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A systematic review of nutrigenetics, omega-3 and plasma lipids/lipoproteins/apolipoproteins with evidence evaluation using the GRADE approach

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Running Head: Nutrigenetics, omega-3 and lipids/lipoproteins

Data described in the manuscript will be made available upon request pending approval from the corresponding author.

Abbreviations: ALA (alpha-linolenic acid); CV (coefficient of variation); DHA (docosahexaenoic acid); EPA (eicosapentaenoic acid); FDA (Food and Drug Administration); GRADE (Grading of Recommendations Assessment, Development and Evaluation); HCP (healthcare professional); LD (linkage disequilibrium); nutri-GRS (nutrigenetic risk score); SNP (single nucleotide polymorphism)

ABSTRACT

Objectives: Despite the uptake of nutrigenetic testing through direct-to-consumer services and healthcare professionals, systematic reviews determining scientific validity are limited in this field. The objective of this review was to: retrieve, synthesize and assess the quality (level) of evidence for nutrigenetic approaches related to the effect of genetic variation on plasma lipid, lipo- and apolipoprotein responsiveness to omega-3 fatty acid intake.

Design: A systematic review was conducted using three search engines. Included studies assessed dietary interventions or associations between genetic variants and plasma lipid, lipo- and apolipoprotein levels based on omega-3 fatty acid intake. Studies were selected for evidence grading if there were statistically significant nutrigenetic findings for the same SNP(s) and lipid/lipoprotein/apolipoprotein outcome in at least two independent studies. Risk of bias was assessed in individual studies. Evidence was evaluated using the GRADE approach. This systematic review was registered with PROSPERO (CRD42020185087).

Results: Out of 1830 articles screened, 65 met the inclusion criteria (*n*=23 observational, *n*=42 interventional); of these, 25 met the criteria for evidence evaluation using GRADE. Overall, current evidence is insufficient for gene-diet associations related to omega-3 fatty acid intake on plasma apolipoproteins, total cholesterol, HDL-cholesterol, LDL-cholesterol and LDL particle size. However, there is strong (GRADE rating: moderate quality) evidence to suggest that male *APOE*-E4 carriers (rs429358, rs7412) exhibit significant triglyceride reductions in response to omega-3-rich fish oil with a dose-response effect. Moreover, strong (GRADE rating: high quality) evidence suggests that a 31-SNP nutrigenetic risk score can predict plasma triglyceride responsiveness to omega-3-rich fish oil in adults with overweight/obesity from various ethnicities.

Conclusions: Most evidence in this area is weak, but two specific nutrigenetic interactions exhibited strong evidence, with limited generalizability to specific populations.

Keywords: nutrigenomics, nutrigenetics, nutritional genomics, genetic risk score, nutrigenetic risk score, triglycerides, lipids, lipoproteins, omega-3 fatty acid, *APOE*

STRENGTHS AND LIMITATIONS

- Strength: Comprehensive systematic review guided by PRSIMA
- Strength: Critical appraisal of the evidence guided by GRADE
- Limitation: Inability to conduct a meta-analysis given the comprehensive overview of studies and thus heterogeneity
- Limitation: Several included studies without replication; most evidence was low or very low quality according to GRADE

INTRODUCTION

Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research demonstrates that there is significant inter-individual variability in cardiometabolic risk factor levels, in part based on a combination of genetic and nutrition-related risk factors (2,3). Consumers indicate great interest in personalized nutrition based on genetics (4,5), however, a lack of industry oversight (6,7) has led to highly variable scientific validity of nutrigenetic tests available to consumers. While recognizing that some groups question whether genetic testing for personalized nutrition is ready for 'prime time', Gorman and colleagues suggested that there are certain specific nutrigenetic interactions with strong evidence that could be considered for implementation into clinical practice by expert committees who are responsible for creating dietary guidelines (8). With this in mind, systematic reviews that include an evaluation of levels of evidence are urgently needed in order to determine if there are any nutrigenetic associations that may warrant potential implementation into practice.

The dominant omega-3 polyunsaturated fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which typically come from marine sources (e.g. fish oil), and alpha-linolenic acid (ALA), which are rich in plant sources (e.g., canola oil) (10,11). It is well established that higher intakes of omega-3 fatty acids from foods or supplements (herein after referred to as "omega-3s"), particularly from long-chain EPA and DHA, tend to improve indicators of cardiometabolic health (11,12). In terms of their lipid and lipoprotein lowering effects, omega-3s have consistently demonstrated an impact on triglycerides (TG) (13). High-quality evidence from population-based studies

suggests that long-chain omega-3s (EPA and DHA) reduce plasma TG by about 15% (13). There is also high-quality evidence suggesting that EPA and DHA can raise high-density lipoprotein (HDL) cholesterol (13). Some studies have further demonstrated an effect of omega-3 on HDL-cholesterol (14), low-density lipoprotein (LDL)-cholesterol (14), total cholesterol (15–17), apolipoproteins (18), and LDL particle size (19). Despite several studies with significant findings for these outcomes, when reviewing the evidence, studies have demonstrated conflicting results for the impact of omega-3 on many lipid profile outcomes (13). Genetic variation could explain this heterogeneity. EPA and DHA have been shown to significantly impact the expression of thousands of genes including those involved in inflammatory and atherogenic pathways (20,21). Evidence now demonstrates that the health impacts of omega-3 intake could differ based on genetic variation (22,23). Despite the potential for omega-3s to have a significant positive impact on health outcomes, population intakes of omega-3s tend to be low (24). While the World Health Organization's Adequate Intake level for adults is 200-250 mg EPA+DHA daily (25,26), the mean reported intake of EPA+DHA in the United States is only approximately 100 mg daily (24). Nutrigenetic interventions have the potential to motivate improvements in dietary intake beyond population-based interventions (27). Additionally, evidence suggests that genetic variability affects health responses to omega-3s (22). Thus, critically appraising and grading the evidence for nutrigenetic interactions related to omega-3s and plasma lipids, lipoproteins and apolipoproteins is an important research priority. The most recent systematic review on nutrigenetic interactions related to omega-3s and intermediate phenotypes of cardiovascular disease was conducted nearly a decade ago, and this study did not evaluate the quality of

evidence using an established methodology (28). Therefore, we aimed to provide a comprehensive summary of current evidence related to inter-individual variability in plasma lipid, lipoprotein and apolipoprotein responses to omega-3 intake (plant and marine sources) based on genetic variations. Overall, the specific objective of this study was to: systematically search, identify (select), summarize, synthesize and assess the quality of evidence for gene-diet effects on cardiometabolic risk factors - more specifically, plasma lipid, lipoprotein and apolipoprotein responsiveness to omega-3s.

Methods

Patient and Public Involvement: No patient involvement.

Literature Search

The systematic review protocol was registered with PROSPERO (CRD42020185087). The review process was guided by previously established methods, including a previously outlined five-step systematic review process (29,30). The search engines Embase, Web of Science and Medline OVID were used to conduct the search and screen for articles meeting inclusion criteria, using the comprehensive search terms outlined in Supplementary Table 1, properly combined by Boolean operators. The literature was searched up until August 1, 2020. A PRISMA diagram (Figure 1) guided the article screening process (31).

Inclusion and Exclusion Criteria

Original studies were included if they were written in English or French. Inclusion criteria were developed using the Population, Intervention, Comparison, Outcomes, (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (32,33) for

interventional and observational research, respectively. There were no limitations to the population characteristics (all populations/patient samples were included). Animal studies were excluded. Dietary interventions and observational studies involving omega-3s (total omega-3 or various types; supplemental and/or dietary intake) and comparing lipid and/or lipoprotein and/or apolipoprotein outcomes between different genetic variations based on omega-3 dietary or supplemental intake (and not blood fatty acid levels; e.g. EPA and DHA in red blood cells) were included. In included studies, samples had to be stratified on the basis of genetic variation. Specific lipid and lipoprotein outcomes of interest were: HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and triglycerides (TG). Studies that reported ratios of the aforementioned lipid parameters (e.g. HDL-cholesterol to total cholesterol ratio) were also included. Both observational and interventional studies were included, as well as single-gene, polygenic and genome-wide association studies (GWAS). Differences in study designs and methods were considered when developing the overall evidence grades, as further detailed below.

Article Selection and Data Extraction

Two independent investigators (JH and VG) screened articles using the computer software *Covidence* (including title, abstract, and full-text screening) and extracted data from the included articles. Reference lists of included articles and of a systematic review on a similar topic (34) were also screened for relevant articles. Data extraction templates were piloted by two independent investigators (JH and VG) on ten included studies and revised accordingly. The final data extraction templates included the following components for each study: first author name and year, study design, genetic approach, population and sample size, study duration (interventional studies only), genes and single

nucleotide polymorphisms (SNPs) analyzed with rs numbers, quantity and type of omega-3, comparisons (e.g. a control group or different amount/type of omega-3s as well as genetic grouping), lipid/lipoprotein outcome(s), whether or not the study reported that they followed STREGA guidelines and a summary of statistically significant study findings relevant to the research question. Corresponding authors of included studies were contacted as needed to provide clarity and/or additional information about the included studies.

Evidence Grading

Upon reading all full-text articles included, and summarizing the body of evidence, SNPs/nutrigenetic risk scores (nutri-GRSs) and subsequent lipid/lipoprotein/apolipoprotein outcomes were systematically selected for evidence grading based on the following predetermined replication criteria: statistically significant nutrigenetic results for the same SNP(s)/nutri-GRS [or SNPs in strong linkage disequilibrium (LD)] and lipid/lipoprotein outcome in at least two studies. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach indicates that a single study rarely (if ever) results in strong evidence, but two studies (typically RCTs) can indicate strong evidence if they are graded highly using the GRADE criteria (35). Prior to selecting the genetic variants and lipid/lipoprotein/apolipoprotein outcomes for evidence grading, LD was assessed using the SNIPA SNP Annotator Software (36) for genes located on the same chromosome and arm (determined using the Online Mendelian Inheritance in Man® [OMIM] database) as outlined in the summary of results' tables in the column labelled 'Cytogenic Location of Gene(s)' (Tables 1 and 2). Strong LD was defined as $r^2>0.8$ and location <250 kb away

from the index SNP location. SNPs in strong LD were considered together for the purposes of evidencing grading.

Based on our abovementioned predetermined criteria for study selection for evidence grading, SNPs that were not included in the evidence grading process likely have weak evidence (at minimum due to lack of replication). According to the GRADE guidelines, when only a single study exists indicating significant findings for an outcome of interest (especially when the study is observational), the overall quality of the evidence is generally rated to be low or very low (37). Therefore, our study selection prioritization process aimed to filter out evidence that would be deemed low or very low quality. Two authors (JH and VG) critically appraised the selected nutrigenetic interactions using the GRADE methodology (37,38). Nutrigenetic interactions were grouped according to studies assessing the same SNP(s)/nutri-GRS and lipid/lipoprotein/apolipoprotein outcome, and the quality of the body of evidence was rated; this process was guided by the GRADE Evidence Profile, which included consideration of risk of bias, inconsistency, indirectness, imprecision, publication bias, plausible confounding, dose-response and other factors (37). For example, different sources of omega-3s (e.g. EPA+DHA vs. ALA; food sources vs. supplementation) were taken into consideration when grading the evidence through the analysis of indirectness within the GRADE approach (37,38). Risk of bias was assessed in each of the included interventional and observational studies using the National Institutes of Health Study Quality Assessment Tools, in line with recently published recommendations for risk of bias assessments (39). To assess measures of precision, coefficients of variation (CV) were calculated based on outcome means (mean change or absolute values – whichever was used for the analyses)

and standard deviations. In cases where standard errors of the mean were reported, these were converted to standard deviation to calculate the CV. The nutrigenetic interactions were each given an evidence grade of high, moderate, low or very low.

