UNITED STATES DEPARTMENT OF AGRICULTURE

Seafood Consumption during Childhood and Adolescence and Cardiovascular Disease: A Systematic Review

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USDA and HHS implemented a process to identify topics and scientific questions to be examined by the 2020 Dietary Guidelines Advisory Committee. The Committee conducted its review of evidence in subcommittees for discussion by the full Committee during its public meetings. The role of the Committee members involved establishing all aspects of the protocol, which presented the plan for how they would examine the scientific evidence, including the inclusion and exclusion criteria; reviewing all studies that met the criteria they set; deliberating on the body of evidence for each question; and writing and grading the conclusion statements to be included in the scientific report the 2020 Committee submitted to USDA and HHS. The NESR team with assistance from Federal Liaisons and Project Leadership, supported the

[i] Under contract with the Food and Nutrition Service, United States Department of Agriculture.

Committee by facilitating, executing, and documenting the work necessary to ensure the reviews were completed in accordance with NESR methodology. More information about the 2020 Dietary Guidelines Advisory Committee, including the process used to identify topics and questions, can be found at www.DietaryGuidelines.gov. More information about NESR can be found at NESR.usda.gov.

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INTRODUCTION

This document describes a systematic review conducted to answer the following question: What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and risk of cardiovascular disease? This systematic review was conducted by the 2020 Dietary Guidelines Advisory Committee, supported by USDA's Nutrition Evidence Systematic Review (NESR).

More information about the 2020 Dietary Guidelines Advisory Committee is available at the following website: www.DietaryGuidelines.gov.

NESR specializes in conducting food- and nutrition-related systematic reviews using a rigorous, protocol-driven methodology. More information about NESR is available at the following website: NESR.usda.gov.

NESR's systematic review methodology involves developing a protocol, searching for and selecting studies, extracting data from and assessing the risk of bias of each included study, synthesizing the evidence, developing conclusion statements, grading the evidence underlying the conclusion statements, and recommending future research. A detailed description of the systematic reviews conducted for the 2020 Dietary Guidelines Advisory Committee, including information about methodology, is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews. In addition, starting on page 21, this document describes the final protocol as it was applied in the systematic review. A description of and rationale for modifications made to the protocol are described in the 2020 Dietary Guidelines Advisory Committee Report, Part D: Chapter 9. Dietary Fats and Seafood.

List of abbreviations

Abbreviation	Full name
BMI	Body mass index
CHD	Coronary heart disease
CVD	Cardiovascular disease
HDL	High-density lipoprotein
HHS	United States Department of Health and Human Services
LDL	Low-density lipoprotein
NESR	Nutrition Evidence Systematic Review
PCS	Prospective cohort study
RCT	Randomized controlled trial
SD	Standard deviation
TC	Total cholesterol
U.K.	United Kingdom
U.S.	United States
USDA	United States Department of Agriculture

WHAT IS THE RELATIONSHIP BETWEEN SEAFOOD CONSUMPTION DURING CHILDHOOD AND ADOLESCENCE (UP TO 18 YEARS OF AGE) AND RISK OF CARDIOVASCULAR DISEASE?

PLAIN LANGUAGE SUMMARY

What is the question?

- The question is: What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and risk of cardiovascular disease?

What is the answer to the question?

- Insufficient evidence is currently available to accurately determine the relationship between seafood consumption during childhood and adolescence and risk of developing cardiovascular disease.

Why was this question asked?

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.

How was this question answered?

- The 2020 Dietary Guidelines Advisory Committee, Dietary Fats and Seafood Subcommittee, conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.

What is the population of interest?

- For the intervention or exposure, generally healthy children and adolescents, ages 18 years and younger. For the outcome, children and adolescents, ages 2 years and older, and adults, ages 19 years and older for blood lipids or blood pressure and adults for cardiovascular disease endpoint outcomes.

What evidence was found?

- This review identified four articles that met inclusion criteria.
- Few studies examined the relationship between seafood intake during childhood and adolescence and blood pressure and/or lipid levels in childhood and adulthood, or cardiovascular-related mortality in adulthood.
- The 2020 Advisory Committee could not draw conclusions due to serious methodological limitations of the included studies.

How up-to-date is this systematic review?

- This review searched for studies from January 2000 to July 2019.

TECHNICAL ABSTRACT

Background

- This important public health question was identified by the U.S. Departments of Agriculture (USDA) and Health and Human Services (HHS) to be examined by the 2020 Dietary Guidelines Advisory Committee.
- The 2020 Dietary Guidelines Advisory Committee, Dietary Fats and Seafood Subcommittee conducted a systematic review to answer this question with support from the Nutrition Evidence Systematic Review (NESR) team.
- The goal of this systematic review was to examine the following question: What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and risk of cardiovascular disease?

Conclusion Statement and Grade

- Insufficient evidence is currently available to accurately determine the relationship between seafood consumption during childhood and adolescence and risk of developing cardiovascular disease. (Grade: Grade not assignable)

Methods

- A literature search was conducted using four databases (i.e., PubMed, Cochrane, Embase, and CINAHL) to identify articles that evaluated the intervention or exposure of seafood consumption during childhood and adolescence and the outcomes of cardiovascular disease. A manual search was conducted to identify articles that may not have been included in the electronic databases searched. Articles were screened by two NESR analysts independently for inclusion based on pre-determined criteria.
- Data extraction and risk of bias assessment were conducted for each included study, and both were checked for accuracy. The Committee qualitatively synthesized the body of evidence to inform development of a conclusion statement, and graded the strength of evidence using pre-established criteria for risk of bias, consistency, directness, precision, and generalizability.

Summary of the evidence

- Four articles, two randomized controlled trials and two prospective cohort studies, met inclusion criteria for this systematic review.
- The 2020 Dietary Guidelines Advisory Committee used the following seafood definition: marine animals that live in the sea and in freshwater lakes and rivers. Seafood includes fish (e.g., salmon, tuna, trout, and tilapia) and shellfish (e.g., shrimp, crab, and oysters).
- Few articles were identified that examined the relationship between seafood intake during childhood and adolescence and blood pressure, lipid levels, and cardiovascular-related mortality, and no articles examined the relationship with incidence of cardiovascular disease.
- Two of four included articles had serious methodological limitations that made interpretation of the results difficult.
- Evidence was insufficient and no conclusion could be drawn.

FULL REVIEW

Systematic review question

What is the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and risk of cardiovascular disease?

Conclusion statement and grade

Insufficient evidence is currently available to accurately determine the relationship between seafood consumption during childhood and adolescence and risk of developing cardiovascular disease. (Grade: Grade not assignable)

Summary of the evidence

- Four articles,[1-4] two randomized controlled trials and two prospective cohort studies, met inclusion criteria for this systematic review.
- Seafood was defined as marine animals that live in the sea and in freshwater lakes and rivers. Seafood includes fish (e.g., salmon, tuna, trout, and tilapia) and shellfish (e.g., shrimp, crab, and oysters).
- Few articles were identified that examined the relationship between seafood intake during childhood and adolescence and blood pressure, lipid levels, and cardiovascular-related mortality, and no articles examined the relationship with incidence of cardiovascular disease.
- Studies had serious methodological limitations that made interpretation of the results difficult.
- Evidence was insufficient and no conclusion could be drawn.

Description of the evidence

Four articles,[1-4] two randomized controlled trials (RCTs)[1,3] and two prospective cohort studies (PCSs),[2,4] met inclusion criteria for this systematic review that examined the relationship between seafood consumption during childhood and adolescence (up to 18 years of age) and risk of cardiovascular disease (CVD; **Table 1**).

Randomized controlled trial characteristics

Two RCTs evaluated the effect of oily fish (i.e., grouper, sea bream, kingfish, emperor, snapper)[1] or tuna,[3] among schoolchildren on intermediate CVD outcomes. In the Fish Feeding Study conducted in Oman, children age 10 years were randomized to receive a school meal with either 100 grams of oily fish (n=96) or a cheese/salad sandwich (control; n=102) five times per week for 12 weeks.[1] Total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides were measured at post-intervention. An RCT conducted in Mexico examined the effect of 6, 7, or 8 grams of tuna (n~20-32); however, the number of meals provided, length of intervention, and control conditions were not described. Blood pressure, total cholesterol, and triglycerides were assessed following an unknown period, and results were stratified by sex.[3] Compliance was not reported in either study.

Prospective cohort study characteristics

Two PCSs, one from the OPUS School Meal Study (Denmark) and one from the Boyd Orr Cohort (United Kingdom [U.K.]) assessed fish intake, analyzed continuously[2] or in quartiles,[4] respectively. The OPUS School Meal Study, assessed fish intake at age 10 years using a 7-day dietary record at baseline, 3 months follow-up, and 6 months follow-up.[2] Intermediate outcomes were assessed after 3 and 6 months, including diastolic blood pressure, HDL cholesterol, and triglycerides. In the Boyd Orr Cohort, fish intake at age 7.5 years was indirectly assessed between 1937 and 1939 using a 7-day household inventory, dividing the total food expenditure by the total number of household members.[4] This long-term longitudinal study followed these children for 60 years at which time stroke mortality and coronary heart disease (CHD) mortality were assessed.[4]

Evidence synthesis

Intermediate outcomes (cardiovascular risk factor assessment)

Blood pressure: One RCT and one PCS did not find a significant relationship between intake of 6, 7, or 8 grams of tuna (length of intervention unknown and control group unspecified) or fish intake (grams per day), respectively, and blood pressure at approximately age 10-12 years.[2,3]

Blood lipid levels: One RCT found a statistically significant relationship between fish intake and blood lipids: obese girls age 11-12 years who consumed 6, 7, or 8 grams of tuna had lower total cholesterol levels compared to controls. This was not significant in obese boys. Additionally, obese boys and girls age 11-12 years who consumed 6, 7, or 8 grams of tuna had significantly lower triglycerides compared to the control group.[3] This study did not report the frequency or duration of the intervention; therefore, it was difficult to interpret the effect of the intervention. The OPUS PCS detected a statistically significant association between fish intake at age 10 years and fasting triglyceride levels three months later; these data were not reported.[2] However, interpretation of data on triglyceride change is difficult when not reported concurrently with a validated surrogate endpoint for CVD such as LDL cholesterol. In contrast, an RCT did not find an effect of an oily fish meal intervention (100 grams per meal, 5 times per week for 12 weeks; n=96) on triglyceride levels compared to cheese/salad sandwich (control, n=102).[1]

