versus positional therapy* *Including shoulder-head elevation pillows and devices worn on the back	2 weeks to 1 month of study duration Dropout rate range: 0% to 7% Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • Cognitive functions • QoL (measured by SF-36, FOSQ, HADS, UWIST mood adjective checklist, and GHQ)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
		Intensive weight-loss programs versus inactive controls					
		RCTs (n = 3) 2009	345 patients Mean age range: 50 to 61 years) % male range: 42% to 100% Mild-to-severe OSA (mean AHI range: 9 to 37 events/hour) Obese (mean BMI range: 31.4 to 36.7 kg/m^2); diabetes	Intensive weight-loss programs* versus inactive controls** *Including intensive lifestyle interventions, low-energy diet, and very-low-calorie diet with lifestyle changes **Including diabetes support and education, usual diet, and general counselling	9 weeks to 1 year of study duration Dropout rate range: 3% to 17% Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • Treatment response • BP (measured by SBP and DBP) • A1C • AEs	None
		TRDs plus posture alarm versus no treatment					
		RCT (n = 1) 1991	60 patients Age: NR 100% male Mild-to-severe	TRDs plus posture alarm versus no treatment	Study duration: NR Loss to follow-up: NR	• OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Review Methods, Including Databases and Time Frames Searched, QA Tool Used	Study Types, Number, and Publication Years of Primary Studies Included	Number, Age, Sex, OSA Severity, Comorbidities, and Surgical History (for Surgical Interventions Only) of Patients Included	Intervention and Comparator (Number of Primary Studies Included)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported from SRs	Subgroup or Meta-Regression Analysis of Interest
			OSA (AHI threshold: > 12.5 events/hour) Comorbidities: NR		Adherence level: NR		

A1C = glycated hemoglobin; AE = adverse events; AF = atrial fibrillation; AHI = Apnea–Hypopnea Index; AHRQ = Agency for Healthcare Research and Quality; BDI = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; BSI = brief symptom inventory; BSI-A = Brief Symptom Inventory–Anxiety Subscale; BSI-D = Brief Symptom Inventory–Depression Subscale; CBD = cerebrovascular disease; CENTRAL = Cochrane Central Register of Controlled Trials; CES-D = Center for Epidemiological Studies Depression Scale; CONSORT = Consolidated Standards of Reporting Trials; CPAP = continuous positive airway pressure; CV = cardiovascular; CVD = cardiovascular disease; CVE = cardiovascular event; DBP = diastolic blood pressure; DI = desaturation index; EDS = excessive daytime sleepiness; EPAP = expiratory positive airway pressure; EPHPP = Effective Public Health Practice Project; EPOC = Effective Practice and Organisation of Care; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; GHQ = General Health Questionnaire; GP = genioplasty; GQL = glaucoma quality of life; GRADE = Grading of Recommendations Assessment, Development and Evaluation; GTA = genial tubercle advancement; HADS-A = Hospital Anxiety and Depression Scale–Anxiety Subscale; HADS-D = Hospital Anxiety and Depression Scale–Depression Subscale; HAM-D = Hamilton Rating Scale for Depression; HF = heart failure; MA = meta-analysis; MAD = mandibular advancement device; MADRS = Montgomery–Åsberg Depression Rating Scale; MAS = mandibular advancement splint; MI = myocardial infarction; MMA = maxillomandibular advancement; MMPI = Minnesota Multiphasic Personality Inventory; MMPI-Pt = Minnesota Multiphasic Personality Inventory–Psychasthenia Subscale; NHP = Nottingham Health Profile; NICE = National Institute for Health and Care Excellence; NMA = network meta-analysis; NR = not reported; OA = oral appliance; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; POMS-D = Profile of Mood States–Depression Subscale; POMS-T = Profile of Mood States–Tension and Anxiety Subscale; PTCA = percutaneous transluminal coronary angiography; QA = quality assessment; QoL = quality of life; QSQ = Quebec Sleep Questionnaire; RCT = randomized controlled trial; RDI = respiratory disturbance index; RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies; SAHS = sleep apnea/hypopnea syndrome; SAQLI = Calgary Sleep Apnea Quality of Life Index; SBP = systolic blood pressure; SD = standard deviation; SDS = Zung Self-Rating Depression Scale; SF-12 = Short Form (12) Health Survey; SF-36 = Short Form (36) Health Survey; SR = systematic review; SSS = Stanford Sleepiness Scale; STAI = State-Trait Anxiety Inventory; TAS = Tension Anxiety Scale; TRD = tongue-retaining device; TSD = tongue-stabilizing device; UK = United Kingdom; UMACL = University of Wales Mood Adjective Checklist; UPPP = uvulopalatopharyngoplasty; US = United States; UWIST = University of Wales Institute of Science and Technology; WHO-5 = World Health Organization–Five Well-Being Index; WHOQOL = World Health Organization Quality of Life questionnaire.

Appendix 7: Characteristics of Included Systematic Reviews Arranged by Comparisons (Research Question 1)

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
1. CPAP Versus Inactive Controls			
Fu 2016[52] 11 cohort studies	3,112,644 patients (sample size range: 124 to 3,079,514 patients): • OSA severity: NR • Comorbidities: NR • Study duration: 5 to 10.3 years • Loss to follow-up: NR • Adherence level: NR	• Mortality (all-cause or CV)	None
Guo 2016[53] 18 RCTs (2006 to 2015)	4,146 patients (sample size range: 35 to 1,098 patients): • Moderate-to-severe OSA (mean AHI range: 24 to 60 events/hour) • Overweight to obese (mean BMI range: 28 to 40 kg/m^2) • 22.3% diabetes (% range: 28% to 63%, where reported); 34.7% smoking (% range: 12% to 84%, where reported) • Study duration: 2 to 60 months • Loss to follow-up: 13.6% of patients (% range: 2.4 to 24.3% of patients) • Adherence level: see outcome	• EDS (measured by ESS) • BP (measured by SBP and DBP) • CVEs • Stroke • Mortality (all-cause) • CPAP adherence level	Subgroup analysis on CVEs, stroke, and mortality: • Study duration (i.e., < 12 or ≥ 12 months)
Gupta 2016[54] 10 RCTs and 16 single-arm trials (1988 to 2013)	895 patients (sample size range: 7 to 300 patients): • Mild-to-severe OSA (mean AHI range: 11 to 71.5 events/hour) • Overweight to obese (mean BMI range: 27.8 to 38 kg/m^2) • Study duration: 11 days to 2 years • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI or RDI) • QoL (measured by SF-36, GQL, SF-12, WHOQOL, NHP-2, GHQ-28, WHO-5, or FOSQ) • Psychological functions (i.e., depression and anxiety)	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
Iftikhar 2016[55] Network MA: 80 RCTs (1985 to 2015)	7,882 patients (sample size range: 10 to 725 patients): • Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	None
Kim 2016[56] 1 RCT, 5 prospective cohort studies, and 2 administrative database studies (2005 to 2015)	60,186 patients (sample size range: 168 to 33,274 patients): • Mild-to-severe OSA (AHI threshold range: ≥ 5 to ≥ 20 events/hour) • Previous CVD (excluded from the RCT and 1 cohort study but included in the other studies) • Study duration: 48 to 132 months • Loss to follow-up: NR • Adherence level: see outcome	• CVEs • Stroke • Mortality (caused by stroke or CVEs) • CPAP adherence level	Subgroup analysis on hypertension and CVEs: • CPAP adherence (i.e., ≥ 4 hours/night)
Liu 2016[57] 5 RCTs (2010 to 2015)	446 patients (sample size range: 35 to 194 patients): • Moderate-to-severe OSA (mean AHI range: 20 to 52.7 events/hour) • Overweight to obese (mean BMI range: 29.8 to 34.1 kg/m^2) • 100% resistant hypertension • Study duration: 3 to 8 months • Loss to follow-up: NR • Adherence level: see outcome	• BP (measured by 24-hour ambulatory and daytime and nighttime SBP and DBP) • CPAP adherence level	Subgroup analysis on 24-hour ambulatory DBP: • ESS (i.e., < 10 or ≥ 10) • AHI (i.e., < 30 or > 30 events/hour) • Baseline SBP/DBP (i.e., < 140/90 or ≥ 140/90 mm hg) • BMI (i.e., ≤ 32 or > 32 kg/m^2) • CPAP adherence (i.e., ≤ 5 or > 5 hours/night) • Study duration (i.e., ≤ 12 or > 12 weeks) •

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
Sharples 2016[59] 52 RCTs (1996 to 2013)	5,382 patients (sample size range: 10 to 1,105 patients): • Mild-to-severe OSA (mean AHI or DI range: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 35.1 kg/m^2) • Study duration: 2 to 156 weeks • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	Subgroup analysis on ESS and AHI: • Baseline ESS (i.e., normal/mild, moderate, or severe) • Baseline AHI (i.e., mild, moderate, or severe) • Study duration (i.e., 2 to 4, 5 to 12, or > 12 weeks)
Bratton 2015[62] Pairwise MA: 54 RCTs (1997 to 2015) Network MA: 67 RCTs (1997 to 2015)	6,873 patients (sample size range: 16 to 1,098 patients): • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension) • Study duration: 1 to 157 weeks • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS)	Meta-regression analysis on ESS: • Baseline ESS • Baseline AHI • Baseline ODI • Age • CPAP adherence level (hours/night) • Study duration
Bratton 2015[63] Pairwise MA: 47 RCTs (1996 to 2015) Network MA: 51 RCTs (1996 to 2015)	4,888 patients (sample size range: 12 to 725 patients): • Mild-to-severe OSA (mean AHI range: 13 to 64 events/hour) • Overweight to obese (mean BMI range: 26-37 kg/m^2) • Other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder) • Study duration: 1 to 157 weeks • Loss to follow-up: NR • Adherence level: NR	• BP (measured by 24-hour ambulatory, morning, daytime ambulatory, nighttime, or office SBP and DBP)	Meta-regression analysis on SBP and DBP: • Baseline AHI • Baseline ODI • Baseline SBP and DBP • CPAP adherence level (hours/night) • Study duration

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
Feng 2015[64] 2 RCTs and 4 prospective observational studies (1994 to 2012)	128 patients (sample size range: 9 to 44 patients): • OSA severity: NR • Obese (mean BMI range: 33.6 to 42.7 kg/m^2) • 100% diabetes • Study duration: 1 to 4 months • Loss of follow-up: NR • Adherence level: see outcome	• A1C • Insulin sensitivity • CPAP adherence level	Subgroup analysis on A1C: • CPAP adherence level (i.e., ≤ 5 or > 5 hours/night)
Hu 2015[65] 7 RCTs (2006 to 2014)	794 patients (sample size range: 35 to 340 patients): • Moderate-to-severe OSA (mean AHI range: 28.1 to 58.3 events/hour) • Obese (mean BMI range: 30.8 to 35.7 kg/m^2) • 100% hypertension (in 3 RCTs) or 100% resistant hypertension (in 4 RCTs) • Study duration: 1 to 6 months • Loss of follow-up: NR • Adherence level: see outcome	• BP (measured by 24-hour ambulatory, daytime, or nighttime SBP and DBP) • CPAP adherence level	Subgroup analysis on SBP and DBP: • Hypertension (non-resistant or resistant) Meta-regression analysis on SBP and DBP: • Baseline ESS • Baseline AHI • Baseline SBP • Age • Sex • BMI • CPAP adherence level (hours/night) • Study duration
Pan 2015[66] 13 RCTs (1994 to 2012)	1,744 patients (sample size range: 16 to 1,098 patients): • Mild-to-severe OSA (mean AHI range: 10 to 55.4 events/hour) • Overweight to obese (mean BMI range: 27.8 to 37.1 kg/m^2) • Study duration: 1 to 24 weeks • Loss to follow-up: NR	• Cognitive functions (i.e., attention, vigilance, processing speed, working memory, memory, verbal fluency, and visuoconstructive skills) • CPAP adherence level	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	• Adherence level: see outcome		
Qureshi 2015[67] 1 RCT and 7 prospective cohorts (2003 to 2013)	4,516 patients (sample size range: 56 to 3,000 patients): • % severe OSA range 10% to 100% • Overweight to obese (mean BMI range: 25 to 35 kg/m^2) • 100% AF; hypertension (% range: 24% to 70%); diabetes (% range: 15% to 24%, where reported) • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• CVEs (i.e., recurrence of AF)	Meta-regression analysis on CVEs: • Hypertension • Diabetes • Age • Sex • BMI
Wang 2015[69] 11 RCTs and observational studies (2005 to 2015)	4,620 patients (sample size range: 96 to 1,010 patients): • Moderate-to-severe OSA (in 5 studies) or unselected OSA (in 6 studies) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• Non-fatal CVEs (e.g., MI, stroke, coronary artery bypass surgery, and PTCA) • CV death	Subgroup analysis on CV death: • OSA severity (i.e., moderate-to-severe)
Wang 2015[70] 5 RCTs (2001 to 2015)	307 patients (sample size range: 30 to 226 patients): • Moderate-to-severe OSA (mean AHI range: 24 to 51.5 events/hour) • 100% nocturia • Study duration: 1 to 12 months • Loss to follow-up: none • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	None
Fava 2014[10] 29 RCTs (1996 to 2012)	1,820 patients (sample size range: 12 to 359 patients): • Mild-to-severe OSA (mean AHI range: 12.9 to 63.8 events/hour) • Overweight to obese (mean BMI range:	• BP (measured by SBP and DBP) • CPAP adherence level	Subgroup analysis on SBP and DBP: • Baseline ESS (i.e., < 10 or ≥ 10) • Baseline AHI (i.e., ≤ 30 or

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	27.2 to 37 kg/m^2) • Hypertension (% range: 0% to 100%, where reported) • Study duration: 2 to 52 weeks • Loss to follow-up: NR • Adherence level: see outcome		> 30 events/hour) • Hypertension (i.e., yes or no) • Age (i.e., < 50 or ≥ 50 years) • Study duration (i.e., ≤ 9 or > 9 weeks) • CPAP adherence level (i.e., < 4 or ≥ 4 hours/night) Meta-regression analysis on SBP: • Baseline AHI (events/hour)
Povitz 2014[75] 19 RCTs (1998 to 2013)	1,355 patients (sample size range: 18 to 391 patients): • Mild-to-severe OSA (mean AHI range: 10 to 65.1 events/hour) • (for the 1,732 patients included in the SR) Normal-to-obese (mean BMI range: 24.7 to 42.5 kg/m^2) • Study duration: 1 to 24 weeks • Loss to follow-up: NR • Adherence level: see outcome	• Depression (measured by BDI, BSI, HADS-D, POMS-D, and SF-36) • CPAP adherence level	Subgroup analysis: • AHI (i.e., mild-to-moderate or severe) • Baseline depression (i.e., yes or no) • Study duration (i.e., < 4, 4 to 8, or > 8 weeks) • CPAP adherence level (i.e., < 4 or ≥ 4 hours/night)
Antonopoulos 2011[47] 21 studies of unknown designs (1989 to 2007)	1,331 patients (sample size range: 14 to 547 patients): • Moderate-to-severe OSA (mean AHI range: 24.8 to 73 events/hour) • Overweight to obese (mean BMI range: 29.5 to 39 kg/m^2) • Study duration: 6 to 36 months • Loss to follow-up: NR • Adherence level: NR	• Real accidents • Near-miss accidents	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
Balk 2011[5] 22 RCTs (1994 to 2010)	*CPAP versus inactive controls* 1,116 patients: • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 27.3 to 43.8 kg/m^2) • Study duration: 1 to 12 months • Dropout rate range: 0% to 33% • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP (measured by SBP and DBP) • A1C • Cognitive functions • Psychological functions • QoL (measured by FOSQ, SF-36, NHP, GHQ-28, UMACL, SAHS-related symptoms questionnaire, or SAQLI)	None
Balk 2011[5] 24 RCTs (1999 to 2010)	*CPAP versus sham CPAP* 1,076 patients: • Moderate-to-severe OSA (mean AHI range: 22 to 68 events/hour) • Overweight to obese (mean BMI range: 27.2 to 42.6 kg/m^2) • Study duration: 1 week to 3 months • Dropout rate range: 0% to 47% • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP • Cognitive functions • QoL (measured by SF-36 and SAQLI)	None
2. EPAP Pre Versus Post			
Riaz 2015[68] 3 RCTs, 5 cohort studies, and 10 conference abstracts (2008 to 2015)	920 patients (sample size range: 6 to 229 patients): • Mild-to-severe OSA (mean AHI range: 14.4 to 43.3 events/hour) • Overweight to obese (mean BMI range: 27 to 34.9 kg/m^2) • Study duration: 1 night to 12 months • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI or ODI) • Snoring	None
3. OA Versus Inactive Controls			
Bartolucci 2016[51] 13 RCTs (2000 to 2010)	514 patients (sample size range: 12 to 95 patients): • Moderate-to-severe OSA (mean AHI range:	• Success rate* *Defined as [(mean AHI at baseline – mean	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	16.2 to 50.4 events/hour) • Overweight to obese (mean BMI range: 25.9 to 32.3 kg/m^2) • Study duration: 3 weeks to 1 year • Loss to follow-up: NR • Adherence level: NR	AHI after treatment) / mean AHI at baseline]	
Iftikhar 2016[55] Network MA: 80 RCTs (1985 to 2015)	7,882 patients (sample size range: 10 to 725 patients): • Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	None
Serra-Torres 2016[58] Prospective (n = 21) and retrospective (n = 1) observational studies (2004 to 2014)	1,495 patients (sample size range: 10 to 922 patients): • Mild-to-severe OSA (mean AHI range: 14-45.5 events/hour) • Overweight to obese (mean BMI range: 25.9 to 32.3 kg/m^2) • Study duration: 0.5 to 84 months • Loss to follow-up: 222 patients (range 0 to 117 patients) • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • AEs • Snoring	None
Sharples 2016[59] 12 RCTs (1997 to 2014)	629 patients (sample size range: 21 to 90 patients): • Mild-to-severe OSA (mean AHI or DI range: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 35.1 kg/m^2) • Study duration: 4 to 26 weeks • Loss to follow-up: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	Subgroup analysis on ESS and AHI: • Baseline ESS (i.e., moderate or severe) • Baseline AHI (i.e., mild, moderate, or severe) • Study duration (i.e., ≤ 12 or > 12 weeks)

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	• Adherence level: NR		
Bratton 2015[62] Pairwise MA: 8 RCTs (2002 to 2014) Network MA: 67 RCTs (1997 to 2015)	6,873 patients (sample size range: 16 to 1,098 patients): • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension) • Study duration: 1 to 157 weeks • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS)	None
Bratton 2015[63] Pairwise MA: 6 RCTs (2004 to 2014) Network MA: 51 RCTs (1996 to 2015)	4,888 patients (sample size range: 12 to 725 patients): • Mild-to-severe OSA (mean AHI range: 13 to 64 events/hour) • Overweight to obese (mean BMI range: 26 to 37 kg/m^2) • Other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder) • Study duration: 1 to 157 weeks • Loss to follow-up: NR • Adherence level: NR	• BP (measured by 24-hour ambulatory, morning, daytime ambulatory, nighttime, or office SBP and DBP)	None
Zhu 2015[71] 16 RCTs and 1 cohort study (1997 to 2015)	840 patients (sample size range: 15 to 91 patients): • Moderate-to-severe OSA (mean AHI ± SD: 23.2 ± 8.2 events/hour [for OA group] or 22.6 ± 7.6 events/hour [for control group]) • Comorbidities: NR • Study duration: 1 week to 6 months • Loss to follow-up: NR • Adherence level: NR	• OSA severity (measured by AHI) • EDS (measured by ESS)	Subgroup analysis on ESS and AHI: • OSA severity (i.e., mild-to-moderate or mild-to-severe)

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
Okuno 2014[74] 3 RCTs (2005 to 2011)	106 patients (sample size range: 24 to 63 patients): • Moderate-to-severe OSA (mean AHI range: 22.1 to 39.1 events/hour [for OA group] and 20.1 to 32.6 events/hour [for control group]) • Comorbidities: NR • Study duration: 1 to 6 months • Loss to follow-up: 23 patients • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • QoL (measured by SF-36)	None
Povitz 2014[75] 5 RCTs (2004 to 2008)	418 patients (sample size range: 24 to 114 patients): • Moderate-to-severe OSA (mean AHI range: 21.3 to 34.7 events/hour) • (for the 1,732 patients included in the SR) Normal-to-obese (mean BMI range: 24.7 to 42.5 kg/m^2) • Study duration: 4 to 12 weeks • Loss to follow-up: NR • Adherence level: see outcome	• Depression (measured by BDI, BSI, HADS-D, POMS-D, and SF-36) • MAD adherence level	None
Balk 2011[5] 5 RCTs (2000 to 2008)	*MADs versus inactive controls*		
	301 patients: • Moderate-to-severe OSA (mean AHI range: 19 to 34 events/hour) • Overweight to obese (mean BMI range: 27.3 to 31.3 kg/m^2) • Exclusion of patients with heart disease and diabetes • Study duration: 1 to 10 weeks • Dropout rate range: 0-14% • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP (measured by SBP and DBP) • Cognitive functions • QoL (measured by FOSQ or SAQLI)	None
Balk 2011[5] 5 RCTs (1997 to 2008)	*MADs versus sham OAs*		
	186 patients: • Moderate-to-severe OSA (mean AHI range:	• EDS (measured by ESS) • OSA severity (measured by AHI)	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	25 to 36 events/hour) • Overweight to obese (mean BMI range: 29 to 32 kg/m^2) • Study duration: 8 days to 6 weeks • Dropout rate range: 0% to 29% • Adherence level: NR	• BP (measured by SBP and DBP) • Cognitive functions • QoL (measured by SF-36)	
4. Surgery Versus Inactive Controls			
GP or GTA pre versus post			
Song 2016[24] 9 pre-and-post studies (1994 to 2015)	61 patients: • Moderate-to-severe OSA (mean AHI range: 13.0 to 88.2 events/hour) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• OSA severity (measured by AHI)	None
MMA Pre Versus Post			
Zaghi 2016[60] 1 RCT and 44 observational studies (1986 to 2014)	518 patients: • Severe OSA (mean AHI: 57.2 events/hour) • Obese (mean BMI: 33.8 kg/m^2 [from 82 patients]) • Study duration: 2 to 6 months • Loss to follow-up: NR Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI or RDI) • Success rate* • Cure rate** *% patients with > 50% reductions in AHI to < 20, < 15, or < 10 events/hour after MMA **% patients with reductions in AHI to < 5 events/hour after MMA	Subgroup analysis on change in AHI: Baseline AHI (i.e., < 30, 30 to < 60, 60 to < 90, or ≥ 90 events/hour)
5. Lifestyle Interventions Versus Inactive Controls			
Aiello 2016[50] 6 RCTs and 2 single-arm trials (2000 to 2014)	180 patients (sample size range: 8 to 43 patients): • Mild-to-severe OSA (mean AHI range: 3.47 to 42.3 events/hour) • Overweight to obese (mean BMI range: 25.9 to 35.5 kg/m^2) • Study duration: 2 to 6 months	• EDS (measured by ESS) • OSA severity (measured by AHI)	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	• Loss to follow-up: NR • Adherence level: NR		
Iftikhar 2016[55] Network MA: 80 RCTs (1985 to 2015)	7,882 patients (sample size range: 10 to 725 patients): • Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	None
Ashrafian 2015[61] 7 RCTs and 13 prospective observational studies (1987 to 2014)	825 patients (sample size range: 8 to 139 patients): • Moderate-to-severe OSA (mean AHI range: 10 to 90 events/hour) • Overweight to obese (mean BMI range: 29.8 to 54 kg/m^2) • Study duration: 1 to 94.3 months • Loss to follow-up: NR • Adherence level: NR	• OSA severity (measured by AHI)	None
Mitchell 2014[73] 8 RCTs (1985 to 2013)	618 patients (sample size range: 11 to 264 patients): • Mild-to-severe OSA (AHI: 21.4 to 49 events/hour [in mean range] or 5 to 15 events/hour [in threshold]) • Overweight to obese (BMI range: 25 to 40 kg/m^2) • Study duration: 8 weeks to 48 months • Loss to follow-up: NR • Adherence level: NR	• OSA severity (measured by AHI and ODI) • EDS (measured by ESS)	None
Araghi 2013[76] 7 RCTs and 14 before-after studies (1987 to 2011)	893 patients (sample size range: 8 to 264 patients): • Mild-to-severe OSA (mean AHI range: 10 to	• OSA severity (measured by AHI and ODI) • EDS (measured by ESS)	Subgroup analysis on AHI: • Baseline AHI (i.e., < 15, 15 to 25, or ≥ 25