Results

Figure 1 outlines the PRISMA Flow Diagram, which was used to guide the systematic review. Tables 1 and 2 provide a summary of the 65 included studies. The results columns of Tables 1 and 2 (far right) indicate only nutrigenetic findings that were statistically significant. Any results related to the studies' analyzed SNPs and outcomes of interest that were not statistically significant are not indicated in the results column. No studies explicitly reported that they followed STREGA guidelines. LD analysis of SNPs tested in different studies revealed strong LD in several SNPs from the *FADS* gene cluster (see Table 3 footnote). As such, LD was taken into consideration in the selection of nutrigenetic interactions selected for evidence grading.

Observational Studies

Of the 65 included studies, 23 were observational with the majority of these being cross-sectional, as outlined in Table 1. A total of 62,221 participants were included in the observational studies. These studies assessed correlations among a number of different genetic variations and outcomes, with several studies assessing genetic variations in the *FADS* gene cluster (40–46), *TNFα* (47–49) and *PPARα* (50–52). Most studies (n=13) assessed total omega-3s (40,45–47,49,52–59). The intake and type of omega-3s, lipid/lipoprotein/apolipoprotein outcomes and associations revealed from these studies were variable as further detailed in Table 1. In the observational studies assessing genetic

variation in the *FADS* gene cluster, some studies indicated significant gene-diet findings related to HDL-cholesterol, LDL-cholesterol, TG, total-cholesterol while other studies demonstrated no significant gene-diet interactions for these outcomes thus indicating notable inconsistency among the results, while considering that SNPs differed by studies (40–46). In the observational studies focused on genetic variation in the *TNFα* gene, there was some evidence of a gene-diet relationship for omega-3 and LDL-cholesterol, total-cholesterol and total-cholesterol:HDL-cholesterol ratio, but again, results differed between studies (47–49). For gene-diet relationships and *PPARα* genetic variation, individual studies indicated significant findings related to total-cholesterol, LDL-cholesterol, TG, apoC-III and LDL peak particle diameter (50–52). Comprehensive details of the observational studies are outlined in Table 1.

Interventional Studies

Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-randomized studies included single arm clinical trials and sequential non-randomized cross-over interventions. For interventional studies, n=6,225 upon combining all sample sizes of the included studies. Again, these studies assessed relationships between a number of different genetic variants and study outcomes. In more recent years, several studies (n=8) used a nutri-GRS or polygenic approaches (60–67) given the plausibility that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are polygenic in nature. Numerous studies assessed genetic variations in the *FADS* gene cluster (60,61,68–70), *APOE* (60,70–79), *CD36* (66,80,81), *PPARγ2* (61,66,82–84) and *PPARα* (82,85,86). Among these studies, results related to significant gene-diet (omega-3) associations influencing lipid/lipoprotein outcomes were generally inconsistent except for

APOE (rs429358 and rs7412), omega-3 and TG in males only (70–74,76–79), and for a 31-SNP nutri-GRS, omega-3 and TG (64,65). There was also consistent evidence to indicate a lack of association among *PPARγ2* (rs1801282) genetic variation, EPA+DHA and LDL cholesterol (61,66,83,84,87). Most studies (n=40) used supplemental EPA and/or DHA sources of omega-3s for the dietary intervention (see Table 2). The dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages ranging from 0.5-3.7 g/day across different studies, and one study with an ALA intervention dosage of 8.1 g/day, as further detailed in Table 2.

Levels of Evidence Using GRADE

A total of 25 articles were included in the evidence grading process, representing 11 unique nutrigenetic interactions as outlined in Tables 3 and 4, and Supplementary Table 2. Through the GRADE process, it was determined that there is strong evidence (GRADE rating: moderate quality) for *APOE* genotypes (rs7412, rs429358), omega-3s and TG lowering in male adults only (70–74,76–79). This evidence suggests that adult males (but not females) with the APOE-E3/E4 or E4/E4 genotype (rs429358, rs7412) tend to experience significant reductions in TG in response to 0.7-3.7 g/day of EPA and/or DHA, with higher dosages demonstrating greater TG lowering effects (70–74,76–79). Furthermore, it was determined that there is strong evidence (GRADE rating: high quality) for using a 31-SNP nutri-GRS to assess the effectiveness of omega-3s for TG lowering in adults with overweight/obesity in various ethnicities (64,65). The evidence suggests that in adults with overweight/obesity, lower genetic risk scores demonstrate greater responsiveness to omega-3 supplementation (64,65).

All other evidence that was evaluated was determined to be weak (GRADE rating: low or very low quality), as further detailed in Table 3. Imprecision, indirectness, and inconsistency were common reasons for downgrading the evidence (refer to Table 3 footnote). There was evidence for a plausible mechanism of action for most of the nutrigenetic interactions that were graded; evidence of a dose response was less common.

Table 1: Summary of observational studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3[1]	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[2]
Bouchard-Mercier et al. 2011 (88)	Cross-Sectional	Single SNP	Healthy Caucasian men and women from INFOGENE study (n=674)	*PPARα*, L162V (rs1800206) *PPARγ*, P12A (rs1801282) *PPARδ*, –87T→ C (rs2016520)	*PPARα*: 22q13.31 *PPARγ*: 3p25.2 *PPARδ*: 6p21.31	Mean: L162: 2.8 g/day V162: 2.9 g/day (unclear if food and/or supplement sources)	Minor allele carriers vs. Non-carriers	LDL-PPD	**LDL-PPD:** In a model including age, sex, TG, BMI, energy and omega-3 intakes and PPAR*α* L162V (rs1800206) polymorphism, the interaction of PPAR*α*162V and omega-3 intakes explained 0.62% of the variance in LDL-PPD.
Bodhini et al. 2017 (89)	Cross-Sectional	Single SNP	Adults with normal glucose tolerance (n=821) and adults with type 2 diabetes (n=861)	*MC4R*, rs17782313 *TCF7L2*, rs12255372 *TCF7L2*, rs7903146	*MC4R:* 18q21.32 *TCF7L2:* 10q25.2-q25.3	**Low:** 0.38 g/day ALA **Moderate:** 0.58 g/day ALA **High:** 0.89 g/day ALA (means) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c	**HDL-c:** 'T' allele carriers of *TCF7L2* rs12255372 within the lowest tertile of ALA intake (mean=0.38 g/day) exhibited higher levels of HDL-c compared to GG homozygotes in the lowest tertile of ALA intake (mean=0.38 g/day)
Chen et al. 2019 (40)	Cross-Sectional Analysis within a Prospective Cohort	Single SNP, Haplotype and Gene-Centric	Adults of Swedish ancestry from the GLACIER cohort (n=5160)	All variations in the *FADS1-FADS2-FADS3* gene cluster and variation within 200kb upstream and downstream of the *FADS* region	*FADS1:* 11q12.2 *FADS2:* 11q12.2 *FADS3:* 11q12.2	**High:** >1.6 g/day **Low:** <1.6 g/day (food)	Entire FADS region gene-centric analysis and Variation in individual FADS cluster SNPs: rs174570, rs174602, rs74771917, rs3168072, rs12577276, rs7115739 and Haplotype analysis	HDL-c LDL-c TG Total-c	**HDL-c:** Significant interaction of rs174570 and omega-3 on HDL-c **LDL-c:** Significant interaction of rs174602 and omega-3 on LDL-c **TG:** Gene-centric analyses demonstrated a significant interaction between variation in the *FADS* gene cluster and omega-3 intake on TG **Total-c:** Significant interaction of rs174602 and omega-3 on total-c ('C' allele carriers exhibited lower total-c with low omega-3 intake, while no such relationship was observed with high omega-3 intake)
Ching et al. 2019 (90)	Cross-Sectional	Single SNP	Vegetarian adults of Malaysian ancestry (n=200)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low:** ≤0.45 g/day ALA **Moderate:** 0.46-0.64 g/day ALA **High:** >0.64 g/day ALA (means) (food)	Comparison between three genotypes	HDL-c TG	**HDL-c:** The TT genotype had significantly lower HDL-c when ALA intake was in the moderate intake range, but there were no significant gene-omega-3 interaction on lipid levels
Dumont et al.	Cross-	Single SNP	Adolescents of	*FADS1*,	*FADS1:* 11q12.2	**High**: >1.4 g/day	Major allele	HDL-c	**Total-c:** Significant interaction whereby the minor allele

2011 (42)	Sectional		European ancestry (n=573)	rs174547		ALA **Low**: ≤1.4 g/day ALA (unclear if food and/or supplement sources)	homozygotes vs. Minor allele carriers	LDL-c TG Total-c	(CT+TT genotype) was associated with lower total-c when ALA intake is high as compared to when intake is low. This remained significant after assessing the interaction using ALA intake as a continuous variable.
Dumont et al. 2018 (43)	Cross-Sectional	Single SNP	Men and women aged 35 to 74 years from the MONA LISA Study of three French populations (n=3069)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low**: 0.6 g/day ALA (mean) **Median**: 0.8 g/day ALA (stratified by median for analyses) **High**: 1.3 g/day ALA (mean) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c	--
Fallaize et al. 2016 (53)	Cross-Sectional (Baseline) and Longitudinal Analyses within a Randomized Intervention	Single SNP*	Healthy adults enrolled in the Food4Me European trial (*n*=1466)	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**High**: >0.67 %kcal **Low**: <0.67 %kcal **Increased Intake:** reduced omega-3 intake from baseline **Decreased Intake:** decreased omega-3 intake from baseline (unclear if food and/or supplement sources)	*APOE*-E4- vs. *APOE*-E4+	Total-c	**Total-c:** Cross-sectional (baseline) analysis demonstrated a significant genotype effect for *APOE,* omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for *APOE,* change in omega-3 intake (increase or decrease) and total-c.
Fontaine-Bisson and El-Sohemy 2007 (91)	Cross-Sectional	Genetic Score	Men and women aged 20-29 years (n=595)	*TNFα,* rs361525, rs1800629	*TNFα:* 6p21.33	Intake range: 0.2-4.6 %kcal (mean intakes were 0.7 %kcal for 0/0, 0.7% kcal for 0/1 and 0.6%kcal for 1/0) (food)	No minor allele ('A') for both SNPs (0/0) vs. One minor allele for rs361525 (1/0) vs. One minor allele for rs1800625 (0/1)	HDL-c	--
Fontaine-Bisson et al. 2009 (92)	Cross-Sectional	Single SNP	Healthy men and women aged 20-29 years (n=593)	*NF-κB* -94Ins/Del ATTG (rs28362491)	*NF-κB:* 4q24	Mean intake: 0.7 %kcal (unclear if food and/or supplement sources)	Ins/Ins vs. Ins/Del vs. Del/Del	HDL-c	**HDL-c:** Significant interaction between *NF-κB* genotype and omega-3 intake on HDL-c
Hellstrand et al. 2012 (93)	Cross-Sectional	Single SNP	Healthy men and women aged 45-68 years from Sweden (n=4635)	*FADS,* rs174547	*FADS:* 11q12.2	**Low:** ≤0.14 %kcal long-chain omega-3 **Moderate:** 0.14-0.28 %kcal long-chain omega-3 **High:** >0.28 %kcal long-chain omega-3 (tertiles	TT vs. TC vs. CC	HDL-c LDL-c TG	**LDL-c:** Significant interaction between *FADS* rs174547 genotype and long-chain omega-3 on LDL-c whereby the 'C' allele was significantly associated with lower LDL-c when long-chain omega-3 intake was in the lowest tertile (but not in the moderate or highest tertile). High long-chain omega-3 intake was associated with significantly higher LDL-c for CC and TC genotypes but not TT genotypes. Stratified analysis based on sex demonstrated that these significant interactions remained for men, but not women, however there was not a