Two studies (one RCT and one PCS) did not find a significant relationship between fish intake and HDL cholesterol levels.[1,2] Only one study (an RCT) assessed LDL cholesterol levels and did not find a statistically significant effect of oily fish intake.[1]

CVD Endpoint outcomes

CVD-related mortality: One PCS (N=4,028) detected a statistically significant linear trend between greater fish intake at age 7.5 years and greater risk of stroke mortality after 60 years of follow-up. When examining comparisons between quartiles of intake, there was a statistically significant association between the highest quartile of fish intake at age 7.5 years (mean=44.5 grams, standard deviation [SD]=15.5), compared to the lowest quartile (mean=1.8 grams, SD=2.4) of intake and greater risk of stroke mortality approximately 60 years later.[4] There was not a statistically significant difference in risk of stroke mortality between the second and third quartiles of fish intake (means=11.3 and 21.6 grams, respectively) and the lowest intake quartile. No association was detected between oily fish intake at age 7.5 years and stroke mortality (n=4,028). However, there was no statistically significant association between either fish intake or oily fish intake at age 7.5 years and CHD mortality after approximately 60 years. Results were interpreted with caution because this study had a serious limitation related to the method of fish assessment. Specifically, the dietary assessment completed between 1937 and 1939 was based on a weighed inventory of all foods available in the household divided by the total number of household members. Thus, no information was provided regarding the validity or accuracy of the actual intake of fish among children.

Assessment of the evidence[ii]

As outlined and described below, the body of evidence examining seafood consumption during childhood and adolescence and risk of CVD was assessed for the following elements used when grading the strength of evidence.

Risk of Bias:

- RCTs (**Table 2**)
    - Risk of bias due to randomization: it was unclear whether one trial randomized participants using a non-biased method.[3]
    - Risk of bias due to deviations from intended interventions:
        - Dietary compliance was not reported in either trial.[1,3]
        - Results were difficult to interpret due to incomplete information on fish intake, the control group, and timing of outcome assessment in one trial.[3]
- PCSs (**Table 3**)
    - Risk of bias due to confounding: both studies did not control for all key confounders, particularly family history of CVD.[2,4]
    - Risk of bias due to selection of participants: follow-up period may have been different for all participants in one study.[4]
    - Risk of bias due to classification of exposures: fish intake was measured indirectly using a non-validated 7-day household inventory and a non-validated 7-day dietary record.[2,4]
    - Risk of bias due to missing data: participants were excluded for missing data on other variables besides the exposure and outcome data in both studies.[2]

Consistency:

- Consistency could not be assessed due to an insufficient number of studies and serious methodological limitations.

Directness:

- Three studies were designed to examine seafood intake during childhood and

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[ii] A detailed description of the methodology used for grading the strength of the evidence is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

adolescence and CVD outcomes.
- One PCS was derived from a cluster randomized crossover trial designed to examine the effect of school lunches based on the new Nordic diet on metabolic syndrome and cognition.[2]

Precision:
- In one study, subgroupings had relatively small sample sizes.[3]

Generalizability:
- Two studies were conducted in Europe (U.K. and Denmark),[2,4] one in Mexico,[3] and one in Oman.[1]
- One study exclusively enrolled obese adolescents.[3]
- In the one study that provided information on parental education level, 66% reported having had “higher education”.[2]

Other considerations:

A large, comprehensive search was conducted in multiple databases for this systematic review. Risk of publication bias is always of potential concern, however, both relatively small and large studies were included in this review, reporting both null and statistically significant results. Therefore, risk of publication bias is likely low across this body of evidence.

Research recommendations

In order to better assess the relationship between seafood consumption during childhood and adolescence and risk of cardiovascular disease, additional research is warranted that:

- Employs validated and reliable dietary assessment methods to quantify amount, frequency, type, source, and preparation method of seafood consumed during childhood, accompanied by clinical measures of cardiovascular risk factors including systolic and diastolic blood pressure, fasting blood lipid/lipoprotein measures, and body mass index (BMI);
- Specifies the frequency, duration, type, source and preparation method of the seafood intervention, controls for baseline levels of seafood and non-seafood intakes, adjusts for and reports in detail how compliance was derived;
- Employs RCTs and PCSs to explore seafood consumption during childhood and adolescence and validated short-term intermediate CVD risk factor measures and long-term cardiovascular outcomes;
- Accounts for or examines mercury contamination (if relevant) and key confounders, particularly family history of CVD;
- Includes diverse populations.

Included articles

1. Al-Ghannami SS, Sedlak E, Hussein IS, et al. DHA-enriched re-esterified triacylglycerol fish oil supplementation and oily fish consumption enhance red blood n-3 fatty acid index in Omani pre-adolescent schoolchildren. *Prostaglandins Leukot Essent Fatty Acids*. 2018;135:74-82. doi:10.1016/j.plefa.2018.07.005.
2. Damsgaard CT, Ritz C, Dalskov SM, et al. Associations between school meal-induced dietary changes and metabolic syndrome markers in 8-11-year-old Danish children. *Eur J Nutr*. 2016;55(5):1973-1984. doi:10.1007/s00394-015-1013-z.
3. García-Cervera E, Figueroa-Valverde L, Gómez EP, et al. Effect of omega-3 fatty acids on triglycerides and BMI levels in obese children. *Curr Pediatr Res*. 2015;19(1-2):1-8.
4. Ness AR, Maynard M, Frankel S, et al. Diet in childhood and adult cardiovascular and all cause mortality: the Boyd Orr cohort. *Heart*. 2005;91(7):894-898. doi:10.1136/hrt.2004.043489.

Table 1. Evidence examining the relationship between seafood intake during childhood and adolescence and risk of cardiovascular disease[iii]

Article and Population Characteristics	Intervention/Exposure and Outcomes	Results (statistically significant results bolded)	Key Confounders, Study Limitations and Funding
Randomized Controlled Trials			
Al-Ghannami, 2018[1] **RCT Cluster, Fish Feeding Study, Oman** Baseline N=NR Analytic N=198 (Attrition: NA) **Participant characteristics at baseline:** • Child age (Mean±SD): 9.8y ± 0.4 • Female: 53.5% • Race/ethnicity: NR • SES: NR • Health characteristics (Mean±SD): Weight (kg): 29.6±7.5; Height (cm): 133.3±6.6 • Infant feeding practices: NR • Smoking: NR • SBP (Mean±SD): 107.2±10.4 mmHg • DBP (Mean±SD): 63.8±10.3 mmHg • Triglycerides (Mean±SD): 0.61±0.3 mmol/L • TC (Mean±SD): 4.32±0.68 mmol/L • HDL (Mean±SD): 1.38±0.32 mmol/L • LDL (Mean±SD): 2.66±0.55 mmol/L **Child seafood intake:** NR **Seafood nutrient exposure, (Mean±SD):** • Baseline RBC FA composition: EPA: 0.36% ±0.14; DHA: 3.63% ±1.45 • n-3 content of study fish: 243.9mg ± 60.5 (range: 200-390mg) **Summary of findings:** Following oily fish (100 grams) or cheese/salad sandwich consumption 5x/wk for 12 wk, no differences in blood pressure, triglyceride, total cholesterol, HDL cholesterol, or LDL cholesterol were detected between groups.	**Intervention:** Three groups of children (9-10y) received school meals 5x/wk for 12wk containing either: • Oily fish (n=96): 100g lightly grilled fish (grouper, sea bream, kingfish, emperor, snapper) sandwich • Control (n=102): Cheese/salad sandwich • Fish oil (n=77): DHA enriched fish oil with cheese/salad sandwich *(Fish oil is out of scope for review)* Compliance assessment: Dietary compliance monitored by teachers (NR); post RBC DHA and EPA statistically higher in the oily fish group compared to the control. **Outcomes and assessment methods:** • Blood lipids: TC, LDL-C, HDL-C, Triglyceride Assessment timing: 12wk post-intervention	*Oily fish vs control, categorical* **TC**, post-intervention (mean ± SD) All: Oily fish (n=96): 4.49 mmol/L ± 0.71 Control (n=102): 4.47 mmol/L ± 0.65, P>0.05 Males: Oily fish (n=46): 4.57 mmol/L ± 0.80 Control (n=46): 4.52 mmol/L ± 0.65, P>0.05 Females: Oily fish (n=50): 4.43 mmol/L ± 0.63 Control (n=50): 4.44 mmol/L ± 0.65, P>0.05 **HDL**, post-intervention (mean ± SD) All: Oily fish (n=96): 1.41 mmol/L ± 0.33 Control (n=102): 1.39 mmol/L ± 0.29, P>0.05 Males: Oily fish (n=46): 1.46 mmol/L ± 0.33 Control (n=46): 1.41 mmol/L ± 0.28, P>0.05 Females: Oily fish (n=50): 1.37 mmol/L ± 0.32 Control (n=56): 1.38 mmol/L ± 0.31, P>0.05 **LDL**, post-intervention (mean ± SD) All: Oily fish (n=96): 2.79 mmol/L ± 0.54 Control (n=102): 2.80 mmol/L ± 0.54, P>0.05 Males: Oily fish (n=46): 2.81 mmol/L ± 0.66 Control (n=46): 2.83 mmol/L ± 0.56 Females: Oily fish (n=50): 2.76 mmol/L ± 0.44 Control (n=56): 2.75 mmol/L ± 0.52 **Triglyceride**, post-intervention (mean ± SD) All: Oily fish (n=96): 0.65 mmol/L ± 0.23 Control (n=102): 0.64 mmol/L ± 0.35, P>0.05 Males: Oily fish (n=46): 0.64 mmol/L ± 0.24 Control (n=46): 0.59 mmol/L ± 0.37, P>0.05 Females: Oily fish (n=50): 0.65 mmol/L ± 0.22 Control (n=56): 0.67 mmol/L ± 0.33, P>0.05	**Model adjustments:** Child age, race/ethnicity, SES **Limitations:** • Baseline sample size NR and therefore, attrition is unknown. • Did not adjust for or report compliance. • Did not account for baseline lipid/BP measures. **Funding sources:** 8th Five year Development Plan; Ministry of Agriculture and Fisheries Wealth, Sultanate of Oman