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	66.5 events/hour) • Overweight to obese (mean BMI range: 26.5 to 54.6 kg/m^2) • Study duration: 4 weeks to 24 months • Loss to follow-up: NR • Adherence level: NR		events/hour) • Change in BMI (i.e., 0 to 3, 3 to 5, or ≥ 5 kg/m^2) • Study duration (i.e., ≤ 12 or > 12 weeks) Meta-regression analysis on AHI: • Baseline AHI • Weight loss
Thomasouli 2013[19] 6 RCTs (2008 to 2012)	483 patients (sample size range: 21 to 264 patients): • Mild-to-severe OSA (mean AHI range: 9.7 to 46.2 events/hour) • Overweight to obese (mean BMI range: 28.2 to 36.7 kg/m^2) • Study duration: 2 to 12 months • Loss to follow-up: NR • Adherence level: NR	• OSA severity (measured by AHI) • EDS (measured by ESS)	None
Balk 2011[5] 3 RCTs (2009)	345 patients: • Mild-to-severe OSA (mean AHI range: 9 to 37 events/hour) • Obese (mean BMI range: 31.4 to 36.7 kg/m^2) • Diabetes • Study duration: 9 weeks to 1 year • Dropout rate range: 3% to 17% • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • Treatment response • BP (measured by SBP and DBP) • A1C • AEs	None
6. CPAP Versus OAs			
Gupta 2016[54] 2 RCTs (2004 and 2013)	139 patients (sample size range: 25 to 114 patients): • Moderate OSA (mean AHI range: 21.3 to 26.2 events/hour)	• EDS (measured by ESS or SSS) • OSA severity (measured by AHI) • Psychological functions (i.e., depression and anxiety)	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	• Overweight to obese (mean BMI range: 27.8 to 31.1 kg/m^2) • Study duration: 60 days to 3 months • Loss to follow-up: NR • Adherence level: NR	• QoL (measured by SF-36)	
Iftikhar 2016[55] Network MA: 80 RCTs (1985 to 2015)	7,882 patients (sample size range: 10 to 725 patients): • Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9-68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	None
Sharples 2016[59] 13 RCTs (1996 to 2013)	746 patients (sample size range: 20 to 122 patients): • Moderate-to-severe OSA (mean AHI or DI range: NR) • (for the 6,757 patients included in the SR) Overweight to obese (mean BMI range: 28.3 to 35.1 kg/m^2) • Study duration: 4 to 26 weeks • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	Subgroup analysis for CPAP versus MADs on ESS and AHI: • Baseline ESS (i.e., moderate) • Baseline AHI (i.e., moderate or severe) • Study duration (i.e., ≤ 12 or > 12 weeks)
Bratton 2015[62] Pairwise MA: 11 RCTs (1997 to 2014) Network MA: 67 RCTs (1997 to 2015)	6,873 patients (sample size range: 16 to 1,098 patients): • Mild-to-severe OSA (mean AHI range: 10 to 65 events/hour) • Overweight to obese (mean BMI range: 25 to 43 kg/m^2) • Other comorbidities (e.g., Alzheimer disease, CBD, CVD, HF, hypertension, and resistant hypertension)	• EDS (measured by ESS)	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	• Study duration: 1 to 157 weeks • Loss to follow-up: NR • Adherence level: NR		
Bratton 2015[63] Pairwise MA: 4 RCTs (2004 to 2014) Network MA: 51 RCTs (1996 to 2015)	4,888 patients (sample size range: 12 to 725 patients): • Mild-to-severe OSA (mean AHI range: 13 to 64 events/hour) • Overweight to obese (mean BMI range: 26 to 37 kg/m^2) • Other comorbidities (e.g., CVD, HF, hypertension, resistant hypertension, and panic disorder) • Study duration: 1 to 157 weeks • Loss to follow-up: NR • Adherence level: NR	• BP (measured by 24-hour ambulatory, morning, daytime ambulatory, nighttime, or office SBP and DBP)	None
Okuno 2014[74] 3 RCTs (2007 to 2011)	278 patients (sample size range: 43 to 103 patients): • Moderate-to-severe OSA (mean AHI range: 20.9 to 40.3 events/hour) • Comorbidities: NR • Study duration: 8 weeks to 6 months • Loss to follow-up: 14 patients • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • QoL (measured by SF-36)	None
Li 2013[77] 14 RCTs (1996 to 2011)	638 patients (sample size range: 10 to 114 patients): • Mild-to-severe OSA (AHI threshold: ≥ 5 events/hour) • Comorbidities: NR • Study duration: 6 to 48 weeks • Loss to follow-up: NR • Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP (measured by SBP or DBP) • Cognitive functions • Psychological functions • QoL (measured by SF-36) • Treatment usage • Treatment preference • Side effects	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
		• Withdrawals	
Balk 2011[5] 10 RCTs (1996 to 2009)	384 patients: • Moderate-to-severe OSA (mean AHI range: 18 to 40 events/hour) • Overweight to obese (mean BMI range: 26.7 to 34.1 kg/m^2) • Study duration: 2 weeks to 4 months • Dropout rate range: 0% to 24% • Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI) • Cognitive functions • QoL • Adherence • Treatment response	Subgroup analysis on treatment response: • Baseline AHI (i.e., ≤ 30 or > 30 events/hour)
7. CPAP Versus Lifestyle Interventions			
Gupta 2016[54] 1 RCT (2013)	16 patients: • Moderate OSA (mean AHI: 26.2 events/hour) • Overweight (mean BMI: 27.8 kg/m^2) • Study duration: 60 days • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • Psychological functions (i.e., depression and anxiety) • QoL (measured by SF-36)	None
Iftikhar 2016[55] Network MA: 80 RCTs (1985 to 2015)	7,882 patients (sample size range: 10 to 725 patients): • Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	None
Ha 2014[72] 3 RCTs (1999 to 2010)	71 patients (sample size range: 13 to 38 patients): • Mild-to-moderate OSA (mean AHI range: 13 to 22.7 events/hour) • Obese (mean BMI range: 30 to 31 kg/m^2)	• OSA severity (measured by AHI)	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	• Study duration: 3 nights to 9 weeks • Loss to follow-up: NR • Adherence level: NR		
Thomasouli 2013[19] 3 RCTs (1999 to 2004)	261 patients (sample size range: 31 to 125 patients): • Moderate-to-severe OSA (mean AHI range: 20 to 56 events/hour) • Overweight to obese (mean BMI range: 29 to 43.8 kg/m^2) • Study duration: 3 to 24 months • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • QoL	None
Balk 2011[5] 3 RCTs (1999 to 2008)	47 patients: • Moderate OSA (mean AHI range: 18 to 27 events/hour) • Obese (mean BMI range: 30 to 34 kg/m^2) • Study duration: 2 weeks to 1 month • Dropout rate range: 0% to 7% • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • Cognitive functions • QoL	None
8. MADs Versus TRDs			
Balk 2011[5] 1 RCT (2009)	22 patients: • Moderate OSA (mean AHI: 27.0 events/hour) • Overweight (mean BMI: 29.3 kg/m^2) • Study duration: 1 week • Dropout rate: 19% • Adherence level: NR	• OSA severity (measured by AHI)	None
9. MADs Versus Lifestyle Interventions			
Iftikhar 2016[55] Network MA: 80 RCTs (1985 to 2015)	7,882 patients (sample size range: 10 to 725 patients): • Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI)	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	groups] or 9 to 68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR		
10. Diet Versus Exercise			
Iftikhar 2016[55] Network MA: 80 RCTs (1985 to 2015)	7,882 patients (sample size range: 10 to 725 patients): • Mild-to-severe OSA (mean AHI range: 10 to 66.6 events/hour [for intervention groups] or 9-68.1 years [for control groups]) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	None
11. TRDs Plus Positional Therapy Versus Inactive Controls			
Balk 2011[5] 1 RCT (1991)	60 patients: • Mild-to-severe OSA (AHI threshold: > 12.5 events/hour) • Comorbidities: NR • Study duration: NR • Loss to follow-up: NR • Adherence level: NR	• OSA severity (measured by AHI)	None
12. CPAP plus diet programs versus diet programs			
Thomasouli 2013[19] 2 RCTs (1999 and 2001)	230 patients: • Moderate-to-severe OSA (mean AHI range: 20 to 56 events/hour) • Overweight to obese (mean BMI range: 29 to 32 kg/m^2) • 3 to 6 months of study duration	• EDS (measured by ESS) • QoL	None

Study	Population	Outcomes	Subgroup or Meta-Regression Analysis
	• Loss to follow-up: NR • Adherence level: NR		

A1C = glycated hemoglobin; AE = adverse event; AF = atrial fibrillation; AHI = Apnea–Hypopnea Index; AHRQ = Agency for Healthcare Research and Quality; BDI = Beck Depression Inventory; BMI = body mass index; BP = blood pressure; BSI = brief symptom inventory; BSI-A = Brief Symptom Inventory–Anxiety Subscale; BSI-D = Brief Symptom Inventory–Depression Subscale; CBD = cerebrovascular disease; CENTRAL = Cochrane Central Register of Controlled Trials; CES-D = Center for Epidemiological Studies Depression Scale; CONSORT = Consolidated Standards of Reporting Trials; CPAP = continuous positive airway pressure; CV = cardiovascular; CVD = cardiovascular disease; CVE = cardiovascular event; DBP = diastolic blood pressure; DI = desaturation index; EDS = excessive daytime sleepiness; EPAP = expiratory positive airway pressure; EPHPP = Effective Public Health Practice Project; ESS = Epworth Sleepiness Scale; FOSQ = Functional Outcomes of Sleep Questionnaire; GHQ = General Health Questionnaire; GP = genioplasty; GQL = glaucoma quality of life; GRADE = grading of recommendations assessment, development and evaluation; GTA = genial tubercle advancement; HADS-A = Hospital Anxiety and Depression Scale–Anxiety Subscale; HADS-D = Hospital Anxiety and Depression Scale–Depression Subscale; HAM-D = Hamilton Rating Scale for Depression; HF = heart failure; MA = meta-analysis; MAD = mandibular advancement device; MADRS = Montgomery–Åsberg Depression Rating Scale; MAS = mandibular advancement splint; MI = myocardial infarction; MMA = maxillomandibular advancement; MMPI = Minnesota Multiphasic Personality Inventory; MMPI-Pt = Minnesota Multiphasic Personality Inventory–Psychasthenia Subscale; NHP = Nottingham Health Profile; NICE = National Institute for Health and Care Excellence; NR = not reported; OA = oral appliance; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; PAP = positive airway pressure; POMS-D = Profile of Mood States–Depression Subscale; POMS-T = Profile of Mood States –Tension and Anxiety Subscale; PTCA = percutaneous transluminal coronary angiography; QA = quality assessment; QoL = quality of life; QSQ = Quebec Sleep Questionnaire; RCT = randomized controlled trial; RDI = respiratory disturbance index; RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies; SAHS = sleep apnea/hypopnea syndrome; SAQLI = Calgary sleep apnea quality of life index; SBP = systolic blood pressure; SD = standard deviation; SDS = Zung Self-Rating Depression Scale; SF = Short Form Health Survey; SSS = Stanford Sleepiness Scale; STAI = State-Trait Anxiety Inventory; TAS = Tension Anxiety Scale; TRD = tongue-retaining device; TSD = tongue-stabilizing device; UK = United Kingdom; UMACL = University of Wales Mood Adjective Checklist; UPPP = uvulopalatopharyngoplasty; US = United States; UWIST = University of Wales Institute of Science and Technology; WHO-5 = World Health Organization–Five Well-Being Index; WHOQOL = World Health Organization Quality of Life questionnaire.

Appendix 8: Outcomes Reported by Included Systematic Reviews (Research Question 1)

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
1. APAP/BiPAP/CPAP Versus Inactive Controls																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Fu 2016[52]													X				
Guo 2016[53]	X				X	X	X						X	X			
Gupta 2016[54]	X	X								X		X					
Iftikhar 2016[55]	X	X															
Kim 2016[56]						X	X						X	X			
Sharples 2016[59]	X	X															
Bratton 2015[62]	X																
Bratton 2015[63]					X												
Pan 2015[66]											X			X			
Qureshi 2015[67]						X											
Wang 2015[69]						X							X				
Fava 2014[10]					X									X			
Povitz 2014[75]												X		X			
Antonopoulos 2011[47]									X								
Balk 2011[5]	X	X			X			X		X	X	X		X			X
Summary	**X**	**X**			**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**	**X**			**X**
Adults with OSA and specific comorbidities																	
Hypertension or resistant hypertension																	
Liu 2016[57]					X									X			
Hu 2015[65]					X									X			
Summary					**X**												

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
Diabetes																	
Feng 2015[64]								X						X			
Summary								**X**									
Nocturia																	
Wang 2015[70]	X	X															
Summary	**X**	**X**															
SG or MR analysis 1: baseline AHI, ODI, or RDI																	
Liu 2016[57] (SG)					X												
Sharples 2016[59] (SG)	X	X															
Bratton 2015[62] (MR)	X																
Bratton 2015[63] (MR)					X												
Hu 2015[65] (MR)					X												
Wang 2015[69] (SG)													X				
Fava 2014[10] (SG, MR)					X												
Povitz 2014[75] (MR)												X					
Summary	**X**	**X**			**X**							**X**	**X**				
SG or MR analysis 2: baseline ESS																	
Liu 2016[57] (SG)					X												
Sharples 2016[59] (SG)	X	X															
Bratton 2015[62] (MR)	X																
Hu 2015[65] (MR)					X												
Fava 2014[10] (SG)					X												
Summary	**X**	**X**			**X**												
SG or MR analysis 3: comorbidities																	
Baseline BP																	
Liu 2016[57] (SG)					X												

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
Bratton 2015[63] (MR)					X												
Hu 2015[65] (MR)					X												
Summary					**X**												
Hypertension or resistant hypertension																	
Hu 2015[65] (SG)					X												
Qureshi 2015[67] (MR)						X											
Fava 2014[10] (SG)					X												
Summary					**X**	**X**											
Baseline BMI																	
Liu 2016[57] (SG)					X												
Hu 2015[65] (MR)					X												
Qureshi 2015[67] (MR)						X											
Summary					**X**	**X**											
Diabetes																	
Qureshi 2015[67] (MR)						X											
Summary						**X**											
Depression																	
Povitz 2014[75] (SG, MR)												X					
Summary												**X**					
SG or MR analysis 4: sex																	
Hu 2015[65] (MR)					X												
Qureshi 2015[67] (MR)						X											
Summary					**X**	**X**											
SG or MR analysis 5: age																	
Bratton 2015[62] (MR)	X																
Hu 2015[65] (MR)					X												

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
Qureshi 2015[67] (MR)						X											
Fava 2014[10] (SG)					X												
Summary	**X**				**X**	**X**											
SG or MR analysis 6: adherence level																	
Kim 2016[56] (SG)						X											
Liu 2016[57] (SG)					X												
Bratton 2015[62] (MR)	X																
Bratton 2015[63] (MR)					X												
Feng 2015[64] (SG)								X									
Hu 2015[65] (MR)					X												
Fava 2014[10] (SG)					X												
Povitz 2014[75] (MR)												X					
Summary	**X**				**X**	**X**		**X**				**X**					
SG or MR analysis 7: study duration																	
Guo 2016[53] (SG)						X	X						X				
Liu 2016[57] (SG)					X												
Sharples 2016[59] (SG)	X	X															
Bratton 2015[62] (MR)	X																
Bratton 2015[63] (MR)					X												
Hu 2015[65] (MR)					X												
Fava 2014[10] (SG)					X												
Povitz 2014[75] (MR)												X					
Summary	**X**	**X**			**X**	**X**	**X**					**X**	**X**				
2. EPAP Versus Inactive Controls																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Riaz 2015[68]	X	X	X														

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
Summary	X	X	X														
3. OAs Versus Inactive Controls																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Bartolucci 2016[51]															X		
Iftikhar 2016[55]	X	X															
Serra-Torres 2016[58]	X	X	X														X
Sharples 2016[59]	X	X															
Bratton 2015[62]	X																
Bratton 2015[63]					X												
Zhu 2015[71]	X	X															
Okuno 2014[74]	X	X								X							
Povitz 2014[75]												X		X			
Balk 2011[5]	X	X			X					X	X	X					X
Summary	X	X	X		X					X	X	X		X	X		X
SG analysis 1: baseline AHI																	
Sharples 2016[59]	X	X															
Zhu 2015[71]	X	X															
Summary	X	X															
SG analysis 2: baseline ESS																	
Sharples 2016[59]	X	X															
Summary	X	X															
SG analysis 3: study duration																	
Sharples 2016[59]	X	X															
Summary	X	X															
4. Surgery Versus Inactive Controls																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
Song 2016[24]	X	X															
Zaghi 2016[60]	X	X													X		
Summary	**X**	**X**													**X**		
SG analysis 1: baseline AHI																	
Zaghi 2016[60]		X													X		
Summary		**X**													**X**		
5. Lifestyle Interventions Versus Inactive Controls																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Aiello 2016[50]	X	X															
Iftikhar 2016[55]	X	X															
Ashrafian 2015[61]		X															
Mitchell 2014[73]	X	X															
Araghi 2013[76]	X	X															
Thomasouli 2013[19]	X	X															
Balk 2011[5]	X	X			X			X							X		X
Summary	**X**	**X**			**X**			**X**							**X**		**X**
SG or MR analysis 1: baseline AHI																	
Araghi 2013[76] (SG, MR)		X															
Summary		**X**															
SG or MR analysis 2: change in BMI or weight loss																	
Araghi 2013[76] (SG, MR)		X															
Summary		**X**															
SG analysis 3: study duration																	
Araghi 2013[76]		X															
Summary		**X**															

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
6. CPAP Versus OAs																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Gupta 2016[54]	X	X								X		X					
Iftikhar 2016[55]	X	X															
Sharples 2016[59]	X	X															
Bratton 2015[62]	X																
Bratton 2015[63]					X												
Okuno 2014[74]	X	X								X							
Li 2013[77]	X	X			X					X	X	X		X			X
Balk 2011[5]	X	X								X	X			X	X		
Summary	**X**	**X**			**X**					**X**	**X**	**X**		**X**	**X**		**X**
SG analysis 1: baseline AHI																	
Sharples 2016[59]	X	X															
Balk 2011[5]															X		
Summary	**X**	**X**													**X**		
SG analysis 2: baseline ESS																	
Sharples 2016[59]	X	X															
Summary	**X**	**X**															
SG analysis 3: study duration																	
Sharples 2016[59]	X	X															
Summary	**X**	**X**															
7. CPAP Versus Lifestyle Interventions																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Ha 2014[72]		X															
Iftikhar 2016[55]	X	X															
Balk 2011[5]	X	X								X	X						

	Outcomes																
Study	**EDS**	**Sev**	**Sno**	**FT**	**BP**	**CVE**	**Str**	**DBT**	**Acc**	**QoL**	**Cog**	**Psy**	**Mor**	**Com**	**SR**	**FE**	**AE**
Gupta 2016[54]	X	X								X		X					
Thomasouli 2013[19]	X									X							
Summary	**X**	**X**								**X**	**X**	**X**					
8. MADs Versus TRDs																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Balk 2011[5]		X															
Summary		**X**															
9. MADs Versus Lifestyle Interventions																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Iftikhar 2016[55]	X	X															
Summary	**X**	**X**															
10. Diet Versus Exercise																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Iftikhar 2016[55]	X	X															
Summary	**X**	**X**															
11. TRDs Plus Positional Therapy Versus Inactive Controls																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Balk 2011[5]		X															
Summary		**X**															
12. CPAP Plus Diet Programs Versus Diet Programs																	
Adults with OSA (i.e., mixed populations or comorbidities not reported)																	
Thomasouli 2013[19]	X									X							
Summary	**X**									**X**							

Acc = accident; AE = adverse event; AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; BiPAP = bilevel positive airway pressure; BMI = body mass index; BP = blood pressure; Cog = cognitive function; Com = compliance; CPAP = continuous positive airway pressure; CVE = cardiovascular event; DBT = diabetes; EDS = excessive daytime sleepiness; EPAP = expiratory positive airway pressure; ESS = Epworth Sleepiness Scale; FE = facial esthetic; FT = fatigue; MAD = mandibular advancement device; Mor = mortality; MR = meta-regression; OA = oral appliance; ODI = oxygen desaturation index; OSA = obstructive sleep apnea; Psy = psychological function; QoL = quality of life; Sev = OSA severity; SG = subgroup; Sno = snoring; SR = success rate; Str = stroke; TRD = tongue-retaining device.

Appendix 9: Characteristics of Included Primary Studies (Research Question 1)

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Benoist 2016[78] Netherlands and Belgium No funding received	Pre-and-post study	33 positional OSA patients with previous upper airway surgery Mean age ± SD: 52.3 ± 9.7 years 84.8% male Median AHI: 18.3 (IQR: 13.7 to 24.0) events/hour Mean BMI ± SD: 27.9 ± 2.8 kg/m^2	Positional therapy* pre versus post *A sleep position trainer that vibrates to signal to patients to change body positions	3 months of study duration 1 patient lost to follow-up Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI) • Treatment response* • Treatment success** • QoL • Positional therapy adherence level *Defined as > 50% reductions in AHI **Defined as > 50% reductions in AHI to < 5 events/hour	Subgroup analysis on AHI: • Sleep position (i.e., supine versus non-supine)
Levendowski 2016[79]	Pre-and-post study	135 patients	Positional therapy* pre versus post	15 to 52 weeks of study	• Positional therapy	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
US Funding: NR		Patients characteristics: NR	*A neck-positioning device	duration Loss to follow-up: NR Adherence level: see outcome	adherence level • Snoring	
Passeri 2016[80] US Funding from the Harvard Clinical and Translational Science Center, Harvard University, and affiliated academic health care centres	Retrospective cohort study	54 patients (28 in the intervention group; 26 in the control group) Mean age ± SD: 41.9 ± 12.5 years for the intervention group; 21.7 ± 8.6 years for the control group Sex: NR OSA severity: NR Mean BMI ± SD: 29.6 ± 4.7 kg/m^2 for the intervention group; 23.0 ± 3.1 kg/m^2 for the control group Comorbidities* ± SD: 2.4 ± 2.3 for the intervention group; 0.7 ± 1.0 for the control group	MMA plus GA pre versus post* *The control group was out of scope for the report	Study duration: NR No loss to follow-up Adherence level: NR	• Mortality • AEs	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		*Documented medical problems (e.g., obesity, diabetes, or cardiac disease)				
Scarlata 2016[81] Italy Funding: NR	Pre-and-post study	20 patients with positional OSA Mean age ± SD: 64.8 ± 9.5 years 75.0% male Mean AHI ± SD: 16.8 ± 9.5 events/hour Mean BMI ± SD: 28.9 ± 4.0 kg/m^2	Positional therapy* pre versus post *A neck-worn vibrating device that induces positional change to limit supine position in sleeping patients	3 days of study duration No loss to follow-up Adherence level: NR	• OSA severity (measured by AHI, ODI, and RDI)	None
Afrashi 2015[82] Turkey No funding received	Pre-and-post study	29 patients Mean age ± SD: 48.4 ± 10.6 years (range: 26-65 years) 58.6% male Mean AHI ± SD: 15.5 ± 6.2 events/hour Mean BMI ± SD: 28.9 ± 3.2 kg/m^2 (range: 22.2-36.0 kg/m^2)	Positional therapy* pre versus post *A pure prone positioning technique, consisting of a pillow designed to restrict lateral rotations of the neck and keep patients sleep prone	2 nights of study duration No loss to follow-up Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Bidarian-Moniri 2015[83] Sweden Funding from Acta Oto-Laryngologica Foundation	Pre-and-post study	15 patients (recruited) or 14 patients (completed the study) Mean age: 51 years (range: 31 to 70 years) 78.6% male Mean AHI: 26 events/hour (range: 6 to 53 events/hour) Mean BMI: 26 kg/m^2 (range: 21-33 kg/m^2)	Positional therapy* pre versus post *A mattress and a pillow, designed to restrict lateral rotations of the neck and keep patients sleep prone	4 weeks of study duration 1 patient lost to follow-up Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI and ODI) • Positional therapy adherence level	None
Bidarian-Moniri 2015[84] Sweden Funding from Acta Oto-Laryngologica Foundation	Pre-and-post study	32 patients (recruited) or 27 patients (completed the study) Mean age: 51 years (range: 33 to 72 years) 81.5% male Mean AHI: 31 events/hour (range: 5 to 93 events/hour) Mean BMI: 28 kg/m^2 (range: 23 to 36 kg/m^2)	Positional therapy* pre versus post *A mattress and a pillow, designed to restrict lateral rotations of the neck and keep patients sleep prone	2 nights of study duration 5 patients lost to follow-up Adherence level: NR	• OSA severity (measured by AHI and ODI)	Subgroup analysis on AHI: • Positional OSA (i.e., yes versus no)
Chen 2015[85]	Pre-and-post study	25 positional OSA patients	Positional therapy* pre versus post	3 nights of study duration	Primary outcome:	Subgroup analysis on

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Taiwan Funding from the Taiwanese Ministry of Education		Median age: 47.0 years 84% male Median AHI: 7.0 events/hour (IQR: 6.0 to 15.2 events/hour) Median BMI: 24.8 kg/m^2 (IQR: 23.1 to 26.4 events/hour)	*A head-positioning pillow, designed for patients to avoid supine sleep	No loss to follow-up Adherence level: see outcome	• Snoring Secondary outcome: • OSA severity (measured by ODI) • Positional therapy adherence level	ODI, adherence, snoring: • Baseline weight (i.e., normal weight versus overweight)
de Vries 2015[86] Netherlands No industry funding	Retrospective cohort study	53 positional OSA patients (with baseline data) or 40 positional OSA patients (with follow-up data) Mean age ± SD: 51.1 ± 8.3 years (for the 40 patients with follow-up data) 85% male Median AHI: 14.5 events/hour (IQR: 10.7 to 19.6 events/hour) Mean BMI ± SD: 28.0 ± 4.1 kg/m^2	Positional therapy* pre versus post** *A commercial waistband (n = 20) or a self-made construction (n = 20) **Comparing different types of positional therapy was out of scope for the report	Study duration: NR 13 patients lost to follow-up Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI) • Positional therapy adherence level	Subgroup analysis on AHI: • Sleep position (i.e., supine versus non-supine)

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Dieltjens 2015[87] Belgium Funding: NR	RCT	20 patients Mean age ± SD: 52.5 ± 0.5 years 55% male Mean AHI ± SD: 24.6 ± 10.2 events/hour Mean BMI ± SD: 26.4 ± 3.0 kg/m^2	MADs plus positional therapy* versus MADs or positional therapy* *A chest-worn sleep position trainer, designed to vibrate when patients are in the supine position until the patient shifts to a non-supine position	Study duration: NR No loss to follow-up Adherence level: NR	• OSA severity (measured by AHI and ODI)	None
Eijsvogel 2015[88] Netherlands Self-funding	RCT	55 positional OSA patients Mean age ± SD: 50.7 ± 12.2 years for the intervention group; 50.1 ± 10.6 years for the control group 84.6% male for the intervention group;79.3% male for the comparator group Mean AHI ± SD: 13.1 ± 9.1 events/hour for the intervention group; 11.4 ± 4.9 events/hour for the control group	Positional therapy* pre and post** *A tennis ball or a sleep position trainer, designed to vibrate when patients are in the supine position until the patient shifts to a non-supine position **Comparing different types of positional therapy was out of scope for the report	Study duration: NR 7 patients lost to follow-up Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI, ODI, and RDI) • Positional therapy adherence level	Subgroup analysis on AHI: • Sleep position (i.e., supine versus non-supine)

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		Mean BMI ± SD: 26.8 ± 3.0kg/m^2 for the intervention group; 27.6 ± 4.5kg/m^2 for the control group				
Islam 2015[89] UK Funding: NR	Pre-and-post study	26 patients Mean age: 45 ± 7 years 92% male OSA severity: NR Mean BMI ± SD: 28 ± 3 kg/m^2	MMA pre versus post	Study duration: NR No loss to follow-up Adherence level: NR	• Facial aesthetics (measured by VAS)	None
Jackson 2015[90] Australia Funding from the Institute for Breathing and Sleep, the Austin Health Medical Research Foundation, and the Harold and Cora Brennan Benevolent Trust	RCT	86 positional OSA patients Mean age ± SD: 48.0 ± 11.2 years for the intervention group; 51.2 ± 11.4 years for the control group 78.7% male for the intervention group; 76.9% male for the control group Mean AHI ± SD: 20.1 ± 8.8 events/hour for the intervention group; 21.8 ± 10.1 events/hour for the control group	Positional therapy* versus inactive control** *A sleep position modification device and supportive care (see below) **Supportive care, comprising a guide on exercise, weight loss, and sleep positions	4 weeks of study duration 5 patients lost to follow-up Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI) • BP	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		Mean BMI ± SD: 30.0 ± 5.3 kg/m^2 for the intervention group; BMI 30.9 ± 7.7 kg/m^2 for the control group				
Kuscu 2015[91] Turkey Funding: NR	Pre-and-post study	17 patients Mean age: 46 years (range: 30 to 58 years) 94.1% male Mean AHI ± SD: 27.5 ± 8 events/hour Mean BMI ± SD: 30.2 ± 4 kg/m^2	GTA pre versus post	Study duration: NR No loss to follow-up Adherence level: NR	Primary outcomes: • EDS (measured by ESS) • OSA severity (measured by AHI)	None
Roplekar 2015[92] UK No industry funding	Pre-and-post study	20 patients (recruited) or 11 patients (completed the study) Patients characteristics: NR	TRDs pre versus post	4 months of study duration 6 patients lost to follow-up Adherence level: see outcome	• TRD adherence level • EDS (measured by ESS)	None
Chirinos 2014[93] US Funding from the National	RCT	181 patients Mean age: 48.3 years for the weight-loss group; 49.8 years for the CPAP group;	CPAP plus weight loss (n = 62) versus CPAP (n = 58) or weight loss with weekly counselling sessions (n = 61)	24 weeks of study duration 35 patients lost to follow-up	• BP	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Heart, Lung, and Blood Institute		49.0 years for the CPAP plus weight loss group 59% male for the weight-loss group; 60.3% male for the CPAP group; 53.2% male for the CPAP plus weight-loss group Mean AHI ± SD: 39.7 ± 20.3 events/hour for the weight-loss group; 41.2 ± 20.96 events/hour for the CPAP group; 47.1 ± 26.86 events/hour for the CPAP plus weight-loss group Mean BMI ± SD: 38.1 ± 5.8 kg/m^2 for the weight loss group; 39.8 ± 7.1 kg/m^2 for the CPAP group; 38.4 ± 6.4 kg/m^2 for the CPAP plus weight-loss group		Adherence level: NR		
Garreau 2014[94] France Funding: NR	Retrospective cohort study	198 patients Mean age: 46.9 years (range: 20 to 78 years) 67.7% male Moderate-to-severe OSA (moderate = 27.0%, severe =	MADs versus MMA	Study duration: NR Loss to follow-up: NR	• OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		72.1%) for the MMA group; moderate-to-severe OSA (moderate = 46.6%, severe = 53.4%) for the MADs group Mean BMI: 26.6 kg/m^2		Adherence level: NR		
Islam 2014[95] UK Funding: NR	Pre-and-post study	51 patients Mean age ± SD: 44 ± 8 years 90.2% male Mean AHI ± SD: 42 ± 17 events/hour Mean BMI ± SD: 29 ± 3.4 kg/m^2	MMA plus GTA pre versus post	Study duration: NR Loss to follow-up: NR Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	None
Levendowski 2014[96] US Funding from Advanced Brain Monitoring, Inc.	Pre-and-post study	36 positional OSA patients (recruited) or 30 positional OSA patients (completed the study) Mean age ± SD: 51 ± 9 years 73% male Mean AHI ± SD: 24.7 ± 14.7 events/hour	Positional therapy* pre versus post *A neck position therapy device, designed to vibrate when patients are in the supine position until the patient shifts to a non-supine position	30 nights of study duration 6 patients lost to follow-up Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI) • Positional therapy adherence level	Subgroup analysis on AHI: • Sleep position (i.e., supine or non-supine) • Baseline OSA severity (i.e., mild, moderate, or severe)