						of intake reported only for certain significant findings) (food and supplement)			significant difference in interactions by sex.
Hosseini-Esfahani et al. 2017 (94)	Nested Case-Control	Single SNP	Healthy men and women aged ≥18 years from Iran (n=1634)	*ZNT8,* rs13266634	*ZNT8:* 8q24.11	**Tertiles for omega-3:** **Low:** <0.38 %kcal **Moderate:** 0.38-0.54 %kcal **High:** >0.54 %kcal (food)	CC vs. CT+TT	HDL-c TG	**HDL-c:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of low HDL-c whereby CC genotypes exhibited a decreased risk of low HDL-c with increasing intake of omega-3; this was not observed in the CT+TT genotype group. **TG:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of high TG whereby CC genotypes exhibited a decreased risk of high TG with increasing intake of omega-3; this was not exhibited in the CT+TT genotype group.
Jang et al. 2014 (95)	Cross-Sectional	Single SNP	Adult: Men and women aged 40-69 from Korea (n=4205) Children: Boys and girls aged 8-13 years from Korea (n=1548)	*PCSK5,* rs1029035	*PCSK5:* 9q21.13	Based on overall median intake (further detailed elsewhere (95)): **Low:** <0.4 %kcal **High:** >0.4 %kcal (food)	CC vs. CA vs. AA	HDL-c	**HDL-c:** Significant interaction between *PCSK5* rs1029035 and omega-3 on HDL-c in male children and male adults. 'C' allele carriers exhibit a tendency to decrease HDL-c with omega-3, while AA genotypes exhibit the opposite effect.
Joffe et al. 2010 (96)	Cross-Sectional	Single SNP	Black women from South Africa, normal weight or with obesity (n=138)	*TNFα,* rs1800629	*TNFα:* 6p21.33	ALA (amount not reported/cannot determine) (food)	GG vs. GA+AA	HDL-c LDL-c TG Total-c Total-c:HDL-c	**Total-c:HDL-c ratio:** Significant interaction between *TNFα,* rs1800629 genotypes and %kcal from ALA whereby increasing %kcal from ALA was associated with increases in Total-c:HDL-c for GG genotypes but decreases in Total-c:HDL-c ratio for GA+AA genotypes
Joffe et al. 2012 (97)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=263)	*TNFα,* rs361525	*TNFα:* 6p21.33	**Median Intakes:** omega-3: 0.28-0.36 % kcal ALA: 0.21-0.26 %kcal EPA: 0.02 %kcal DHA: 0.04-0.08 %kcal (food)	GG vs. GA(+AA for one participant: black, normal weight)	HDL-c LDL-c TG Total-c Total-c:HDL-c	**LDL-c:** Significant interaction for Caucasian women whereby LDL-c decreased with increasing %kcal from EPA in the GG genotype but not the GA genotype of *TNFα,* rs361525. **Total-c:** Significant interaction for white women whereby total-c decreased with increasing EPA and DHA intakes in the GG genotype group but not the GA genotype group of *TNFα* rs361525 but individual rates were not significant. **Total-c:HDL-c ratio:** Significant interaction for black women whereby Total-c:HDL-c decreased within increasing %kcal from omega-3 in the GA genotype group but not GG of *TNFα* rs361525.
Joffe et al. 2014 (98)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=268)	*IL-6,* −174 G>C, IVS3 (rs1800795), +281 G>T, IVS4 (rs1554606), +869 A>G (rs2069845)	*IL-6:* 7p15.3	Black Women (%kcal/day): 0.28 omega-3, 0.21 ALA, 0.02 EPA, 0.04 DHA (normal weight); 0.36 omega-3, 0.22 ALA, 0.04 EPA, 0.08 DHA (obesity)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	The following results were statistically significant only in white women, but not in black women[3]: **HDL-c:** Significant interaction whereby HDL-c increased with: increasing omega-3 and/or DHA and/or ALA intake in *IL-6* rs1800795 C allele carriers and increasing ALA intake in *IL-6* rs1554606 T allele carriers. HDL-c decreased with: increasing EPA and/or DHA intake in *IL-6* rs2069845 G allele carriers. **TG:** Significant interaction whereby TG reduced with increasing EPA intake in *IL-6* rs1800795 C allele carriers **Total-c:HDL-c:** Significant interaction whereby total-c:HDL-c

						White Women (%kcal/day): 0.33 omega-3, 0.26 ALA, 0.01 EPA, 0.05 DHA (normal weight); 0.32 omega-3, 0.25 ALA, 0.02 EPA, 0.05 DHA (food)			ratio decreased with: increasing EPA intake in *IL-6* rs1800795 CC genotypes and *IL-6* rs1554606 TT genotypes, increasing DHA intake in *IL-6* rs1800795 CC genotypes, and increasing ALA intake in *IL-6* rs1554606 TT genotypes.
Lai et al. 2006 (99)	Cross-Sectional	Single SNP	Men and women from the Framingham Heart Study (n=2148)	*APOA5,* rs662799, rs651821, rs3135506, rs2072560, rs2266788	*APOA5:* 11q23.3	**Mean Intake:** 0.69 %kcal omega-3 **Tertiles for omega-3:** **Low:** <0.58 %kcal **Moderate:** 0.58-0.74 %kcal **High:** >0.74 %kcal (unclear if food and/or supplement sources)	Major allele homozygotes vs. Minor allele carriers	TG	--
Lu et al. 2010 (100)	Cross-Sectional	Single SNP	Men and women of Doetinchem Cohort Study (n=3575)	*FADS,* rs174546, rs482548, rs174570	*FADS:* 11q12.2	Mean intake: 0.5 %kcal (food)	Comparison between three genotypes	HDL-c Total-c	**Total -c**: In high omega-3 intake group, total-c was significantly higher with each added minor 'C' allele of rs174546
Nettleton et al. 2009 (101)	Cross-Sectional	Single SNP	Men and women of Caucasian ancestry (n=8511)	*ANGPTL4* E40K (rs116843064)	*ANGPTL4:* 19p13.2	Not Reported/Cannot Determine (food)	Minor allele carriers vs. Non-allele carriers	HDL-c TG	--
Richardson et al. 2011 (102)	Meta-analysis of the Framingham Offspring Study (FOS) and the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	Single SNP	Men and women from FOS and GOLDN studies (*n*=3605)	*PLIN4*, rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	*PLIN4:* 19p13.3	Mean intakes: **FOS Men:** 1.43 g/d **FOS Women:** 1.37 g/d **GOLDN Men:** 1.83 g/d **GOLDN Women:** 1.48 g/d (food and supplement)	Minor allele carriers vs. Non-allele carriers	TG HDL-c	**TG:** Significant interactions for *PLIN4,* rs884164 whereby TG levels increased in minor allele carriers with higher omega-3 intake for males and females combined, and males individually.
Standl et al. 2012 (46)	Cross-Sectional Analysis (10-year time point) within a 10-year longitudinal cohort study	Single SNP	10 year-old children of the GINIplus and LISAplus birth cohort studies (n=1697)	*FADS1/FADS2,* rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	*FADS1/2:* 11q12.2	Median intake: 0.14 mg/MJ omega-3 (ALA+EPA+DPA +DHA) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c Total-c TG	--

Tai et al. 2005 (103)	Cross-Sectional	Single SNP	Framingham Cohort, men and women (*n*=2106)	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	**High**: >0.69 %kcal **Low**: <0.69 %kcal (food)	PPARα: 162V carriers vs. 162L/162L homozygotes	TG apoC-III	**TG:** 167V carriers had lower TG with high omega-3 intake compared to low omega-3 intake (gene-diet-interaction effects were NS) **apoC-III:** Significant gene-diet interactions; Higher apoC-III in 162V carriers with low omega-3 intake compared to 162V carriers with high omega-3 intake and 162L homozygotes with low omega-3 intake
Volcik et al. 2008 (104)	Cross-Sectional (Baseline) Analysis within a Prospective Cohort	Single SNP	African American (*n*=3480) and Caucasian (*n*=10 134) men and women (*N*=13,614)	*PPARα*, L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	*PPARα*: 22q13.31	African American: **High:** >0.32 g/d EPA+DHA **Low:** ≤0.32 g/d EPA+DHA Caucasian: **High:** >0.22 g/d EPA+DHA **Low:** ≤0.22 g/d EPA+DHA (food)	Comparison between three genotypes for each SNP	HDL-c LDL-c TG Total-c	**Total-c, LDL-c:** African Americans (but not Caucasians) homozygous for *PPARα* (rs3892755) TT genotype with high EPA+DHA intake had significantly lower total-c and LDL-c compared to CT and TT genotypes (both high and low EPA+DHA intake)
Warodomwichit et al. 2009 (105)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	*TCF7L2* rs7903146, rs12255372	*TCF7L2:* 10q25.2-25.3	N/A (Median omega-3: 0.67% of kcal) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c LDL-c particle size TG Total-c	--

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. Intakes are total omega-3 unless otherwise specified

2. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS
Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

3. These results were taken from the full-text manuscript's summary table of IL-6 results. Refer to Supplementary Tables S8-S13 in Joffe et al. 2014 (98) for several other significant results, stratified and un-stratified by ethnicity. Note: There were no corrections for multiple testing in the statistical analyses.

'--' indicates that all of the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε2, ε3 and ε4)

Table 2: Summary of interventional studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Intervention Duration	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[1]
AbuMweis et al. 2018 (70)	Randomized, Crossover Controlled Intervention	Single SNP*	Adults with at least one cardiovascular risk factor (n=129)	4 weeks	*FADS1*, rs174561 *FADS2*, rs174583 *ELOVL2*, rs953413 *ELOVL5*, rs2397142 *CETP*, rs5882 *SCD1*, rs2234970, *PPARα*, rs6008259 *LIPF*, rs814628 and *APOE*, rs429358, rs7412	*FADS1/2:* 11q12.2 *ELOVL2:* 6p24.2 *ELOVL5:* 6p12.1 *CETP:* 16q13 *SCD1:* 10q24.31 *PPARα*: 22q13.31 *LIPF:* 10q23.31 *APOE:* 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except *PPARA* and *LIPF* whereby analyses were major allele homozygotes vs. minor allele carriers) and *APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoA1 apoB HDL-c LDL-c TG Total-c	--
Alsaleh et al. 2014 (106)	Randomized Controlled Intervention	Single SNP and Polygenic	Healthy men and women (n=310)	12 months	CETP, rs3764261, *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5/ABCG*, rs4299376 *TIMD4/HAVCR1*, rs6882076 *GCKR*, rs1260326 *TRIB1*, rs2954029 *ANGPTL3/DOCK7*, rs2131925 *FADS1/2/3*, rs174546 *GALNT2*, rs4846914 *ABCA1*,	*CETP:* 16q13 *LIPC:* 15q21.3 *APOB:* 2p24.1 *ABCG5/ABCG8:* 2p.21 *TIMD4/HAVCR1:* 5q33.3 *GCKR:* 2p23.3 *TRIB1:* 8q24.13 *ANGPTL3/DOCK7:* 1p31.3 *FADS:* 11q12.2 *GALNT2:* 1q42.13 *ABCA1:* 9q31.1 *APOE/APOC1/APOC2:* 19q13.32	**Low Dose:** 0.5 g/day EPA and DHA **Moderate Dose:** 0.9 g/day EPA and DHA **High Dose:** 1.8 g/day EPA and DHA (supplement)	Effect sizes per GRS risk allele after omega-3 treatment *and* Risk allele carriers vs. non-risk allele carriers	HDL-c LDL-c TG Total-c	**TG:** significant interaction whereby 1.8 g/day EPA and DHA significantly reduced TG in T allele carriers (21.6% reduction) vs. CC genotypes (3.5% reduction) of *FADS1* rs174546