Article and Population Characteristics	Intervention/Exposure and Outcomes	Results (statistically significant results bolded)	Key Confounders, Study Limitations and Funding
Garcia-Cervera, 2015[3] **RCT, Mexico** Baseline N=152 Analytic N=152 (Attrition: 0%) **Participant characteristics at baseline:** • Child age: ~11-12y • Female: 49.3% • Race/ethnicity: NR • SES: NR • Health characteristics: 100% obese • Infant feeding practices: NR • Smoking: NR • Baseline lipids: NR **Child seafood intake:** NR **Seafood nutrient exposure:** NR **Summary of findings:** Children who consumed 6, 7 or 8g of tuna, compared to control, had significantly lower triglycerides, but not blood pressure and cholesterol. (Note: statistical tests NR)	**Intervention:** • Fish (tuna) intake of 6, 7, or 8g for unknown duration and unknown frequency • Control not described <u>Compliance assessment</u>: NR **Outcomes and assessment methods:** • <u>Blood pressure:</u> NR • <u>Blood lipids:</u> Fasting blood sample was collected <u>Assessment timing:</u> NR	**<u>SBP</u>,** post-intervention (mean ± SE) *Tuna fish, 6g vs Control* <u>Boys (n=20):</u> Tuna: 107.60 mmHg ± 1.2 Control: 110.22 mmHg ± 1.4 <u>Girls (n=28):</u> Tuna: 102.10 mmHg ± 2.3 Control: 108.18 mmHg ± 1.6 *Tuna fish, 7g vs Control* <u>Boys (n=32):</u> Tuna: 109.22 mmHg ± 1.2 Control: 100.44 mmHg ± 1.6 <u>Girls (n=22):</u> Tuna: 100.60 mmHg ± 1.2 Control: 104.00 mmHg ± 1.4 *Tuna fish, 8g vs Control* <u>Boys (n=25):</u> Tuna: 102.40 mmHg ± 1.2 Control: 99.44 mmHg ± 1.6 <u>Girls (n=25):</u> Tuna: 100.02 mmHg ± 1.2 Control: 106.00 mmHg ± 1.6 **<u>TC</u>**, post-intervention (mean ± SE) *Tuna fish, 6g vs Control* <u>Boys (n=20):</u> Tuna: 165.14 mg/dL ± 2.1 Control: 168.10 mg/dL ± 1.6 **<u>Girls (n=28):</u> Tuna: 166.04 mg/dL ± 1.4** **Control: 170.24 mg/dL ± 1.2** *Tuna fish, 7g vs Control* <u>Boys (n=32):</u> Tuna: 167.12 mg/dL ± 2.1 Control: 172.02 mg/dL ± 1.3 **<u>Girls (n=22):</u> Tuna: 160.14 mg/dL ± 2.1** **Control: 168.24 mg/dL ± 1.2** *Tuna fish, 8g vs Control* <u>Boys (n=25):</u> Tuna: 158.14 mg/dL ± 2.1 Control: 168.02 mg/dL ± 1.3 **<u>Girls (n=25):</u> Tuna: 144.18 mg/dL ± 2.4** **Control: 166.02 mg/dL ± 1.2** **<u>Triglycerides</u>**, post-intervention (mean ± SE) *Tuna fish, 6g vs Control* **<u>Boys (n=20):</u> Tuna: 198.00 mg/dL ± 18.0** **Control: 217.40 mg/dL ± 14.0** **<u>Girls (n=28):</u> Tuna: 200.00 mg/dL ± 18.0**	**Model adjustments**: None **Limitations:** • Intervention duration and frequency is unknown • Compliance was not reported • Study did not control for baseline levels • Statistical test is unknown and NR • Only SBP reported • Small sample size in the 3 intervention arms **Funding sources**: NR

Article and Population Characteristics	Intervention/Exposure and Outcomes	Results (statistically significant results bolded)	Key Confounders, Study Limitations and Funding
		Control: 220.00 mg/dL ± 14.0 *Tuna fish, 7g vs Control* **Boys (n=32): Tuna: 190.00 mg/dL ± 17.0** **Control: 217.40 mg/dL ± 14.0** **Girls (n=22): Tuna: 178.00 mg/dL ± 17.0** **Control: 220.00 mg/dL ± 14.0** *Tuna fish, 8g vs Control* **Boys (n=25): Tuna: 160.00 mg/dL ± 15.0** **Control: 217.40 mg/dL ± 14.0** **Girls (n=25): Tuna: 144.00 mg/dL ± 15.0** **Control: 220.00 mg/dL ± 14.0**	

Article and Population Characteristics	Intervention/Exposure and Outcomes	Results (statistically significant results bolded)	Key Confounders, Study Limitations and Funding
Prospective Cohort Studies			
Damsgaard, 2016[2] **PCS, OPUS School Meal Study, Denmark** Baseline N=834 Analytic N=523 (Attrition: 37%) **Participant characteristics at baseline:** • Child age: Mean=10.0y, SD=0.6 • Female: 48.6% • Race/ethnicity: Non-Danish (two parents born outside Denmark): 10.5% • SES: Parental education: Short education (upper and lower secondary and vocational education) 34%, Higher education (shorter higher education, bachelor's degree and higher) 66% • Health characteristics: Weight status: underweight 10.3%, normal weight 78.2%, overweight/obese 11.5%; BMI-for-age z-score: Mean=0.09, SD=1.03; Waist circumference (cm): Mean=62.3 (range: 59.1, 67.3) • Infant feeding practices: NR • Smoking: NR • DBP (Mean±SD): 68±7 mmHg • HDL (Mean±SD): 1.44±0.30 mmol/L • Triglyceride (Median, IQR): 0.60 (0.50-0.77) mmol/L **Child seafood intake:** Baseline fish intake: Median: 13g/d (IQR: 2-29) **Seafood nutrient exposure:** NR **Summary of findings:** Higher fish intake was associated with lower triglyceride levels (data NR), but not diastolic blood pressure and HDL cholesterol levels.	**Exposure:** • Fish intake (g/d) at 10y (continuous) Assessment method: dietary intake measured for 7 consecutive days at baseline, 3 and 6mo using web-based dietary assessment software developed for the age group with parental help Assessment timing: Baseline, 3mo follow-up, 6mo follow-up **Outcomes and assessment methods:** • Blood pressure: measured by automated device following 10 minute rest performed in triplicate (last 2 measurements averaged for outcome) • Triglycerides and HDL cholesterol: at baseline, 3 and 6mo in morning after overnight fast Assessment timing: Baseline, 3mo follow-up, 6mo follow-up	*Fish intake at 10y, continuous (per g/d increase), longitudinal associations* **DBP:** N=523 NR, P>0.05 **HDL:** N=523 NR, P>0.05 **Triglyceride:** N=523 **NR, P<0.05**	**Key confounders accounted for:** • Child sex, child age, non-fish dietary exposure to n-3 PUFA, anthropometry **Confounders NOT accounted for:** • Race/ethnicity, SES, smoking, family history of CVD **Additional model adjustments:** Puberty, height at all visits, energy under-, normal- and over-reporting, outcome baseline values; random effects: child, sibling, class, year group, school **Limitations:** • Did not account for all key confounders • Directness: Cohort derived from cluster randomized trial designed to examine whether whole-blood DHA and intakes of whole-grain, coarse vegetables and potatoes, dietary fiber, protein and fat were associated with metabolic syndrome markers **Funding sources:** Nordea Foundation; Danaeg A/S, Naturmaelk, Lantmannen A/S, Skaertoft Molle A/S, Kartoffelpartnerskabet, AkzoNobel Danmark, Gloria Mundi and Rose Pountry A/S provided food for study

Article and Population Characteristics	Intervention/Exposure and Outcomes	Results (statistically significant results bolded)	Key Confounders, Study Limitations and Funding
Ness, 2005[4] **PCS, Boyd Orr Cohort, U.K.** Baseline N=4,999 Analytic N=4,028 (Attrition: 19%) **Participant characteristics at baseline:** • Child age: Mean=7.5y, SD=4.8 (IQR: 3.5-11.2) • Female: 50.5% • Race/ethnicity: NR • SES: Father's social class: I 1.5%, II 7.2%, III 19.6%, IV 23.0%, V 14.3%, Unemployed 26.2%, Unclassifiable 8.2%; Townsend score (sum of standardized scores for levels of car ownership, house ownership, overcrowding, unemployment; negative values indicate less deprivation): -1.6 (Range: -2.8 to 0.9) • Health characteristics: NR • Infant feeding practices: NR • Smoking: NR • Baseline lipids: NR **Child seafood intake:** Oily fish intake: Some 43%, No 57% **Summary of findings:** Highest level of fish intake at ~7.5y (SD=4.8), compared to the lowest level of fish intake, was associated with a higher rate of stroke mortality. Fish intake was not associated with coronary heart disease mortality.	**Exposure:** • Fish intake in quartiles (Q): • Q1 (Ref, lowest, Mean=1.8g, SD=2.4) • vs Q2 (Mean=11.3g, SD=2.5) • vs Q3 (Mean=21.6g, SD=3.9) • vs Q4 (highest, Mean=44.5g, SD=15.5) Assessment method: Data collection conducted between 1937 and 1939. Seven-day household inventory. Weighed inventory of all foods available in the household was recorded in a diary at baseline and after survey period. Per capita food and nutrient intake was calculated by dividing daily total food expenditure by total number of household members, taking into account meals missed by family members and meals consumed by visitors. Assessment timing: Baseline **Outcomes and assessment methods:** • CVD mortality: Death certificate Assessment timing: Length of follow-up: ~60y	*Fish intake at 7.5y (RR=Rate Ratio)* **Stroke mortality:** N=4,028 Q1 vs Q2: RR: 0.79, 95% CI: 0.39, 1.60 Q1 vs Q3: RR: 1.13, 95% CI: 0.58, 2.18 **Q1 vs Q4: RR: 2.01, 95% CI: 1.09, 3.69** **P for linear trend = 0.01** **Coronary heart disease mortality:** N=4,028 Q1 vs Q2: RR: 0.99, 95% CI: 0.68, 1.43 Q1 vs Q3: RR: 0.85, 95% CI: 0.58, 1.25 Q1 vs Q4: RR: 1.18, 95% CI: 0.80, 1.76 P for linear trend = 0.6 *Oily fish intake at 7.5y* **Stroke mortality:** N=4,028 No oily fish (57%) vs Some oily fish (43%): NR, P>0.05 **Coronary heart disease mortality:** N=4,028 No oily fish (57%) vs Some oily fish (43%): NR, P>0.05	**Key confounders accounted for:** • Child sex, child age, SES **Key confounders NOT accounted for:** • Race/ethnicity, non-fish dietary exposure to n-3 PUFA, smoking, anthropometry, family history of CVD **Additional model adjustments:** Energy, childhood family food expenditure, district of residence as a child, period of birth, season when studied as a child, Townsend score for current address or place of death **Limitations:** • Did not account for all key confounders • Fish exposure was measured indirectly using a 7d weighed family food inventory divided by total number of household members irrespective of age or sex **Funding sources:** World Cancer Research Fund, Medical Research Council, British Heart Foundation