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		Mean BMI ± SD: 28 ± 3.4 kg/m^2				
van Maanen 2014[97] Netherlands Funding from Achmea Holding, Mediq Tefa, and NightBalance	Pre-and-post study	145 positional OSA patients Median age: 53 years (IQR: 38.7 to 67.3 years) 82.5% male Median AHI: 11.5 events/hour (IQR: 2.5 to 20.5 events/hour) Median BMI: 27.0 kg/m^2 (IQR: 23.0-31.0 kg/m^2)	Positional therapy* pre versus post *A sleep position trainer, designed to vibrate when patients are in the supine position	168 days of study duration 39 patients lost to follow-up Adherence level: see outcome	• EDS (measured by ESS) • Positional therapy adherence level	None
Cohen-Levy 2013[98] France Funding: NR	Pre-and-post study	15 patients Mean age: 42 years (range: 20 to 59 years) 100% male Mean AHI: 50.9 events/hour Mean BMI: 26.60 kg/m^2 (range: 22 to 29 kg/m^2)	MMA pre versus post	Study duration: NR Loss to follow-up: None Adherence level: NR	• Facial aesthetics	None
van Maanen 2013[99] Netherlands	Pre-and-post study	36 positional OSA patients (recruited) or 31 positional OSA patients (completed the study)	Positional therapy* pre versus post *A sleep position trainer	29 ± 2 nights of study duration 5 patients lost	• EDS (measured by ESS) • OSA severity	Subgroup analysis on AHI: • Sleep

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
No funding received		Mean age ± SD: 48.1 ± 11.0 years 87.1% male Median AHI: 16.4 events/hour (IQR: 6.6 to 29.9 events/hour) Mean BMI ± SD: 27.0 ± 3.7 kg/m^2	device, designed to vibrate when patients are in the supine position until the patient shifts to a non-supine position	to follow-up Adherence level: see outcome	(measured by AHI) • Positional therapy adherence level	position (i.e., supine versus non-supine)
Ackel-D'Elia 2012[100] Brazil Funding from Associação Fundo de Incentivo à Pesquisa, Conselho Nacional de Desenvolvimento Científico e Tecnológico, Fundação de Amparo à Pesquisa do Estado de São Paulo, and the FAPESP–Centros de Pesquisa, Inovação e Difusão	RCT	47 patients (recruited) or 32 patients (completed the study) Age range: 25 to 65 years (inclusion criteria) 100% male Mean AHI ± SD: 40.5 ± 22.9 events/hour for the CPAP plus exercise group; 42.3 ± 21.6 events/hour for the CPAP group Mean BMI ± SD: 28.0 ± 3.1 kg/m^2 for the CPAP plus exercise group; 28.5 ± 2.2 kg/m^2 for the CPAP group	CPAP plus exercise (n = 13) versus CPAP (n = 19)	6 months of study duration 15 patients lost to follow-up Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Dort 2012[101] Canada No industry funding	Pre-and-post study	44 patients (recruited) or 41 patients (completed the study) Mean age ± SD: 54.2 ± 10.0 years Sex: NR Mean RDI ± SD: 33.5 ± 15.9 events/hour Mean BMI ± SD: 32.2 ± 5.8 kg/m^2	MADs plus TRDs pre versus post	< 20 weeks of study duration 6 patients lost to follow-up Adherence level: NR	Primary outcome: • OSA severity (measured by RDI) Secondary outcome: • EDS (measured by ESS)	None
Heinzer 2012[102] Switzerland Funding from Lausanne University, the Swiss Pulmonary Society, and the Lancardis Foundation	Pre-and-post study	16 positional OSA patients Mean age ± SD: 58.4 ± 15.1 years 81.2% male Mean AHI ± SD: 26.7 ± 17.5 events/hour Mean BMI ± SD: 25.4 ± 4.1 kg/m^2	Positional therapy* pre versus post *A tennis ball	3 months of study duration No loss to follow-up Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI) • Positional therapy adherence level	Subgroup analysis on AHI: • Sleep position (i.e., supine versus non-supine)
Liu 2012[103] China	Pre-and-post study	12 patients Mean age ± SD: 39.8 ± 2.4 years	MMA pre versus post	6 months of study duration	• Facial aesthetics	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
No funding received		91.7% male Mean AHI ± SD: 60.53 ± 12.66 events/hour Mean BMI ± SD: 27.4 ± 2.1 kg/m^2		No loss to follow-up Adherence level: NR		
van Maanen 2012[104] Netherlands No funding received	Pre-and-post study	30 positional OSA patients Mean age ± SD: 48.0 ± 9.5 years 85.7% male Mean AHI ± SD: 27.7 ± 2.4 events/hour Mean BMI ± SD: 27.7 ± 3.6 kg/m^2	Positional therapy* pre versus post *A small apparatus, designed to vibrate when patients are in the supine position until the patient shifts to a non-supine position	18 months of study duration No loss to follow-up Adherence level: NR	• OSA severity (measured by AHI)	Subgroup analysis on AHI: • Sleep position (i.e., supine versus non-supine)
Bignold 2011[105] Australia Funding from the Flinders Medical Centre Foundation Grant	Pre-and-post study	16 patients (recruited) or 15 patients (completed the study) Mean age ± SD: 58.2 ± 13.9 years 81.3% male Mean AHI ± SD: 24.1 ± 10.5 events/hour	Positional therapy* pre and post *Supine avoidance, with a device	30 months of study duration 1 patient lost to follow-up Adherence level: NR	• OSA severity (measured by AHI) • Snoring	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		Mean BMI ± SD: 28.8 ± 2.5 kg/m^2				
El-Solh 2011[106] US Funding from the American Sleep Foundation	Three-intervention pre-and-post study	14 patients (recruited) or 10 patients (completed the study) Mean age ± SD: 56.9 ± 6.1 years 60% male Mean AHI ± SD: 23.5 ± 13.4 events/hour Mean BMI ± SD: 26.9 ± 3.2 kg/m^2	CPAP plus MADs (n = 10) versus CPAP (n = 10) or MADs (n = 10)	8 weeks of study duration 1 patient lost to follow-up Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by AHI)	None
Johansson 2011[107] Sweden Funding from Cambridge Weight Plan and Novo Nordisk	Prospective cohort study	63 patients Age range: 30 to 65 years Sex: NR Mean AHI ± SD: 36 ± 15 events/hour BMI range: 30 to 40 kg/m^2	CPAP plus diet versus CPAP	1 year of study duration Loss to follow-up: NR Adherence level: see outcome	Primary outcomes: • EDS (measured by ESS) • OSA severity (measured by AHI) Secondary outcomes: • CPAP plus diet adherence level	Subgroup analysis on AHI: • Sleep position (i.e., supine)

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Kim 2011[108] South Korea Funding from the Korea science and Engineering Foundation	Pre-and-post study	14 positional OSA patients Mean age ± SD: 53.5 ± 6.8 years 85.7% male Mean AHI ± SD: 22.8 ± 9.3 events/hour Mean BMI ± SD: 26.3 ± 3.6 kg/m^2	Positional therapy* pre versus post *A free snoring vest, with chambers that inflate to prevent the patient from sleeping in the supine position	Study duration: NR No loss to follow-up Adherence level: NR	• OSA severity (measured by AHI and ODI)	Subgroup analysis on AHI: • Sleep position (i.e., supine versus non-supine)
Sutherland 2011[109] Australia Funding: NR	Prospective cohort study	39 patients Mean age ± SD: 50 ± 10.7 years 64% male Mean AHI ± SD: 26.9 ± 17.1 events/hour Mean BMI ± SD: 29.2 ± 5.5 kg/m^2	MADs versus TSDs	Study duration: NR No loss to follow-up Adherence level: NR	• OSA severity (measured by AHI)	None
Fujii 2010[110] Japan Funding from Dokkyo Medical University	Pre-and-post study	10 patients Mean age ± SD: 50.7 ± 7.8 years 100% male	CPAP plus weight loss pre versus post	4 months of study duration No loss to follow-up	• EDS (measured by ESS)	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		Mean AHI ± SD: 59.0 ± 20.9 events/hour Mean BMI ± SD: 30.7 ± 2.5 kg/m^2		Adherence level: NR		
McDoniel 2010[111] US Funding: NR	Pre-and-post study	11 patients Mean age ± SD: 49.1 ± 8.2 years 54.5% male Mean AHI ± SD: 64.2 ± 28.2 events/hour Mean BMI ± SD: 41.7 ± 6.8 kg/m^2	CPAP plus weight loss pre versus post	12 weeks of study duration No loss to follow-up Adherence level: NR	• EDS (measured by ESS)	None
Bignold 2009[112] Australia No industry funding	Pre-and-post study	108 patients Mean age ± SD: 59.6 ± 12.1 years for questionnaire respondents; 53.8 ± 18.1 years for non-respondents 87.0% male Mean AHI ± SD: 32.4 ± 35.2 events/hour	Positional therapy* pre versus post *A tennis ball	Study duration: NR 41 patients lost to follow-up Adherence level: see outcome	• Positional therapy adherence level	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		Mean BMI ± SD: 28.7 ± 4.2 kg/m^2 for questionnaire respondents; 29.3 ± 8.5 kg/m^2 for non-respondents				
Lazard 2009[113] France No industry funding	Pre-and-post study	84 patients Mean age ± SD: 55 ± 11.0 years 76.2% male Mean AHI ± SD: 37 ± 19.5 events/hour Mean BMI ± SD: 26 ± 3.8 kg/m^2	TRDs pre versus post	Study duration: NR 21 patients lost to follow-up Adherence level: see outcome	• EDS (measured by ESS) • OSA severity (measured by AHI) • TRD adherence level	None
Bruno 2008[114] Italy Funding: NR	Pre-and-post study	20 patients Mean age: 45 years 100% male RDI threshold: > 35 events/hour Comorbidities: NR	MMA plus modified GA pre versus post	Study duration: NR No loss to follow-up Adherence level: NR	• OSA severity (measured by RDI)	None
Dort 2008[115] Canada	Crossover RCT	38 patients (enrolled or 32 patients (completed the study)	TRDs* pre and post** *Prefabricated, one-	Study duration: NR	Primary outcome: • OSA severity	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
Funding from the Alberta Heritage Fund for Medical Research		Mean age ± SD: 48 ± 10.00 years 68.8% male Mean AHI ± SD: 15.5 ± 17.7 events/hour Mean BMI ± SD: 29.4 ± 5.7 kg/m^2	sized TRDs, with or without suction **Comparing different features of TRDs was out of scope for the report	6 patients lost to follow-up Adherence level: NR	(measured by RDI) Secondary outcome: • EDS (measured by ESS)	
Loord 2007[116] Sweden Funding from the County Council of South-East Sweden and Silent Sleep AB	Pre-and-post study	23 positional OSA patients (recruited) or 18 positional OSA patients (completed the study) Mean age: 60.4 years for women; 49.8 years for men 72.2% male Mean AHI ± SD: 21.8 ± 12.0 events/hour Comorbidities: NR	Positional therapy* pre versus post *The Positioner, designed to prevent the supine position	10 months of study duration 5 patients lost to follow-up Adherence level: NR	• EDS (measured by ESS) • OSA severity (measured by RDI)	None
Santos Junior 2007[117] Brazil Funding: NR	Pre-and-post study	10 patients Age range: 30 to 57 years 70% male	GTA pre versus post	Study duration: NR No loss to follow-up	• OSA severity (measured by AHI)	None

First Author, Publication Year, Country, Funding Sources	Study Design, Study Name (if reported)	Patient Characteristics	Intervention and Comparator(s)	Study Duration, Loss to Follow-up, Treatment Adherence Level	Primary and Secondary Outcomes Reported	Subgroup Analyses of Interest
		AHI range: 5 to 30 events/hour BMI threshold: < 30 kg/m^2 (inclusion criteria)		Adherence level: NR		
Oksenberg 2006[118] Israel Funding: NR	Pre-and-post study	78 positional OSA patients Mean age ± SD: 51.3 ± 12.1 years 91% male Mean AHI ± SD: 25.5 ± 17.3 events/hour Mean BMI ± SD: 28.1 ± 3.7 kg/m^2	Positional therapy* pre versus post *A tennis ball	6 months of study duration No loss to follow-up Adherence level: see outcome	• OSA severity (measured by AHI) • Positional therapy adherence level	Subgroup analysis on AHI: • Sleep position (i.e., supine versus non-supine)

AE = adverse event; AHI = Apnea–Hypopnea Index; BMI = body mass index; BP = blood pressure; CPAP = continuous positive airway pressure' CRP = C-reactive protein; DFD = dentofacial deformity; ESS = Epworth Sleepiness Scale; GA = genioglossus advancement; GTA = genial tubercle advancement; HPP = head-positioning pillow; IQR = interquartile range; MAD = mandibular advancement device; MAS = mandibular advancement splint; MMA = maxillomandibular advancement; NR = not reported; ODI = oxygen desaturation index; PSG = polysomnography; PSQI = Pittsburgh sleep quality index; PT = positional therapy; QoL = quality of life; RCT = randomized controlled trials; RDI = respiratory disturbance index; SD = standard deviation; SPMD = sleep position modification device; TRD = tongue-retaining device; TSD = tongue-stabilizing device; UPPP = uvulopalatopharyngoplasty; UK = United Kingdom; US = United States; VAS = visual analogue scale.

Appendix 10: Summary of Quality or Risk of Bias Assessments Conducted by Included Systematic Reviews (Research Question 1)

First Author, Publication Year	Quality or RoB Assessment Tool(s) Used, Included Study Types and Number	Quality or RoB Assessment Summary
Aiello 2016[50]	Jadad[a] RCTs (n = 6) and single-arm trials (n = 2)	The Jadad score was 1 in 3 studies, 3 in 4 studies, and 4 in 1 study, on a scale of 0 to 5. The mean score across all studies was 2.4. *Overall quality: mixed*
Bartolucci 2016[51]	EPHPP's quality assessment tool,[b] Cochrane RoB tool,[c] and GRADE[d] RCTs (n = 13)	The EPHPP rating was weak in 3 studies, moderate in 5 studies, and strong in 5 studies, on a scale of weak to strong quality. The studies were assessed to generally be strong in study design, data collection methods, and withdrawals and dropout rates but moderate in selection bias and mixed in confounders and blinding. The Cochrane RoB rating was low or unclear for all studies, on a scale of low to high risk. There was low RoB in all studies for incomplete outcome data addressed and selective outcome reporting. However, most studies were unclear in sequence generation and allocation concealment. Seven studies had no blinding. The GRADE rating on the success rate for MADs versus inactive controls was moderate, on a scale of very low to high quality. The main reason for lowering the quality of the evidence was indirectness. *Overall quality: moderate to high*
Fu 2016[52]	Newcastle–Ottawa scale[e] (n = 27)	The Newcastle–Ottawa score was 6 in 4 studies, 8 in 2 studies, and 9 in 5 studies, on a scale of 0 to 9, where a score of < 3, 4 to 6, and 7 to 9 was considered to be of low, moderate, and high quality, respectively. *Overall quality: moderate to high*
Guo 2016[53]	Select RoB criteria[c] RCTs (n = 18)	The RoB rating was generally low for all criteria (i.e., 50% to 75% of all RCTs), on a scale of low to high risk. Of the 18 RCTs, 14 reported details of randomization, 12 used satisfactory methods of concealment allocation, and 8 reported blinding of both participants and personnel. There was low risk of attrition bias and reporting bias in most studies. *Overall quality: high*
Gupta 2016[54]	Cochrane RoB tool[c] and GRADE[d] RCTs (n = 10) and single-arm trials (n = 16)	The Cochrane RoB rating was mixed across the included studies, on a scale of low to high risk. Of the 10 RCTs, 2 had adequate randomization procedures, and allocation concealment was described in 1 of the 4 possibilities. Across the included studies, there was high RoB in blinding but low RoB in incomplete outcome data or selective reporting.

First Author, Publication Year	Quality or RoB Assessment Tool(s) Used, Included Study Types and Number	Quality or RoB Assessment Summary
		The GRADE rating on various outcomes for CPAP versus inactive controls was generally very low to low, and that for CPAP versus OAs was low, on a scale of very low to high quality. *Overall quality: very low to low*
Iftikhar 2016[55]	Cochrane RoB[c] tool RCTs (n = 80)	The RoB rating was generally low for all criteria (i.e., 61% to 100% of all RCTs), on a scale of low to high risk. Of the 80 RCTs, 73 reported details of randomization, 64 used satisfactory methods of concealment allocation, and 49 reported blinding of both participants and personnel. There was low risk of attrition bias in 58 RCTs and reporting bias in all 80 RCTs. *Overall quality: high*
Kim 2016[56]	Cochrane RoB[c] tool (for RCTs) and RoBANS[f] (for observational studies) RCT (n = 1), prospective cohort studies (n = 5), and administrative database studies (n = 2)	The Cochrane RoB rating for the RCT was low for all criteria, on a scale of low to high risk. The RoBANS rating for the 7 non-RCTs was mixed for all criteria except selective outcome reporting, which was assessed to be low, on a scale of low to high risk. For selection of participants, allocation concealment, measurement of exposures, and incomplete outcome data, half the studies were rated as having low RoB, while the other half as having high RoB. For blinding of outcome assessment, half the studies were rated as unclear, while the other half as having low or high RoB. *Overall quality: high (for the RCT) or mixed (for the non-RCTs)*
Liu 2016[57]	Jadad[a] RCTs (n = 5)	The Jadad score was 3 in 4 RCTs and 4 in 1 RCT, on a scale of 0 to 5, where a score from 0 to 2 was considered low quality, and from 3 to 5, high quality. The mean score across all RCTs was 3.2. *Overall quality: high*
Serra-Torres 2016[58]	CONSORT criteria Prospective (n = 21) and retrospective (n = 1) observational studies	The CONSORT rating was high in 16 studies and medium in 6 studies, on a scale of low to high quality. *Overall quality: moderate to high*
Sharples 2016[59]	Jadad[a] RCTs (n = 71)	The mean Jadad score was 3.1 for CPAP versus inactive controls, 2.9 for MADs versus inactive controls, and 2.3 for CPAP versus MADs, on a scale of 0 to 5. *Overall quality: moderate*
Song 2016[24]	NICE QA tool[9] Pre-and-post studies (n = 9)	Of the 8 NICE QA criteria, 1 study met 2, 1 study met 3, 6 studies met 4, and 1 study met 5. *Overall quality: low*
Zaghi 2016[60]	Quality control questionnaire[h]	The mean quality score was 5.11, on a scale of 0 to 10. The description and characteristics of participants and surgical technical

First Author, Publication Year	Quality or RoB Assessment Tool(s) Used, Included Study Types and Number	Quality or RoB Assessment Summary
	RCT (n = 1) and observational studies (n = 44)	quality scored high (i.e., met in ≥ 80% of all studies). However, sleep study test quality and independence of sleep study interpretation scored low (i.e., met in < 40% of all studies), and sample size and cohort assembly scored moderate (i.e., met in 46.7% to 64.6% of all studies). *Overall quality: moderate*
Ashrafian 2015[61]	Modified Newcastle–Ottawa scale[e] RCTs (n = 7) and prospective observational studies (n = 13)	The modified Newcastle–Ottawa score ranged from 4 to 14, on a scale of 0 to 15. Of the 20 studies, 10 were of high quality, scoring ≥ 7. *Overall quality: mixed*
Bratton 2015[62]	Cochrane RoB tool[c] RCTs (n = 67)	The Cochrane RoB rating was largely low for incomplete outcome data (i.e., 70% of all RCTs) but largely high for blinding (i.e., 60% of all RCTs) and unclear for random sequence generation and allocation concealment (i.e., 60% of all RCTs), on a scale of low to high risk. *Overall quality: moderate*
Bratton 2015[63]	Cochrane RoB tool[c] RCTs (n = 51)	The Cochrane RoB rating was largely low for all criteria (i.e., 61% to 98% of all RCTs) except for allocation concealment, which was largely unclear (i.e., 59% of all RCTs), on a scale of low to high risk. *Overall quality: high*
Feng 2015[64]	Cochrane RoB tool[c] RCTs (n = 2) and prospective observational studies (n = 4)	The Cochrane RoB rating was low for incomplete outcome data and selective reporting (i.e., 100% of all studies) but high for all other criteria (i.e., 67% of all studies), on a scale of low to high risk. *Overall quality: low*
Hu 2015[65]	Jadad[a] RCTs (n = 7)	The Jadad score was 2 in 1 RCT, 3 in 3 RCTs, 4 in 2 RCTs, and 5 in 1 RCT, on a scale of 0 to 5, where scores ≥ 3 were considered high quality. The mean score across all RCTs was 3.4. *Overall quality: high*
Pan 2015[66]	Jadad[a] RCTs (n = 13)	The Jadad score was 3 in 6 RCTs, 4 in 3 RCTs, and 5 in 4 RCTs, on a scale of 0 to 5, where scores ≥ 3 were considered high quality. The mean score across all RCTs was 3.8. *Overall quality: high*
Qureshi 2015[67]	*Cochrane Handbook for Systematic Reviews of interventions*[i] RCT (n = 1) and prospective cohort	The *Cochrane Handbook* score for the cohort studies ranged from 15 to 22, on a scale of 0 to 22. The score for the RCT was 18, on a scale of 0 to 28. Across the included studies, research questions, design, methods, and participants were assessed to be appropriate and sufficiently described, and the variance was reported for main outcomes and results supporting conclusions. However, ratings were

First Author, Publication Year	Quality or RoB Assessment Tool(s) Used, Included Study Types and Number	Quality or RoB Assessment Summary
	studies (n = 7)	mixed for the appropriateness of sample sizes, analysis, confounding, and results reporting. *Overall quality: moderate*
Riaz 2015[68]	NICE QA tool[g] RCTs (n = 3), cohort studies (n = 5), and conference abstracts (n = 10)	Of the 8 NICE QA criteria, 3 studies met 6, 3 studies met 7, and 2 studies met all 8. *Overall quality: high*
Wang 2015[69]	Downs and Black RCTs and observational studies (n = 11)	The Downs and Black score ranged from 20 to 24, on a scale of 0 to 27, where a score ≥ 20 was considered good quality, and < 20 poor quality. *Overall quality: high*
Wang 2015[70]	Select RoB criteria[c] RCTs (n = 5)	The RoB rating was low for 1 RCT and moderate for 4 RCTs, on a scale of low to high risk. Across the included studies, sequence allocation, loss to follow-up, calculation of sample size, statistical analysis, and intention-to-treat analysis were assessed to be at low risk. However, allocation concealment and blinding were assessed to be at moderate risk. *Overall quality: moderate*
Zhu 2015[71]	Cochrane RoB tool[c] and GRADE[d] RCTs (n = 16) and cohort study (n = 1)	The RoB rating was low for 1 study, medium for 3 studies, and high for 13 studies, on a scale from low to high risk. Across the included studies, sequence generation, allocation concealment, and other bias were assessed to largely be at low risk. However, incomplete outcome and selective reporting were assessed to largely be at high risk. The GRADE rating on various outcomes for OA versus inactive control was generally very low to low, on a scale of very low to high quality. The main reasons for lowering the quality of the evidence were study limitations, indirectness, and imprecision. *Overall quality: low*
Fava 2014[10]	Jadad[a] and GRADE[d] RCTs (n = 29)	The Jadad score was 1 in 3 RCTs, 2 in 9 RCTs, 3 in 8 RCTs, 4 in 9 RCTs, and 5 in 1 RCT, on a scale from 0 (i.e., very poor) to 5 (i.e., rigorous). The mean score across all RCTs was 3.0. The GRADE score was 1 in 7 RCTs, 2 in 14 RCTs, 3 in 8 RCTs, and 4 in 1 RCT, on a scale from 1 (very low quality) to 4 (high quality). *Overall quality: low to moderate*
Ha 2014[72]	Cochrane RoB tool[c] and quality criteria[k]	The Cochrane RoB was significantly identified in the blinding of patients and outcome assessment across the included studies.

First Author, Publication Year	Quality or RoB Assessment Tool(s) Used, Included Study Types and Number	Quality or RoB Assessment Summary
	RCTs (n = 3)	The quality criteria score was 4 in 1 RCT and 5 in 2 RCTs, on a scale of 0 to 8. All studies had high risk of bias for blinding. *Overall quality: moderate*
Mitchell 2014[73]	Cochrane RoB tool[c] RCTs (n = 8)	The Cochrane RoB rating was largely low for random sequence generation, blinding of participants and personnel, and incomplete data reporting (i.e., 69% to 100% of all RCTs), largely unclear for allocation concealment, blinding of outcome assessment, and selective reporting (i.e., 47% to 100% of all RCTs), and largely high for other bias (i.e., 69% of all RCTs), on a scale of low to high risk. *Overall quality: high (for the RCTs included in the MA)*
Okuno 2014[74]	Cochrane RoB[c] tool and GRADE[d] RCTs (n = 5)	The Cochrane RoB rating was largely low for allocation sequence, allocation concealment, and other bias, but mixed for blinding, and high for incomplete outcome data, on a scale from low to high risk. The GRADE rating on various outcomes for CPAP versus OAs was very low to moderate, on a scale of very low to high quality. The main reason for lowering the quality of the evidence was study limitations. *Overall quality: low to moderate*
Povitz 2014[75]	Cochrane RoB tool[c] RCTs (n = 24)	The Cochrane RoB rating varied across the included studies. Most of the included studies reported inclusion and exclusion criteria, loss to follow-up, and power calculations. However, about half the studies reported the method of randomization, allocation concealment, and blinding, and fewer studies reported baseline differences and conducted intention-to-treat analysis. *Overall quality: mixed*
Araghi 2013[76]	Cochrane RoB tool[c] (for RCTs) and Cochrane EPOC RoB[l] (for before-and-after studies) RCTs (n = 7) and before-and-after studies (n = 14)	Across the included RCTs, the Cochrane RoB rating was largely low for sequence generation, incomplete outcome data, and selective outcome reporting (i.e., 75% of all RCTs) and largely unclear for allocation concealment, blinding, and other bias (i.e., 50% to 62.5% of all RCTs). Across the included before-and-after studies, the Cochrane EPOC RoB score ranged from 3 to 11, on a scale of 0 to 11. *Overall quality: mixed*
Li 2013[77]	Cochrane RoB tool[c] RCTs (n = 14)	The Cochrane RoB rating was largely unclear for randomization, allocation concealment, and participant blinding (i.e., 50% to 79% of all RCTs). Follow-up was clearly reported in all RCTs. *Overall quality: low*
Thomasouli 2013[19]	Jadad[a] RCTs (n = 12)	The Jadad score was 2 in 3 RCTs, 3 in 4 RCTs, 4 in 4 RCTs, and 5 in 1 RCT, on a scale of 0 to 6, where a score ≥ 4 was considered good quality. The mean score across all RCTs was 3.25.