					rs4149268 *APOE/APOC1/ APOC2,* rs439401					
Armstrong et al. 2012 (107)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	*ALOX5,* dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	*ALOX5:* 10q11.21	Fish oil: 5.0 g/day containing 2.0 g/day EPA and 1.0 g/day DHA Control oil: 5.0 g/day corn/soy oil (supplement)	dd vs. d5 vs. 55	TG Mean lipoprotein particle diameter, total number of particles and particle concentration for: HDL-c and LDL-c	**TG:** significant interaction whereby decreases in TG from omega-3 supplementation were specific to d5 genotype group **HDL-c particle concentration:** significant decrease with omega-3 intervention in the d5 and 55 genotype groups compared to placebo, but no decreases in the dd genotype group **Medium HDL-c particles and HDL-c (mmol/L):** significant gene-treatment interaction but no significant differences after post-hoc analysis for comparisons among genotypes
Binia et al. 2017 (82)	Single-Arm Clinical Trial	Single SNP	Mexican adults 18-40 years (n=191)	6 weeks	*PPARα,* L162V (rs1800206), *PPARγ2*, P12A (rs1801282)	*PPARα*: 22q13.31 *PPARγ2*: 3p25.2	Fish oil: 2.7 g/day containing 1.9 g/d EPA and 0.8 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c	**LDL-c:** significant increase in LDL-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2 **Total-c:** significant increase in total-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2
Bouchard Mercier et al. 2013 (108)	Single Arm Clinical Trial	Single SNP	Healthy adults aged 18-50 years (n=208)	6 weeks	*SREBF1,* rs4925115, rs4925118, rs12953299 *ACLY,* rs8071753, rs8065502, rs2304497 *ACACA* rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	*SREBF1:* 17p11.2 *ACLY:* 17q21.2 *ACACA:* 17q12	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** Significant gene-diet interaction whereby individuals with the GG genotype of *ACLY* rs8071753 and individuals with the GG or CG genotype of *ACACA* rs1714987 exhibited greater TG lower effects following omega-3 supplementation; these two SNPs explained approximately 8% of the variance in plasma TG responses to omega-3 supplementation. There were significant differences in genotype frequencies of *ACLY* rs8071753 for responders and non-responders to omega-3 for TG lowering.
Bouchard-Mercier et al. 2014 (109)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*RXRA* (12 SNPs), *CPT1A* (9 SNPs), *ACADVL* (1 SNP), *ACAA2* (6 SNPs), *ABCD2* (8 SNPs), *ACOX1* (8 SNPs), *ACAA1* (3 SNPs) [outlined in Supplementary	*RXRA:* 9q34.2 *CPT1A:* 11q13.3 *ACADVL:* 17p13.1 *ACAA2:* 18q21.1 *ABCD2:* 12q12 *ACOX1:* 17q25.1 *ACAA1:* 3p22.2	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** There were significant gene-diet interaction effects on TG responses to omega-3 for RXRA rs11185660 genotype dependent on total fat intake, RXRA rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and ACOX1 rs17583163 dependent on total polyunsaturated fat intake

					Table 2]					
Bouchard-Mercier et al. 2014 (110)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*GCK* (13 SNPs) [outlined in Supplementary Table 3]	*GCK:* 7p13	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** CC genotypes of *GCK* rs741038 exhibited significantly greater TG reduction in response to omega-3 when their carbohydrate intake was high (>48.6%kcal) compared to those with the CC genotype of rs741038 with low carbohydrate intake (≤48.6%kcal) and compared to CT or TT genotypes with either high or low carbohydrate intake.
Caron-Dorval et al. 2008 (111)	Single Arm Clinical Trial	Single SNP	Healthy men of Caucasian ancestry aged 18-55 years (n=28)	6 weeks	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	V162 carriers vs. non-carriers	apoB-100 HDL-c LDL-c TG Total-c Total-C:HDL-c	--
Carvalho-Wells et al. 2012 (112)	Sequential Non-Randomized, Cross-Over Dietary Intervention	Single SNP*	Healthy men and women aged 35-70 years (*n*=88)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**Low-Fat**: 4.0 mg/day EPA, 10.6 mg/d DPA, 11.7 mg/d DHA **High-SFA**: 20.2 mg/d EPA, 27.1 mg/d DPA, 15.4 mg/d DHA **High-SFA+DHA**: 524.3 mg/d EPA, 215.5 mg/d DPA, 3017.3 mg/d DHA [actual intakes reported (113)] (supplemental DHA for High-SFA+DHA; others from food sources)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c sdLDL-c TG Total-c	**TG:** Significant diet x genotype interaction for TG; greater TG lowering response to high-SFA+DHA diet in *APOE*-E3/4 carriers (compared to high-SFA diet alone)
Caslake et al. 2008 (114)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men and women aged 20-70 years (*n*=312)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Control oil: 0.0 g/d EPA and DHA Fish oil: 0.7 g/d EPA and DHA Fish oil: 1.8 g/d EPA and DHA (supplement)	*APOE*-E2/E2 + E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	**TG:** Significant interaction between treatment x sex x genotype whereby *APOE*-E3/E4 + E4/E4 males exhibited the greatest TG reductions with both 0.7 g/d EPA and DHA as well as 1.8 g/d EPA and DHA compared to other genotypes
Cormier et al. 2012 (115)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*FADS* gene cluster (19 SNPs) [outlined in Supplementary Table 3]	*FADS:* 11q12.2	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	TG	--
Dang et al. 2015 (73)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	*APOE*-E4+ vs. *APOE*-E4-	HDL-c LDL-c TG Total-c	--
Dawczynski et	Randomized,	Single SNP	Men and	10 weeks	*CD36,*	*CD36:* 7q21.11	Yogurt with lower	Comparison between	HDL-c	**HDL-c**: In response to omega-3 supplementation (0.8-3.0

al. 2013 (81)	Placebo-Controlled, Double-Blind Intervention		women with TG ≥ 1.7 mmol/L, otherwise healthy (n=47)		rs1761667, rs1049673		dose fish oil: 0.8g/day omega-3 containing 0.01g ALA, 0.44g EPA, 0.06g DPA and 0.31g DHA (fish oil) Yogurt with higher dose fish oil: 3.0 g/day omega-3 containing 0.07g ALA, 1.59g EPA, 0.23g DPA and 1.12g DHA (fish oil) Control yogurt: commercial whole fruit yogurt with 3.5% milk fat (food)	three genotypes	TG	g/day), HDL-c increased in GA genotype of *CD36* rs1761667 and CG genotype of *CD36* rs1049673. **TG**: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of *CD36* rs1761667.
Ferguson et al. 2010 (116)	Randomized Intervention and Cross-Sectional (Baseline) Analysis	Single SNP	Men and women with metabolic syndrome from LIPGENE cohort (*n*=450)	12 weeks	*NOS3,* rs11771443, rs1800783, rs1800779, rs1799983, rs3918227, rs743507	*NOS3:* 7q36.1	1.24 g/d EPA+DHA supplement (intervention); quantity of omega-3 not reported for observational analyses	Major allele homozygotes vs. Minor allele carriers	apoA-1 apoB apoB-48 apoC-II apoC-III apoE HDL-c LDL-c TG Total-c	**TG:** For *NOS3* rs1799983 minor-allele (A) carriers only, the observational analysis indicated higher TG with lower EPA+DHA intake (and lower TG with higher EPA+DHA intake). Post-intervention with omega-3 supplementation indicated that only minor-allele (A) carriers exhibited significant TG reduction (accompanied by increases in plasma omega-3).
Harsløf et al. 2014 (61)	Randomized, Controlled Intervention	Single SNP and Genetic Score	Infants of Danish ancestry (n=133)	9 months	*PPARγ2*, Pro12Ala (rs1801282), *FADS1,* rs1535, *FADS2,* rs174575, *FADS3,* rs174448 *COX2,* rs5275, rs689466	*PPARγ2*: 3p25.2 *FADS:* 11q12.2 *COX2:* 1q25.2-q25.3	5.0 mL/day fish oil (median reported intake: 3.8 g/day containing 630 mg/day EPA and 620 mg/day DHA) (supplement)	*PPARγ2* genotype analyses were by major allele homozygotes vs. heterozygotes and *FADS* genotype analyses were by the number of DHA-increasing alleles and *COX2* genotype analyses were by major allele homozygotes vs.	HDL-c LDL-c TG Total-c	**TG:** *PPARγ2* heterozygotes exhibited reduced TG in response to omega-3 when compared to *PPARγ2* heterozygotes in the control (sunflower oil) group

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								heterozygotes vs. minor allele homozygotes		
Itariu et al. 2012 (83)	Randomized, Controlled Intervention	Single SNP	Men and women without diabetes with a BMI ≥40 kg/m^2 aged 20-65 years (n=55)	8 weeks	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 3.4 g/day EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	apoB HDL-c LDL-c TG Total-c	**apoB:** Significant increases in apoB with omega-3 intervention in Ala12 carriers when compared to Pro12 carriers. **Total-c:** Significant interaction effect whereby increases in total-c were exhibited with omega-3 intervention in Ala12 carriers when compared to the Pro12Pro genotype.
Jackson et al. 2012 (74)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	8 weeks and 480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c TG Total-c	**TG:** *APOE*-E3/E4 exhibited reduced fasting TG in response to a high saturated fat + DHA intervention when compared to the high saturated fat diet alone. There was also a significant interaction (meal x time x genotype) for the postprandial TG lowering response whereby *APOE*-E3/4 consuming a high saturated fat + DHA intervention exhibited significantly lower postprandial TG, TG area under the curve, and TG maximum concentration compared to those consuming the high saturated fat diet alone.
Jackson et al. 2017 (117)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB-48 apoB-100	--
Lindi et al. 2003 (84)	Randomized Intervention	Single SNP	Healthy men and women aged 30-65 years (*n*=150)	3 months	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	HDL-c LDL-c TG Total-c	**TG:** Compared to Pro12Pro, Ala12 carriers exhibited significantly greater TG reductions in response to omega-3 supplementation only when total fat intake was ≤37 %kcal or SFA intake was ≤10 %kcal
Lindman et al. (118)	Randomized, Controlled Intervention	Single SNP	Men at high risk of cardiovascular disease aged 65-75 years (n=204)	6 months	*FVII,* rs6046	*FVII:* 13q34	Fish oil containing 2.4 g/d EPA + DHA Dietary advice including recommendations to increase omega-3 (supplement and food)	Major allele homozygotes vs. Minor allele carriers	TG	--
Madden et al. 2008 (80)	Non-Randomized Intervention	Single SNP	Healthy men aged 43-84 years (*n*=111)	12 weeks	*CD36,* rs1527483, rs1049673, rs1761667, rs1984112	*CD36:* 7q21.11	Fish oil containing 1.02 g/d EPA and 0.69 g/d DHA (supplement)	For each SNP: AA vs. AG vs. GG	HDL-c LDL-c LDL-c:HDL-c TG	**TG:** In response to omega-3 supplementation, TG significantly reduced only in individuals with the GG genotype, for each SNP individually (i.e. for rs1527483, rs1049673, rs1761667 and rs1984112 individually) **LDL-c:** In response to omega-3 supplementation, LDL-c increased only in individuals with the rs1761667 AA genotype as well as for individuals with the rs1984112 AA genotype **HDL-c:** In response to omega-3 supplementation, HDL-c significantly increased in individuals with rs1761667 AA or AG as well as for individuals with the CC or CG genotype for either rs1984112, rs1527483 and/or rs1049673; NOTE: rs1527483 results should be interpreted with caution due to low sample sizes for AA and AG genotypes thus reducing statistical power)
Markovic et	Single-Arm	Single SNP	Healthy men	12 weeks	*TNFα,* -308	*TNFα:* 6p21.33	Fish oil containing	Major allele	TG	**TG:** Significant negative correlation between pre-