[iii] Abbreviations: CI – confidence interval, d – day(s), DBP – diastolic blood pressure, DHA – docosahexaenoic acid, EPA – eicosapentaenoic acid, FA – fatty acids, HDL – HDL cholesterol, IQR – interquartile range, LDL – LDL cholesterol, mo – month(s), n-3 – omega-3, NA – not applicable, NR – not reported, RBC – red blood cell, RR – rate ratio, SBP – systolic blood pressure, SD – standard deviation, SE – standard error, SES – socioeconomic status, TC – total cholesterol, wk – week(s), x – times, y – year(s)

Table 2. Risk of bias for randomized controlled trials examining seafood consumption during childhood and adolescence and risk of cardiovascular disease[iv,v]

	Randomization	Identification of participants - randomization	Deviations from intended interventions - Intention to treat	Missing outcome data	Outcome measurement	Selection of the reported result
Al-Ghannami, 2018,[1] RCT cluster	Low	Low	Some concerns	Low	Low	Low
Garcia-Cervera, 2015,[3] RCT	Some concerns	Not applicable	Some concerns	Low	Low	Some concerns

Table 3. Risk of bias for observational studies examining seafood consumption during childhood and adolescence and risk of cardiovascular disease[vi]

	Confounding	Selection of participants	Classification of exposures	Deviations from intended exposures	Missing data	Outcome measurement	Selection of the reported result
Damsgaard, 2015[2]	Serious	Low	Moderate	Low	Moderate	Low	Moderate
Ness, 2005[4]	Serious	Moderate	Serious	Low	Moderate	Low	Moderate

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[iv] A detailed description of the methodology used for assessing risk of bias is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews and in Part C of the following reference: Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC..

[v] Possible ratings of low, some concerns, or high determined using the "Cochrane Risk-of-bias 2.0" (RoB 2.0) (August 2016 version)" (Higgins JPT, Sterne JAC, Savović J, Page MJ, Hróbjartsson A, Boutron I, Reeves B, Eldridge S. A revised tool for assessing risk of bias in randomized trials In: Chandler J, McKenzie J, Boutron I, Welch V (editors). Cochrane Methods. *Cochrane Database of Systematic Reviews* 2016, Issue 10 (Suppl 1). dx.doi.org/10.1002/14651858.CD201601.)

[vi] Possible ratings of low, moderate, serious, critical, or no information determined using the "Risk of Bias for Nutrition Observational Studies" tool (RoB-NObs) (Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.)

METHODOLOGY

The NESR team used its rigorous, protocol-driven methodology to support the 2020 Dietary Guidelines Advisory Committee in conducting this systematic review.

NESR's systematic review methodology involves:

- Developing a protocol,
- Searching for and selecting studies,
- Extracting data from and assessing the risk of bias of each included study,
- Synthesizing the evidence,
- Developing conclusion statements,
- Grading the evidence underlying the conclusion statements, and
- Recommending future research.

A detailed description of the methodology used in conducting this systematic review is available on the NESR website: https://nesr.usda.gov/2020-dietary-guidelines-advisory-committee-systematic-reviews, and can be found in the 2020 Dietary Guidelines Advisory Committee Report, Part C: Methodology.[vii] This systematic review was peer reviewed by Federal scientists, and information about the peer review process can also be found in the Committee's Report, Part C. Methodology. Additional information about this systematic review, including a description of and rationale for any modifications made to the protocol can be found in the 2020 Dietary Guidelines Advisory Committee Report, Part D. Chapter 9. Dietary Fats and Seafood.

Below are details of the final protocol for the systematic review described herein, including the:

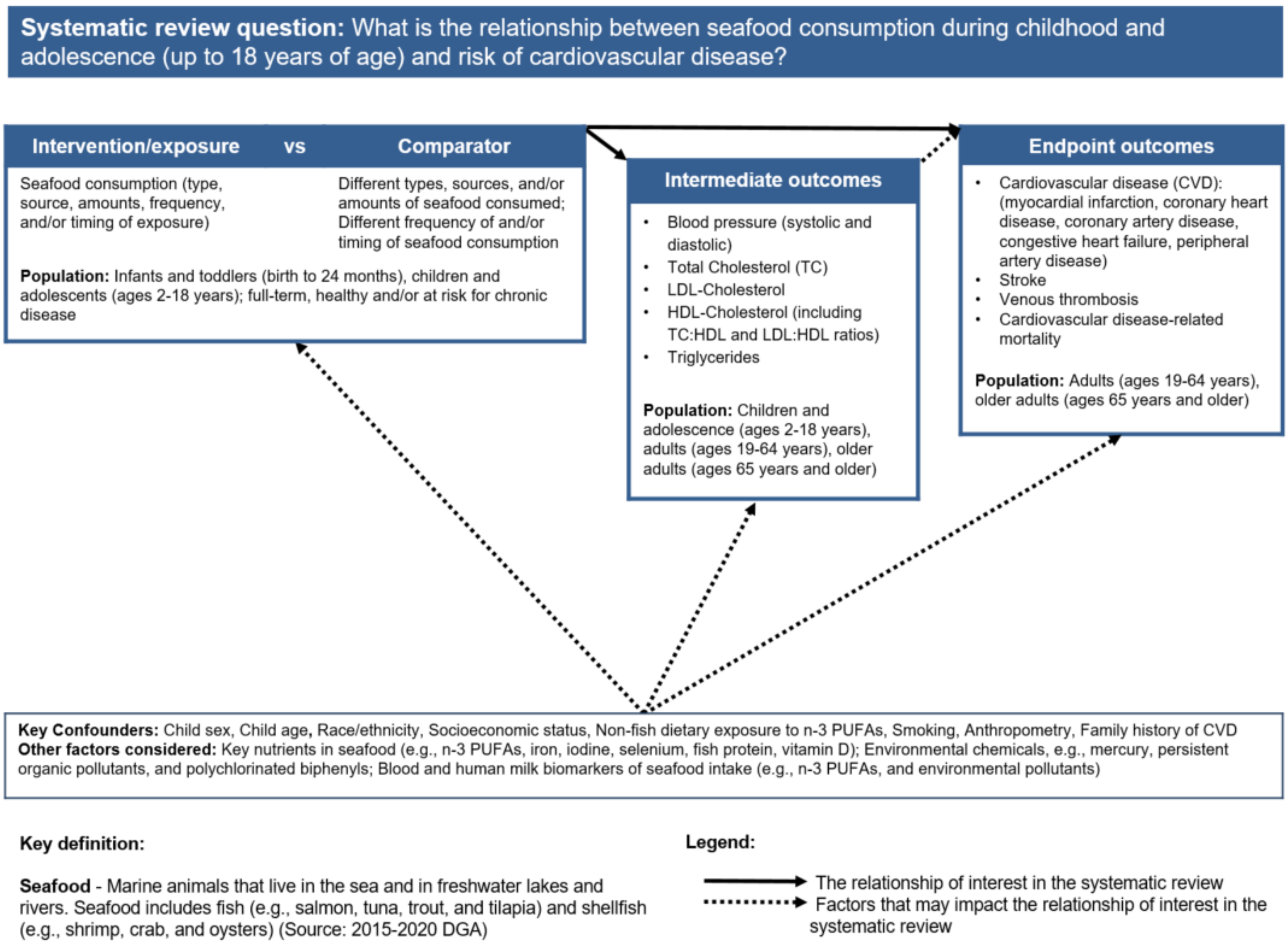
- Analytic framework
- Literature search and screening plan
- Literature search and screening results

[vii] Dietary Guidelines Advisory Committee. 2020. *Scientific Report of the 2020 Dietary Guidelines Advisory Committee: Advisory Report to the Secretary of Agriculture and the Secretary of Health and Human Services*. U.S. Department of Agriculture, Agricultural Research Service, Washington, DC.

ANALYTIC FRAMEWORK

The analytic framework (**Figure 1**) illustrates the overall scope of the systematic review, including the population, the interventions and/or exposures, comparators, and outcomes of interest. It also includes definitions of key terms and identifies key confounders considered in the systematic review. The inclusion and exclusion criteria that follow provide additional information about how parts of the analytic framework were defined and operationalized for the review.

Figure 1: Analytic framework



LITERATURE SEARCH AND SCREENING PLAN

Inclusion and exclusion criteria

This table (**Table 4**) provides the inclusion and exclusion criteria for the systematic review. The inclusion and exclusion criteria are a set of characteristics used to determine which articles identified in the literature search were included in or excluded from the systematic review.