First Author, Publication Year	Quality or RoB Assessment Tool(s) Used, Included Study Types and Number	Quality or RoB Assessment Summary
		Overall quality: mixed
Antonopoulos 2011[47]	RoBANS[f,m] Studies of unknown designs (n = 8 of 10 in English and full text)	The RoBANS rating for the 8 studies was mixed for 5 criteria and high for 3 criteria, on a scale of low to high risk. For comparability, exposure measurement, blinding of assessors, and incomplete outcome data, about half the studies were rated as having low RoB, with the other half as having high RoB. For selection of patients, about half the studies were rated as unclear, while the other half was rated as having high RoB. *Overall quality: low*
Balk 2011[5]	AHRQ methods guide[n] RCTs (n = 74)	On a scale from A (highest quality, least likely to have significant bias) to C (lowest quality, most likely to have significant bias), the AHRQ rating was as follows: • CPAP versus inactive controls (22 RCTs): ○ B for 11 RCTs and C for 11 RCTs ○ *Overall quality: low to moderate* • CPAP versus sham CPAP (24 RCTs): ○ A for 5 RCTs, B for 13 RCTs, and C for 6 RCTs ○ *Overall quality: mixed* • MADs versus inactive controls (5 RCTs): ○ B for 4 RCTs and C for 1 RCT ○ *Overall quality: moderate* • MADs versus sham OAs (5 RCTs): ○ B for 4 RCTs and C for 1 RCT ○ *Overall quality: moderate* • MADs versus TRDs (1 RCT): ○ B for the RCT ○ *Overall quality: moderate* • CPAP versus MADs (10 RCTs): ○ B for 9 RCTs and C for 1 RCT ○ *Overall quality: moderate* • CPAP versus positional therapy (3 RCTs): ○ B for all 3 RCTs ○ *Overall quality: moderate* • Intensive weight-loss programs versus inactive controls (3 RCTs): ○ A for 1 RCT and B for 2 RCTs ○ *Overall quality: moderate*

First Author, Publication Year	Quality or RoB Assessment Tool(s) Used, Included Study Types and Number	Quality or RoB Assessment Summary
		• TRD plus posture alarm versus no treatment (1 RCT): ○ C for the RCT ○ *Overall quality: low*

AHRQ = Agency for Healthcare Research and Quality; CONSORT = consolidated standards of reporting trials; CPAP = continuous positive airway pressure; EPHPP = Effective Public Health Practice Project; EPOC = Effective Practice and Organisation of Care; GRADE = Grading of Recommendations Assessment, Development and Evaluation; MA = meta-analysis; MAD = mandibular advancement device; NICE = National Institute for Health and Care Excellence; OA = oral appliance; QA = quality assessment; RCT = randomized controlled trial; RoB = Risk of Bias; RoBANS = Risk of Bias Assessment Tool for Nonrandomized Studies; TRD = tongue-retaining device.

[a] Based on randomization, blinding, and withdrawals and dropouts of participants.

[b] Based on selection bias, study design, confounders, blinding, data collection methods, and withdrawals and dropouts of participants.

[c] Based on sequence generation, allocation concealment, blinding, incomplete outcome data addressed, and selective outcome reporting, with or without other bias (undefined).

[d] Based on risk of bias, inconsistency, indirectness, imprecision, and publication bias.

[e] Based on participant selection, group comparability, and exposure or outcome assessment.

[f] Based on selection of participants, confounding variables, measurement of exposures, blinding of outcome assessment, incomplete outcome data, and selective outcome reporting.

[g] Based on the following questions: case series collected in more than one centre?; is the hypothesis/aim/objective of the study clearly described?; are the inclusion and exclusion criteria clearly reported?; is there a clear definition of the outcomes reported?; were data collected prospectively?; is there an explicit statement that patients were recruited consecutively?; are the main findings of the study clearly described?; and are outcomes stratified?

[h] Based on clinical description and characteristics of participants, sleep study test quality, independence of sleep study interpretation, surgical technical quality, sample size, and cohort assembly.

[i] Based on the following criteria: question sufficiently described; design evident and appropriate to answer study question; method of subject selection described and appropriate; random allocation to treatment reported; blinding of subjects reported, outcome well defined and robust/assessment reported; sample size appropriate; analysis described and appropriate; variance reported for main outcomes; controlled for confounding; results reported in sufficient detail; and results support conclusions.

[j] Based on sequence generation, allocation concealment, blinding, loss to follow-up, calculation of sample size, statistical analysis, and intention-to-treat analysis.

[k] Based on methods of patient allocation, randomization procedures with concealed allocation, mechanism used to implement the random allocation sequence, eligibility criteria for patients and settings for data collection, interventions for each group with sufficient details, pre-specified primary and secondary outcome measures, estimation of required sample size, and methods of blinding.

[l] Based on patient selection, confounding variables, outcome measurement and reporting, and other sources of bias.

[m] QA performed by authors of clinical review of this report.

[n] Based on risk of bias, study consistency, directness of evidence, and degree of certainty of findings.

Appendix 11: Quality Assessment of Included Systematic Reviews (Research Question 1)

Quality Assessment of Included Systematic Reviews																	
	Aiello 2016[50]	Bartolucci 2016[51]	Fu 2016[52]	Guo 2016[53]	Gupta 2016[54]	Iftikhar 2016[55]	Kim 2016[56]	Liu 2016[57]	Serra-Torres 2016[58]	Sharples 2016[59]	Song 2016[24]	Zaghi 2016[60]	Ashrafian 2015[61]	Bratton 2015[62]	Bratton 2015[63]	Feng 2015[64]	Hu 2015[65]
ROBIS Domain 1: study eligibility criteria																	
1.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Low	Low	High	High	Low	Low	High	High	Moderate	Moderate	Low	Moderate	High	Low	Low	Moderate	Moderate
ROBIS Domain 2: identification and selection of studies																	
2.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Low	Low	Moderate	Low	Low	Moderate	Low	Low	Moderate	Low	Moderate	Low	Low	Low	Low	Low	Moderate
ROBIS Domain 3: data collection and study appraisal																	
3.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Moderate	Low	Moderate	Low	Low	Low	Low	Low	High	Low	Moderate	Low	Moderate	Low	Low	Low	Low
ROBIS Domain 4: synthesis and findings																	
4.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.3	●	●	●	●	●		●	●	●	●	●	●	●	●	●	●	●
4.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Quality Assessment of Included Systematic Reviews																	
	Aiello 2016[50]	Bartolucci 2016[51]	Fu 2016[52]	Guo 2016[53]	Gupta 2016[54]	Iftikhar 2016[55]	Kim 2016[56]	Liu 2016[57]	Serra-Torres 2016[58]	Sharples 2016[59]	Song 2016[24]	Zaghi 2016[60]	Ashrafian 2015[61]	Bratton 2015[62]	Bratton 2015[63]	Feng 2015[64]	Hu 2015[65]
4.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.6	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Low	Low	Low	Low	Low	Low	Low	Low	Moderate	Low	Low	Moderate	Moderate	Low	Low	Low	Low
Select criteria from AMSTAR																	
5.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
5.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
5.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
5.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Quality Assessment of Included Systematic Reviews (continued)																	
	Pan 2015[66]	Qureshi 2015[67]	Riaz 2015[68]	Wang 2015[69]	Wang 2015[70]	Zhu 2015[71]	Fava 2014[10]	Ha 2014[72]	Mitchell 2014[73]	Okuno 2014[74]	Povitz 2014[75]	Araghi 2013[76]	Li 2013[77]	Thomasouli 2013[19]	Antonopoulos 2011[47]	Balk 2011[5]
ROBIS Domain 1: study eligibility criteria																
1.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
1.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Moderate	Low	Low	Unclear	High	Low	Low	High	High	Low	Low	Low	Moderate	Moderate	Moderate	Moderate
ROBIS Domain 2: identification and selection of studies																
2.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
2.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Moderate	Low	Low	Moderate	Low	Low	Low	Low	Moderate	Low	Low	Low	Moderate	Low	Low	Low
ROBIS Domain 3: data collection and study appraisal																
3.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

Quality Assessment of Included Systematic Reviews (continued)																
	Pan 2015[66]	Qureshi 2015[67]	Riaz 2015[68]	Wang 2015[69]	Wang 2015[70]	Zhu 2015[71]	Fava 2014[10]	Ha 2014[72]	Mitchell 2014[73]	Okuno 2014[74]	Povitz 2014[75]	Araghi 2013[76]	Li 2013[77]	Thomasouli 2013[19]	Antonopoulos 2011[47]	Balk 2011[5]
3.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
3.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Moderate	Low	Low	Moderate	High	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low
ROBIS Domain 4: synthesis and findings																
4.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.5	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
4.6	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Low	Low	Low	Low	Moderate	Low	Moderate	Moderate	Moderate	High	Low	Low	High	Low	Low	Low
Select criteria from AMSTAR																
5.1	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
5.2	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
5.3	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
5.4	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●

● = yes; ● = probably yes; ● = probably no; ● = no; ● = no information; Y = yes; N = no

Appendix 12: Quality Assessment of Included Network Meta-Analyses (Research Question 1)

Quality Assessment of Included Network Meta-Analyses			
	Iftikhar 2016[55]	**Bratton 2015[62]**	**Bratton 2015[63]**
ISPOR Domain 1: relevance			
1.1	Yes, the population was relevant	Yes, the population was relevant	Yes, the population was relevant
1.2	Yes, some relevant interventions were missing	Yes, some relevant interventions were missing	Yes, some relevant interventions were missing
1.3	Yes, some relevant outcomes were missing	Yes, some relevant outcomes were missing	Yes, some relevant outcomes were missing
1.4	Yes, the context was applicable	Yes, the context was applicable	Yes, the context was applicable
ISPOR Domain 2: credibility			
2.1	Yes, attempts were made to identify and include all relevant RCTs	Yes, attempts were made to identify and include all relevant RCTs	Yes, attempts were made to identify and include all relevant RCTs
2.2	Yes, the included RCTs formed a connected network	Yes, the included RCTs formed a connected network	Yes, the included RCTs formed a connected network
2.3	Yes, poor-quality studies were included, and no subgroup analysis on high-quality studies only was conducted	No, poor-quality studies were not included in a subgroup analysis	No, poor-quality studies were not included in a subgroup analysis
2.4	No, bias was not induced by selective outcome reporting	No, bias was not induced by selective outcome reporting	No, bias was not induced by selective outcome reporting
2.5	Cannot answer whether there were systematic differences in treatment effect modifiers	Yes, there were systematic differences in treatment effect modifiers	Yes, there were systematic differences in treatment effect modifiers
2.6	Not applicable (since the answer to Question 2.5 was not “Yes”)	Cannot answer whether the systematic differences in treatment effect modifiers were identified before comparing individual study results	Cannot answer whether the systematic differences in treatment effect modifiers were identified before comparing individual study results
ISPOR Domain 3: analysis			
3.1	Yes, statistical methods were used to preserve within-study randomization	Yes, statistical methods were used to preserve within-study randomization	Yes, statistical methods were used to preserve within-study randomization
3.2	Yes, consistency was evaluated, but the results were not presented	Yes, consistency was evaluated	Yes, consistency was evaluated
3.3	Yes, both direct and indirect comparisons were included	Yes, both direct and indirect comparisons were included	Yes, both direct and indirect comparisons were included
3.4	No, inconsistency was not handled in the analysis	Yes, inconsistency was handled in the analysis through meta-regression	Yes, inconsistency was handled in the analysis through meta-regression
3.5	Yes, a valid rationale was provided for the use of random-effects models	Yes, a valid rationale was provided for the use of random-effects models	Yes, a valid rationale was provided for the use of random-effects models
3.6	No, heterogeneity was not explored	Yes, heterogeneity was explored	Yes, heterogeneity was explored
3.7	No, subgroup or meta-regression analyses were not conducted to account for heterogeneity	Yes, meta-regression analyses with pre-specified covariates were conducted to account for heterogeneity	Yes, meta-regression analyses with pre-specified covariates were conducted to account for heterogeneity
ISPOR Domain 4: reporting quality and transparency			
4.1	No, a graphical representation of the evidence network did not provide the numbers of RCTs per comparison	Yes, a graphical representation of the evidence network provided the numbers of RCTs per comparison	Yes, a graphical representation of the evidence network provided the numbers of RCTs per comparison

Quality Assessment of Included Network Meta-Analyses			
	Iftikhar 2016[55]	**Bratton 2015[62]**	**Bratton 2015[63]**
4.2	No, individual study results were not reported	Yes, individual study results were reported	Yes, individual study results were reported
4.3	No, results of direct comparisons were not reported	Yes, results of both direct and indirect comparisons were reported	Yes, results of both direct and indirect comparisons were reported
4.4	Yes, all pairwise contrasts and 95% CIs were reported	Yes, all pairwise contrasts and 95% CIs were reported	Yes, all pairwise contrasts and 95% CIs were reported
4.5	Yes, a ranking of interventions was provided No, uncertainty was not reported	No, a ranking of interventions was not provided	No, a ranking of interventions was not provided
4.6	No, there was no evaluation of patient characteristics on the outcomes	Yes, there was an evaluation of some patient characteristics on the outcomes	Yes, there was an evaluation of some patient characteristics on the outcomes
ISPOR Domain 5: interpretation			
5.1	Cannot answer whether the conclusions are appropriate for CPAP comparisons, due to potential bias from inconsistency	Yes, the conclusions are appropriate	Yes, the conclusions are appropriate
ISPOR Domain 6: conflict of interest			
6.1	Yes, some authors declared past funding from OSA device companies	No, no conflict of interest was declared	No, no conflict of interest was declared
6.2	Cannot tell how the potential for conflict of interest from past funding was mitigated	Not applicable (since the answer to Question 6.1 was not “Yes”)	Not applicable (since the answer to Question 6.1 was not “Yes”)

CI = confidence interval

Appendix 13: Quality Assessment of Included Primary Studies With Cochrane Risk of Bias (Research Question 1)

Quality Assessment of Included Primary Studies With Cochrane Risk of Bias						
	Dieltjens 2015[87]	Eijsvogel 2015[88]	Jackson 2015[90]	Chirinos 2014[93]	Ackel-D'Elia 2012[100]	Dort 2008[115]
Cochrane Risk of Bias						
Sequence Generation	●	●	●	●	●	●
Allocation Concealment	●	●	●	●	●	●
Blinding of Participants and Personnel	NA	NA	●	NA	NA	NA
Blinding of Outcome Data	●	●	●	●	●	●
Incomplete Outcome Data	●	●	●	●	●	●
Selective Outcome Reporting	●	●	●	●	●	●
Other Potential Threats to Validity	●	●	●	●	●	●
Concerns	Unclear	Low	Low	Unclear	Unclear	Unclear

● = yes; ● = no; ● = unclear; NA = not applicable

Appendix 14: Quality Assessment of Included Primary Studies With Robans (Research Question 1)

Quality Assessment of Included Primary Studies With RoBANS																	
	Benoist 2016[78]	Levendowski 2016[79]	Passeri 2016[80]	Scarlata 2016[81]	Afrashi 2015[82]	Bidarian-Moniri 2015[83]	Bidarian-Moniri 2015[84]	Chen 2015[85]	de Vries 2015[86]	Islam 2015[89]	Kuscu 2015[91]	Roplekar 2015[92]	Garreau 2014[94]	Islam 2014[95]	Levendowski 2014[96]	van Maneen 2014[97]	Cohen-Levy 2013[98]
RoBANS																	
Comparability	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Selection of Patients	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Confounder	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Exposure Measurement	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blinding of Assessors	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	●	NA	NA	NA	NA
Outcome Assessment	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Incomplete Outcome Data	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Selective Outcome Reporting	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Low	Low	Low	Low	Low	Low	Low	Low	Low	High	Low	Low	Low	Low	Low	Low	Low

Quality Assessment of Included Primary Studies With RoBANS (continued)																		
	van Maneen 2013[99]	Dort 2012[101]	Heinzer 2012[102]	Liu 2012[103]	van Maneen 2012[104]	Bignold 2011[105]	El-Solh 2011[106]	Johansson 2011[107]	Kim 2011[108]	Sutherland 2011[109]	Fujii 2010[110]	McDoniel 2010[111]	Bignold 2099[112]	Lazard 2009[113]	Bruno 2008[114]	Loord 2007[117]	Santos Junior 2007[117]	Oksenberg 2006[118]
RoBANS																		
Comparability	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Selection of Patients	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Confounder	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Exposure Measurement	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Blinding of Assessors	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Outcome Assessment	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Incomplete Outcome Data	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Selective Outcome Reporting	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●	●
Concerns	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Low	Medium	High	Medium	Unclear	High	Low	High

● = low. ● = high. ● = unclear. NA = not applicable

Appendix 15: Validity of Outcomes Measures

Aim

To summarize the validity and minimal clinically important difference (MCID) of the following outcome measures:

- Apnea–Hypopnea Index (AHI)
- Epworth Sleepiness Scale (ESS)

Findings

The above outcome measures are briefly summarized in Table 118.

Table 118: Validity and MCID of Outcome Measures

Instrument	Type	Evidence of Validity	MCID (or similar parameter)	References
AHI	The frequency of obstructive events per hour of sleep, measured with a polysomnography	Yes	5 events/hour[a]	Emami et al. 2009[334]
ESS	The amount of excessive daytime sleepiness, measured with a self-administered questionnaire	Yes	Unknown	Johns 2016[335]

AHI = Apnea–Hypopnea Index; ESS = Epworth Sleepiness Scale; MCID = minimal clinically important difference.
[a] Based on expert opinion.

Apnea–Hypopnea Index

AHI, also referred to as the respiratory disturbance index, is a measure to quantify the severity of sleep apnea and is used to diagnose obstructive sleep apnea (OSA) (i.e., AHI is ≥ 15 events/hour and if there is no underlying condition).[15] The American Academy of Sleep Medicine defines the severity of OSA with the following AHI cut-offs: mild, ≥ 5 and < 15 events/hour; moderate, ≥ 15 and < 30 events/hour; and severe, ≥ 30 events/hour.[15] The frequency of obstructive events (i.e., apnea and hypopnea), is measured during sleep with a polysomnography (PSG). The American Academy of Sleep Medicine has published standardized definitions for both apnea and hypopnea.[336] In adults, apnea is defined when there is a total cessation (≥ 90%) of airflow for ≥ 10 seconds, while hypopnea is defined as a reduction (≥ 30%) of airflow for ≥ 10 seconds in association with either ≥ 3% arterial oxygen desaturation or an arousal.

Measures of scoring respiratory events have only been weakly and inconsistently correlated with the degree of sleepiness.[334] The predictive validity of AHI scores to cardiovascular events and motor vehicle accidents in patients with sleep-related breathing disorders are described and discussed in detail in one paper.[334] In summary, the paper suggests there is evidence supporting a modest to moderate correlation between blood pressure and AHI and further, following continuous positive airway pressure (CPAP) treatment, both blood pressure and severity of sleep apnea were found to be reduced. There are some data that AHI can be predictive of cardiovascular disease. While the majority of case-control studies that looked at retrospectively determined accident rates reported a correlation with higher AHI values, this was not observed in studies that utilized patient self-reported crashes (a study found that non-commercial drivers tend to under-report motor vehicle events when under a research setting). These studies imply that, for motor vehicle accidents, patients with higher AHI values (> 20 to 30) are at a higher risk, although sleepiness may be important in those with lower AHI values. There remains some debate on the validity of AHI, as there is no correlation between AHI and quality of life.[337]

It has been noted that, despite attempts at standardization, there is substantial between-laboratory variation in the AHI measurement due to differences in devices and the criteria used to define apnea and hypopneas.[338-340] This may be for several reasons, including the possibility of confounding effects of different methods used to measure sleepiness, coexisting sleep disorders or medical conditions that may cause sleepiness, and any underlying mechanism in the cause and development of the sleepiness in patients who have sleep-related breathing disorders.[334] MCID in AHI is determined as five events per hour.[334] This MCID was formulated based on the opinion of expert clinicians using the Delphi method.

Epworth Sleepiness Scale

ESS is a measure to quantify excessive daytime sleepiness, assessed with a self-administered questionnaire. The questionnaire includes eight questions on the likelihood of falling asleep in various situations. The scale has a range of 0 to 3: 0 indicating there is no chance of dozing, 1 indicating there is a slight chance of dozing, 2 indicating there is a moderate chance of dozing, and 3 indicating there is a high chance of dozing.[341] The ESS score is the sum of the responses to each of the eight questions and can range from 0 to 24, with higher scores indicative of a person's higher average sleep propensity in daily life.[342] The scale is patient reported and patients using the scale may use symptoms of fatigue as a proxy, as opposed to excessive daytime sleepiness. Additionally, ESS is not a suitable tool in patients with cognitive impairment.[335]

Although ESS can be a good indicator for OSA, ESS cannot be used as the sole diagnostic tool for OSA.[341] As noted in the above section, the external criterion validity of the ESS has also been tested by examining the relationship between ESS scores and AHI in patients with OSA. It appears there is a weak correlation in the relationship between ESS and AHI.[335] Another study concluded that ESS showed correlation with AHI for normal and severe levels, but not for mild and moderate severities.[343] The study recommends the use of the ESS for the follow-up post-operative period, but should not replace the PSG as a diagnostic tool for OSA.[343]

Evidence supporting the validity of ESS can be found in multiple studies where higher-than-normal ESS scores in patients with OSA returned to normal (ESS score 0 to 10) after successful treatment with CPAP.[344] Research notes that ESS does not accurately predict a person's crash risk, although an exception may exist among patients with a very high ESS scores (> 15).[335]

The reliability of the ESS has been previously reported.[335] The test–retest reliability of ESS scores, which has been measured over a few weeks to a few months, has been tested with an intra-class correlation coefficient ranging from 0.81 to 0.93 in five separate investigations.[335] There appears to be limited evidence of an MCID for ESS among individuals with OSA.

Appendix 16: Overlap of Primary Studies Across Included Systematic Reviews (Research Question 1)

Excessive Daytime Sleepiness

Appendix 16.1: CPAP Versus Inactive Controls								
Primary Studies	**Systematic Reviews**							**Times Cited**
	Guo 2016[53] n = 7	**Gupta 2016[54] n = 17**	**Iftikhar 2016[55] n = 44**	**Sharples 2016[59] n = 38**	**Bratton 2015[62] n = 54**	**Wang 2015[70] n = 2**	**Balk 2011[5] n = 28**	
Aarab 2011			+	+				2
Ballester 1999			+	+	+		+	4
Barbe 2001			+	+	+		+	4
Barbe 2010							+	1
Barbe 2012	+		+	+	+			4
Barnes 2002			+	+	+			3
Barnes 2004		+	+	+	+		+	5
Becker 2003			+	+	+		+	4
Campos-Rodriguez 2006			+	+	+		+	4
Castronovo 2009		+						1
Chakravorty 2002			+	+	+		+	4
Chasens 2014					+			1
Chong 2006					+			1
Coughlin 2007			+	+	+		+	4
Craig 2012			+	+	+			3
Dal-Fabbro 2014			+		+			2
Diaferia 2013			+		+			2
Diamanti 2013		+						1
Drager 2007			+	+	+			3
Duran-Cantolla 2010	+		+	+	+			4
Egea 2008			+		+		+	3
El-Sherbini 2011		+						1
Engleman 1997		+	+	+	+		+	5
Engleman 1998		+	+	+	+		+	5
Engleman 1999		+		+	+		+	4
Faccenda 2001			+	+	+		+	4
Ferini-Strambi 2003		+						1
Guilleminault 2004						+		1
Haensel 2007			+					1
Henke 2001			+	+	+			3
Herold 2011		+						1

Appendix 16.1: CPAP Versus Inactive Controls								
Primary Studies	**Systematic Reviews**							**Times Cited**
	Guo 2016[53] n = 7	**Gupta 2016[54] n = 17**	**Iftikhar 2016[55] n = 44**	**Sharples 2016[59] n = 38**	**Bratton 2015[62] n = 54**	**Wang 2015[70] n = 2**	**Balk 2011[5] n = 28**	
Hoyos 2012			+	+	+			3
Huang 2015	+				+			2
Hui 2006			+	+	+		+	4
Jenkinson 1999				+	+		+	3
Jones 2013					+			1
Kaneko 2003			+					1
Kawahara 2005		+						1
Kohler 2008					+			1
Kohler 2011					+			1
Kritikou 2014					+			1
Kushida 2012	+		+	+	+			4
Lam 2007			+	+	+		+	4
Lam 2010					+		+	2
Lee 2012			+					1
Loredo 2006					+		+	2
Lozano 2010			+	+	+			3
Mansfield 2004			+	+	+		+	4
Marshall 2005		+	+	+	+		+	5
Martinez-Garcia 2013	+		+		+			3
Martinez-Garcia 2015			+		+			2
McArdle 2001					+			1
McMillan 2014	+		+		+	+		4
Monasterio 2001			+	+	+		+	4
Montserrat 2001			+	+	+		+	4
Norman 2006			+					1
O'Donoghue 2012		+						1
Pedrosa 2013			+		+			2
Pepperell 2002			+	+				2
Phillips 2011	+		+	+	+			4
Redline 1998			+	+	+		+	4
Robinson 2006			+	+	+		+	4
Rossi 2013					+			1
Ryan 2011			+		+			2
Sharma 2011				+				1
Schutz 2013		+						1
Schwartz 2005		+						1
Schwartz 2007		+						1

Appendix 16.1: CPAP Versus Inactive Controls								
Primary Studies	**Systematic Reviews**							**Times Cited**
	Guo 2016[53] n = 7	**Gupta 2016[54] n = 17**	**Iftikhar 2016[55] n = 44**	**Sharples 2016[59] n = 38**	**Bratton 2015[62] n = 54**	**Wang 2015[70] n = 2**	**Balk 2011[5] n = 28**	
Siccoli 2008			+	+			+	3
Simpson 2013			+					1
Skinner 2004			+					1
Skinner 2008			+	+				2
Smith 2007			+		+		+	3
Spicuzza 2006			+					1
Tomfohr 2011			+	+				2
von Kanel 2006			+					1
Weaver 2012			+	+	+			3
Weinstock 2012			+					1
West 2007			+	+	+		+	4
West 2009							+	1
Woodson 2003			+		+			2
Yamamoto 2000		+						1
Ye 2009		+						1
Zhao 2010					+			1

CPAP = continuous positive airway pressure.

Appendix 16.2: OAs Versus Inactive Controls								
Primary Studies	**Systematic Reviews**							**Times Cited**
	Iftikhar 2016[55] n = 11	**Serra-Torres 2016[58] n = 9**	**Sharples 2016[59] n = 9**	**Bratton 2015[62] n = 8**	**Zhu 2015[71] n = 12**	**Okuno 2014[74] n = 3**	**Balk 2011[5] n = 6**	
Aarab 2011	+		+			+		3
Banhiran 2014		+						1
Barnes 2004	+		+	+	+		+	5
Blanco 2005	+		+	+	+	+		5
Dal-Fabbro 2014	+			+	+			3
Dieltjens 2013		+						1
Dort 2008					+			1
Duarte 2012		+						1
Duran-Cantolla 2015					+			1
Ghazal 2009		+						1
Giannasi 2013		+						1
Gotsopoulos 2002	+		+					2

Appendix 16.2: OAs Versus Inactive Controls								
Primary Studies	**Systematic Reviews**							**Times Cited**
	Iftikhar 2016[55] n = 11	**Serra-Torres 2016[58] n = 9**	**Sharples 2016[59] n = 9**	**Bratton 2015[62] n = 8**	**Zhu 2015[71] n = 12**	**Okuno 2014[74] n = 3**	**Balk 2011[5] n = 6**	
Gotsopoulos 2004				+				1
Hans 1997	+		+		+		+	4
Itzhaki 2007		+						1
Johnston 2002	+		+	+	+		+	5
Lam 2007	+		+	+			+	4
Lawton 2005		+						1
Maguire 2010					+			1
Mehta 2001	+							1
Naismith 2005					+		+	2
Petri 2008	+		+	+	+	+	+	6
Quinnell 2014	+		+	+	+			4
Vanderveken 2008		+						1
Zhang 2009					+			1
Zhou 2012		+						1

OA = oral appliance.