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al. 2004 (119)	Clinical Trial		(n=159)		(rs1800629) *LT-α,* +252 (rs909253) *IL-1β,* -511 (rs16944) *IL-6,* -174 (rs1800795)	*LT-α:* 6p21.33 *IL-1β:* 2q14.1 *IL-6:* 7p15.3	1.8 g/d EPA+DHA (supplement)	homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)		supplementation TG and change of TG during omega-3 supplementation for all genotypes of genes studied except for *LT-α* rs909253 GG genotype and *IL-1β* rs16944 TT genotype. In *LT-α* rs909253 AA genotype and *TNFα* rs1800629 AA genotype, signification association between BMI (divided in tertiles) and TG changes.
McColley et al. 2011 (120)	Crossover Intervention	Single SNP	Healthy post-menopausal women (n=16)	8 weeks per diet	*FABP2,* rs1799883	*FABP2:* 4q26	**High-Fat:** 50 %kcal from dietary fat **Low-Fat:** 20 %kcal from dietary fat **Low-Fat + omega-3:** 23% kcal from dietary fat with 3 %kcal from omega-3 (food)	Major allele homozygotes vs. Minor allele carriers	TG	--
Minihane et al. 2000 (121)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men aged 30-70 years at risk of atherogenic lipoprotein phenotype (*n*=50)	6 weeks per diet and 480 minute postprandial	*APOE,* rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.0 g/d EPA and DHA, Control oil: 6.0 g/d olive oil capsule (supplement)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c Total-c:HDL	**TG:** Postprandial: Significantly greater reduction in TG incremental area under postprandial TG curve in *APOE*-E2/E3 relative to other *APOE* genotype categories **Total-c:** 6-week: *APOE*-E3/E4 + E4/E4 genotype group exhibited significantly different changes in total-c (increase), relative to other *APOE* genotypes, whereby reductions in total-c occurred
Olano-Martin et al. 2010 (77)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemic men (*n*=38)	4 weeks per diet	*APOE,* rs429358, rs7412	*APOE:* 19q13.32	EPA-rich fish oil: 3.3 g/d EPA DHA-rich fish oil: 3.7 g/d DHA Control oil: 80:20 palm olein:soyabean (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4 (carriers)	apoB apoE HDL-c LDL-c TG TG:HDL-c Total-c	**apoB, LDL-c:** In *APOE*-E4 carriers only, DHA-rich oil treatment resulted in significant increases in apoB and LDL-c **TG:** Significant reduction in TG in response to both EPA and DHA in *APOE*-E3/E3 group; significant reduction in TG in *APOE*-E4 carriers with EPA only. No significant interactions. **Total-c:** Significant genotype x treatment interaction whereby *APOE*-E4 carriers exhibit total-c reductions in response to EPA-rich oil.
Ouellette et al. 2013 (122)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*GPAM* (3 SNPs), *AGPAT3* (13 SNPs), *AGPAT4* (35 SNPs) [outlined in Supplementary Table 3]	*GPAM:* 10q25.2 *AGPAT3:* 21q22.3 *AGPAT4:* 6q26	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	HDL-c LDL-c TG Total-c	**LDL-c:** Significant *GPAM*, rs2792751 genotype x supplementation interaction on LDL-c **TG:** Significant genotype x supplementation interaction on TG for *GPAM,* rs2792751 and rs17129561 as well as *AGPAT4,* rs9458172 and rs3798943
Ouellette et al. 2014 (123)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18-50 years (*n*=208)	6 weeks	*MGLL* (18 SNPs) [outlined in Supplementary Table 3]	*MGLL:* 3q21.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele	apoB HDL-c LDL-c LDL particle size TG Total-c	**LDL-c:** Significant interactions for *MGLL* rs6776142, rs555183, rs782444, rs6787155 and rs1466571 whereby omega-3 supplementation modulated LDL-c levels; rs782444 and rs555183 minor allele homozygotes more likely to be negative responders to omega-3 supplementation (i.e. exhibit reduced LDL-c); rs6780384, rs782444 and rs6787155 major allele homozygotes more likely to be negative responders to omega-3 supplementation

								frequencies)		**LDL particle size:** Significant interactions for *MGLL* rs782440, rs13076543 and rs9877819 whereby omega-3 supplementation modulated LDL particle size; rs549662 minor allele homozygotes more likely to be positive responders to omega-3 supplementation (i.e. exhibit increased LDL particle size)
Paschos et al. 2005 (78)	Single-Arm Clinical Trial	Single SNP*	Men with dyslipidemia, aged 35 to 67 years (n=50)	12 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4	ApoA-I ApoB HDL-c LDL-c TG Total-c	**ApoA-I:** Significant decrease in E3/E3 **HDL-c:** Significant decrease in E3/E3
Pishva et al. 2010 (124)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	*FABP2*, Ala54Thr (rs1799883)	*FABP2:* 4q26	2.0 g/day pure EPA (supplement)	Ala54Ala (GG) vs. Thr54 carriers (GT+TT)	ApoB ApoC-III HDL-c LDL-c TG Total-c	**ApoC-III:** In response to EPA supplementation, significantly greater reductions in ApoC-III in GT+TT genotypes of rs1799883 compared to GG genotype. **HDL-c:** In response to EPA supplementation, significantly greater increases in HDL-c in GT+TT genotypes of rs1799883 compared to GG genotype. **LDL-c:** In response to EPA supplementation, LDL-c significantly decreased in GG genotypes of rs1799883 but not GT+TT genotypes. **TG:** In response to EPA supplementation, significantly greater reductions in TG in GT+TT genotypes of rs1799883 compared to GG genotype.
Pishva et al. 2014 (125)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	*PPARα*, Leu162Val (rs1800206) *PPARα*, Intron 7 SNP	*PPARα* : 22q13.31	2.0 g/day pure EPA (supplement)	Leu162 vs. Val162 carriers *and* Intron 7 GG vs Intron 7 GC	ApoB ApoCIII HDL-c LDL-c TG Total-c	--
Roke and Mutch, 2014 (68)	Single-Arm Clinical Trial	Single SNP	Men aged 18-25 years (n=12)	12 weeks (+8 week washout)	*FADS1*, rs174537 *FADS2*, rs174576 (LD=1.0 therefore presented results for rs174537)	*FADS1/2:* 11q12.2	Fish oil containing 1.8 g/d EPA+DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c Total-c:HDL-c	--
Rudkowska et al. 2014 (126)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*SCD1*, rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	*SCD1 :* 10q24.31	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	**TG:** For *SCD1* rs508384, AA genotype was associated with lower TG than CA and CC genotypes both pre- and post-supplementation.
Rudkowska et al. 2014 (2)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Healthy men and women	6 weeks	Genetic Risk Score	*IQCJ-SCHIP1:* 3q25.32	Fish oil containing 1.9-2.2 g/d EPA +	Responders versus non-responders (i.e.	TG	Thirteen SNPs were associated with TG response to omega-3 supplementation and 10 were used in the GRS calculation.

			aged 18-50 (*n*=141) + Replication of GRS in FINGEN study (n=310)		including: *IQCJ-SCHIP1* (4 SNPs), *SLIT2* (3 SNPs), *PHF17* (3 SNPs), *MYB* (1 SNP), *NXPH1* (1SNP), *NELL1* (1SNP) [outlined in Supplementary Table 3]	*SLIT2:* 4p15.31 *PHF17:* 4q28.2 *MYB:* 6q23.3 *NXPH1:* 7p21.3 *NELL1:* 11p15.1	1.1 g/d DHA (supplement)	TG response) to supplementation		The GRS was significantly associated with TG response. **TG**: The GRS explained 21.5% of the variation in TG response when adjusted for age, sex and BMI. Replication of this GRS in the FINGEN study: the GRS explained 2.0% of the TG change but the association as NS (adjusted for age, sex and BMI).
Scorletti et al. 2015 (127)	Randomized, Placebo-Controlled, Double-Blind Intervention	Single SNP	Men and women with non-alcoholic fatty liver disease (n=95)	15-18 months	*PNPLA3, I148M (rs738409) TM6SF2, E167K (rs58542926)*	*PNPLA3:* 22q13.31 *TM6SF2:* 19p13.11	1.8 g/day EPA+ 1.5 g/day DHA (supplement)	Comparison between three genotypes *and* Major allele homozygotes vs. Minor allele carriers	TG	--
Thifault et al. 2013 (128)	Single-Arm Clinical Trial	Single SNP*	Healthy men and women with overweight or obesity aged 18-50 (*n*=210)	6 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	*APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoB HDL-c LDL-c TG Total-c	--
Tremblay et al. 2015 (129)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (*n*=208)	6 weeks	*PLA2G2A* (5 SNPs), *PLA2G2C* (6 SNPs), *PLA2G2D* (8 SNPs), *PLA2G2F* (6 SNPs), *PLA2G4A* (22 SNPs), *PLA2G6* (5 SNPs), *PLA2G7* (9 SNPs) [outlined in Supplementary Table 3]	*PLA2G2A:* 1p36.13 *PLA2G2C*: 1p36.13 *PLA2G2D*: 1p36.12 *PLA2G2F*: 1p36.12 *PLA2G4A:* 1q31.1 *PLA2G6:* 22q13.1 *PLA2G7:* 6p12.3	Fish oil containing 1.9 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	apoB-100 HDL-c LDL-c TG Total-c	**TG:** omega-3 supplementation significantly reduced TG in *PLA2G7* rs1805018 as well as *PLA2G4A* rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs 10752979 and rs1160719 together explained 5.9% of post-supplementation TG levels
Vallée Marcotte et al. 2016 (130)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Men and woman aged 18-50 years (*n*=208)	6 weeks	*IQCJ* (16 SNPs), *NXPH1* (34 SNPs), *PHF17* (8 SNPs), *MYB* (9 SNPs) [outlined in	*IQCJ:* 3q25.32 *NXPH1:* 7p21.3 *PHF17:* 4q28.2 *MYB:* 6q23.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	TG	**TG:** Significant gene-diet interaction on TG levels pre- vs. post-supplementation for the following SNPs: *IQCJ* (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), *NXPH1* (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), *MYB* (3 SNPs: rs9321493, rs11154794, rs210962). Four SNPs were still significant after applying the false discovery rate to account for multiple testing: rs1449009,