Table 4. Inclusion and exclusion criteria

Category	Inclusion Criteria	Exclusion Criteria
Study design	• Randomized controlled trials • Non-randomized controlled trials, including quasi-experimental and controlled before-and-after studies • Prospective cohort studies • Retrospective cohort studies • Nested case-control studies	• Uncontrolled trials • Case-control studies • Cross-sectional studies • Uncontrolled before-and-after studies • Narrative reviews • Systematic reviews • Meta-analyses
Intervention/ exposure	• Seafood consumption measured prior to outcome assessment ○ Type (e.g., salmon, tuna, bass) ○ Source (e.g., sea, fresh water, farmed, wild) ○ Amount/frequency of intake ○ Timing of exposure (e.g., age at intake) ○ Dietary intake (e.g., from food frequency questionnaires, dietary recall, fish/seafood screeners) may be validated with biomarkers for polyunsaturated fatty acid or methylmercury, but not substituted.	• No measure of seafood consumption (i.e., studies that only examined biomarkers for consumption) • omega-3 supplement studies which do not evaluate seafood consumption • Studies evaluating infant formula with added docosahexaenoic acid (DHA) and/or eicosapentaenoic acid (EPA)
Comparator	• Different types, sources, amounts, frequency, and/or timing of exposure of seafood consumption	• No comparator

Category	Inclusion Criteria	Exclusion Criteria
Outcomes	• Intermediate Outcomes ○ Blood pressure (systolic and diastolic) ○ Total Cholesterol (TC) ○ LDL-Cholesterol ○ HDL-Cholesterol (including TC:HDL and LDL:HDL ratios) ○ Triglycerides • Endpoint Outcomes ○ Cardiovascular disease (myocardial infarction, coronary heart disease, coronary artery disease, congestive heart failure, peripheral artery disease) ○ Stroke ○ Venous thrombosis ○ Cardiovascular disease mortality	
Date of publication	• January 2000 to July 2019	• Articles published prior to January 2000 or after July 2019
Publication status	• Articles that have been peer-reviewed	• Articles that have not been peer-reviewed and are not published in peer-reviewed journals, including unpublished data, manuscripts, reports, abstracts, and conference proceedings
Language of publication	• Articles published in English	• Articles published in languages other than English
Country[viii]	• Studies conducted in countries ranked as high or very high human development	• Studies conducted in countries ranked as medium or lower human development

[viii] The Human Development classification was based on the Human Development Index (HDI) ranking (1) from the year the study intervention occurred or data were collected. If the study did not report the year in which the intervention occurred or data were collected, the HDI classification for the year of publication was applied. HDI values are available from 1990 to present. If a study was conducted in 2018 or 2019, the most current HDI classification was applied. If a study was conducted prior to 1990, the HDI classification from 1990 was applied. When a country was not included in the HDI ranking, the current country classification from the World Bank (2) is used instead.

1. UN Development Program. HDI 1990-2017 HDRO calculations based on data from UNDESA (2017a), UNESCO Institute for Statistics (2018), United Nations Statistics Division (2018b), World Bank (2018b), Barro and Lee (2016) and IMF (2018). Available from: http://hdr.undp.org/en/data.
2. The World Bank. World Bank country and lending groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-country-and-lending-groups

Category	Inclusion Criteria	Exclusion Criteria
Study participants	• Human participants	• Non-human subjects (e.g., animal models or in-vitro models)
Age of study participants	• Age at intervention or exposure: ○ Infants and toddlers (0-24 months) ○ Children and adolescents (ages 2-18 years) • Age at intermediate outcomes: ○ Children and adolescents (ages 2-18 years) ○ Adults (ages 19-64 years) ○ Older adults (ages 65 years and older) • Age at endpoint outcomes: ○ Adults (ages 19-64 years) ○ Older adults (ages 65 years and older)	
Health status of study participants	• Studies that enroll participants who are healthy and/or at risk for chronic disease, including those with obesity • Studies that **exclusively** enroll participants with high blood pressure or high cholesterol and are evaluating cardiovascular disease endpoint outcomes • Studies that enroll **some** participants diagnosed with cardiovascular disease endpoint outcomes. • Studies that enroll **some** participants diagnosed with a disease or hospitalized with and illness or injury • Studies that enroll infants born full-term (≥37 weeks and 0/7 days gestational age) • Studies that enroll **some** infants born preterm (gestational age <37 weeks and 0/7 days), infants with low birth weight (<2500g), and/or infants born small for gestational age	• Studies that **exclusively** enroll participants diagnosed with a disease (e.g., diabetes, renal disease), or hospitalized with an illness or injury (For this criterion, studies that exclusively enroll participants with obesity will not be excluded) • Studies that **exclusively** enroll participants with cardiovascular disease endpoint outcomes (i.e., studies that aim to treat participants who have already been diagnosed with cardiovascular disease) • Studies that **exclusively** enroll participants with high blood pressure or high cholesterol and are evaluating blood pressure or cholesterol outcomes (i.e., studies that aim to treat participants who already have high blood pressure or high cholesterol)

Electronic databases and search terms

PubMed

- Provider: U.S. National Library of Medicine
- Date(s) Searched: July 29, 2019
- Date range searched: January 1, 2000-July 29, 2019
- Search Terms:

#1 - "Seafood"[Mesh] OR seafood* OR sea food* OR “fish consumption” OR "Fishes"[Mesh] OR fish[tiab] OR fishes[tiab] OR “fish products” OR fatty fish[tiab] OR shellfish[tiab] OR "Fish Proteins, Dietary"[Mesh] OR shellfish protein* OR "Mercury Poisoning"[Mesh] OR mercury poisoning* OR methylmercury[tiab] OR sharks[tiab] OR swordfish[tiab] OR tuna[tiab] OR salmon[tiab] OR sardines[tiab] OR pollock[tiab] OR flounder[tiab] OR cod[tiab] OR tilapia[tiab] OR shrimp[tiab] OR "Ostreidae"[Mesh] OR oysters[tiab] OR "Mya"[Mesh] OR "Bivalvia"[Mesh] OR clams[tiab] OR "Pectinidae"[Mesh] OR scallops[tiab] OR "Brachyura"[Mesh] OR crab[tiab] OR mackerel[tiab] OR catfish*[tiab] OR trout[tiab] OR lobster[tiab] OR "Decapodiformes"[Mesh] OR squid[tiab] OR halibut[tiab] OR “mahi mahi” OR crawfish[tiab] OR anchov*[tiab] OR herring[tiab] OR rockfish OR marine product* OR "Fatty Acids, Omega-3"[Mesh]

#2 - "Cardiovascular Diseases"[Mesh:NoExp] OR cardiovascular disease*[tiab] OR coronary artery disease[tiab] OR heart disease*[tiab] OR "Heart Failure"[Mesh] OR heart failure[tiab] OR "Myocardial Infarction"[Mesh] OR myocardial infarction*[tiab] OR "Myocardial Ischemia"[Mesh] OR Myocardial Ischemia*[tiab] OR "Stroke"[Mesh] OR stroke[tiab] OR angina[tiab] OR heart attack[tiab] OR "Venous Thrombosis"[Mesh] OR venous thrombosis[tiab] OR hypertension[tiab] OR high blood pressure[tiab] OR "Lipids/blood"[Mesh] OR "Cholesterol, HDL"[Mesh] OR HDL cholesterol[tiab] OR "Cholesterol, LDL"[Mesh] OR LDL cholesterol[tiab] OR total cholesterol[tiab] OR "Triglycerides"[Mesh] OR triglycerides[tiab]

#3 - "Child"[Mesh] OR child[tiab] OR children[tiab] OR youth* OR "Adolescent"[Mesh] OR adolescence[tiab] OR adolescent* OR teen[tiab] OR teens[tiab] OR teenager* OR preteen* OR pre-teen* OR pre-adolesc* OR preadolesc* OR preschool* OR pediatric* OR paediatric* OR boy[tiab] OR boys[tiab] or girl[tiab] OR girls[tiab] OR schoolchild* OR middle school* OR high school* OR juvenile[tiab] OR pubescent[tiab] OR pre pubescent[tiab] OR prepubescent[tiab] OR kid[tiab] OR kids[tiab] OR early childhood[tiab] OR early years[tiab] OR pre-k[tiab] OR pre-primary[tiab] OR under five*[tiab] OR young child*[tiab] OR head start[tiab] OR prekindergarten[tiab] OR pre-kindergarten[tiab]

#4 - (#1 AND #2 AND #3)

#5 - (#1 AND #2 AND #3) NOT ("Animals"[Mesh] NOT ("Animals"[Mesh] AND "Humans"[Mesh])) NOT (editorial[ptyp] OR comment[ptyp] OR news[ptyp] OR letter[ptyp] OR review[ptyp] OR systematic review[ptyp] OR systematic review[ti] OR meta-analysis[ptyp] OR meta-analysis[ti] OR meta-analyses[ti] OR retracted publication[ptyp] OR retraction of publication[ptyp] OR retraction of publication[tiab] OR retraction notice[ti]) Filters: Publication date from 2000/01/01 to 2019/07/29; English

Cochrane Central Register of Controlled Trials (CENTRAL)

- Provider: John Wiley & Sons
- Date(s) Searched: July 29, 2019
- Date range searched: January 1, 2000-July 29, 2019
- Search Terms:

#1 - [mh "Seafood"] OR [mh "Fishes"] OR [mh "Fish Proteins, Dietary"] OR [mh "Mercury Poisoning"] OR [mh "Ostreidae"] OR [mh "Mya"] OR [mh "Bivalvia"] OR [mh "Pectinidae"] OR [mh "Brachyura"] OR [mh "Decapodiformes"] OR [mh "Fatty Acids, Omega-3"]

#2 - (seafood* OR "sea food*" OR "fish consumption" OR fish OR fishes OR "fish products" OR "fatty fish" OR shellfish OR "shellfish protein*" OR "mercury poisoning*" OR methylmercury OR sharks OR swordfish OR tuna OR salmon OR sardines OR pollock OR flounder OR cod OR tilapia OR shrimp OR oysters OR clams OR scallops OR crab OR mackerel OR catfish* OR trout OR lobster OR squid OR halibut OR "mahi mahi" OR crawfish OR anchov* OR herring OR rockfish OR "marine product*"):ti,ab,kw