Appendix 16.3: Lifestyle Interventions Versus Inactive Controls							
Primary Studies	**Systematic Reviews**						**Times Cited**
	Aiello 2016[50] n = 4	**Iftikhar 2016[55] n = 10**	**Mitchell 2014[73] n = 2**	**Araghi 2013[76] n = 6**	**Thomasouli 2013[19] n = 2**	**Balk 2011[5] n = 2**	
Barnes 2009				+			1
Desplan 2014		+					1
Guimaraes 2009	+						1
Johansson 2009		+	+	+		+	4
Johansson 2011				+			1
Kemppainen 2008		+					1
Kline 2011	+	+			+		3
Kuna 2013		+					1
Nerfeldt 2010				+			1
Ng 2015		+					1
Schutz 2013	+						1
Sengul 2011	+	+		+			3

Appendix 16.3: Lifestyle Interventions Versus Inactive Controls							
Primary Studies	Systematic Reviews						Times Cited
	Aiello 2016[50] n = 4	Iftikhar 2016[55] n = 10	Mitchell 2014[73] n = 2	Araghi 2013[76] n = 6	Thomasouli 2013[19] n = 2	Balk 2011[5] n = 2	
Servantes 2012		+					1
Smith 1985		+					1
Tuomilehto 2009		+	+	+	+	+	5

Appendix 16.4: CPAP Versus OAs								
Primary Studies	Systematic Reviews							Times Cited
	Gupta 2016[54] n = 2	Iftikhar 2016[55] n = 13	Sharples 2016[59] n = 10	Bratton 2015[62] n = 11	Okuno 2014[74] n = 3	Li 2013[77] n = 8	Balk 2011[5] n = 7	
Aarab 2011		+	+	+	+			4
Barnes 2004	+	+	+	+		+	+	6
Dal-Fabbro 2014		+		+				2
Engleman 2002		+	+	+		+	+	5
Ferguson 1996		+						1
Ferguson 1997		+	+	+		+		4
Fleetham 1998			+					1
Gagnadoux 2009		+	+	+		+	+	5
Hoekema 2007						+		1
Hoekema 2008		+	+	+	+	+	+	6
Lam 2007		+	+	+	+	+	+	6
Phillips 2013		+	+	+				3
Randerath 2002		+						1
Schutz 2013	+	+		+				3
Skinner 2004							+	1
Tan 2002		+	+	+		+	+	5

CPAP = continuous positive airway pressure; OA = oral appliance

Appendix 16.5: CPAP Versus Lifestyle Interventions					
Primary Studies	**Systematic Reviews**				**Times Cited**
	Gupta 2016[54] n = 1	**Iftikhar 2016[55] n = 1**	**Thomasouli 2013[19] n = 2**	**Balk 2011[5] n = 3**	
Ballester 1999			+		1
Jokic 1999				+	1
Monasterio 2001			+		1
Schutz 2013	+	+			2
Skinner 2004				+	1
Skinner 2008				+	1

CPAP = continuous positive airway pressure

Obstructive Sleep Apnea Severity

Appendix 16.6: CPAP Versus Inactive Controls						
Primary Studies	**Systematic Reviews**					**Times Cited**
	Gupta 2016[54] n = 6	**Iftikhar 2016[55] n = 44**	**Sharples 2016[59] n = 25**	**Wang 2015[70] n = 2**	**Balk 2011[5] n = 15**	
Aarab 2011		+	+			2
Ballester 1999		+				1
Barbe 2001		+				1
Barbe 2012		+				1
Barnes 2002		+				1
Barnes 2004	+	+	+		+	4
Becker 2003		+	+		+	3
Campos-Rodriguez 2006		+				1
Chakravorty 2002		+	+		+	3
Coughlin 2007		+				1
Craig 2012		+				1
Dal-Fabbro 2014		+				1
Diaferia 2013		+	+			2
Drager 2006			+			1
Drager 2007		+				1
Duran-Cantolla 2010		+				1
Egea 2008		+			+	2
Engleman 1997		+				1
Engleman 1998		+				1
Facenda 2001		+				1
Guilleminault 2004				+		1
Haensel 2007	+	+	+		+	4
Henke 2001		+	+			2
Herold 2011	+					1
Hoyos 2012		+	+			2

Appendix 16.6: CPAP Versus Inactive Controls						
Primary Studies	**Systematic Reviews**					**Times Cited**
	Gupta 2016[54] n = 6	**Iftikhar 2016[55] n = 44**	**Sharples 2016[59] n = 25**	**Wang 2015[70] n = 2**	**Balk 2011[5] n = 15**	
Hui 2006		+				1
Ip 2004					+	1
Kanekos 2003		+	+		+	3
Kushida 2012		+				1
Lam 2007		+	+		+	3
Lee 2012		+	+			2
Loredo 1999					+	1
Loredo 2006					+	1
Lozano 2010		+				1
Mansfield 2004		+	+		+	2
Marshall 2005		+				1
Martinez-Garcia 2013		+				1
Martinez-Garcia 2015		+				1
McMillan 2014		+				1
Mills 2006					+	1
Miyauchi 2015				+		1
Monasterio 2001		+	+		+	3
Montserrat 2001		+				1
Norman 2006		+	+		+	3
Pedrosa 2013		+				1
Pepperell 2002		+	+			2
Phillips 2011		+	+			2
Redline 1998		+				1
Robinson 2006		+				1
Ryan 2011		+				1
Schutz 2013	+					1
Schwartz 2005	+					1
Siccoli 2008		+				1
Simpson 2012			+			1
Simpson 2013		+				1
Skinner 2004		+	+			2
Skinner 2008		+	+			2
Smith 2007		+				1
Spicuzza 2006		+	+		+	3
Tomfohr 2011		+	+			2
von Kanel 2006		+	+			2
Weaver 2012		+	+			2
Weinstock 2012		+	+			2
West 2007		+				1

Appendix 16.6: CPAP Versus Inactive Controls						
Primary Studies	**Systematic Reviews**					**Times Cited**
	Gupta 2016[54] n = 6	**Iftikhar 2016[55] n = 44**	**Sharples 2016[59] n = 25**	**Wang 2015[70] n = 2**	**Balk 2011[5] n = 15**	
Woodson 2003		+				1
Yu 1999	+					1

CPAP = continuous positive airway pressure

Appendix 16.7: OAs Versus Inactive Controls							
Primary Studies	**Systematic Reviews**						**Times Cited**
	Iftikhar 2016[55] n = 11	**Serra-Torres 2016[58] n = 18**	**Sharples 2016[59] n = 11**	**Zhu 2015[71] n = 13**	**Okuno 2014[74] n = 3**	**Balk 2011[5] n = 7**	
Aarab 2010		+					1
Aarab 2011	+		+	+	+		4
Banhiran 2014		+					1
Barnes 2004	+		+	+		+	4
Blanco 2005	+		+	+	+		4
Bloch 2000						+	1
Chan 2010		+					1
Dal-Fabbro 2014	+			+			2
De Lima 2013		+					1
Dieltjens 2013		+					1
Duarte 2012		+					1
Duran 2002			+				1
Duran-Cantolla 2015				+			1
Gasparini 2013		+					1
Ghazal 2009		+					1
Giannasi 2008		+					1
Giannasi 2013		+					1
Gotsopoulos 2002	+		+				2
Gotsopoulos 2004				+			1
Hans 1997	+		+				2
Itzhaki 2007		+					1
Johnston 2002	+		+	+		+	4
Kurtulmus 2009		+					1
Lam 2007	+		+			+	3
Lawton 2005		+					1
Lettieri 2011		+					1
Marklund 2015				+			1
Mehta 2001	+		+			+	3

Appendix 16.7: OAs Versus Inactive Controls							
Primary Studies	**Systematic Reviews**						**Times Cited**
	Iftikhar 2016[55] n = 11	**Serra-Torres 2016[58] n = 18**	**Sharples 2016[59] n = 11**	**Zhu 2015[71] n = 13**	**Okuno 2014[74] n = 3**	**Balk 2011[5] n = 7**	
Naismith 2005				+		+	2
Petri 2008	+		+	+	+	+	5
Poon 2008		+					1
Quinnell 2014	+		+	+			3
Teixeira 2013				+			1
Tsuiki 2004		+					1
Vanderveken 2008		+					1
Zhang 2009				+			1
Zhou 2012		+					1

OA = oral appliance.

Appendix 16.8: Lifestyle Interventions Versus Inactive Controls								
Primary Studies	**Systematic Reviews**							**Times Cited**
	Aiello 2016[50] n = 7	**Iftikhar 2016[55] n = 10**	**Ashrafian 2015[61] n = 20**	**Mitchell 2014[73] n = 4**	**Araghi 2013[76] n = 16**	**Thomasouli 2013[19] n = 6**	**Balk 2011[5] n = 3**	
Ackel-D'Elia 2012	+					+		2
Barnes 2009			+		+			2
Cavagnolli 2014	+							1
Desplan 2014		+						1
Dixon 2012			+					1
Ferland 2009			+					1
Foster 2009			+	+		+	+	4
Fredheim 2013			+					1
Guimaraes 2009	+							1
Habdank 2006					+			1
Hernandez 2009					+			1
Johansson 2009		+		+	+		+	4
Johansson 2011			+		+			2
Kansanen 1998			+					1

Appendix 16.8: Lifestyle Interventions Versus Inactive Controls								
Primary Studies	**Systematic Reviews**							**Times Cited**
	Aiello 2016[50] n = 7	**Iftikhar 2016[55] n = 10**	**Ashrafian 2015[61] n = 20**	**Mitchell 2014[73] n = 4**	**Araghi 2013[76] n = 16**	**Thomasouli 2013[19] n = 6**	**Balk 2011[5] n = 3**	
Kemppainen 2008		+			+	+		3
Kline 2011	+	+			+	+		4
Kuna 2013		+						1
Nerfeldt 2008				+				1
Nerfeldt 2010			+		+			2
Ng 2015		+						1
Norman 2000	+				+			2
Pahkala 2014			+					1
Papandreou 2012			+			+		2
Pasquali 1990			+		+			2
Phillips 2009			+					1
Rajala 1991			+					1
Rubinstein 1988			+					1
Sampol 1998			+		+			2
Schutz 2013	+							1
Schwartz 1991			+					1
Sengul 2011	+	+	+		+			4
Servantes 2012		+						1
Sleep AHEAD 2009					+			1
Smith 1985		+						1
Suratt 1987 & 1992			+		+			2
Tuomilehto 2009		+		+	+	+	+	5
Tuomilehto 2010			+					1
Ueno 2009					+			1
Yee 2007			+					1

Appendix 16.9: CPAP Versus OAs							
Primary Studies	Systematic Reviews						Times Cited
	Gupta 2016[54] n = 2	Iftikhar 2016[55] n = 13	Sharples 2016[59] n = 13	Okuno 2014[74] n = 3	Li 2013[77] n = 9	Balk 2011[5] n = 9	
Aarab 2011		+	+	+	+		4
Barnes 2004	+	+	+		+	+	5
Clark 1996						+	1
Dal-Fabbro 2014		+					1
Engleman 2002		+	+		+		3
Ferguson 1996		+	+		+	+	4
Ferguson 1997		+	+		+		3
Fleetham 1998			+				1
Gagnadoux 2009		+	+			+	3
Hoekema 2008		+	+	+	+	+	5
Lam 2007		+	+	+	+	+	5
Phillips 2013		+	+				2
Olson 2002			+				1
Randerath 2002		+	+		+	+	4
Schutz 2013	+	+					2
Skinner 2004						+	1
Tan 2002		+	+		+	+	4

CPAP = continuous positive airway pressure; OA = oral appliance.

Appendix 16.10: CPAP Versus Lifestyle Interventions					
Primary Studies	Systematic Reviews				Times Cited
	Gupta 2016[54] n = 1	Iftikhar 2016[55] n = 1	Ha 2014[72] n = 3	Balk 2011[5] n = 3	
Jokic 1999			+	+	2
Permut 2010			+		1
Schutz 2013	+	+			2
Skinner 2004				+	1
Skinner 2008			+	+	2

CPAP = continuous positive airway pressure.

Appendix 16.11: CPAP Versus Inactive Controls							
Primary Studies	**Systematic Reviews**						**Times Cited**
	Guo 2016[53] n = 7	**Liu 2016[57] n = 5**	**Bratton 2015[63] n = 47**	**Hu 2015[65] n = 7**	**Fava 2014[10] n = 29**	**Balk 2011[5] n = 19**	
Arias 2005			+		+	+	3
Barbe 2001			+		+	+	3
Barbe 2010					+	+	2
Barbe 2012			+				1
Barnes 2002			+		+	+	3
Barnes 2004			+		+		2
Becker 2003			+		+	+	3
Campos-Rodriguez 2006			+	+	+	+	4
Comondore 2009			+		+	+	3
Coughlin 2007			+		+	+	3
Craig 2012			+				1
Cross 2008			+		+	+	3
Dal-Fabbro 2014			+				1
de Oliveira 2014		+	+				2
Drager 2007			+		+	+	3
Drager 2011	+		+		+		3
Duran-Cantolla 2010	+		+	+	+		4
Egea 2008			+		+	+	3
Elizabeth 2015	+	+					2
Engleman 1996			+		+	+	3
Faccenda 2001			+		+		2
Gottlieb 2014	+		+				2
Hall 2014			+				1
Hoyos 2012			+				1
Hoyos 2015			+				1
Huang 2015			+				1
Hui 2006			+		+	+	3
Ip 2004			+		+		2
Jones 2013			+				1
Kaneko 2003						+	1
Kohler 2011			+				1
Lam 2007			+		+		2
Lam 2010			+			+	2
Lloberes 2014	+			+			2
Litvin 2013			+				1
Lozano 2010		+	+	+	+		4
Mansfield 2004					+		1

Appendix 16.11: CPAP Versus Inactive Controls							
Primary Studies	**Systematic Reviews**						**Times Cited**
	Guo 2016[53] n = 7	**Liu 2016[57] n = 5**	**Bratton 2015[63] n = 47**	**Hu 2015[65] n = 7**	**Fava 2014[10] n = 29**	**Balk 2011[5] n = 19**	
Martinez-Garcia 2013	+	+	+	+			4
McMillan 2014			+				1
Mills 2006					+	+	2
Monasterio 2001			+		+	+	3
Muxfeldt 2015			+				1
Nguyen 2010			+		+		2
Noda 2007			+		+		2
Norman 2006			+			+	2
Pamidi 2015			+				1
Pedrosa 2013		+	+	+			3
Pepperell 2002			+		+		2
Robinson 2006	+		+	+	+	+	5
Rossi 2013			+				1
Ruttanaumpawan 2008			+		+		2
Takaesu 2012			+		+		2
Weaver 2012			+				1

CPAP = continuous positive airway pressure.

Blood Pressure

Appendix 16.12: CPAP Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Bratton 2015[63] n = 6	**Balk 2011[5] n = 1**	
Andren 2013	+		1
Barnes 2004	+		1
Dal-Fabbro 2014	+		1
Gotsopoulos 2002		+	1
Gotsopoulos 2004	+		1
Lam 2007	+		1
Quinnell 2014	+		1

CPAP = continuous positive airway pressure.

Appendix 16.13: CPAP Versus OAs			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Bratton 2015[63] n = 4	**Li 2013[77] n = 3**	
Barnes 2004	+		1
Dal-Fabbro 2014	+		1
Engleman 2002		+	1
Lam 2007	+	+	2
Phillips 2013	+		1
Trzepizur 2009		+	1

CPAP = continuous positive airway pressure; OA = oral appliance.

Diabetes

Appendix 16.14: CPAP Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Feng 2015[64] n = 6	**Balk 2011[5] n = 1**	
Babu 2005	+		1
Brooks 1994	+		1
Comondore 2009		+	1
Dawson 2008	+		1
Harsch 2004	+		1
Myhill 2012	+		1
West 2007	+		1

CPAP = continuous positive airway pressure.

Cardiovascular Events

Appendix 16.15: CPAP Versus Inactive Controls					
Primary Studies	**Systematic Reviews**				**Times Cited**
	Guo 2016[53] n = 6	**Kim 2016[56] n = 5**	**Qureshi 2015[67] n = 8**	**Wang 2015[69] n = 6**	
Barbe 2012	+	+		+	3
Bazan 2013			+		1
Buchner 2007		+			1
Campos-Rodriguez 2014		+			1
Craig 2008			+		1
Doherty 2005		+		+	2
Fein 2013			+		1
Gottlieb 2014	+				1
Huang 2015	+				1
Jongnarangsin 2008			+		1
Kanagala 2003			+		1
Kushida 2012	+				1
Lamberts 2014		+			1

Appendix 16.15: CPAP Versus Inactive Controls					
Primary Studies	**Systematic Reviews**				**Times Cited**
	Guo 2016[53] n = 6	**Kim 2016[56] n = 5**	**Qureshi 2015[67] n = 8**	**Wang 2015[69] n = 6**	
Marin 2005				+	1
Martinez-Garcia 2012				+	1
McMillan 2014	+				1
Naruse 2013			+		1
Neilan 2013			+		1
Nishihata 2015				+	1
Parra 2015	+			+	2
Patel 2010			+		1

CPAP = continuous positive airway pressure.

Cerebrovascular Events

Appendix 16.16: CPAP Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Guo 2016[53] n = 4	**Kim 2016[56] n = 4**	
Barbe 2012	+		1
Buchner 2007		+	1
Campos-Rodriguez 2014		+	1
Doherty 2005		+	1
Gottlieb 2014	+		1
Huang 2015	+		1
Lamberts 2014		+	1
Parra 2015	+		1

CPAP = continuous positive airway pressure.

Cognitive Functions

Appendix 16.17: CPAP Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Pan 2015[66] n = 13	**Balk 2011[5] n = 15**	
Barbe 2001	+	+	2
Bardwell 2001	+		1
Barnes 2002		+	1
Barnes 2004	+	+	2
Engleman 1994	+	+	2
Engleman 1997	+	+	2
Engleman 1998	+	+	2
Engleman 1999	+	+	2
Gast 2006	+		1
Haensel 2007		+	1

Appendix 16.17: CPAP Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Pan 2015[66] n = 13	**Balk 2011[5] n = 15**	
Henke 2001		+	1
Kushida 2012	+		1
Lojander 1996, 1999		+	1
Loredo 1999		+	1
Loredo 2006		+	1
Marshall 2005	+	+	2
Mills 2006		+	1
Monasterio 2001	+	+	2
Pelletier-Fleury 2004	+		1
Prilipko 2012	+		1

CPAP = continuous positive airway pressure.

Appendix 16.18: CPAP Versus OAs			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Li 2013[77] n = 3	**Balk 2011[5] n = 2**	
Barnes 2004	+		1
Engleman 2002	+	+	2
Gagnadoux 2009	+	+	2

CPAP = continuous positive airway pressure; OA = oral appliance.

Psychological Functions

Appendix 16.19: CPAP Versus Inactive Controls				
Primary Studies	**Systematic Reviews**			**Times Cited**
	Gupta 2016[54] n = 24	**Povitz 2014[75] n = 19**	**Balk 2011[5] n = 6**	
Amin 2011		+		1
Bardwell 2007		+		1
Barnes 2002		+	+	2
Barnes 2004	+	+	+	3
Borak 1996	+			1
Castronovo 2009	+			1
Craig 2012		+		1
Derderian 1988	+			1
Diaferia 2013		+		1
Diamanti 2013	+			1
El-Sherbini 2011	+			1
Engleman 1994	+		+	2
Engleman 1997	+		+	2
Engleman 1998	+	+	+	3

Appendix 16.19: CPAP Versus Inactive Controls				
Primary Studies	**Systematic Reviews**			**Times Cited**
	Gupta 2016[54] n = 24	**Povitz 2014[75] n = 19**	**Balk 2011[5] n = 6**	
Engleman 1999	+	+	+	3
Ferrini-Strambi 2003	+			1
Haensel 2007	+	+		2
Herold 2011	+			1
Jenkinson 1999		+		1
Kawahara 2005	+			1
Lam 2007		+		1
Lee 2012	+	+		2
Marshall 2005	+	+		2
Montserrat 2001		+		1
O'Donoghue 2012	+			1
Papparigopoulos 2009	+			1
Ramos-Platon 1992	+			1
Ryan 2011		+		1
Sanchez 2001	+			1
Sandberg 2001		+		1
Schutz 2013	+			1
Schwartz 2005	+			1
Siccoli 2008		+		1
Smith 2007		+		1
Yamamoto 2000	+			1
Yu 1999	+	+		2

CPAP = continuous positive airway pressure.

Appendix 16.20: OAs Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Povitz 2014[75] n = 5	**Balk 2011[5] n = 2**	
Barnes 2004	+	+	2
Blanco 2005	+		1
Gotsopoulos 2002		+	1
Lam 2007	+		1
Naismith 2005	+		1
Petri 2008	+		1

OA = oral appliance.

Appendix 16.21: CPAP Versus OAs			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Gupta 2016[54] n = 2	**Li 2013[77] n = 2**	
Barnes 2004	+		1
Engleman 2002		+	1
Hoekema 2008		+	1
Schutz 2013	+		1

CPAP = continuous positive airway pressure; OA = oral appliance.

Quality of Life

Appendix 16.22: CPAP Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Gupta 2016[54] n = 11	**Balk 2011[b] n = 17**	
Ballester 1999		+	1
Barbe 2001		+	1
Barnes 2002		+	1
Barnes 2004	+	+	2
Castronovo 2009	+		1
Diamanti 2013	+		1
Egea 2008		+	1
Engleman 1994	+	+	2
Engleman 1997	+	+	2
Engleman 1998	+	+	2
Engleman 1999	+	+	2
Faccenda 2001		+	1
Herold 2011	+		1
Lam 2007		+	1
Mansfield		+	1
Marshall 2005	+	+	2
Monasterio 2001		+	1
Montserrat 2001		+	1
Papparigopoulos 2009	+		1
Schuts 2013	+		1
Siccolli 2008		+	1
Smith 2007		+	1

CPAP = continuous positive airway pressure.

Appendix 16.23: OAs Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Okuno 2014[74] n = 2	**Balk 2011[5] n = 3**	
Blanco 2005	+		1
Barnes 2004		+	1
Lam 2007		+	1
Petri 2008	+	+	2

OA = oral appliance.

Appendix 16.24: CPAP Versus OAs					
Primary Studies	**Systematic Reviews**				**Times Cited**
	Gupta 2016[54] n = 2	**Okuno 2014[74] n = 2**	**Li 2013[77] n = 5**	**Balk 2011[5] n = 7**	
Aarab 2011			+		1
Barnes 2004	+		+	+	3
Engleman 2002			+	+	2
Gagnadoux 2009				+	1
Hoekema 2008		+	+	+	3
Lam 2007		+	+	+	3
Schutz 2013	+				1
Skinner 2004				+	1
Tan 2002				+	1

CPAP = continuous positive airway pressure; OA = oral appliance.

Appendix 16.25: CPAP Versus Lifestyle Interventions				
Primary Studies	**Systematic Reviews**			**Times Cited**
	Gupta 2016[54] n = 1	**Thomasouli 2013[19] n = 2**	**Balk 2011[5] n = 3**	
Ballester 1999		+		1
Jokic 1999			+	1
Monasterio 2001		+		1
Schutz 2013	+			1
Skinner 2004			+	1
Skinner 2008			+	1

CPAP = continuous positive airway pressure.

Mortality

Appendix 16.26: CPAP Versus Inactive Controls					
Primary Studies	**Systematic Reviews**				**Times Cited**
	Fu 2016[52] n = 11	**Guo 2016[53] n = 4**	**Kim 2016[56] n = 3**	**Wang 2015[69] n = 11**	
Anandam 2013	+			+	2
Barbe 2012		+		+	2
Buchner 2007	+		+		2
Campos-Rodriguez 2009				+	1
Campos-Rodriguez 2012	+		+	+	3
Cassar 2007				+	1
Doherty 2005	+		+	+	3
Huang 2015		+			1
Jennum 2015	+				1
Kushida 2012		+			1
Marin 2005	+			+	2
Marrone 2013	+				1
Martinez-Garcia 2012	+			+	2
Martinez-Garcia 2012 (b)				+	1
Molnar 2015	+				1
Nishihata 2015				+	1
Ou 2015	+				1
Parra 2015		+		+	2
Yuan 2015	+				1

CPAP = continuous positive airway pressure.

Adverse Events

Appendix 16.27: OAs Versus Inactive Controls			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Serra-Torres 2016[58] n = 5	**Balk 2011[5] n = 5**	
Doff 2013	+		1
Engleman 2002		+	1
Ferguson 1996		+	1
Johnston 2002		+	1
Lawton 2005	+		1
Marklund 2007	+		1
Martinez-Gomis 2010	+		1
Petri 2008		+	1
Walker-Engstrom 2002		+	1
Zhou 2012	+		1

OA = oral appliance.

Adherence

Appendix 16.28: CPAP Versus OAs			
Primary Studies	**Systematic Reviews**		**Times Cited**
	Li 2013[77] n = 6+5	**Balk 2011[5] n = 1**	
Aarab 2011	+		1
Barnes 2004	+		1
Engleman 2002	+		1
Gagnadoux 2009		+	1
Hoekema 2007	+		1
Hoekema 2008a	+		1
Hoekema 2008b	+		1
Lam 2007	+		1

CPAP = continuous positive airway pressure; OA = oral appliance.

Appendix 17: Coverage in Canada (Research Question 2)

	BC	AB	SK	MB	NL	NB	NS	PE	YK	NT	NU	Veterans Affairs
Dentistry	N	N	N	N	N	N	N	N	N	N	N	Y
CPAP[a]	N	Y(c)	Y	Y	Y	N	N	N	Y	Y(c)	Y	Y
Surgery	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

AB = Alberta; BC = British Columbia; C = criteria; MB = Manitoba; N = no; NB = New Brunswick; NL = Newfoundland and Labrador; NS = Nova Scotia; NT = Northwest Territories; NU = Nunavut; PAP = positive airway pressure; PE = Prince Edward Island; SK = Saskatchewan; Y = yes.