					Supplementary Table 3]					rs2621309, rs61332355 in *IQCJ*; rs7805772 in *NXPH1*. There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in *IQCJ*, rs7805772 in *NXPH1* and rs11154794 in *MYB*. Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for *IQCJ* rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, *NXPH1* rs7806226, rs7805772, *MYB* rs11154794 and rs210936.
Vallée Marcotte et al. 2019 (131)	Single-Arm Clinical Trial (replication of GRS in a novel cohort)	Nutrigenomic GWAS	Healthy adults of Mexican descent aged 18-40 years (n=191)	6 weeks	Genetic Risk Score including 103 SNPs: [outlined in Supplementary Table 3]	NA	Fish oil containing 1.9 g/day EPA + 0.8 g/day DHA (supplement)	Responders versus non-responders (i.e. TG response) to supplementation	TG	**TG:** A first 7-SNP GRS [SNPs selected based on previously developed GRS (2,130)] did not explain TG variation. A second GRS calculated from 103 SNPs significantly explained 4.4% of TG variation. A third GRS including the 5 most relevant SNPs significantly explained 11.0% of TG variation (*NXPH1* rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and *IQCJ-SCHIP1* rs2595241). When subjects with the lowest TG change were not included, this third GRS explained more TG variation. Including only the 28 responders and 28 non-responders with the greatest TG variation, this third GRS explained 29.1% of TG variation.
Vallée Marcotte et al. 2019 (132)	Single-Arm Clinical Trial	Nutrigenomics GWAS (polygenic)	Men and woman aged 18-50 years with overweight or obesity (*n*=208)	6 weeks	GWAS; GRS included 31 SNPs [outlined in Supplementary Table 3]	NA	Fish oil containing 1.9-2.2g/d EPA + 1.1g/d DHA (supplement)	Responders to omega-3 supplementation for TG reduction vs. Non-Responders	TG	**TG:** 31 SNPs associated with TG response to omega-3 supplementation and used in GRS calculation; Lower GRSs were significantly more responsive to omega-3 supplementation for TG reduction compared to higher GRS (GRS accounted for 49.7% of TG responses); These findings were replicated in the FINGEN study with 23 SNPs (GRS accounted for 3.7% of TG responses).
Vallée Marcotte et al. 2020 (65)	Double-Blind, Randomized, Controlled, Crossover Intervention	Nutrigenomics GWAS (polygenic)	Men and women with abdominal obesity and elevated CRP aged 18-70 years (n=122)	10 weeks per diet	GRS included 30 SNPs [outlined in Supplementary Table 3]	NA	Control oil: 3 g/d corn oil Pure EPA: 2.7 g/d Pure DHA: 2.7 g/d (supplement)	Responders to different types of omega-3 supplementation for TG reduction vs. Non-Responders vs. Adverse Responders *and* Responders vs. Adverse Responders	TG	**TG:** The GRS was significantly associated with responsiveness to EPA for TG reduction when comparing responders vs. non-responders vs. adverse responders (trend, p=0.08, for DHA). The GRS was significantly associated with responsiveness to both EPA and DHA for TG reduction when comparing responders vs. adverse responders.
Wu et al. 2014 (133)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP	Men and women with moderate risk of CVD (n=84)	8 weeks	*eNOS* Glu298Asp (rs1799983)	*NOS3:* 7q36.1	Fish oil containing 0.9 g/day EPA + 0.6 g/day DHA (supplement)	Major allele homozygotes (GG) vs. Minor allele carriers (GT+TT)	LDL-c HDL-c TG Total-c	--
Zheng et al. 2018 (134)	Double-Blind, Randomized, Controlled Intervention	Single SNP and Polygenic	Men and women with type 2 diabetes aged 35-80 years for men or postmenopausa	25 weeks	*CD36,* rs1527483 NOS3, rs1799983 *PPARγ2*, rs1801282	*CD36:* 7q21.11 *NOS3:* 7q36.1 *PPARγ2*: 3p25.2	Fish oil: 2.0 g/d EPA and DHA Flaxseed oil: 2.5 g/d ALA Control oil: corn oil (supplement)	Major allele homozygotes vs. Minor allele carriers and High vs. low genetic score calculated	HDL-c LDL-c TG Total-c:HDL-c Total-c	**LDL-c:** significant interaction for *PPARγ2* rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of *PPARγ2* rs1801282 compared to CC genotype *only in the control* (corn oil) group **TG:** omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the *CD36* rs1527483 GG genotype (significant interaction); significant interaction

			l and 80 years for women (*n*=139)					based on three SNPs		between genetic score and omega-3 on TG levels whereby omega-3 (fish oil and flaxseed oil) supplementation significantly reduced TG levels compared to control only in individuals with high genetic scores

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, omega-3: omega-3, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS

Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

'--' indicates that all of the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε2, ε3 and ε4)

Table 3. GRADE Evidence Profile: Genetic Variation, Omega-3 and Lipids

Nutrigenetic interactions for omega-3 and plasma lipid/lipoprotein outcomes									
Patient or Population: adults **Intervention/Exposure: dietary or supplemental omega-3 (EPA and/or DHA and/or ALA)** **Comparison/Control: genetic variation, different omega-3 intakes** **Outcomes: plasma lipids and lipoproteins**									
***Gene* rs Number and Lipid: Number and Type of Studies (total *n*)**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Dose Response**	**Biological Plausibility***	**Quality**	**Conclusion**
***CD36* rs1761667 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (80,135)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the AA genotype of *CD36* rs1761667 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1761667 and TG**: 1 RCT and 1 single arm trial (*n*=115) (80,135)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the GG genotype of *CD36* rs1761667 could lead to significant reductions in TG in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1049673 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (80,135)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	No serious imprecision	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or possibly the CC genotype of *CD36* rs1049673 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1527483 and TG**: 1 RCT and 1 single arm trial (*n*=250) (66,80)	Serious limitations[f]	No serious inconsistency	Serious indirectness[g]	Very serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GG genotype of *CD36* rs1527483 could lead to significant decreases in TG in response to approximately 2.0 g/day of EPA+DHA (but not ALA).
***APOE* rs429358, rs7412 and TG:** 4 RCTs and 5 single arm trials (1 single arm trial consisted of a	No serious limitations	No serious inconsistency	Serious indirectness[h]	No serious imprecision	Undetected	Evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that adult males (but not females) with the *APOE*-E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

subset sample of another single arm trial) (n=980) (70–74,76–79)									response to 0.7-3.7 g/day of EPA and/or DHA. Higher dosages may have greater TG lowering effects.
***APOE* rs429358, rs7412 and Total-c:** 4 RCTs, 5 single arm trials (1 single arm trial consisted of a subset sample of another single arm trial), 1 cross-sectional and longitudinal analysis within an RCT (*n*=2,446) (53,70–74,76–79)	No serious limitations	Serious inconsistency[i]	Serious indirectness[h]	No serious imprecision	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate: Males and Females) and ⊕⊕⊖⊖ (Low: Males)	In males and females combined, strong evidence suggests that there is no nutrigenetic interaction between EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, *APOE* (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c.
31-SNP Nutri-GRS and TG: 1 RCT, 1 single arm trial (*n*=330) (64,65)	No serious limitations	No serious inconsistency	Serious indirectness[j]	No serious imprecision	Undetected	Evidence of a gradient[k]	Some evidence of a mechanism of action[l]	⊕⊕⊕⊕ High	Strong evidence suggests that in adults with overweight/obesity, a 31-SNP genetic risk score can predict TG responsiveness to EPA+DHA supplementation. Individuals with lower genetic risk scores demonstrate greater responsiveness to EPA+DHA for TG lowering.
***PPARg2* rs1801282 and LDL-c:** 4 RCTs, 1 single arm trial (*n*=670) (61,66,83,84,87)	No serious limitations	No serious inconsistency	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence LDL-c responses to omega-3s (EPA+DHA).
***PPARg2* rs1801282 and Total-c:** 4 RCTs, 1 single arm trial (*n*=670) (61,66,83,84,87)	No serious limitations	Serious inconsistency[o]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or GG genotype of *PPARg2* (rs1801282) could lead to significant increases in total-c in response to approximately 3 g/day of omega-3s (EPA+DHA) in individuals with overweight or obesity, but not for individuals without overweight or obesity.
***PPARg2* rs1801282 and TG:** 4 RCTs, 1 single arm trial (*n*=670) (61,66,83,84,87)	No serious limitations	Very serious inconsistency[p]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence total-c responses to omega-3s (EPA+DHA), but when dietary total fat and saturated fat intake are low, nutrigenetic interactions may exist.
***FADS* (rs174547**) and Total-c:** 2 RCTs, 1 single-arm trial, 4 cross-	Very serious risk of bias[q]	No serious inconsistency	Very serious indirectness[r]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊖⊖⊖ (Very Low)	Weak evidence suggests that genetic variation in *FADS* (rs174547**) does not influence total-c responses to omega-3.

sectional studies (*n*=9365) (42,43,45,46,60,68,70)									

*Direct mechanisms of action were considered

**FADS rs174547 was in strong LD with the following SNPs from other included studies and therefore these SNPs were also included in the selection of studies assessing FADS genetic variation, n-3 intake and LDL-c: rs174546, rs174599, rs174601, rs174583, rs1353, rs174561, rs174556, rs174545, rs174537 and rs174576.

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

a. Small sample sizes, especially among homozygous groups in the RCT (with a larger heterozygous group, potentially affecting the results)
b. Some variation in results by genotype
c. One study sample consisted of all males while the other sample consisted of both men and women; differences in age and n-3 dosages (with some overlap)
d. Coefficient of variation >1 for all significant values
e. Coefficient of variation substantially >1 for several values
f. Small sample size within genotype groups for minor allele homozygote and heterozygote groups in the RCT
g. One study sample consisted of all men while the other consisted of men and postmenopausal women with type 2 diabetes
h. Differences in age, omega-3 dosages, and types (with some overlap), and dietary interventions even when considering studies with male study samples separate from male + female study samples
i. Serious inconsistency for men subgroup only; men + women samples were consistent
j. EPA and DHA separate on one study and EPA+DHA in the other, sample stratified into two groups in one study (responders and non-responders) and separated into three groups (responders, non-responders and adverse responders)
k. Evidence of a gradient for GRS and TG responsiveness to omega-3 supplementation
l. Some evidence of a potential mechanism of action for *IQCJ-SCHIP1, NXPH1, PHF17, MYB and NELL1* as discussed by Rudkowska et al. (62), Vallée Marcotte et al. (63)
m. Differences in population (healthy adults, adults with chronic disease or obesity, infants), some variation in length of follow-up
n. Downgraded precision as it was not possible to assess precision in most studies due to lack of reporting of means and SD/SEM
o. Some variation in results even when considering differences in BMI and populations among studies
p. Major variability in results even when considering differences in BMI and populations among studies
q. Risk of bias detected in every study except one
r. Major differences in populations, types and amounts of omega-3 and follow-up for interventional studies

Table 4. Summary of Risk of Bias Across SNPs and Outcomes Following Omega-3 Exposure/Intervention

***CD36*, rs1761667 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1761667 and TG**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1049673 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1527483 and TG**	
Study	**Risk of Bias**
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
***ApoE*, rs429358, rs7412 and TG**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
***ApoE*, rs429358, rs7412 and Total-c**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Fallaize et al. 2016	⊖
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
31-SNP Nutri-GRS and TG	
Study	**Risk of Bias**
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

PPARg2, rs1801282 and LDL-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and Total-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and TG	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
FADS, rs174547 and Total-c	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Alsaleh et al. 2014	⊕
Lu et al. 2010	⊖
Standl et al. 2012	⊖
Dumont et al. 2011	⊖
Dumont et al. 2018	⊖
Roke and Mutch 2014	⊖

⊕ no serious risk of bias; ⊖ serious risk of bias; ⊖⊖ very serious risk of bias (for study design type using NIH Study Quality Assessment Tools)

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

DISCUSSION

Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and high quality evidence) for only a limited amount of evidence in this area: *APOE* (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity. Limited evidence exists for individual genetic-based responsiveness of omega-3s on apolipoprotein and/or LDL particle size, with no studies from the present comprehensive review meeting the criteria for evidence. This highlights the need for more replication studies in this area. While more research exists on omega-3 responsiveness for other lipid outcomes such as total-c, HDL-c and LDL-c, the level of evidence for nutrigenetic interactions related to these outcomes remains low. Again, more studies are needed related to these outcomes, including replication studies of previously identified nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the same type and amount of omega-3s as the original study), and recruit samples with similar characteristics to the original study. Once replication is established, research should then seek to expand the population studied to improve generalizability and explore the effectiveness of different interventions (i.e. different formulations and doses of omega-3s). The variability of the interventions and sample sizes in the studies conducted to date often resulted in the quality of evidence being downgraded (see Table 3). It should also be noted that study heterogeneity precluded the ability to conduct a meta-analysis. Thus, the GRADE approach worked well for evaluating the quality of the evidence given that this approach takes into consideration several factors when determining the quality of

evidence such as risk of bias, indirectness of evidence, inconsistency or results, imprecision and publication bias (37).