#3 - #1 OR #2

#4 - [mh ^"Cardiovascular Diseases"] OR [mh "Heart Failure"] OR [mh "Myocardial Infarction"] OR [mh "Myocardial Ischemia"] OR [mh Stroke] OR [mh "Venous Thrombosis"] OR [mh Lipids/BL] OR [mh "Cholesterol, HDL"] OR [mh "Cholesterol, LDL"] OR [mh "Triglycerides"]

#5 - ("cardiovascular disease*" OR "coronary artery disease" OR "heart disease" OR "heart failure" OR "myocardial infarction*" OR "myocardial ischemia*" OR stroke OR angina OR "heart attack" OR "venous thrombosis" OR "hypertension" OR "high blood pressure" OR "HDL cholesterol" OR "LDL cholesterol" OR "total cholesterol" OR triglycerides):ti,ab,kw

#6 - #4 OR #5

#7 - [mh "Child"] OR [mh "Adolescent"]

#8 - (child OR children OR youth* OR adolescence OR adolescent* OR teen OR teens OR teenager* OR preteen* OR pre-teen* OR pre-adolesc* OR preadolesc* OR preschool* OR pediatric* OR paediatric* OR boy OR boys OR girl OR girls OR schoolchild* OR "middle school*" OR "high school*" OR juvenile OR pubescent OR "pre pubescent" OR prepubescent OR kid OR kids OR "early childhood" OR "early years" OR pre-k OR pre-primary OR "under five*" OR "young child*" OR "head start" OR prekindergarten OR pre-kindergarten):ti,ab,kw

#9 - #7 OR #8

#10 - #3 AND #6 AND #9" with Publication Year from 2000 to 2019, in Trials (Word variations have been searched)

Embase

- Provider: Elsevier
- Date(s) Searched: July 29, 2019
- Date range searched: January 1, 2000-July 29, 2019
- Search Terms:

#1 - 'sea food'/exp OR 'fish'/exp OR 'fish protein'/exp OR 'mercurialism'/exp OR 'oyster'/exp OR 'mya'/de OR 'bivalve'/exp OR 'scallop'/exp OR 'brachyura'/exp OR 'decapodiformes'/exp OR 'omega 3 fatty acid'/de

#2 - seafood*:ab,ti OR 'sea food*':ab,ti OR 'fish consumption':ab,ti OR fish:ab,ti OR fishes:ab,ti OR 'fish products':ab,ti OR 'fatty fish':ab,ti OR shellfish:ab,ti OR 'shellfish protein*':ab,ti OR 'mercury poisoning*':ab,ti OR methylmercury:ab,ti OR sharks:ab,ti OR swordfish:ab,ti OR tuna:ab,ti OR salmon:ab,ti OR sardines:ab,ti OR pollock:ab,ti OR flounder:ab,ti OR cod:ab,ti OR tilapia:ab,ti OR shrimp:ab,ti OR oysters:ab,ti OR clams:ab,ti OR scallops:ab,ti OR crab:ab,ti OR mackerel:ab,ti OR catfish*:ab,ti OR trout:ab,ti OR lobster:ab,ti OR squid:ab,ti OR halibut:ab,ti OR 'mahi mahi':ab,ti OR crawfish:ab,ti OR anchov*:ab,ti OR herring:ab,ti OR rockfish:ab,ti OR 'marine product*':ab,ti

#3 - #1 OR #2

#4 - 'cardiovascular disease'/exp OR 'heart failure'/exp OR 'heart infarction'/exp OR 'heart muscle ischemia'/exp OR 'cerebrovascular accident'/exp OR 'venous thromboembolism'/exp OR 'lipids in blood'/de OR 'high density lipoprotein cholesterol'/de OR 'low density lipoprotein cholesterol'/de OR 'triacylglycerol'/exp

#5 - 'cardiovascular disease*':ab,ti OR 'coronary artery disease':ab,ti OR 'heart disease':ab,ti OR 'heart failure':ab,ti OR 'myocardial infarction*':ab,ti OR 'myocardial ischemia*':ab,ti OR stroke:ab,ti OR angina:ab,ti OR 'heart attack':ab,ti OR 'venous thrombosis':ab,ti OR 'hypertension':ab,ti OR 'high blood pressure':ab,ti OR 'hdl cholesterol':ab,ti OR 'ldl cholesterol':ab,ti OR 'total cholesterol':ab,ti OR triglycerides:ab,ti

#6 - #4 OR #5

#7 - 'child'/exp OR 'adolescent'/exp

#8 - child:ab,ti OR children:ab,ti OR youth*:ab,ti OR adolescence:ab,ti OR adolescent*:ab,ti OR teen:ab,ti OR teens:ab,ti OR teenager*:ab,ti OR preteen*:ab,ti OR 'pre teen*':ab,ti OR 'pre adolesc*':ab,ti OR preadolesc*:ab,ti OR preschool*:ab,ti OR pediatric*:ab,ti OR paediatric*:ab,ti OR boy:ab,ti OR boys:ab,ti OR girl:ab,ti OR girls:ab,ti OR schoolchild*:ab,ti OR 'middle school*':ab,ti OR 'high school*':ab,ti OR juvenile:ab,ti OR pubescent:ab,ti OR 'pre pubescent':ab,ti OR prepubescent:ab,ti OR kid:ab,ti OR kids:ab,ti OR 'early childhood':ab,ti OR 'early years':ab,ti OR 'pre k':ab,ti OR 'pre primary':ab,ti OR 'under five*':ab,ti OR 'young child*':ab,ti OR 'head start':ab,ti OR prekindergarten:ab,ti OR 'pre kindergarten':ab,ti

#9 - #7 OR #8

#10 - #3 AND #6 AND #9

#11 - #3 AND #6 AND #9 AND [humans]/lim AND [english]/lim AND [2000-2019]/py NOT ([conference abstract]/lim OR [conference paper]/lim OR [conference review]/lim OR [editorial]/lim OR [erratum]/lim OR [letter]/lim OR [note]/lim OR [review]/lim OR [systematic review]/lim OR [meta analysis]/lim)

Cumulative Index of Nursing and Allied Health Literature (CINAHL Plus)

- Provider: EBSCO*host*
- Date(s) Searched: July 29, 2019
- Date range searched: January 1, 2000-July 29, 2019
- Search Terms:

#S1- (MH "Seafood+") OR (MH "Fish") OR (MH "Shellfish") OR (MH "Mercury Poisoning") OR (MH "Mollusca") OR (MH "Fatty Acids, Omega-3+")

#S2 - seafood* OR “sea food*” OR “fish consumption” OR fish OR fishes OR “fish products” OR “fatty fish” OR shellfish OR “shellfish protein*” OR “mercury poisoning*” OR methylmercury OR sharks OR swordfish OR tuna OR salmon OR sardines OR pollock OR flounder OR cod OR tilapia OR shrimp OR oysters OR clams OR scallops OR crab OR mackerel OR catfish* OR trout OR lobster OR squid OR halibut OR “mahi mahi” OR crawfish OR anchov* OR herring OR rockfish OR “marine product*”

#S3 - S1 OR S2

#S4 - (MH "Cardiovascular Diseases") OR (MH "Heart Failure+") OR (MH "Myocardial Infarction+") OR (MH "Myocardial Ischemia+") OR (MH "Stroke+") OR (MH "Venous Thrombosis+") OR (MH "Lipids/BL") OR (MH "Lipoproteins, HDL Cholesterol") OR (MH "Lipoproteins, LDL Cholesterol") OR (MH "Triglycerides")

#S5 - “cardiovascular disease*” OR “coronary artery disease” OR “heart disease*”OR “heart failure” OR “myocardial infarction*” OR “myocardial Ischemia*” OR stroke OR angina OR “heart attack” OR “venous thrombosis” OR hypertension OR “high blood pressure” OR “HDL cholesterol” OR “LDL cholesterol” OR “total cholesterol” OR triglycerides