[a] For details on the extent to which PAP therapy is covered, please refer to INNESS publication by Potvin et al., 2014.[2]

Appendix 18: Characteristic of Existing Published Economic Evaluations on Treatments for Obstructive Sleep Apnea (Research Question 2)

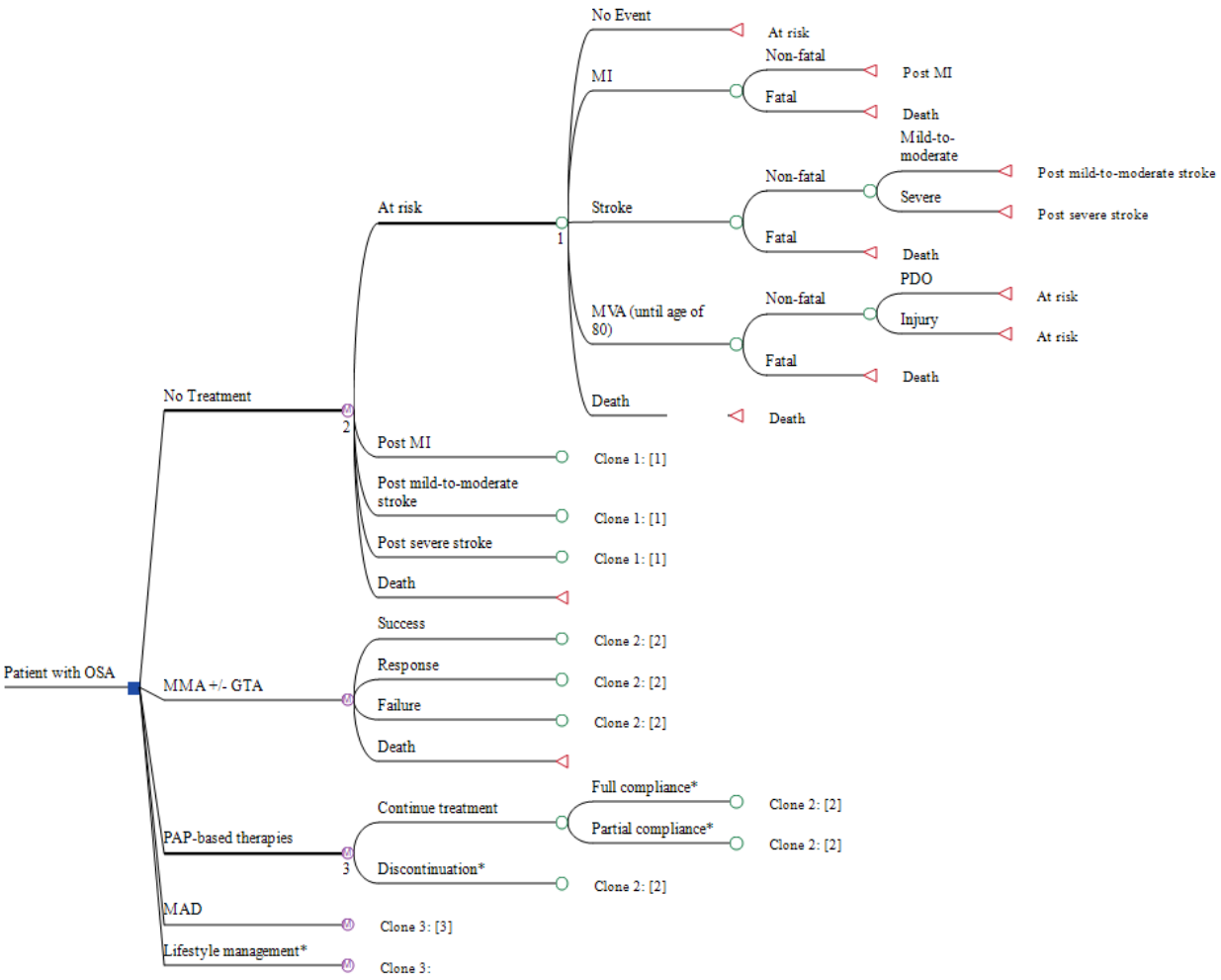
First Author	Country, perspective	Population	Comparators	Modelling Approach	Clinical Outcomes modelled
McMillan[120]	UK, TPP	Patients from PREDICT trial: ≥ 65 years of age, newly diagnosed with OSA (oxygen desaturation index ≥ 4% desaturation threshold level for > 7.5 events/hr and ESS ≥ 9)	CPAP + BSC BSC	Trial-based economic evaluation (short-term) Markov cohort model (long-term)	
Sharples[28] Quinell[180]	UK, TPP	Patients from TOMADO trial: adults, 50.9 years of age, 80% males, with AHI 5 to < 30/h and ESS ≥ 9	Oral appliances (i.e., thermoplastic boil and bite, semi-bespoke, bespoke MAD) No treatment	Trial-based economic evaluation (RCT)	Based on EQ-5D-3L
Trakada[121]	Greece, NR	Patients, 55 years of age, with severe OSA (AHI ≥ 30/h) and ESS > 10	CPAP No treatment	Markov cohort model	• CVD • Mortality
Guest[122]	UK, TPP	Patients defined by case-control study: 54 years of age with OSA and type 2 diabetes	CPAP No treatment	Trial-based economic evaluation (case-control study)	Based on EQ-5D-3L
Sadatsafavi[123]	US, TPP	Moderate-severe OSA (AHI ≥ 15/h)	CPAP Dental devices No treatment	Markov cohort model	• MVA • MI, Stroke • Mortality
Weatherly[124]	UK, TPP	Male, 50 years of age	CPAP Dental devices Lifestyle advice	Markov cohort model	• MVA, • CHD, Stroke • Mortality
Guest[125]	UK, TPP	55 years of age, with severe OSA (AHI > 30/h and ESS ≥ 12)	CPAP No treatment	Markov cohort model	• MVA, • MI, Stroke • Mortality
Tan[39]	Canada, TPP	Drivers, 30 to 59 years of age, newly diagnosed moderate-to-severe OSA	CPAP No treatment	Markov cohort model	• MVA • Mortality
Ayas[126]	US, TPP and societal	Moderate-to-severe OSA (AHI ≥ 15/h)	CPAP No treatment	Markov cohort model	• MVA • Mortality
Mar[127]	Spain, TPP	Male, 50 years of age, with moderate-to-severe OSA (AHI > 30/h and ESS > 10)	CPAP No treatment	Markov cohort model	• MVA, • CHD, Stroke • Mortality

First Author	Country, perspective	Population	Comparators	Modelling Approach	Clinical Outcomes modelled
Pietzsch[128]	US, TPP	Patients from STAR trial: 54.5 years of age, 83% male, mean AHI 32/h	Upper airway stimulation No treatment	Markov cohort model	• MVA • *Hypertension* • MI, Stroke • Mortality
Poullié[129]	France, TPP	Mild-to-moderate OSA (5/h ≤ AHI ≤ 30/h), patient characteristics defined from European cohort studies and French national database	CPAP Dental devices Lifestyle* No treatment	Markov cohort model	• MVA • CV event (in cohort with high CV risk) • Mortality
Tan[130]	US, TPP	Male, 50 years of age, with severe OSA (AHI ≥ 30/h) intolerant of CPAP and who are candidates of OSA surgery	CPAP Surgery (i.e., PRS or MLS) No treatment	Markov cohort model	• MVA, • MI, Stroke • Surgical complications • Mortality

AHI = Apnea–Hypopnea Index; BSC = best supportive care; CHD = coronary heart disease; CPAP = continuous positive airway pressure; CV = cardiovascular; CVD = cardiovascular disease; ESS = Epworth Sleepiness Scale; EQ-5D-3L = EuroQol 5-Dimensions 3-Levels questionnaire; MAD = mandibular advancement device; MI = myocardial infarction; MLS = multilevel surgery; MVA = mortality vehicle accident; NR = not reported; OSA = obstructive sleep apnea; PRS = palatopharyngoplasty reconstructive surgery; RCT = randomized controlled trial; TPP = third-party payer; UK = United Kingdom; US = United States of America

*Mentioned in methods as a comparator but results are not presented

Appendix 19: Simplified Diagrammatic Representation of the Decision-Analytic Model (Research Question 2)



MAD = mandibular advancement device; MI = myocardial infarction; MVA = motor vehicle accident; PAP = positive airway pressure; PDO = property damage only.
Note: The square node represents a decision to treat OSA with either no therapy, PAP-based therapy, MAD, MMA with or without GTA, or lifestyle management. For simplicity, only three submodel structures are presented. It is important to note that patients in post-MI or post-stroke states that have no event in a subsequent cycle return to post-MI or post-stroke "no event" health state.

Appendix 20: Description of Key Clinical Characteristics in Which Data Were Taken as Treatment Estimates for the Economic Model (Research Question 2)

Author	Description	Comparison	Demographics						
			Age (SD)	% Male	AHI (SD)	Baseline ESS	SBP	BMI	Follow-up duration
AHI									
Sharples[55]	MA of 77 RCTs; 52 studies compared CPAP against inactive control; 12 studies compared MAD against inactive controlled 5400 patients (CPAP) 629 patients (MAD)	PAP therapy vs. inactive control MAD vs. inactive control PAP therapy vs. MAD	Total: 44.0 to 59.2	Total: 65% to 100%	NR	NR		Total: 28.3 to 35.1	2 to 156 weeks
Araghi[76]	MA of 7 RCTs 519 patients	Weight loss vs. inactive control/usual care	46 to 61	NR	10 to 37	NR		29.7 to 43.8	6 weeks to one year
Riaz[68]	MA of 18 randomized and observational studies; AHI analysis based on 10 studies 920 patients (AHI, n = 345)	EPAP vs. inactive control	Total: 50.2 (12.7)	NR	AHI analysis: 27.32 (22.24)	NR		Total: 32.2 (6.7)	One night to 12 months
Zaghi[60]	MA of 45 pre-post studies 518 patients (AHI, n = 455)	MMA without adjunctive procedures	Total: 45.3	83%	57.2 events/hr	13.5 (SD: 5.2)		33.8 (9.7)	2 to 6 months
Jackson[90]	RCT 86 patients (47 patients)	Positional therapy vs. control	48. (11.2)	79%	21.8 (10.1) [C] vs. 20.1 (8.8) [I]	10.0 (5.9) [C] vs. 9.9 (4.7) [I]		30.0 (7.7) [C] vs. 30 (5.3) [I]	4 weeks
Blood Pressure									
Bratton[63]	NMA of 51 RCTs Total: 4533 patients	PAP therapy vs. MAD vs. inactive control	Ranges from 55.3 (CPAP vs. C) to 46.2 (CPAP vs. MAD vs. C)	Ranges from 79% (3-way comparison) to 81% (CPAP vs. MAD)	Ranges from 36.9 (CPAP vs. C) to 20.7 (MAD vs. C)	Ranges from 9.1 (CPAP vs. MAD) to 11.5 (MAD vs. C)	Ranges from 127.9 (3-way comparison) to 135 (OA vs. C)	Ranges from 29.1 (3-way comparison) to 32.1 (CPAP vs. C)	Ranges from 4.3 (CPAP vs. MAD) to 15.1 weeks (CPAP vs. C)

Author	Description	Comparison	Demographics						
			Age (SD)	% Male	AHI (SD)	Baseline ESS	SBP	BMI	Follow-up duration
Balk[5]	SR, 1 relevant RCT 72 obese patients (35 in lifestyle modification group) Inclusion criteria: mild OSA (5-15 events/h)	Weight reduction vs. control	51.8 [C] vs. 50.9 [I]	72% [C] vs. 74% [I]	9.3 (3) [C] vs. 10 (3) [I]	9.9 (4.8) [C] vs. 10.1 (5.0) [I]	130 (12.8) [C] vs. 131.2 (10.2) [I] Antihypertensive medication: 41% [C] vs. 51% [I]	31.4 [C] vs. 33.4 [I]	1 year
Boyd[162]	Before-after study w/out comparator group 30 patients Inclusion criteria: moderate-to-severe OSA (AHI > 15 events/h); inability to tolerate or adequately adhere to CPAP	MMA	50.5	80%	49	12.1 (4.9)	136.0 (13) 26.7% diagnosed w/ hypertension	29.1 (4.1)	> 6 years post MMA

AHI = Apnea–Hypopnea Index; C = control; CPAP = continuous PAP; EPAP = expiratory PAP; I = (active) intervention; MA = meta-analysis; MAD = mandibular advancement device; MMA = maxillomandibular advancement; NR = not reported; OSA = obstructive sleep apnea; PAP = positive airway pressure; RCT = randomized controlled trial; SBP = systolic blood pressure; SD = standard deviation; SR = systematic review; UPPP = uvulopalatopharyngoplasty.

Appendix 21: Sensitivity Analysis Results Under a Lifetime Perspective (Research Question 2)

Sensitivity Analysis	Mild, AHI = 5 ICUR($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
Base case	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 175,543 (0.00) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,058 (0.03) 9,276 (0.93) Dominated (0.05)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,420 (0.79) Dominated (0.03) Dominated (0.17)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 17,125 (0.99)
Modelled time horizon, 7 years	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1) 301,322 (0) Ext. Dom (0) 3,056,840 (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,119 (0.28) 31,421 (0.72) Dominated (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,605 (0.98) Dominated (0.01) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.62) Ext. Dom (0.01) Dominated (0) 59,552 (0.37)
Modelled time horizon, 10 years	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1) 266,814 (0) 864,730 (0) 3,971,066 (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,145 (0.12) 18,318 (0.88) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,459 (0.97) Dominated (0.02) Dominated (0.01)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.36) Ext. Dom (0.02) Dominated (0) 43,047 (0.63)
Discontinuation for severe OSA, Guest's rates[125]	Not impacted				No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,361 (0.79) Dominated (0.03) Dominated (0.18)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 17,027 (0.99)
Adherence rate, higher end of 95% CI	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 168,922 (0.00) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 7,975 (0.03) 9,344 (0.93) Dominated (0.04)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,418 (0.80) Dominated (0.05) Dominated (0.16)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.02) Dominated (0) Ext. Dom (0.00) 16,868 (0.98)

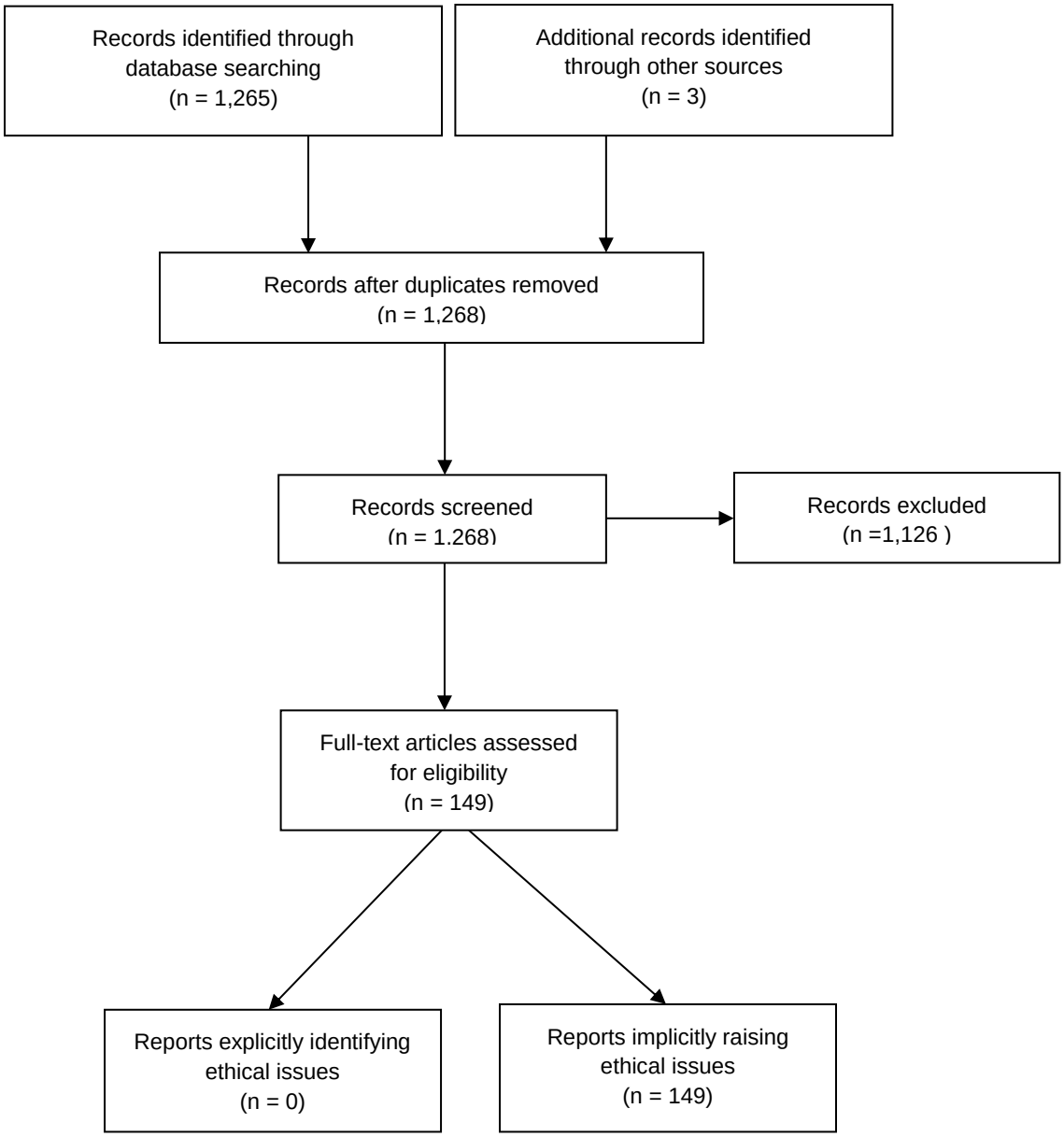
Sensitivity Analysis	Mild, AHI = 5 ICUR($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
Adherence rate, lower end of 95% CI	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 182.912 (0) 2,530,385 (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,085 (0.03) 9,681 (0.92) Dominated (0.05)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7.486 (0.79) Dominated (0.01) Dominated (0.19)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 17,132 (0.99)
Adherence rate for CPAP lower, 17%	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 175,448 (0) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) Ext. Dom (0.01) 8,243 (0.95) Dominated (0.04)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,207 (0.73) Dominated (0.04) 11,966,342 (0.24)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.01) Ext. Dom (0) Dominated (0) 16,981 (0.99)
Perfect adherence, MAD only	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 168,893 (0) Dominated (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,079 (0.02) 8,783 (0.93) Dominated (0.05)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,453 (0.79) Dominated (0.04) Dominated (0.17)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 16,965 (0.99)
RR mortality following cardiovascular event, 1	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 181,182 (0) 1,620,197 (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,045 (0.03) 9,545 (0.92) Dominated (0.05)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 7,635 (0.80) Dominated (0.03) Dominated (0.17)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.02) Dominated (0) Ext. Dom (0.00) 17,189 (0.98)
Effects of surgery on AHI based on lower bound of 95% CI	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 174,993 (0.00) Dominated (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,002 (0.03) 9,421 (0.97) Dominated (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,482 (0.89) Dominated (0.03) Dominated (0.08)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.03) Dominated (0) Ext. Dom (0.00) 20,159 (0.97)
Effects of surgery on blood	No Treatment	-ref- (1.00)	No	-ref- (0)	No	-ref- (0)	No	-ref- (0.02)

Sensitivity Analysis	Mild, AHI = 5 ICUR($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
pressure similar to MAD	PAP therapy MAD MMA ± GTA	Ext. Dom (0.00) 175,226 (0) Dominated (0)	Treatment PAP therapy MAD MMA ± GTA	8,193 (0.03) 9,346 (0.93) Dominated (0.04)	Treatment PAP therapy MAD MMA ± GTA	7,464 (0.80) Dominated (0.03) Dominated (0.18)	Treatment MAD PAP therapy MMA ± GTA	Dominated (0) Ext. Dom (0.00) 17,075 (0.98)
Effects of surgery on blood pressure similar to PAP therapy	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 175,735 (0) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,068 (0.03) 9,290 (0.93) Dominated (0.04)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,465 (0.80) Dominated (0.03) Dominated (0.17)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.02) Dominated (0) Ext. Dom (0.00) 17,115 (0.98)
8% rate of relapse from surgery, applied to the first year post-procedure	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 174,489 (0) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,133 (0.03) 9,247 (0.96) Dominated (0.01)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,481 (0.84) Dominated (0.04) Dominated (0.12)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.02) Dominated (0) Ext. Dom (0.00) 18,167 (0.98)
No additional mortality risk if treatment adherent despite remaining severe OSA (e.g., RR death = 1)	Not impacted				No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.00) 7,403 (0.04) Dominated (0.78) Dominated (0.19)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.00) Ext. Dom (0.12) Ext. Dom (0.00) 16,972 (0.88)
All patients prescribed CPAP under PAP therapy strategy	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0.00) 175,246 (0) 82,323,137 (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0.00) 8,042 (0.03) 9,552 (0.93) Dominated (0.05)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,449 (0.79) Dominated (0.03) Dominated (0.18)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.02) Dominated (0) Ext. Dom (0.00) 17,123 (0.98)
All patients prescribed APAP under PAP therapy	No Treatment PAP therapy	-ref- (1.00) Ext. Dom (0.00)	No Treatment PAP therapy	-ref- (0.00) 7,990 (0.27)	No Treatment	-ref- (0)	No Treatment	-ref- (0.01)

Sensitivity Analysis	Mild, AHI = 5 ICUR($/QALY)		Moderate, AHI = 15 ICUR ($/QALY)		Severe, AHI = 30 ICUR ($/QALY)		Severe, AHI = 60 ICUR ($/QALY)	
strategy	MAD MMA ± GTA	175,937 (0) 42,586,786 (0.00)	MAD MMA ± GTA	9,183 (0.93) Dominated (0.04)	PAP therapy MAD MMA ± GTA	7,492 (0.79) Dominated (0.03) Dominated (0.17)	MAD PAP therapy MMA ± GTA	Dominated (0) Ext. Dom (0.00) 16,938 (0.98)
Lifespan for PAP therapy, 5 years	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 174,765 (0) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8.066 (0.04) 8,701 (0.92) Dominated (0.04)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,571 (0.79) Dominated (0.03) Dominated (0.18)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.02) Dominated (0) Ext. Dom (0.00) 17,153 (0.98)
Lifespan for PAP therapy, 10 years	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. Dom (0) 174,414 (0) Dominated (0.00)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,971 (0.03) 10,120 (0.92) Dominated (0.05)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,396 (0.78) Dominated (0.03) Dominated (0.18)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 16,995 (0.98)
Lifespan for MAD, 10 years	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.95) 85,302 (0.05) Dominated (0) 27,530,989 (0.00)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.00) 3,973 (0.99) Dominated (0) Dominated (0.01)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0) Ext. Dom (0.04) 7,424 (0.78) Dominated (0.18)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 17,097 (0.99)
Cost of CT includes technical fee ($625)[191]	No Treatment PAP therapy MAD MMA ± GTA	-ref- (1.00) Ext. dom (0) 174,736 (0.00) 1.82 x10^{10} (0)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 8,034 (0.03) 9,629 (0.94) Dominated (0.04)	No Treatment PAP therapy MAD MMA ± GTA	-ref- (0) 7,429 (0.80) Dominated (0.04) Dominated (0.16)	No Treatment MAD PAP therapy MMA ± GTA	-ref- (0.01) Dominated (0) Ext. Dom (0.00) 17,641 (0.98)

AHI = Apnea–Hypopnea Index; CI = confidence interval; CPAP = continuous positive airway pressure; CT = computed tomography; Ext Dom = extendedly dominated; GTA = genial tubercle advancement; MAD = mandibular advancement device; MMA = maxillomandibular advancement; OSA = obstructive sleep apnea; PAP = positive airway pressure; QALY = quality-adjusted life-year.

Appendix 22. PRISMA Flow Diagram of Literature Search and Selection Process (Research Question 2)



Appendix 23: Potentially Relevant Reports (Research Question 2)

1. Experiences with CPAP treatment in patients with obstructive sleep apnea syndrome and obesity. Adv Physiother. 2012 Dec;14(4):166-74.
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Appendix 24: Data Abstraction Form (Research Question 3)

STUDY CHARACTERISTICS	
Ref ID	
First Author	
Publication Title	
Publication Year	
Quality	☐ Good ☐ Fair ☐ Poor
Country (Where Data Were generated)	
Data Collection Method	☐ Questionnaire ☐ Interview ☐ Focus group ☐ Observation ☐ Document review ☐ Other (specify):
Research Question	
Emergent Concepts	
OSA Intervention	
Sample Size	
Participant Characteristics	
Age	
Sex	
Mean Age	
Patient Comorbidities	
OSA Severity	
Experience With Treatment	
Study Characteristics	
Duration of Treatment	
Access to Treatment	
Bed Partners Included	
Setting	
Population Notes	

Appendix 25: Quality Assessment Instrument — Qualitative Studies (Research Question 3)

STUDY CHARACTERISTICS	
Ref ID	
First author	
Publication year	
1. Was ethics approval obtained?	□ Yes □ No □ Unclear Comments:
STUDY DESIGN	
2. Was the study design clearly stated and justified?	□ Yes □ No □ Unclear Comments:
RESEARCH QUESTIONS AND OBJECTIVES	
3. Are the research questions and/or objectives clearly stated?	□ Yes □ No □ Unclear Comments:
4. Are the research questions suited to qualitative inquiry?	□ Yes □ No □ Unclear Comments:
PARTICIPANTS AND SAMPLING	
5. Is the sampling strategy clearly described?	□ Yes □ No □ Unclear Comments:
6. Is the sampling strategy congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
7. Did sampling continue until data saturation was reached?	□ Yes □ No □ Unclear Comments:

DATA COLLECTION	
8. Are the data collection strategies described with sufficient detail?	□ Yes □ No □ Unclear Comments:
9. Are the data collection strategies congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
DATA ANALYSIS	
10. Are the data analysis strategies described with sufficient detail?	□ Yes □ No □ Unclear Comments:
11. Are the data analysis strategies congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
RESULTS	
12. Are the results supported by and consistent with the data?	□ Yes □ No □ Unclear Comments:
13. Is it clear how the themes and concepts were derived from the data?	□ Yes □ No □ Unclear Comments:
14. Are results rooted in participants' own perspectives?	□ Yes □ No □ Unclear Comments:
15. Has the diversity of perspective and content been explored?	□ Yes □ No □ Unclear Comments:

CONFIRMABILITY	
16. Is the role of the researcher clearly described?	□ Yes □ No □ Unclear Comments:
17. Have the assumptions and biases of the researcher been clearly described?	□ Yes □ No □ Unclear Comments:
18. Have the effects of the researcher throughout the study process been clearly described?	□ Yes □ No □ Unclear Comments:
TRANSFERABILITY	
19. Is the study setting described with sufficient detail?	□ Yes □ No □ Unclear Comments:
20. Are study participants described with sufficient detail?	□ Yes □ No □ Unclear Comments:
CREDIBILITY	
21. Which of the following techniques were used to enhance credibility of results?	☐ Member checking ☐ Peer debriefing ☐ Attention to negative cases ☐ Independent analysis by more than one researcher ☐ Reporting of verbatim data ☐ Other (specify):
22. Were the applied techniques to enhance credibility sufficient and appropriate?	□ Yes □ No □ Unclear Comments:

DEPENDABILITY	
23. Which of the following techniques were used to enhance dependability of results?	☐ Peer review ☐ Debriefing ☐ Audit trail ☐ Triangulation ☐ Other (specify):
24. Were the applied techniques to enhance dependability sufficient and appropriate?	□ Yes □ No □ Unclear Comments:

Appendix 26: Quality Assessment Instrument — Survey Studies (Research Question 3)

STUDY CHARACTERISTICS	
Ref ID	
First author	
Publication year	
1. Was ethics approval obtained?	□ Yes □ No □ Unclear Comments:
RESEARCH QUESTION AND STUDY DESIGN	
2. Are the research questions and/or objectives clearly stated?	□ Yes □ No □ Unclear Comments:
3. Are the research questions suitable for a cross-sectional design?	□ Yes □ No □ Unclear Comments:
PARTICIPANTS AND SAMPLING	
4. Is the sampling strategy clearly described?	□ Yes □ No □ Unclear Comments:
5. Is the sampling strategy congruent with the research questions and/or objectives?	□ Yes □ No □ Unclear Comments:
6. Is the sample of participants representative of the target sample, or the population to which the findings will be generalized?	□ Yes □ No □ Unclear Comments:
7. Could the way the sample was obtained introduce selection bias?	□ Yes □ No □ Unclear Comments:

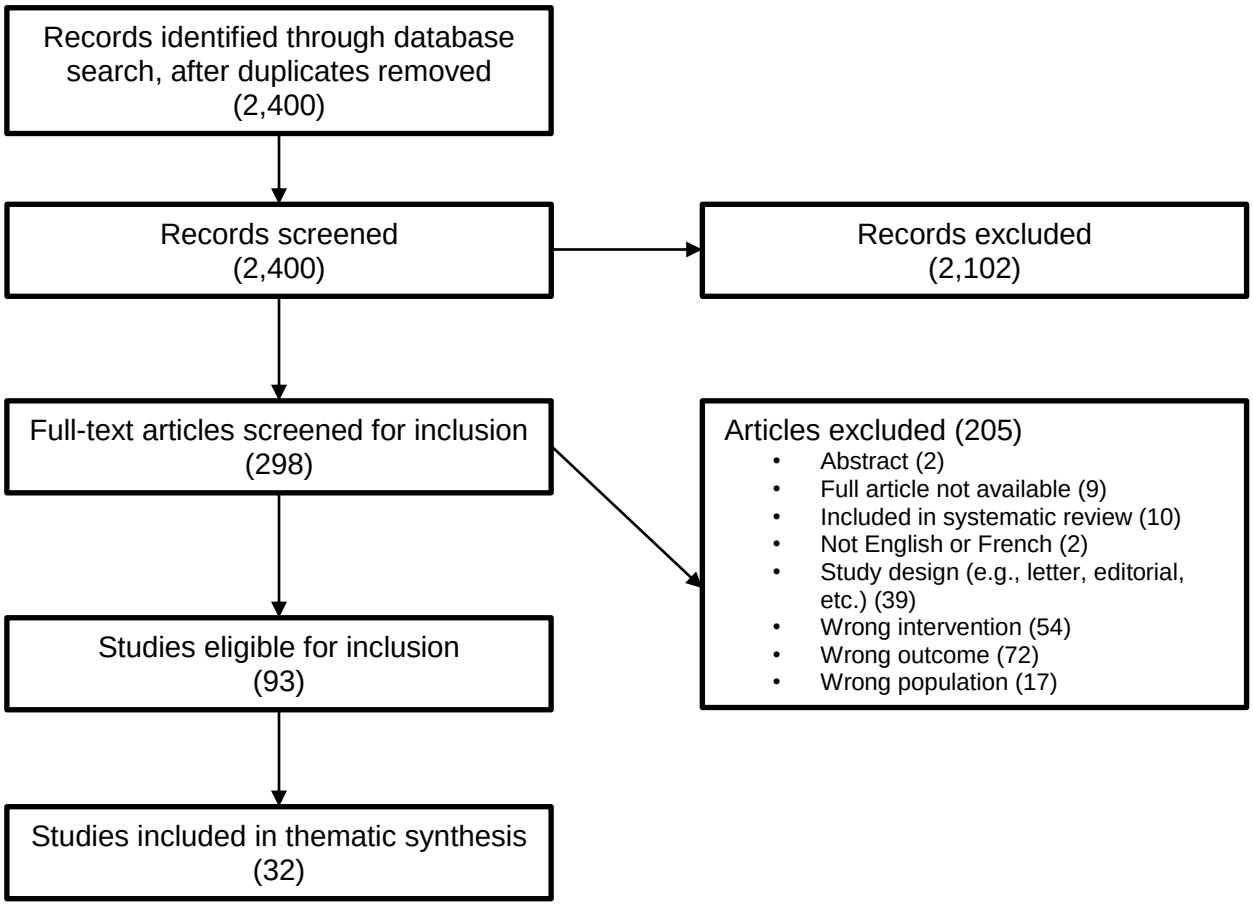
8. Was a sufficient sample size calculation provided?	□ Yes □ No □ Unclear Comments:
DATA COLLECTION	
9. Was a pilot test of data collection methods conducted?	□ Yes □ No □ Unclear Comments:
10. Was the study questionnaire valid?	□ Yes □ No □ Unclear Comments:
11. Was the study questionnaire reliable?	□ Yes □ No □ Unclear Comments:
DATA ANALYSIS	
12. Were the data analysis strategies appropriate for the type of data collected?	□ Yes □ No □ Unclear Comments:
13. Were all analyses planned a priori?	□ Yes □ No □ Unclear Comments:
RESULTS	
14. Was a satisfactory response rate achieved?	□ Yes □ No □ Unclear Comments:
15. Were all significant and non-significant quantitative results been reported?	□ Yes □ No □ Unclear Comments:

16. Were all qualitative results, resulting from open-ended questions, summarized and reported?	□ Yes □ No □ Unclear Comments:
DISCUSSION AND CONCLUSIONS	
17. Have the researchers drawn an appropriate link between the data and their conclusions?	□ Yes □ No □ Unclear Comments:
18. Have all potential biases been identified and discussed?	□ Yes □ No □ Unclear Comments:

Appendix 27: Quality Assessment Instrument — Systematic Review (Research Question 3)

JBI Checklist	
1. Is the review question clearly and explicitly stated?	□ Yes □ No □ Unclear □ Not applicable
2. Were the inclusion criteria appropriate for the review question?	□ Yes □ No □ Unclear □ Not applicable
3. Was the search strategy appropriate?	□ Yes □ No □ Unclear □ Not applicable
4. Were the sources of studies adequate?	□ Yes □ No □ Unclear □ Not applicable
5. Were the criteria for appraising studies appropriate?	□ Yes □ No □ Unclear □ Not applicable
6. Was critical appraisal conducted by two or more reviewers independently?	□ Yes □ No □ Unclear □ Not applicable
7. Were there methods to minimize errors in data extraction?	□ Yes □ No □ Unclear □ Not applicable
8. Were the methods used to combine studies appropriate?	□ Yes □ No □ Unclear □ Not applicable
9. Was the likelihood of publication bias assessed?	□ Yes □ No □ Unclear □ Not applicable
10. Were recommendations for policy and/or practice supported by the reported data?	□ Yes □ No □ Unclear □ Not applicable
11. Were the specific directives for new research appropriate?	□ Yes □ No □ Unclear □ Not applicable

Appendix 28: Selection of Included Studies (Research Question 3)



Appendix 29: List of Included Studies (Research Question 3)

Almeida FR, Henrich N, Marra C, Lynd LD, Lowe AA, Tsuda H, et al. Patient preferences and experiences of CPAP and oral appliances for the treatment of obstructive sleep apnea: a qualitative analysis. Sleep Breath. 2013 May;17(2):659-66.

Bakker JP, O'Keeffe KM, Neill AM, Campbell AJ. Continuous positive airway pressure treatment for obstructive sleep apnoea: Māori, Pacific and New Zealand European experiences. J Prim Health Care. 2014;6(3):221-8.

Baron KG, Gunn HE, Czajkowski LA, Smith TW, Jones CR. Spousal involvement in CPAP: does pressure help? J Clin Sleep Med. 2012 Apr 15;8(2):147-53.

Bates CJ, McDonald JP. Patients' and sleeping partners' experience of treatment for sleep-related breathing disorders with a mandibular repositioning splint. Br Dent J. 2006 Jan 28;200(2):95-101.

Bignold JJ, Deans-Costi G, Goldsworthy MR, Robertson CA, McEvoy D, Catcheside PG, et al. Poor long-term patient compliance with the tennis ball technique for treating positional obstructive sleep apnea. J Clin Sleep Med. 2009 Oct 15;5(5):428-30.

Bishop B, Verrett R, Girvan T. A randomized crossover study comparing two mandibular repositioning appliances for treatment of obstructive sleep apnea. Sleep Breath. 2014 Mar;18(1):125-31.

Broström A, Fridlund B, Ulander M, Sunnergren O, Svanborg E, Nilsen P. A mixed method evaluation of a group-based educational programme for CPAP use in patients with obstructive sleep apnea. J Eval Clin Pract. 2013 Feb;19(1):173-84.

Broström A, Johansson P, Strömberg A, Albers J, Martensson J, Svanborg E. Obstructive sleep apnoea syndrome--patients' perceptions of their sleep and its effects on their life situation. J Adv Nurs. 2007 Feb;57(3):318-27.

Butterfield KJ, Marks PL, McLean L, Newton J. Quality of life assessment after maxillomandibular advancement surgery for obstructive sleep apnea. J Oral Maxillofac Surg. 2016 Jun;74(6):1228-37.

Cohen-Levy J, Petelle B, Vieille E, Dumitrache M, Fleury B. Changes in facial profile after maxillomandibular advancement surgery for obstructive sleep apnea syndrome. Int Orthod. 2013 Mar;11(1):71-92.

Dickerson SS, Obeidat R, Dean G, Aquilina A, Brock ET, Smith P, et al. Development and usability testing of a self-management intervention to support individuals with obstructive sleep apnea in accommodating to CPAP treatment. Heart Lung. 2013 Sep;42(5):346-52.

Elfström M, Karlsson S, Nilsen P, Fridlund B, Svanborg E, Brostrom A. Decisive situations affecting partners' support to continuous positive airway pressure-treated patients with obstructive sleep apnea syndrome: a critical incident technique analysis of the initial treatment phase. J Cardiovasc Nurs. 2012 May;27(3):228-39.

Fung CH, Igodan U, Alessi C, Martin JL, Dzierzewski JM, Josephson K, et al. Human factors/usability barriers to home medical devices among individuals with disabling conditions: in-depth interviews with positive airway pressure device users. Disabil Health J. 2015 Jan;8(1):86-92.

Fung CH, Martin JL, Igodan U, Jouldjian S, Alessi C. The association between difficulty using positive airway pressure equipment and adherence to therapy: a pilot study. Sleep Breath. 2013 May;17(2):853-9.

Gauthier L, Laberge L, Beaudry M, Laforte M, Rompre PH, Lavigne GJ. Efficacy of two mandibular advancement appliances in the management of snoring and mild-moderate sleep apnea: a cross-over randomized study. Sleep Med. 2009 Mar;10(3):329-36.

Goodday RH, Bourque SE, Edwards PB. Objective and subjective outcomes following maxillomandibular advancement surgery for treatment of patients with extremely severe obstructive sleep apnea (Apnea–Hypopnea Index > 100). J Oral Maxillofac Surg. 2016 Mar;74(3):583-9.

Henry D, Rosenthal L. "Listening for his breath:" the significance of gender and partner reporting on the diagnosis, management, and treatment of obstructive sleep apnea. Soc Sci Med. 2013 Feb;79:48-56.

Hu ST, Yu CC, Lee PS, Tsao LI. Life experiences among obstructive sleep apnoea patients receiving continuous positive airway pressure therapy. J Clin Nurs. 2014 Jan;23(1-2):268-78.

Igelström H, Martin C, Emtner M, Lindberg E, Asenlöf P. Physical activity in sleep apnea and obesity-personal incentives, challenges, and facilitators for success. Behav Sleep Med. 2012;10(2):122-37.

Islam S, Aleem F, Ormiston IW. Subjective assessment of facial aesthetics after maxillofacial orthognathic surgery for obstructive sleep apnoea. Br J Oral Maxillofac Surg. 2015 Mar;53(3):235-8.

Luyster FS, Dunbar-Jacob J, Aloia MS, Martire LM, Buysse DJ, Strollo PJ. Patient and partner experiences with obstructive sleep apnea and CPAP treatment: a qualitative analysis. Behav Sleep Med. 2016 Jan;14(1):67-84.

Nolan GM, Ryan S, O'Connor TM, McNicholas WT. Comparison of three auto-adjusting positive pressure devices in patients with sleep apnoea. Eur Respir J. 2006 Jul;28(1):159-64.

Rodgers B. Breaking through limbo: experiences of adults living with obstructive sleep apnea. Behav Sleep Med. 2014;12(3):183-97.

Shoukry G, Wong K, Bartlett D, Saini B. Treatment experience of people with obstructive sleep apnoea seeking continuous positive airways pressure device provision through community pharmacies: a role for pharmacists? Int J Pharm Pract. 2011 Oct;19(5):318-27.

Sporndly-Nees S, Igelstrom H, Lindberg E, Martin C, Asenlof P. Facilitators and barriers for eating behaviour changes in obstructive sleep apnoea and obesity - a qualitative content analysis. Disabil Rehabil. 2014;36(1):74-81.

Stalkrantz A, Brostrom A, Wiberg J, Svanborg E, Malm D. Everyday life for the spouses of patients with untreated OSA syndrome. Scand J Caring Sci. 2012 Jun;26(2):324-32.

Tegelberg Å, Nohlert E, Bergman LE, Andrén A. Bed partners' and patients' experiences after treatment of obstructive sleep apnoea with an oral appliance. Swed Dent J. 2012;36(1):35-44.

Thickett EM, Hirani S, Williams A, Hodgkins J. A prospective evaluation assessing the effectiveness of the 'Dynamax' mandibular appliance in the management of obstructive sleep apnoea. Surg. 2009 Feb;7(1):14-7.

Ward K, Hoare KJ, Gott M. What is known about the experiences of using CPAP for OSA from the users' perspective? A systematic integrative literature review. Sleep Med Rev. 2014 Aug;18(4):357-66.

Willman M, Igelström H, Martin C, Asenlöf P. Experiences with CPAP treatment in patients with obstructive sleep apnea syndrome and obesity. Adv Physiother. 2012;14(4):166-74.

Appendix 30: List of Remaining Eligible Studies (Research Question 3)

Acar M, Kaya C, Catli T, Hanci D, Bolluk O, Aydin Y. Effects of nasal continuous positive airway pressure therapy on partners' sexual lives. Eur Arch Otorhinolaryngol. 2016 Jan;273(1):133-7.

Bachour A, Vitikainen P, Virkkula P, Maasilta P. CPAP interface: satisfaction and side effects. Sleep Breath. 2013 May;17(2):667-72.

Bachour P, Bachour A, Kauppi P, Maasilta P, Makitie A, Palotie T. Oral appliance in sleep apnea treatment: respiratory and clinical effects and long-term adherence. Sleep Breath. 2016 May;20(2):805-12.

Balachandran JS, Yu X, Wroblewski K, Mokhlesi B. A brief survey of patients' first impression after CPAP titration predicts future CPAP adherence: a pilot study. J Clin Sleep Med. 2013 Mar 15;9(3):199-205.

Baltzan MA, Elkholi O, Wolkove N. Evidence of interrelated side effects with reduced compliance in patients treated with nasal continuous positive airway pressure. Sleep Med. 2009 Feb;10(2):198-205.

Baron KG, Smith TW, Czajkowski LA, Gunn HE, Jones CR. Relationship quality and CPAP adherence in patients with obstructive sleep apnea. Behav Sleep Med. 2009;7(1):22-36.

Baron KG, Smith TW, Berg CA, Czajkowski LA, Gunn H, Jones CR. Spousal involvement in CPAP adherence among patients with obstructive sleep apnea. Sleep Breath. 2011 Sep;15(3):525-34.

Boyaci H, Gacar K, Baris SA, Basyigit I, Yildiz F. Positive airway pressure device compliance of the patients with obstructive sleep apnea syndrome. Adv Clin Exp Med. 2013 Nov;22(6):809-15.

Boyd SB, Walters AS, Waite P, Harding SM, Song Y. Long-term effectiveness and safety of maxillomandibular advancement for treatment of obstructive sleep apnea. J Clin Sleep Med. 2015 Jul;11(7):699-708.

Campbell T, Pengo MF, Steier J. Patients' preference of established and emerging treatment options for obstructive sleep apnoea. J Thorac Dis. 2015 May;7(5):938-42.

Chai-Coetzer CL, Pathinathan A, Smith BJ. Continuous positive airway pressure delivery interfaces for obstructive sleep apnoea. Cochrane Database Syst Rev. 2006;(4):CD005308. Assessed as up-to-date: 2011 Jan 14.

Chai-Coetzer CL, Antic NA, Rowland LS, Reed RL, Esterman A, Catcheside PG, et al. Primary care vs specialist sleep center management of obstructive sleep apnea and daytime sleepiness and quality of life: a randomized trial. JAMA. 2013 Mar 13;309(10):997-1004.

Cheng YL, Hsu DY, Lee HC, Bien MY. Clinical verification of patients with obstructive sleep apnea provided with a customized cushion for continuous positive airway pressure. J Prosthet Dent. 2015 Jan;113(1):29-34.

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Appendix 31: List of Excluded Studies, With Reasons (Research Question 3)

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Appendix 32: Characteristics of Included Studies (Research Question 3)

First Author, Publication Year, Country of Origin[1]	Study Objectives	Study Design	OSA Intervention	Sample Size	Data Collection Methods	Perspectives of Bed Partners Included
Almeida 2013, Canada[209]	The aim of this study is to better understand patients' perspectives and preferences about treatment with CPAP and OA devices for OSA.	Qualitative description	CPAP and OA	22	Focus groups	Yes — as reported by patients
Bakker 2014, New Zealand[210]	This study aimed to explore Māori, Pacific, and NZ European patients' experience of CPAP treatment.	Qualitative description	CPAP	18	Focus groups	No
Bates 2006, United Kingdom[223]	To determine in detail the complications associated with the use of MRS to treat sleep-related breathing disorders.	Survey	MAD	121	Questionnaire	Yes
Bignold 2009, Australia[112]	The purpose of this study was to investigate long-term patient adherence with TBT.	Survey	Positional therapy — TBT	108	Questionnaire	No
Bishop 2014, United States[227]	The purpose of this study was to determine whether treatment outcomes vary according to the design of the MRA.	RCT with survey	MAD	18	Questionnaire	No
Broström 2013, Sweden[230]	The aim was to describe adherence to CPAP treatment and knowledge about OSA/CPAP, as well as OSA patients' perceptions of participating in a group-based program using problem-based learning for CPAP initiation.	Sequential explanatory mixed methods approach	CPAP	25	Questionnaire and interviews	Yes — as reported by patients

First Author, Publication Year, Country of Origin[1]	Study Objectives	Study Design	OSA Intervention	Sample Size	Data Collection Methods	Perspectives of Bed Partners Included
Broström 2007, Sweden[211]	This paper reports a descriptive study of how untreated patients with OSAS perceived their sleep situation and how the syndrome affected their life situation.	Qualitative description	Untreated	20	Interview	Yes
Butterfield 2016, Canada[232]	The present study was undertaken to investigate the effect of MMA on patient perceived QoL in OSA.	Cross-sectional	MMA	22	Questionnaire	Yes
Cohen-Levy 2013, France[98]	The aim of this study was to assess changes in the profile of adult male patients treated for OSAS with MMA surgery and to measure patients' perception of changes compared with that of different panels.	Survey	MMA	15	Questionnaire	No
Dickerson 2013, United States[212]	Development and usability testing of a self-management intervention to promote CPAP adherence.	Qualitative description	CPAP	10	Interview	No
Elfström 2012, Sweden[213]	The aim of this study was to explore and describe decisive situations affecting partners' support to patients with OSAS and how the partners manage these situations in the initial phase of CPAP treatment.	Qualitative description	CPAP	25	Interview	Yes — study included only spouses
El-Solh 2010, US[229]	To determine the short-term PAP adherence rates and to identify non–mask-related risk factors associated with 30-day nonadherence to PAP in a population of veterans with OSA and PTSD.	Retrospective	CPAP	148 PTSD patients; 148 Control group	Interview and chart review	No

First Author, Publication Year, Country of Origin[1]	Study Objectives	Study Design	OSA Intervention	Sample Size	Data Collection Methods	Perspectives of Bed Partners Included
Fung 2015, United States[214]	The purpose of this study was to explore in detail the types of difficulties experienced by patients with physical or sensory impairments who use PAP devices, as an initial step in designing a questionnaire to survey users about this topic.	Qualitative description	PAP	9	Interview	No
Fung 2013, United States[231]	This pilot project aims to determine whether perceived difficulty with the mechanics of using PAP equipment is associated with nonadherence.	Mixed methods	CPAP	148	Questionnaire	No
Gauthier 2009, Canada[228]	The aim of this study is to assess the efficacy of and subject satisfaction with two mandibular advancement appliances in the management of OSAS.	RCT with survey	MAD	16	Questionnaire	Yes
Glazer Baron 2012, United States[224]	Aims of this observational study were to assess perceptions of spousal involvement and evaluate associations between involvement and adherence.	Survey	CPAP	23	Questionnaire	Yes — as reported by patients
Goodday 2016, Canada[233]	The purpose of this study was to evaluate objective and subjective treatment outcomes after MMA surgery for the treatment of OSAS in patients with a preoperative AHI score higher than 100.	Cohort study	MMA	13	Questionnaire	No

First Author, Publication Year, Country of Origin[1]	Study Objectives	Study Design	OSA Intervention	Sample Size	Data Collection Methods	Perspectives of Bed Partners Included
Henry 2013, United States[197]	This cross-sectional, exploratory, mixed methods study […] was done in 2006 to illuminate the significance of gender and partner-reporting in shaping the lay diagnosis, management, and treatment of OSA.	Mixed methods	CPAP	12 patients and 12 partners	Interview (qualitative and quantitative)	Yes
Hu 2014, Taiwan[221]	To generate a descriptive theoretical framework for experiences among OSA patients undergoing CPAP therapy.	Ground theory	CPAP	22	Interview	No
Igelström 2012, Sweden[215]	The purpose of this study was to explore aspects of engagement in physical activity in persons with OSA and who are overweight.	Qualitative description	Lifestyle modification — physical activity	15	Interview	No
Islam 2014, United Kingdom[89]	We aimed to evaluate the subjective perception of facial appearance by patients after maxillofacial surgery for OSA, and explored the possible correlation between satisfaction and surgical outcome.	Survey	MMA	26	Questionnaire	No
Luyster 2016, United States[216]	This qualitative research study explored patients' and partners' experiences of CPAP and facilitators and barriers to CPAP use, and elicited suggestions for a first-time CPAP user program.	Qualitative description	CPAP	8 focus groups; 15 patients and 12 partners	Focus groups	Yes
Moreira 2008, UK[220]	This paper reports on how persons diagnosed with a chronic condition, OSAS, use the most widely prescribed therapy for this condition, CPAP, at home to manage their illness.	Qualitative content analysis	CPAP	One website; 1,500 messages	Qualitative analysis on message board threads that had more than 2 members responding to the initial message	NR

First Author, Publication Year, Country of Origin[1]	Study Objectives	Study Design	OSA Intervention	Sample Size	Data Collection Methods	Perspectives of Bed Partners Included
Nolan 2006, Ireland[198]	The present study was designed to compare the effect of three APAP devices on adherence, QoL, and side effects of treatment in patients with OSAS, who were already established on fixed-pressure CPAP therapy.	RCT with survey	APAP	27	Questionnaire	No
Rodgers 2014, United States[199]	This grounded theory study was focused on the experiences of a diverse group of 82 adults who were at various points in the process of obtaining a diagnosis and living with OSA.	Grounded theory	PAP	82	Interview	No
Shoukry 2011, Australia[217]	This study aimed to explore the unique experiences of people with OSA who source their treatment through community pharmacies.	Qualitative description	CPAP	20	Interview	Yes
Sporndly-Nees 2014, Sweden[218]	The aim of this study was to identify personal conceptions of prerequisites for eating behaviour change.	Qualitative description	Lifestyle modification — diet and weight loss	15	Interview	No
Stalkrantz 2012, Sweden[222]	The aim of this study was to generate a theoretical model describing concerns for spouses of patients with untreated OSAS and how they manage these concerns in their everyday life.	Grounded theory	Untreated	12 partners	Interview	Yes — study included only spouses
Tegelberg 2012, Sweden[225]	The purpose of the study was to evaluate bed partners' and patients' self-reports of general well-being, physical strength, and mental energy after treatment for OSA with a mandibular advancement OA.	Survey	OA	134 patients, 85 partners	Questionnaire	Yes

First Author, Publication Year, Country of Origin[1]	Study Objectives	Study Design	OSA Intervention	Sample Size	Data Collection Methods	Perspectives of Bed Partners Included
Thickett 2009, United Kingdom[226]	The aim of this study was to assess patients' satisfaction with, and the effectiveness of, the Dynamax appliance for the treatment of mild-to-moderate OSA.	Survey	OA	35	Questionnaire	Yes
Ward 2014, New Zealand[a,207]	To synthesize international evidence regarding personal experiences using CPAP for OSA.	Integrative review	CPAP	22 papers including 5,760 patients and 21 partners	Systematic review	Yes — for some studies
Willman 2012, Sweden[219]	The purpose of this study was to describe patients' experiences of CPAP treatment in obese individuals with moderate-to-severe OSAS.	Qualitative description	CPAP	15	Interview	No

APAP = autotitrating positive airway pressure; CPAP = continuous positive airway pressure; MAD = mandibular advancement device; MMA = maxillomandibular advancement; MRA = mandibular repositioning appliance; MRS = mandibular repositioning splints; OA = oral appliance; OSA = obstructive sleep apnea; OSAS = obstructive sleep apnea syndrome; PAP = positive airway pressure; PTSD = post-traumatic stress disorder; QoL = quality of life; RCT = randomized controlled trial; TBT = tennis ball technique.

[a] First author is from New Zealand.