It is important to note that our results demonstrating strong evidence for interactions between *APOE* genotypes and lipid responses to omega-3s have notable ethical implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk of developing Alzheimer's disease (136). Moreover, *APOE* genotypes are significantly associated with CVD risk including risk of coronary artery disease and hyperlipidemia (137–139). Interestingly, the pathology of Alzheimer's disease has been linked to cardiovascular mechanisms (136). Future research should explore nutrigenetic interactions, with risk of developing Alzheimer's disease as the study endpoint/outcome of interest. Despite the current lack of knowledge about how diet may play a role in mitigating the genetic-based risk of Alzheimer's disease, several potentially modifiable risk factors account for around 40% of dementia and Alzheimer's disease globally (140), and the link between Alzheimer's disease risk and *APOE* is well-established (141). Therefore, despite the strong scientific validity identified in the present review, there are other factors that must be considered before this test can be recommended for implementation in a practice setting; this includes ethical, legal and social implications (142).

In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness to omega-3s in men but not women speaks to the importance of taking biological sex into account in nutrigenetics research. The importance of this has been further highlighted

elsewhere, where it has been noted that the results of nutrigenetic research may differ in men and women (143). As more studies are completed, researchers may find that certain nutrigenetic interactions differ depending on biological sex, ethnicity, age or other factors, similar to our findings on *APOE,* omega-3s and TG in which there was evidence of a nutrigenetic interaction in males only. Researchers may also find explanations for this, which are currently poorly understood. In general, it is becoming increasingly recognized that health-related responses to different interventions may vary based on biological sex; this is an important consideration of personalized nutrition (143). Nutrigenetic research often groups men and women together, but stratifying based on biological sex could provide further insights for specific nutrigenetic interactions and could also help explain why some replication studies have not demonstrated significant findings (143). Moreover, biomedical research in general historically has been conducted more in men than women; yet such research findings are often generalized to women despite limited research conducted in samples of women, which is problematic for a number of reasons (144). In the present review, the evidence was strong for the *APOE* findings in men only, but not women in part because there were more studies conducted in men. Specifically, there were five studies conducted in men and women (combined) (70,72,73,112,128), and four studies conducted in samples of only men (74,77,78,121), yet no studies conducted in samples of only women. This brings to light important issues of equity and warrants further discussion and consideration.

As research continues to develop, it appears likely that lipid and lipoprotein responses are polygenic in nature. Therefore, future research should consider using nutri-GRSs or other

polygenic methods of assessing responsiveness to nutrition interventions. This work should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs, such as establishing them from genetic-wide association studies. In addition to the two studies meeting the criteria for evidence grading (64,65), a modified version of the 31-SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs (64). While this did not meet our inclusion criteria for evidence grading given that a different GRS was used, the 23-SNP GRS was significantly associated with TG responsiveness to omega-3 supplementation in this population as well, providing further evidence for the scientific validity of this nutrigenetic interaction (64).

While we used the GRADE approach to evaluate the body of evidence, several tools are available for evaluating the quality of scientific evidence, though no generally accepted methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a set of guidelines to assess the scientific validity of genotype-based dietary advice (29). While we originally intended to use these guidelines for assessing the evidence, we came across some limitations that ultimately led us to use the GRADE guidelines. Specifically, Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines should be included in the assessment of scientific validity (29). However, limiting the evidence to only these studies could result in several important studies being missed. In the present review, none of the included studies explicitly indicated that they followed STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA guidelines to assess risk of bias (29). However, the STREGA checklist is only intended for observational genetic association studies - not interventional research (145). In the

present review, 42 of the 65 included studies were interventional (65%) (Table 2). In addition, the STREGA guidelines are intended to improve the transparency and adequate reporting of genetic association studies, but it is not intended to be used as a study quality assessment tool (145). However, Grimaldi et al. nicely highlighted the importance of understanding the nature of the genetic variation, at a functional level, when assessing scientific validity (29). This is not included in the standard GRADE approach but is an important niche component of nutrigenetic research. As such, an analysis of functional SNPs (biological plausibility) was included as an additional component of the standard GRADE process, as indicated in the methods section above. Overall, we found that the methods used in this systematic review were effective and can be used to synthesize and evaluate nutrigenetic studies assessing other gene-nutrient-health outcome interactions.

The additional consideration of functional SNPs to the standard GRADE approach helped to strengthen this review, as biological mechanistic evidence can help ensure that study findings did not occur by chance alone, and this is a component of evidence evaluation frameworks in medical genetics (146,147). Transcriptomic and pathway analyses can help inform the direction of future nutrigenetic studies by generating hypotheses about the impact of specific genetic variations on varying responses to nutrition on health-related outcomes. For example, using transcriptomics and pathway analyses to identify changes in lipid metabolism following omega-3 supplementation, Rudkowska and colleagues identified six genes expressed in opposite directions between responders and non-responders to omega-3 supplementation for TG lowering: *FADS2, PLA2G4A, ALOX15, PEMT, MGLL and GPAM* (148). Tremblay et al. then built on this knowledge

and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a significant impact on the TG lowering effect of omega-3 supplementation (129). Others have built on this mechanistic knowledge as well (122). Future research should now seek to replicate this work given that we found that there have been no replication studies completed and thus, this research (122,129) did not meet the criteria for evidence grading.

In the current body of literature, there are some limitations that should be highlighted. Given the variability in allele frequencies for each SNP, it should be noted that study limitations can arise with small sample sizes whereby some genotype groups may not be adequately powered to detect significant differences. For example, Dawczynski et al. (2013) detected significant changes in TG among the GA genotype group of *CD36* rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA: n=8, GG: n=7) exhibited a significant difference, despite similar directions and magnitudes of effect among the GA and GG genotypes (81). It is thus possible that this study was not adequately powered. Some researchers aim to mitigate this issue of small numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for the minor allele) (68). However, such an approach precludes the possibility to detect an allele-dosage effect. From a physiological perspective, an allele dosage effect would be expected whereby a significant change among a heterozygote group would likely be accompanied by a significant change in one of the homozygote groups but with an even

greater magnitude of the effect. This consideration highlights the importance of having an adequately powered sample size, while factoring in the prevalence of each genotype.

While single SNP research provides important information about individual gene-nutrient interactions, the results of this review indicate that individual responses to omega-3s for altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus, we encourage researchers to further explore the use of nutri-GRSs to improve the accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et al., which obtained a high quality evidence grade in the present review (64,65). This is further exemplified in the analyses recently conducted by Chen et al. (40), which has yet to be replicated and thus was not selected for evidence grading.

The present analysis of scientific validity provides an important first step towards the eventual development of clinical practice guidelines for genetic-based responses to dietary intake. With questionable and variable scientific validity of existing consumer nutrigenetic tests, the development of clinical practice guidelines is an important next step as these can be used by HCPs and industry alike to help promote evidence-based practice in personalized nutrition. Ideally, industry should use future clinical practice guidelines to inform the nutrigenetic associations and related dietary recommendations included in their reports. Decision aids can also be useful to guide clinical practice for HCPs (149), and future research should seek to develop a decision aid related to omega-3s and lipid/lipoprotein outcomes based on genetic variation.

Overall, we have provided a comprehensive overview the body of evidence related to nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing an overview of levels of evidence in this field. To our knowledge, this is the first systematic review with evidence grading in the broader field of nutrigenetics. The results of this work should be used in clinical practice guideline development, to ultimately guide evidence-based practice in personalized nutrition and move this emerging field forward.

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Data Sharing Statement: Data are available upon reasonable request.

Figure Legend:

Figure 1. PRISMA Flow Diagram

*The original PRISMA Flow Diagram indicated the number of studies included in meta-analysis in this box. This has been revised for the purposes of this research

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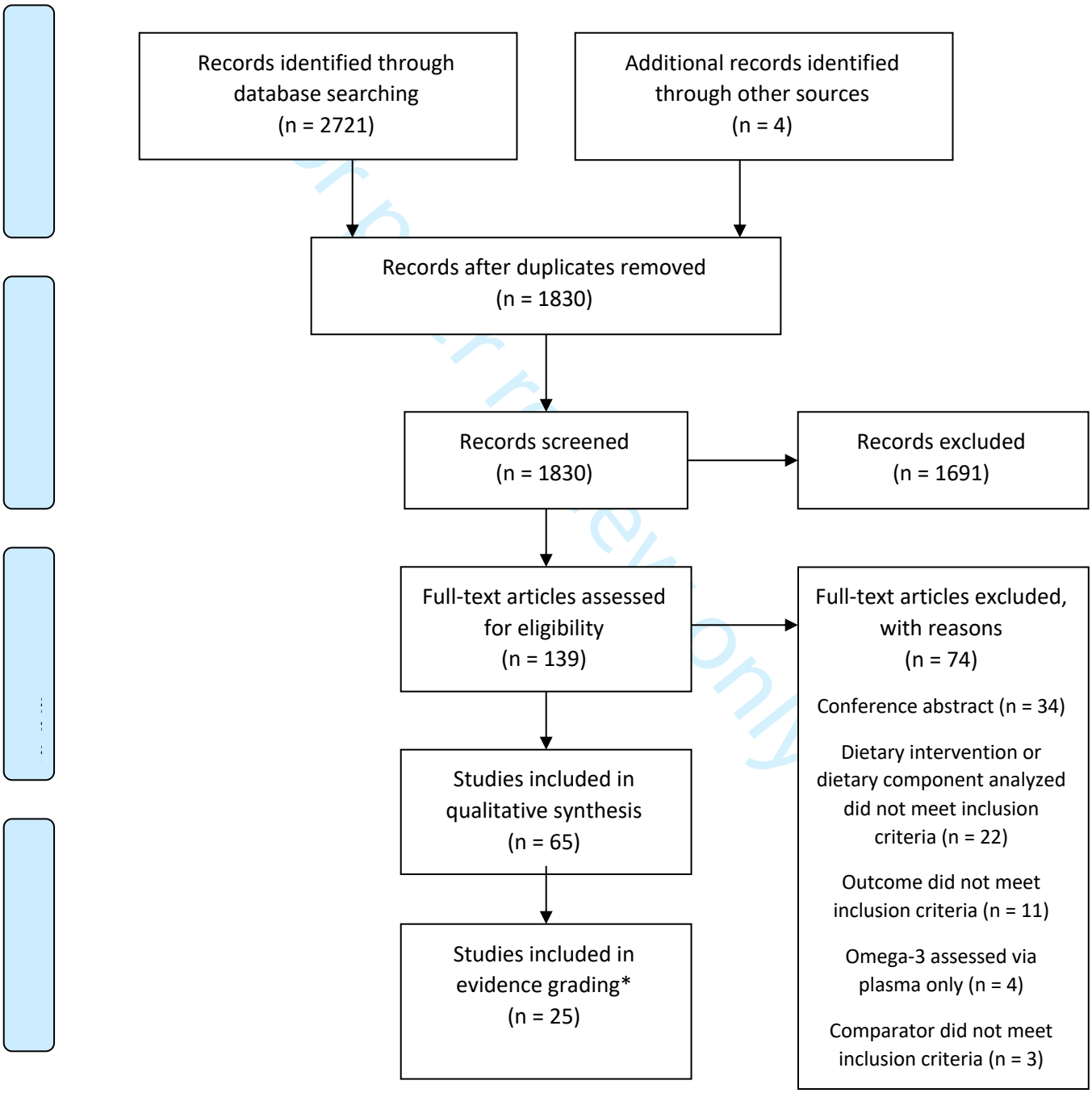
Figure 1: PRISMA 2009 Flow Diagram