#S6 - S4 OR S5

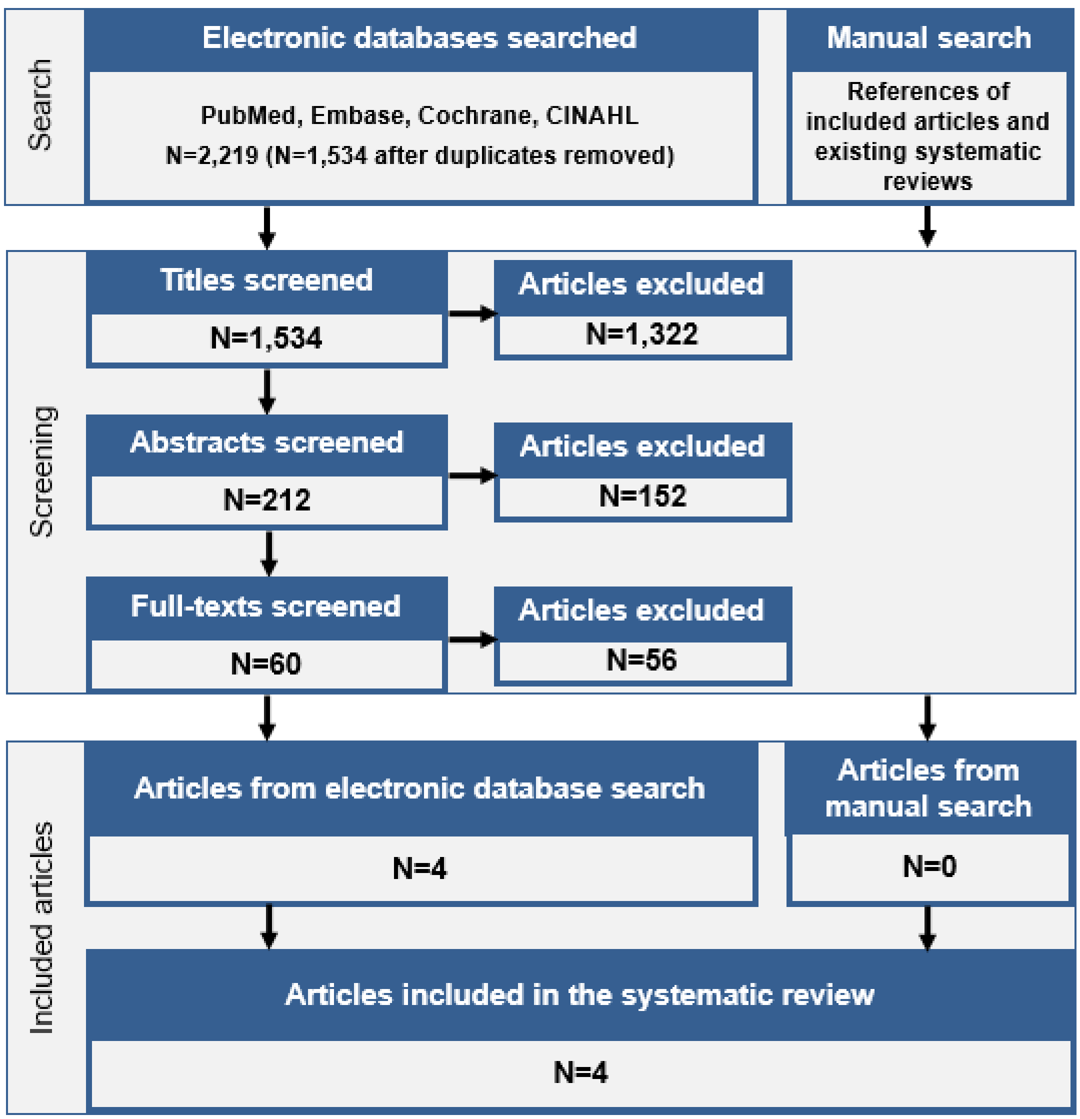
#S7 - (MH "Child+") OR (MH "Adolescence+") OR child OR children OR youth* OR adolescence OR adolescent* OR teen OR teens OR teenager* OR preteen* OR pre-teen* OR pre-adolesc* OR preadolesc* OR preschool* OR pediatric* OR paediatric* OR boy OR boys OR girl OR girls OR schoolchild* OR “middle school*” OR “high school*” OR juvenile OR pubescent OR “pre pubescent” OR prepubescent OR kid OR kids OR “early childhood” OR “early years” OR pre-k OR pre-primary OR “under five*” OR “young child*” OR “head start” OR prekindergarten OR pre-kindergarten

#S8 - (S3 AND S6 AND S7) NOT (MH "Literature Review" OR MH "Meta Analysis" OR MH "Systematic Review" OR MH "News" OR MH "Retracted Publication" OR MH "Retraction of Publication”) Limiters - Publication Year: 2000-2019; Peer Reviewed; English Language; Human

LITERATURE SEARCH AND SCREENING RESULTS

The flow chart (**Figure 2**) below illustrates the literature search and screening results for articles examining the systematic review question. The results of the electronic database searches, after removal of duplicates, were screened independently by two NESR analysts using a step-wise process by reviewing titles, abstracts, and full-texts to determine which articles met the inclusion criteria. Refer to **Table 5** for the rationale for exclusion for each excluded full-text article. A manual search was done to find articles that were not identified when searching the electronic databases; all manually identified articles are also screened to determine whether they meet criteria for inclusion.

Figure 2: Flow chart of literature search and screening results



Excluded articles

The table below (**Table 5**) lists the articles excluded after full-text screening, and includes columns for the categories of inclusion and exclusion criteria (see **Table 4**) that studies were excluded based on. At least one reason for exclusion is provided for each article, as indicated by an "X" in one of the columns, though this may not reflect all possible reasons for exclusion. Information about articles excluded after title and abstract screening is available upon request.

Table 5. Articles excluded after full-text screening with rationale for exclusion

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
1.	Aadland EK, Lavigne C, Graff IE, et al. Lean-seafood intake reduces cardiovascular lipid risk factors in healthy subjects, results from a randomized controlled trial with a crossover design. *Am J Clin Nutr.* 2015;102(3),582-92. doi:10.3945/ajcn.115.112086.			X		
2.	Al-Ghannami SS, Sedlak E, Hussein IS, et al. Lipid-soluble nutrient status of healthy Omani school children before and after intervention with oily fish meal or re-esterified triacylglycerol fish oil. *Nutrition.* 2016;32,73-78. doi:10.1016/j.nut.2015.07.014.				X	
3.	Ayer JG, Harmer JA, Xuan W, et al. Dietary supplementation with n-3 polyunsaturated fatty acids in early childhood, effects on blood pressure and arterial structure and function at age 8 y. *Am J Clin Nutr.* 2009;90(2),438-46. doi:10.3945/ajcn.2009.27811.		X			
4.	Bastida S, Sanchez-Muniz FJ, Cuena R, Perea S, Aragones A. High density lipoprotein-cholesterol changes in children with high cholesterol levels at birth. *Eur J Pediatr.* 2002;161(2),94-8. doi:10.1007/s00431-001-0863-y.		X			
5.	Bradlee ML, Singer MR, Daniels SR, Moore LL. Eating patterns and lipid levels in older adolescent girls. *Nutr Metab Cardiovasc Dis.* 2013;23(3),196-204. doi:10.1016/j.numecd.2011.10.010.		X			
6.	Brox J, Bjornstad, E, Olaussen K, Osterud, B, Almdahl S, Lochen ML. Blood lipids fatty acids diet and lifestyle parameters in adolescents from a region in northern Norway with a high mortality from coronary heart disease. *Eur J Clin Nutr.* 2002;56(7),694-700. doi:10.1038/sj.ejcn.1601381.		X			

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
7.	Çöl N, Gökçen C, Demırcıoğlu Kiliç, B, Karadağ, M. Prevalence of obesity/hypertension in children and adolescents with ADHD and evaluation of total body composition. *Anadolu Psikiyatri Dergisi.* 2019;20(1),93-100.		X		X	
8.	Colussi G, Catena C, Dialti V, Mos L, Sechi LA. Effects of the consumption of fish meals on the carotid IntimaMedia thickness in patients with hypertension, a prospective study. *J Atheroscler Thromb.* 2014;21(9),941-56. doi:10.5551/jat.22921.			X		
9.	Couch SC, Crandell J, King I, et al. Associations between long chain polyunsaturated fatty acids and cardiovascular lipid risk factors in youth with type 1 diabetes, SEARCH Nutrition Ancillary Study. *J Diabetes Complications.* 2017;31(1),67-73. doi:10.1016/j.jdiacomp.2016.10.002.		X			
10.	Cundiff DK, Lanou AJ, Nigg CR. Relation of omega-3 fatty acid intake to other dietary factors known to reduce coronary heart disease risk. *Am J Cardiol.* 2007;99(9),1230-3. doi:10.1016/j.amjcard.2006.12.032.			X	X	
11.	Damsgaard CT, Dalskov SM, Laursen RP, et al. Provision of healthy school meals does not affect the metabolic syndrome score in 8-11-year-old children but reduces cardiometabolic risk markers despite increasing waist circumference. *Br J Nutr.* 2014;112(11),1826-36. doi:10.1017/S0007114514003043.		X			
12.	Dewailly E, Blanchet C, Gingras S, Lemieux S, Holub BJ. Fish consumption and blood lipids in three ethnic groups of Quebec (Canada). *Lipids.* 2003;38(4),359-65. doi:10.1007/s11745-003-1070-4. doi:10.1007/s11745-003-1070-4.			X		
13.	Dias CB, Wood LG, Garg ML. Effects of dietary saturated and n-6 polyunsaturated fatty acids on the incorporation of long-chain n-3 polyunsaturated fatty acids into blood lipids. *Eur J Clin Nutr.* 2016;70(7),812-8. doi:10.1038/ejcn.2015.213.		X	X		
14.	Dorea JG, de Souza JR, Rodrigues P, Ferrari I, Barbosa AC. Hair mercury (signature of fish consumption) and cardiovascular risk in Munduruku and Kayabi Indians of Amazonia. *Environ Res.* 2005;97(2),209-19. doi:10.1016/j.envres.2004.04.007.		X	X		

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
15.	Dumont J, Huybrechts I, Spinneker A, et al. FADS1 genetic variability interacts with dietary alpha-linolenic acid intake to affect serum non-HDL-cholesterol concentrations in European adolescents. *J Nutr.* 2011;141(7),1247-53. doi:10.3945/jn.111.140392.		X			
16.	Fillion M, Mergler D, Sousa Passos CJ, Larribe F, Lemire M, Guimaraes JR. A preliminary study of mercury exposure and blood pressure in the Brazilian Amazon. *Environ Health.* 2006;5,29. doi:10.1186/1476-069X-5-29.	X		X		
17.	Garneau V, Rudkowska I, Paradis AM, et al. Association between plasma omega-3 fatty acids and cardiovascular disease risk factors. *Appl Physiol Nutr Metab.* 2013;38(3),243-8. doi:10.1139/apnm-2012-0238.			X		
18.	Gopinath B, Moshtaghian H, Flood VM, et al. Pattern of omega-3 polyunsaturated fatty acid intake and fish consumption and retinal vascular caliber in children and adolescents, A cohort study. *PLoS One.* 2017;12(2),e0172109. doi:10.1371/journal.pone.0172109.				X	
19.	Guerendiain M, Montes R, López-Belmonte G, et al. Changes in plasma fatty acid composition are associated with improvements in obesity and related metabolic disorders, A therapeutic approach to overweight adolescents. *Clin Nutr.* 2018;37(1),149-156. doi:10.1016/j.clnu.2016.11.006.		X			
20.	Gump BB, MacKenzie JA, Dumas AK, et al. Fish consumption low-level mercury lipids and inflammatory markers in children. *Environ Res.* 2012;112,204-11. doi:10.1016/j.envres.2011.10.002.	X				
21.	Güneş Ö, Soylu M, İnanç N, et al. Relationship between red blood cell membrane fatty acid composition and dietary fatty acids level in obese adolescents with/without metabolic syndrome. *Prog Nutr.* 2018;20(4),648-658. doi:10.23751/pn.v20i4.6039.		X			
22.	Haraldsdottir A, Torfadottir JE, Valdimarsdottir UA, et al. Fish and fish-liver oil consumption in adolescence and midlife and risk of CHD in older women. *Public Health Nutr.* 2016;19(2),318-25. doi: 10.1017/S1368980015001020.	X				