Appendix 33: Characteristics of the Included Study Participants (Research Question 3)

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Almeida 2013, Canada[209]	59% male; 41% female	60[a] (range 36 to 85)	NR	Baseline ESS: 8.1 (CPAP), 9.7 (OA); baseline AHI: 29.1 (CPAP), 17.8 (OA)	2.4 and 8.3 years of experience with CPAP and OA, respectively; some patients had experience with both devices	yes	Married or living with someone = 73%; dating = 5%; single = 18%; NR = 5%	NR
Bakker 2014, New Zealand[210]	61% male; 39% female	Māori = 39.3 (6.2); Pacific Peoples = 43.5 (11.2); NZ European = 58.1 (8.5)	Māori, Pacific Peoples, NZ European	End-trial mean ESS: Māori = 5.8 (6.4); Pacific Peoples = 5.0 (2.0); NZ Europeans = 7.0 (3.8)	Mean days of use at time of focus group: Māori = 90.0 (87.9); Pacific Peoples = 198.0 (27.7); NZ Europeans = 116.4 (30.9)	Yes	NR	NR
Bates 2006, United Kingdom[223]	68% male; 32% female	Responders: 51.4 Non-responders: 47.2		Mean AHI Responders: 17.9 Non-responders: 14.0 Mean ESS Responders 9.7 non-responders 8.7	questionnaire: 3 months after provision of the appliance.	Yes	NR	NR
Bignold 2009, Australia[112]	87% male; 13% female	59.6 ± 12.1	NR	AHI, events/h Respondents: 29.6 ± 13.6 Non-respondents: 36.8 ± 45.6	Follow-up (mean ± SD) 2.5 ± 1.0 years	Yes	NR	NR

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Bishop 2014, United States[227]	94% male; 6% female	Mean age 47.4	NR	ESS Mild Appliance K 6.8 ± 1.2 Appliance T 6.7 ± 1.2 Moderate Appliance K 9.0 ± 1.6 Appliance T 5.6 ± 1.6 Severe Appliance K 9.5 ± 2.7 Appliance T 17.5 ± 2.7	3 to 4 weeks	No	NR	NR
Broström 2013, Sweden[230]	54% male; 44% female	mean age 59.6 years, (range 49–65)	NR	Reported for each individual	6 months	Yes	18 married 5 unmarried 2 divorced	NR
Broström 2007, Sweden[211]	65% male; 35% female	Age mean (range) (years) Men: 53 (33 to 72) Women: 60 (54 to 66)	NR	AHI mean (range) Men: 45 (30 to 94) Women: 39 (33 to 45)	N/A	No	Marital status Married: 8 men, 4 women Unmarried: 3 men, 1 woman Divorced: 1 man, 1 woman Widowed: 1 man, 1 woman	Other diagnosis: hypertension, ischemic heart disease, myocardial infarction, chronic heart failure, stroke

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Butterfield 2016, Canada[232]	86% male; 14% female	45.9 (11.6) at the time of the completion of questionnaire	NR	NR	4 weeks post-operative	Yes	NR	NR
Cohen-Levy 2013, France[98]	100% male	42 (20 to 59)	NR	AHI baseline: 51.07 ± 15.21 After MMA 10.3 ± 7.24 (P 7.2 × 10^{-4})	3 months	Yes	NR	NR
Dickerson 2013, United States[212]	40% male; 60% female	42.7 (13.4), 24 to 61	30% were African-American and 70% white	Sleep apnea severity (self-identified) Moderate 4 (40%) Severe 6 (60%)	Length of time using CPAP: Just started: 40% 6 months: 50% 3 years: 10%	Yes	Marital status: Single: 2 (20%) Divorced: 2 (20%) Married: 6 (60%)	One patient had a new cancer diagnosis
Elfström 2012, Sweden[213]	28% male; 72% female	NR — age ranges for individuals	NR	Mean AHI = 40 (17 to 75) Mean ESS = 10 (2 to 18)	4 to 21 weeks	Yes	20 married 5 cohabitant	CVD, COPD, RA, depression
El-Solh 2010, USA[229]	100% male	PTSD: 59.7 ± 7.9; Control 61.5 ± 8.3	PTSD: Caucasian (89%), African-American (7%), Hispanic (3%) Control: Caucasian (85%), African-American (12%), Hispanic (1%)	ESS: PTSD 13.0 ± 5.7; control 14.2 ± 6.4	NR	Yes	NR	Hypertension, cardiac diseases, diabetes mellitus, depression, alcohol or substance abuse

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Fung 2015, United States[214]	89% male; 11% female	NR	NR	NR	NR	Yes	3/9 (33%) lived alone	Tremor (e.g., Parkinson disease), weakness (e.g., carpal tunnel syndrome, stroke), decreased range of motion (e.g., rotator cuff injury, osteoarthritis, rheumatoid arthritis), loss of digits (e.g., amputation), numbness (e.g., diabetic neuropathy), and visual impairment (e.g., impaired depth perception).
Fung 2013, United States[231]	99% male; 1% female	66.7 years (SD 7.0)	72% of sample was non-Hispanic white	NR	NR	Yes	NR	NR
Gauthier 2009, Canada[228]	69% male; 31% female	47.9 (SD 1.6)	NR	NR	NR	Yes	NR	NR
Glazer Baron 2012, United States[224]	100% male	47.4 (11.8) years	White: 22 (96) Asian/Pacific Islander: 1 (4)	AHI 36.5 (26.4) events/h	3 months	Yes	100% married	Insomnia, n = 2; periodic limb movements and/or restless leg syndrome, n = 8

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Goodday 2016, Canada[233]	85% male; 15% female	38.6 years (SD, 8.4 years)	NR	Baseline: AHI 117.9 SD 9.2 After surgery: AHI 16.1 SD (26.2)	Mean 21 months post-op	Yes	NR	NR
Henry 2013, United States[197]	Patients: 58.3% men	Median age of patients: 49; of spouses: 48	92% Anglo (non-Hispanic); 8% Hispanic	Baseline: AHI range 8 to 135	NR	Yes	100% married	GERD, arthritis, high cholesterol, fibromyalgia, rhinitis, osteoporosis, gout, hypertension, diabetes, psoriasis, anemia, back pain, glaucoma
Hu 2014, Taiwan[221]	82% male; 18% female	Age range between 37 and 68 years	NR	Baseline: AHI mean 60 3/hour	NR	Yes	NR	Hypertension
Igelström 2012, Sweden[215]	53% male; 47% female	Mean 62 SD (8.5)	NR	NR	12 months	Yes	Marital status: Married/cohabitant, n = 9 Single, n = 6	Overweight
Islam 2014, United Kingdom[89]	92% male; 8% female	Mean 45 SD (7)	NR	NR	6 months post-op	Yes	NR	NR
Luyster 2016, United States[216]	Patients = 64% male; partners = 27.2% male	Patients = 55.6 (10.3); Partners = 53.5 (16.6)	"Most were Caucasian"	Self-reported severity: mild (28.6%), moderate (50%), severe (21.4%)	NR	NR	12/15 participants were married	Hypertension and/or diabetes; partners also had some comorbidities

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Moreira 2008, UK[220]	NR	NR	NR	NR	NR	Yes	NR	NR
Nolan 2006, Ireland[198]	92% male; 8% female	Mean 53 range (48 to 67)	NR	Baseline: median (interquartile range) of 53 (37 to 85) Post treatment: median (IQR) AHI: 48 (29–76) median (IQR) ESS score: 15 (9–19)	NR	Yes	NR	NR
Rodgers 2014, United States[199]	65% male; 35% female	Mean 52 (range: 21 to 82)	The majority (n = 78) self-identified as “white.” Two identified as Hispanic, one Asian, and one Middle Eastern.	NR	NR	Yes	NR	NR

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Shoukry 2011, Australia[217]	75% male; 25% female	Range 20 to 75 (mean 57.5 SD ± 14.8)	Observed ethnicity • White/ European, n = 17 • Southeast Asian, n = 1 • Middle Eastern, n = 2	NR	NR	Yes	70% had a bed-sharing partner	Atrial fibrillation, double bypass, triple bypass, heart transplant, asthma, diabetes, obesity, insomnia, asphyxia, osteoarthritis, nasal surgery, depression, fatty liver, Hashimoto's, menopause, prostate cancer — no particular pattern between comorbidities and CPAP use
Sporndly-Nees 2014, Sweden[218]	53% male; 47% female	Mean_SD 56.8_10.2 (Range) 41 to 71	NR	NR	NR	Yes	Single: 6 (40%) Cohabiting/married: 9 (60%)	Obesity
Stalkrantz 2012, Sweden[222]	Partners = 25% male; patients = 75% male	Partner range = 25 to 70; patient range = 31 to 75	NR	Baseline AHI: range 19 to 72	NA[c]	NA[c]	100% married	Patients = hypertension, depression; spouses = rheumatoid arthritis, slipped disc, tinnitus, insomnia, sleep apnea, asthma, migraine, myasthenia gravis

First Author, Publication year, Country of Origin[1]	Sex	Mean Age in Years (SD)	Ethnicity	OSA Severity	Duration of Treatment	Prior Experience With Treatment	Relationship Status	Comorbidities
Tegelberg 2012, Sweden[225]	74% male patients; 18% male bed partners	Patients = 57.6 (10.1); bed partners = 55.8 (9.6)	NR	Patients = 57.6 (10.1); bed partners = 55.8 (9.6)	6 months to year	Yes	Sample included 134 patients, 85 bed partners	NR
Thickett 2009, United Kingdom[226]	85% male; 15% female	51 (range: 29 to 71)	NR	Reported as mild-to-moderate	2 months	Yes	NR	NR
Ward 2014, New Zealand[a,207]	83% male; 17% female	Range: 30 to 75	NR	Moderate to severe (3 studies did not report severity)	Variable	Yes	NR	NR
Willman 2012, Sweden[219]	53% male; 47% female	Mean 56.8 SD (10) Range: 41 to 71	NR	Moderate or severe	2 months to 10 years	yes	9 were married and 6 lived alone	All were obese; 12 also had cardiovascular conditions associated with OSA, such as hypertension or diabetes

AHI = Apnea–Hypopnea Index; APAP = autotitrating positive airway pressure; COPD = chronic obstructive pulmonary disease; CPAP = continuous positive airway pressure; CVD = cardiovascular disease; ESS = Epworth Sleepiness Scale; GERD = gastroesophageal reflux disease; MAD = mandibular advancement device; MMA = maxillomandibular advancement; NA = not applicable; NR = not reported; NZ = New Zealand; OA = oral appliance; OSA = obstructive sleep apnea; PAP = positive airway pressure; PTSD = post-traumatic stress disorder; QoL = quality of life; SD = standard deviation.

[a] Approximation as reported by the study author.

[b] First author is from New Zealand.

[c] Population was untreated, and focused on the experiences of caregivers.

Appendix 34: Critical Appraisal of the Included Studies (Research Question 3)

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
Qualitative Studies		
Almeida 2013,[209] qualitative description, focus groups	• Research objectives and questions were clearly defined. • The research objectives were congruent with the focus group design, and the sampling strategy was congruent with the objectives. • The focus groups are likely to be representative of the population to which the results will be generalized (with the exception of the demographic information listed in the limitations); patients were recruited from a representative clinic. • Data analysis strategies were appropriate for the type of data collected, and were planned a priori. Exemplary quotes, themes and subthemes were provided. • The researchers have drawn an appropriate link between data and conclusions.	• How the questions for the focus groups were developed is uncertain. • The study participants are not clearly described; race or ethnicity of participants was not described, nor was how many patients had experience with both CPAP and OA. • For consistency, it would have been beneficial to conduct a one-to-one interview with an OA user, in addition to the one-to-one interview with the CPAP user. • No techniques described to enhance dependability. • It is uncertain which data analysis strategies were used to identify the common themes.
Bakker 2014,[210] qualitative description, focus groups	• Researchers clearly describe methods to be culturally appropriate, including conducting focus groups at appropriate locations and following culturally appropriate formats. • Member checking of transcripts from the focus groups and verbatim quotes were used to enhance results. • Results are consistent with data and rooted in participants' perspectives. • Data collection strategies are congruent with the research question.	• Justification of study design (focus groups) was not provided. • Sampling strategy is not clearly reported, and it is uncertain how the list of eligible patients was obtained and how patients were recruited from their primary care physicians. • Unclear if data collection and sampling continued until data saturation was reached. • No techniques described to enhance dependability.
Broström 2013,[230] sequential explanatory mixed methods approach, questionnaire and interviews	• Sampling strategy was well defined and congruent with research questions. Maximum variation sampling was used to collect a variety of experiences. • Data collection and analysis strategies were well described and congruent with research questions. Data collection continued until saturation. • Interview questions were provided.	• Strategies to enhance credibility, in addition to verbatim data, were not described. • Mixed method triangulation was used to compare and corroborate the quantitative and qualitative parts of the study; however, this was not well explored in the results or discussion of the report.

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
	• Results are well rooted in participant perspectives, as evidenced with exemplary quotes, and a diversity of perspectives was sought as evidenced by varied patient characteristics. • Academic and clinical backgrounds of the investigators were reported.	
Broström 2007,[211] qualitative description, interviews	• Research objectives were clearly stated and were suitable to qualitative inquiry. • Interview questions were provided. • Data collection and analysis strategies were well described and congruent with research questions. Data collection continued until saturation. • Results are well rooted in participant perspectives, as evidenced with exemplary quotes, and a diversity of perspectives was sought, as evidenced by varied patient characteristics. • Academic and clinical backgrounds of the investigators were reported. Role of investigators is well described. • Methods to enhance credibility and dependability are well described; one interviewer conducted all interviews and repeated discussion was used to develop themes.	• Sampling method was not clear with regard to how they identified the patients eligible to participate in the study. • Study setting is not clearly described.
Dickerson 2013,[212] qualitative description, interviews	• Study design and objective were clearly stated and justified. • Study objectives were suited to qualitative inquiry. • Development of the study intervention, and the theory used to develop this, was well described. • Interview techniques, using a “think-out-loud” technique, were well described. • Results are well rooted in participant perspectives, as evidenced with exemplary quotes, and a diversity of perspectives was sought, as evidenced by varied patient characteristics. • Academic and clinical backgrounds of the investigators were reported.	• It was not explicitly stated if ethics approval was sought or obtained, although implied by the authors saying they obtained participant consent. • It was not stated whether sampling occurred until data saturation was reached. • Participants were offered monetary compensation ($30) for participation in the study and this may have motivated certain persons to participate.
Elfström 2012,[213] qualitative description, interviews	• Objectives and methods were well described and suitable for qualitative inquiry. • Interview methods were well reported and rigorous; interview	• No major limitations were identified.

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
	questions were provided and piloted in 2 test interviews. • Maximum variation sampling was applied to capture a range of participant perspectives. • Investigators reached data saturation. • Investigators used triangulation and comparison to raw data to enhance the dependability of the study.	
Fung 2015,[214] qualitative description, interviews	• The study objectives were clearly described and suitable to qualitative inquiry. • Data analysis methods were clearly described. • Interview questions were provided and the interview process was clearly reported. • The roles of the researchers in the study were clearly described. Researchers without experience with OSA patients also aided in the analysis to mitigate potential preconceived ideas about the patient experience.	• Participants were offered monetary compensation ($50) for participation in the study and this may have motivated certain persons to participate. • A list of barriers and common problems with CPAP were presented to the patients first, then they were asked about barriers not listed; however, this order may have primed patients to reflect and answer a certain way, and may not reflect an accurate view of their experience. • The research was focused on negative aspects of CPAP use and may not reflect the full range of a patient's experience. • It is uncertain whether sampling continued until data saturation was reached.
Henry 2013,[197] mixed methods, interview (qualitative and quantitative)	• Research objectives are clearly stated and congruent with qualitative inquiry. • Data collection strategies were well described, and congruent with the research questions. • Interviews adequately addressed the need to seek patient perspectives and interview questions are provided. • Interviews were consciously conducted in spaces comfortable to the patient, to facilitate the discussion of personal information. • Verbatim data to support the coding analysis were provided.	• There is some concern regarding channelling bias as physicians recruited participants. The majority of couples were of a high socioeconomic status. It is uncertain whether these patients are truly representative of the target population. • Techniques to enhance credibility and dependability were not described. • It is clear that themes and concepts were rooted in the interview data; however, it is unclear if the full range of themes were reported.
Hu 2014,[221] grounded theory, interviews	• Study design and research questions were clearly stated and justified. • Sampling strategy was well defined and congruent with research questions. • Data collection and analysis strategies were well described and	• The researchers' assumptions and biases in particular relation to the research question was made explicit. • Views from participants were provided, but it was difficult to determine whether quotes were reported verbatim or were

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
	congruent with research questions. Interview questions were provided and data collection continued until saturation. • Results are well rooted in participant perspectives and a diversity of perspectives was provided. • Analysis by more than one researcher was used as a strategy to enhance credibility. • Peer review is used as a strategy to enhance dependability.	summative across multiple participants.
Igelström 2012,[215] qualitative description, interview	• Study objectives were clearly described and suitable to qualitative inquiry. • Purposive sampling strategy was well described, and congruent with research questions. • Data collection and analysis strategies were well described and congruent with research questions. Interview questions are provided. • Results are consistent with data and rooted in participants' perspectives. • Credibility was enhanced through independent analyses by more than one researcher and the reporting of verbatim data.	• There is some concern regarding channelling bias, as physicians recruited participants. • The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit.
Luyster 2016,[216] qualitative description, focus groups	• Study objectives were clearly described and suitable to qualitative inquiry. • Data collection strategies were well described, and congruent with the research questions. • Focus groups adequately addressed the need to seek patient and partner perspectives. • Sampling continued until saturation was reached. • Data analysis strategies were well described. Two coders analyzed the concepts and met to discuss discrepancies and emerging themes. Additionally, verbatim data to support the coding analysis were provided.	• The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques were described to enhance dependability.
Moreira 2008,[220] documentary research, qualitative content analysis	• Study design and objective were clearly stated.	• It was uncertain how the website and the patients were sampled and whether the sample was representative of the target population. Very limited demographic information was provided. • Analysis was conducted by only one researcher and any methods

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
		to ensure rigour of methodology were not explored.
Rodgers 2014,[199] grounded theory, interview	• Study design and research questions were clearly stated and justified, and suited for qualitative inquiry. • Data collection and analysis strategies were well described and justified, and are congruent with research questions. • Results are well rooted in participant perspectives and a geographic and socioeconomic diversity of perspectives was represented. • Verbatim quotes are provided to support the coding analysis and results.	• The role of the researcher is not described; nor have the researchers' assumptions and biases in particular relation to the research question been made explicit. • No techniques were described to enhance dependability. • The authors describe how eligible patients were identified to be contacted from the online forums; however, there is no description of when sampling stopped, and whether this was guided by data saturation, or convenience, for example.
Shoukry 2011,[217] qualitative description, interview	• Study design and research questions were clearly stated and justified. • Sampling strategy was well described, and congruent with the research questions. Sampling continued until data saturation was reached. • Data collection and analysis strategies were well described and congruent with the research question. • Results are well rooted in participant perspectives and a diversity of perspectives was sought. • Member checking and independent analysis by more than one researcher were conducted to enhance credibility. • Limitations and biases are discussed.	• Background of the researcher (pharmacy student) may have prompted socially desirable responses from the participants; however, the researchers acknowledged this and reported dissonant responses from participants.
Sporndly-Nees 2014,[218] Qualitative description, Interview	• Study design and research questions were clearly stated and justified. • Sampling strategy well described, and congruent with the research questions. Sampling continued until data saturation was reached. • Data collection and analysis strategies were well described and congruent with the research question. • Interview guide was piloted-tested for relevance and comprehensibility. • Results are well rooted in participant perspectives, and a diversity of perspectives was accounted for.	• Reasons for declining to participant were not reported. • Participants were recruited from one facility, and it is uncertain how representative the sample is of the target population; the majority of participants are well educated and actively employed.

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
	• Independent analysis by more than one researcher was conducted to enhance credibility.	
Stalkrantz 2012,[222] grounded theory, interview	• Study design and research questions were clearly stated and justified. • Sampling strategy was well described, and congruent with the research questions. Sampling continued until data saturation was reached. • Data collection and analysis strategies were well described and congruent with the research question. • Interview guide was pilot tested and refined based on initial interviews. • Results are well rooted in participant perspectives, and a diversity of perspectives was accounted for. Verbatim quotes are provided.	• The researchers' assumptions and biases in particular relation to the research question have not been made explicit, although were mentioned in the limitations section. • There is the potential for the sample to be different from the target population. Patients indicated whether their spouses could be contacted to participate in the study, and it was not reported how many patients gave permission.
Willman 2012,[219] qualitative description, interview	• Study design and research questions were clearly stated and justified. • Sampling strategy was well described, and congruent with the research questions. Sampling continued until data saturation was reached. • Interview guide was pilot tested. • Researcher triangulation was used to enhance dependability. • Analysis was well organized and evident how themes were derived. • Verbatim quotes were provided to enhance credibility.	• It is uncertain whether a diversity of perspectives was obtained. • Participants declining to participate in the study may have been different from those choosing to participate. This was not explored.
Survey Studies		
Bates 2006,[223] survey, questionnaire	• The research questions are clearly stated and suitable for a survey design. • Justification for questionnaire development was provided and the questions were provided in an appendix to the report. • The study was pilot tested. • A satisfactory response rate was achieved and reasons for loss to follow-up were explored. Differences in some characteristics (e.g., age, sex) between responders and non-responders were explored.	• Unclear if ethics approval was sought or obtained. • Unclear if the sample population was representative of the population to which results may be generalized; participants were recruited from one orthodontist and demographic information was lacking (e.g., race and ethnicity, comorbidities). • Unclear whether the questionnaire was valid; as it was investigator derived, and contained only closed-ended questions, it is uncertain whether this captures all pertinent information for users of mandibular repositioning splints.

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
Bignold 2009,[112] survey, questionnaire	• The research questions are clearly stated and suitable for a survey design. • The sampling strategy is clearly defined and congruent with the research objectives. • The questionnaire was included in an appendix to the report, and patients were able to provide other reasons for non-adherence with TBT in addition to the ones listed by the investigator. • Data analysis was appropriate and planned a priori.	• It is unclear whether the way the sample was obtained could introduce response bias; it was a mailed survey and persons without postal addresses or those with low literacy skills may not have been able to complete the questionnaire. Highly motivated patients are likely to have responded. • No pilot test of the questionnaire or sample size calculation was provided. • The study participants are not clearly described and some demographic information is lacking (e.g., race and ethnicity, comorbidities, other device use).
Bishop 2014,[227] randomized controlled trial with survey component, questionnaire	• Ethics approval was sought and obtained. • Research objectives were clearly stated and were suitable for a survey design. • A satisfactory number of patients responded to the questionnaire; this fulfilled an a priori power calculation.	• Dropout rate was higher than expected, although satisfactory, and potential reasons for not responding were not discussed. • The study participants are not clearly described and some demographic information is lacking (e.g., race and ethnicity, comorbidities, other device use). • Sampling method was not clear, and it is uncertain how they identified the patients eligible to participate in the study. • It is uncertain whether the sample population is representative of the target population; only 1 woman was included in the study and this was a much lower female to male ratio than expected. • It was unclear whether the questionnaire portion of the study was valid and reliable; the questionnaire was not provided and how it was conducted was not well described.
Butterfield 2016,[232] cross-sectional, questionnaire	• Sampling strategy is clearly reported. • Significant and non-significant results were reported. • Data analysis techniques were appropriate; data for relevant questions to this review are mainly descriptive (frequencies and proportions). • The researchers have drawn an appropriate link between data and conclusions. • Use of the Ottawa Sleep Apnea	• Methods used to assess the satisfaction and impression of surgical experience was unclear. It is uncertain how these questions were asked and reported. • Justification for study design was not provided. An interview would have been an appropriate approach for these questions. • No open-ended questions were reported. • Minimal details about patient characteristics were given.

First Author Year of Publication, Study Design, Data Collection Methods	Major Strengths	Major Limitations
	Questionnaire covered a variety of patient experiences.	• No pilot test of the questionnaire or sample size calculation was provided.
Cohen-Levy 2013,[98] survey, questionnaire	• Sampling strategy for the patients is clearly reported. • The study used a previously validated questionnaire to assess patient interpretation of their appearance. • Data analysis techniques were appropriate; data for relevant questions to this review are mainly descriptive (frequencies).	• Unclear whether ethics approval was sought or obtained. • It is uncertain whether the sample population is representative of the target population; all patients were recruited from the same physician and only male patients were included. • No pilot test of the questionnaire for this sample was provided. • No sample size calculation was provided, and it is a relatively small sample (15 patients).
El-Solh 2010,[229] cross-sectional, chart review	• Objectives and methods were well described. • Patient characteristics are well described. • Study adds novel information to the review (i.e., information on patients with PTSD).	• Methods used to elicit patient views were not well described. • It is uncertain whether the results ("problems related to PAP adherence") represent the full range of views of the patients or are investigator selected. • No sample size calculation was provided.
Fung 2013,[231] mixed methods, questionnaire	• Ethics approval was obtained. • Sampling strategy is clearly described. • Questionnaire was adapted from a previous questionnaire.	• It is unclear whether the way the sample was obtained could introduce response bias; it was a mailed survey and persons with low literacy skills may not have been able to complete the questionnaire. Additionally, the response rate was relatively low (52%). Highly motivated patients are likely to have responded. • Questionnaire and open-ended question primed patients to negatively reflect on their CPAP experience and does not reflect the full range or experience of patients. • Results from the open-ended question are reported primarily as a frequency, although the authors report a rigorous method for "coding" the data. • No sample size calculation was provided (questionnaire) and no mention was made of whether saturation had been reached (open-ended question).
Gauthier 2009,[228] randomized controlled trial with survey component, questionnaire	• Study design and objective was clearly stated. • Sampling strategy is clearly described.	• The sample may not be generalizable, as all participants were white and French-speaking. This was a noted limitation by the

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	• A sample size calculation was provided and a satisfactory response rate was achieved. • Reasons for loss to follow-up were reported.	study authors. • It is uncertain whether the questionnaires pertaining to activities of daily living and comfort were reliable, although they had face validity (visual analogue scale and the few questions provided were relatively straightforward). It is unlikely that the full range of patient experiences was captured. • Results are reported for seemingly more questions than were described in the methods section. It is uncertain how these results were obtained.
Glazer Baron 2012,[224] survey, questionnaire	• Study objectives are clearly stated and suitable to a survey. • Questionnaires are likely to be valid and reliable. Questionnaires are cited and well described, and their use is justified by the study authors. • Data analysis was appropriate and mainly descriptive statistics.	• It is uncertain whether the centre from which the patients were sampled is representative of the target population. All participants were male, and the majority (96%) are white and well educated (had post-secondary education). • No sample size calculation was provided, and reasons for loss to follow-up were not reported.
Goodday 2016,[233] cohort study, questionnaire	• Ethics approval was obtained. • Sampling strategy is clearly described and congruent with study objectives. • Questionnaires had face validity, and were designed to be easily answered (yes or no questions). • Treatment history and use of other interventions for OSA are well reported and provides context.	• The sample size is very small, and a satisfactory response rate was not achieved (only 9 of 16 patients completed both questionnaires). It is unlikely to be representative of the target population. • Minimal demographic information is presented about the patients and it is uncertain how representative these patients are of the target population. • The questionnaires are not likely to be reliable, as it was not well reported when or how or by whom the questionnaire was delivered. • Potential biases were not identified or discussed.
Islam 2014,[89] survey, questionnaire	• Research questions were clearly stated and were suitable to the survey design. • Analyses were planned a priori and authors drew appropriate links between the data and their conclusions.	• Ethics approval was not clearly reported, although consent was obtained for the photographs used in the report. • It is uncertain how some of the subjective results on patient appearance were collected. • It is unclear if the target population is representative of the general population, and whether the sample was obtained in a way that may introduce selection bias. Reasons for non-participation were

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		not provided. • No sample size calculation was provided.
Nolan 2006,[198] randomized controlled trial with survey component, questionnaire	• Research questions are clearly stated. • Ethics approval was obtained. • Questionnaires were reliable and valid; investigator questionnaire had face validity. • The researchers have drawn an appropriate link between data and conclusions.	• No sample size calculation was provided. It is unclear whether a satisfactory response rate was achieved. • Unclear if the target population is representative of the sample to which it will be generalized, as limited demographic information is provided. • Patient preference for device is briefly described and it is uncertain whether all reasons for choice of device are fully reported or explored.
Tegelberg 2012,[225] survey, questionnaire	• The research objectives were congruent with a survey design. • A satisfactory response rate was achieved (134/164 patients). • The questionnaire included validated scale (ESS) and the investigator-created portion has face validity.	• It was not explicitly stated whether ethics approval was sought or obtained. • No sample size calculation was reported. • It is unclear whether the way the sample was obtained may introduce selection bias. Limited demographic information is provided on the patients and bed partners. • The investigator-created portion of the questionnaire was not pilot tested.
Thickett 2009,[226] survey, questionnaire	• Research questions are clearly stated and suitable for a survey design. • Ethics approval was obtained.	• It was uncertain how the patients were sampled and whether the sample was representative of the target population. Limited demographic information was provided. • It was uncertain how patients were asked about their experience with the device, and how the views of bed partners were ascertained. It is uncertain whether all responses were reported. • It was uncertain whether the questionnaire was valid or reliable. • No sample size calculation was provided and it was uncertain whether statistical analyses were planned a priori.
Systematic Review		
Ward 2014,[207] integrative review, systematic review	• Study objectives were clearly stated. • Choice and number of databases are appropriate; search concepts	• Methods to reduce errors in data extraction were not reported. • The main limitation of the search methods section was that no

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	are logically presented in Table 1 and demonstrate the translation of the research question into search terms adequately. • Inclusion and exclusion criteria were provided and clearly stated. • Stages of synthesis were well described. Identified themes were supported by results. • Critical appraisal tools were well justified. Two researchers conducted quality cross-checking and consensus discussions. • Practice points and areas for research were well supported by the results.	search strategy was provided. • It was not reported whether coding took place in duplicate, nor how many researchers were involved in the synthesis of the data. • The likelihood of publication bias was not assessed.

CPAP = continuous positive airway pressure; ESS = Epworth Sleepiness Scale; OA = oral appliance; OSA = obstructive sleep apnea; PTSD = post-traumatic stress disorder; TBT = tennis ball technique.