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
23.	Harris CP, von Berg A, Berdel D, et al. Association of dietary fatty acids with blood lipids is modified by physical activity in adolescents, Results from the GINIplus and LISA birth cohort studies. *Nutrients.* 2018;10(10). doi:10.3390/nu10101372.	X	X			
24.	Harris C, Buyken A, Koletzko S, et al. Dietary fatty acids and changes in blood lipids during adolescence, the role of substituting nutrient intakes. *Nutrients.* 2017;9(2). doi:10.3390/nu9020127.		X			
25.	Hartiala O, Kajander S, Knuuti J, et al. Life-course risk factor levels and coronary artery calcification. The Cardiovascular Risk in Young Finns Study. *Int J Cardiol.* 2016;225,23-29. doi:10.1016/j.ijcard.2016.09.080.				X	
26.	Jaaskelainen P, Magnussen CG, Pahkala K, et al. Childhood nutrition in predicting metabolic syndrome in adults, the cardiovascular risk in Young Finns Study. *Diabetes Care.* 2012;35(9),1937-43. doi:10.2337/dc12-0019.				X	X
27.	Jang HB, Hwang JY, Park JE,et al. Intake levels of dietary polyunsaturated fatty acids modify the association between the genetic variation in PCSK5 and HDL cholesterol. J Med Genet. 2014;51(12),782-8. doi:10.1136/jmedgenet-2014-102670.		X			
28.	Joki P, Suomalainen H, Jarvinen KM, et al. Cholesterol precursors and plant sterols in children with food allergy. *Am J Clin Nutr.* 2003;77(1),51-5. doi:10.1093/ajcn/77.1.51.		X			
29.	Julian-Almarcegui C, Vandevijvere S, Gottrand F,et al. Association of heart rate and blood pressure among European adolescents with usual food consumption, The HELENA study. *Nutr Metab Cardiovasc Dis.* 2016;26(6),541-8. doi:10.1016/j.numecd.2016.01.014.	X				
30.	Kaikkonen JE, Jula A, Mikkilä V, et al. Childhood serum cholesterol ester fatty acids are associated with blood pressure 27 y later in the cardiovascular risk in young Finns study. *Am J Clin Nutr.* 2012;95(6),1422-31. doi:10.3945/ajcn.111.030387.		X			

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
31.	Katsa ME, Ioannidis A, Zyga S, et al. The effect of nutrition and sleep habits on predisposition for metabolic syndrome in Greek children. *J Pediatr Nurs.* 2018;40,e2-e8. doi:10.1016/j.pedn.2018.01.012.	X				
32.	Kirkhus B, Lamglait A, Eilertsen KE, et al. Effects of similar intakes of marine n-3 fatty acids from enriched food products and fish oil on cardiovascular risk markers in healthy human subjects. *Br J Nutr.* 2012;107(9),1339-49. doi:10.1017/S0007114511004508.			X		
33.	Klein-Platat C, Drai J, Oujaa M, Schlienger J, Simon C. Plasma fatty acid composition is associated with the metabolic syndrome and low-grade inflammation in overweight adolescents. *Am J Clin Nutr.* 2005;82(6),1178-84. doi:10.1093/ajcn/82.6.1178.		X			
34.	Laake I, Pedersen JI, Selmer R, et al. A prospective study of intake of trans-fatty acids from ruminant fat partially hydrogenated vegetable oils and marine oils and mortality from CVD. *Br J Nutr.* 2012;108(4),743-754. doi:10.1017/S0007114511005897.			X		
35.	Lauritzen L, Harslof LB, Hellgren LI, Pedersen MH, Molgaard C, Michaelsen KF. Fish intake erythrocyte n-3 fatty acid status and metabolic health in Danish adolescent girls and boys. *Br J Nutr.* 2012;107(5),697-704. doi:10.1017/S0007114511002418.	X			X	
36.	Lehtovirta M, Pahkala K, Niinikoski H, et al. Effect of dietary counseling on a comprehensive metabolic profile from childhood to adulthood. *J Pediatr.* 2018;195,190-198.e3. doi:10.1016/j.jpeds.2017.11.057.		X			
37.	Liu Y, Buchanan S, Anderson HA, Xiao Z, Persky V, Turyk ME. Association of methylmercury intake from seafood consumption and blood mercury level among the Asian and Non-Asian populations in the United States. *Environ Res.* 2018;160,212-222. doi:10.1016/j.envres.2017.09.031.			X		X
38.	McNaughton SA, Ball K, Mishra GD, Crawford DA. Dietary patterns of adolescents and risk of obesity and hypertension. *J Nutr.* 2008;138(2),364-70. doi:10.1093/jn/138.2.364.	X				

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
39.	Molven I, Retterstol K, Andersen LF, et al. Children and young adults with familial hypercholesterolaemia (FH) have healthier food choices particularly with respect to dietary fat sources compared with non-FH children. *J Nutr Sci.* 2013;2,e32. doi:10.1017/jns.2013.27.	X			X	
40.	Montonen J, Järvinen R, Reunanen A, Knekt P. Fish consumption and the incidence of cerebrovascular disease. *Br J Nutr.* 2010;102(5),750-6. doi:10.1017/S0007114509274782.			X		
41.	Nejatinamini S, Ataie-Jafari A, Ghasemian A, et al. Burden of ischemic heart disease attributable to low omega-3 fatty acids intake in Iran, Findings from the global burden of disease study 2010. *J Tehran Heart Cent.* 2016;11(1),21-29.		X	X		
42.	O'Sullivan TA, Ambrosini GL, Mori TA, Beilin LJ, Oddy WH. Omega-3 Index correlates with healthier food consumption in adolescents and with reduced cardiovascular disease risk factors in adolescent boys. *Lipids.* 2011;46(1),59-67. doi:10.1007/s11745-010-3499-8.	X			X	
43.	Pieniak Z, Verbeke W, Perez-Cueto F, Brunso K, De Henauw S. Fish consumption and its motives in households with versus without self-reported medical history of CVD, a consumer survey from five European countries. *BMC Public Health.* 2008;8,306. doi:10.1186/1471-2458-8-306.	X				
44.	Raghuveer G. Assessment of atherosclerotic cardiovascular risk and management of dyslipidemia in obese children. *Prog Pediatr Cardiol.* 2008;25(2),167-176. doi:10.1016/j.ppedcard.2008.05.005.	X				
45.	Rheinberger CM, Hammitt JK. Risk trade-offs in fish consumption, a public health perspective. *Environ Sci Technol.* 2012;46(22),12337-46. doi:10.1021/es302652m.	X				
46.	Sands SA, Reid KJ, Windsor SL, Harris WS. The impact of age body mass index and fish intake on the EPA and DHA content of human erythrocytes. *Lipids.* 2005;40(4),343-7. doi:10.1007/s11745-006-1392-2			X		

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
47.	Schmedes M, Brejnrod AD, Aadland EK, et al. The effect of lean-seafood and non-seafood diets on fecal metabolites and gut microbiome, results from a randomized crossover intervention study. *Mol Nutr Food Res.* 2019;63(1),e1700976. doi:10.1002/mnfr.201700976.			X		
48.	Skilton Michael R. ω-3 Fatty Acids Impaired Fetal Growth and Cardiovascular Risk, Nutrition as Precision Medicine. *Adv Nutr.* 2018;9(2),99-104. doi:10.1093/advances/nmx012.	X				
49.	Strandvik B, Chen Y, Dangardt F, et al. From the Swedish to the Mediterranean diet and the omega-6/omega-3 balance. *World Rev Nutr Diet.* 2011;102,73-80. doi:10.1159/000327793.	X				
50.	Tam CH, Wang Y, Lee HM, et al. Early gene-diet interaction between glucokinase regulatory protein (GCKR) polymorphism vegetable and fish intakes in modulating triglyceride levels in healthy adolescents. *Nutr Metab Cardiovasc Dis.* 2015;25(10),951-8. doi:10.1016/j.numecd.2015.06.011.	X				
51.	Thorsdottir I, Gunnarsdottir I, Palsson GI. Birth weight growth and feeding in infancy, relation to serum lipid concentration in 12-month-old infants. *Eur J Clin Nutr.* 2003;57(11),1479-85. doi:10.1038/sj.ejcn.1601714.		X			
52.	Thurston SW, Bovet P, Myers GJ, et al. Does prenatal methylmercury exposure from fish consumption affect blood pressure in childhood?. *Neurotoxicology.* 2007;28(5),924-30. doi:10.1016/j.neuro.2007.06.002.		X	X		
53.	Venalainen TM, Viitasalo AM, Schwab US, et al. Effect of a 2-y dietary and physical activity intervention on plasma fatty acid composition and estimated desaturase and elongase activities in children, the Physical Activity and Nutrition in Children Study. *Am J Clin Nutr.* 2016;104(4),964-72. doi:10.3945/ajcn.116.136580.		X			
54.	Verduci E, Radaelli G, Salvioni M, Riva E, Giovannini M. Plasma long-chain fatty acids profile and metabolic outcomes in normolipidaemic obese children after one-year nutritional intervention. *Acta Paediatr.* 2011;100(4),585-9. doi:10.1111/j.1651-2227.2010.02120.x.		X			

	Citation	Study Design	Intervention/ Exposure	Population at Intervention or Exposure	Outcome	Population at Outcome
55.	Washington RL. Diet may lessen heart disease as SGA infants grow up. *J Pediatr.* 2015;166(5),1101-4.	X				
56.	Zhang W, Zhang X, Tian Y, et al. Risk assessment of total mercury and methylmercury in aquatic products from offshore farms in China. *J Hazard Mater.* 2018;354,198-205. doi:10.1016/j.jhazmat.2018.04.039.		X	X		