Supplementary Tables

Supplementary Table 1: Search Strategy

Embase	
#	**Search Strategy**
1	omega-3':ti,ab,kw OR pufa$:ti,ab,kw OR ((acid* NEAR/5 ('n-3' OR polyunsaturated OR linolenic OR eicosapenta$noic OR timnodonic OR docosahexa$noic)):ti,ab,kw) OR docosahexaenoate:ti,ab,kw OR epa:ti,ab,kw OR dha:ti,ab,kw OR ala:ti,ab,kw
2	omega 3 fatty acid'/exp
3	**#1 OR #2**
4	cholesterol*:ti,ab,kw OR hdl:ti,ab,kw OR ldl:ti,ab,kw OR 'high density lipoprotein*':ti,ab,kw OR 'low density lipoprotein*':ti,ab,kw OR 'beta lipoprotein*':ti,ab,kw OR apo*protein*:ti,ab,kw OR apoa:ti,ab,kw OR apob:ti,ab,kw OR apoc:ti,ab,kw OR apod:ti,ab,kw OR apoe:ti,ab,kw OR apoh:ti,ab,kw OR ((apo NEXT/1 (a OR b OR c OR d OR e OR h)):ti,ab,kw) OR triglyceride*:ti,ab,kw OR triacylglycerol*:ti,ab,kw OR (((serum OR plasma) NEXT/1 (lipid* OR tg OR tag)):ti,ab,kw)
5	cholesterol'/exp OR 'lipoprotein'/exp OR 'triacylglycerol'/exp
6	**#4 OR #5**
7	nutrigenomic*:ti,ab,kw OR nutrigenetic*:ti,ab,kw OR (((nutritional OR expression* OR variation* OR variant*) NEAR/2 (genomic* OR genetic* OR gene OR genes)):ti,ab,kw) OR genotype:ti,ab,kw OR ((('nutrient-gene' OR 'gene-nutrient' OR 'gene-diet') NEXT/1 interaction*):ti,ab,kw) OR 'personali?ed nutrition':ti,ab,kw OR 'precision nutrition':ti,ab,kw
8	nutrigenomics'/exp OR 'nutrigenetics'/exp OR 'genetic variation'/exp OR 'genotype'/exp
9	**#7 OR #8**
10	**#3 AND #6 AND #9**
11	[animals]/lim NOT [humans]/lim
12	**#10 NOT #11**

Medline (Ovid)	
#	**Search Strategy**
1	("omega-3" or PUFA? or (acid* adj5 ("n-3" or polyunsaturated or linolenic or eicosapenta?noic or timnodonic or docosahexa?noic)) or docosahexaenoate or EPA or DHA or ALA).ab,kf,ti.
2	exp Fatty Acids, Omega-3/
3	**1 or 2**
4	(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo adj (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) adj (lipid* or TG or TAG))).ab,kf,ti.
5	exp Cholesterol/ or exp Lipoproteins/ or exp Triglycerides/
6	**4 or 5**
7	(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) adj2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") adj interaction*) or "personali#ed nutrition" or "precision nutrition").ab,kf,ti.
8	Nutrigenomics/ or Genetic Variation/ or Genotype/
9	**7 or 8**
10	**3 and 6 and 9**
11	exp animals/ not humans.sh.
12	**10 not 11**

Web of Science
Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan =All years

#	Search Strategy
1	TS=("omega-3" or PUFA$ or (acid* NEAR/5 ("n-3" or polyunsaturated or linolenic or eicosapenta$noic or timnodonic or docosahexa$noic)) or docosahexaenoate or EPA or DHA or ALA)
2	TS=(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo NEAR/0 (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) NEAR/0 (lipid* or TG or TAG)))
3	TS=(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) NEAR/2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") NEAR/0 interaction*) or "personali?ed nutrition" or "precision nutrition")
4	**#1 AND #2 AND #3**
5	TS=(animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)
6	**#4 not #5**

Supplementary Table 2: Genes, SNPs, lipid/lipoprotein outcomes and studies included in evidence grading process and guideline development

Gene, SNP(s)	Outcome	Studies
APOE: rs429358, rs7412 (Genotype)	TG	AbuMweis et al. 2018 (65) Carvalho-Wells et al. 2012 (106) Caslake et al. 2008 (108) Dang et al. 2015 (68) Jackson et al. 2012 (69) Olano-Martin et al. 2010 (72) Minihane et al. 2000 (115) Paschos et al. 2005 (73) Thifault et al. 2013 (122)
APOE: rs429358, rs7412	Total-c	Fallaize et al. 2016 (48) AbuMweis et al. 2018 (65) Carvalho-Wells et al. 2012 (106) Caslake et al. 2008 (108) Dang et al. 2015 (68) Jackson et al. 2012 (69) Olano-Martin et al. 2010 (72) Paschos et al. 2005 (73) Thifault et al. 2013 (122)
PPARγ2: rs1801282	LDL-c	Binia et al. 2017 (77) Harsløf et al. 2014 (56) Itariu et al. 2012 (78) Lindi et al. 2003 (79) Zheng et al. 2018 (128)
PPARγ2: rs1801282	Total-c	Binia et al. 2017 (77) Harsløf et al. 2014 (56) Itariu et al. 2012 (78) Lindi et al. 2003 (79) Zheng et al. 2018 (128)
PPARγ2: rs1801282	TG	Binia et al. 2017 (77) Harsløf et al. 2014 (56) Itariu et al. 2012 (78) Lindi et al. 2003 (79) Zheng et al. 2018 (128)
CD36: rs1761667	HDL-c	Dawczynski et al. 2013 (76) Madden et al. 2008 (75)
CD36: rs1761667	TG	Dawczynski et al. 2013 (76) Madden et al. 2008 (75)
CD36: rs1049673	HDL-c	Dawczynski et al. 2013 (76) Madden et al. 2008 (75)
CD36: rs1527483	TG	Madden et al. 2008 (75) Zheng et al. 2018 (128)
FADS: rs174547*	Total-c	Dumont et al. 2011 (37) Dumont et al. 2018 (38) Lu et al. 2010 (94) Standl et al. 2012 (41) Alsaleh et al. 2014 (100) AbuMweis et al. 2018 (65) Roke et al. 2014 (63)
31-SNP Genetic Risk Score	TG	Vallée Marcotte et al. 2019 (59) Vallée Marcotte et al. 2020 (60)

Supplementary Table 3: Additional list of gene(s) and SNP(s) tested in studies

Study	*Gene(s)*, SNP(s)
Chen et al. Int J Obes;43:808-820 (2019)	*FADS2,* rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276 *FADS3,* rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285 *RAB3IL1,* rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252
Cormier et al. 2012	*FADS* gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567
Vallée Marcotte et al. Am J Clin Nutr;109:176–185 (2019)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Tremblay et al. Lipids in Health and Disease (2015) 14:12	*PLA2G2A*, rs876018, rs955587, rs3753827, rs11573156, rs11573142 *PLA2G2C*, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718 *PLA2G2D*, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671 *PLA2G2F*, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904

	PLA2G4A, rs979924, rs2076075, rs3736741, rs10911949, rs10752979, rs1160719, rs10737277, rs12720702, rs7522213, rs7540602, rs10157410, rs12720497, rs4651331, rs1569480, rs10911935, rs12353944, rs11576330, rs10489410, rs10911946, rs3820185, rs12746200, rs11587539 *PLA2G6*, rs5750546, rs132989, rs133016, rs2235346, rs2284060 *PLA2G7*, rs12195701, rs12528807, rs1421368, rs1421378, rs17288905, rs1805017, rs1805018, rs6929105, rs7756935
Ouellette et al. J Nutrigenet Nutrigenomics;6:268–280 (2013)	*GPAM*, rs17129561, rs10787428, rs2792751 *AGPAT3*, rs999519, rs2838440, rs2838445, rs2838458, rs4818873, rs9978441, rs9982600, rs11700575, rs17004619, rs2838452, rs2838456, rs3788086, rs2838429 *AGPAT4*, rs746731, rs747866, rs1125640, rs2277092, rs2293286, rs3757025, rs3798225, rs3798920, rs3798924, rs3798929, rs3798943, rs3798945, rs3822853, rs3823058, rs4709501, rs6906489, rs6923835, rs7750302, rs7769321, rs9458172, rs10945713, rs10945719, rs11965825, rs12202278, rs17627837, rs12524665, rs1001422, rs6455711, rs9456642, rs2064721, rs3778227, rs3798922, rs11967514, rs7768457, rs12662114
Ouellette et al. Lipids in Health and Disease, 13:86 (2014)	*MGLL,* rs782440, rs16826716, rs6776142, rs9877819, rs555183, rs6780384, rs13076593, rs605188, rs6765071, rs782444, rs549662, rs3773155, rs541855, rs6439081, rs6439082, rs6787155, rs1466571, rs893294
Bouchard-Mercier et al. Genes Nutr 9:395 (2014)	*GCK,* rs2268573, rs2908297, rs2971676, rs758989, rs12673242, rs2908290, rs2284777, rs2300584, rs1990458, rs741038, rs1799884, rs2908277, rs3757838
Bouchard-Mercier et al. Nutrients, 6, 1145-1163 (2014)	*RXRA*, rs10881576, rs7871655, rs12339187, rs11185660, rs11103473, rs10776909, rs12004589, rs3132301, rs1805352, rs3132294, rs1805343, rs1045570 *CPT1A*, rs3019598, rs897048, rs7942147, rs4930248, rs11228364, rs11228368, rs10896371, rs1017640, rs613084 *ACADVL*, rs2017365 *ACAA2*, rs529556, rs10502901, rs631536, rs1942421, rs2276168, rs7237253 *ABCD2*, rs4072006, rs10877201, rs12582802, rs4294600, rs11172696, rs10877173, rs7133376, rs7968837 *ACOX1*, rs10852766, rs3744033, rs12430, rs8065144,

	rs11651351, rs3643, rs7213998, rs17583163 *ACAA1*, rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	*CETP*, rs3764261, rs247616, rs7205804 *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5, ABCG8*, rs4299376 *TIMD4, HAVCR1*, rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 *ANGPTL3, DOCK7*, rs3850634, rs1167998, rs2131925 *FADS1, FADS2, FADS3*, rs174550, rs174547, rs174546, rs174583 *GALNT2*, rs4846914, rs1321257 *ABCA1,* rs4149268 *APOE, APOC1, APOC2,* rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	*IQCJ-SCHIP1, MYB, NELL1, NXPH1, PHF17, SLIT2,* rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	*IQCJ*, rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	NXPH1, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs12537067, rs4318981, rs17153997, rs7801099, rs4725120, rs1859275, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862 PHF17, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308
Vallée Marcotte et al. Nutrients; 11, 737 (2019)	*IQCJ-SCHIP1*, rs12497650, rs4501157, rs13091349, rs2044704, rs1962071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs1449009, rs61332355, rs12485627, rs2595242, rs7639937, rs9820807, rs1375409, rs1967363, rs9824310, rs11915303, rs9835214, rs11921343, rs13066560, rs1675497, rs9839862, rs16829875, rs17795566, rs9860588, rs16830408, rs17798579, rs2364930, rs9865997, rs2595241, rs7632574, rs2621308 *NXPH1*, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs4318981, rs17153997, rs7801099, rs4725120, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862, rs6463808 *PHF17*, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, *SLIT2,* rs2952724 *NELL1*, rs752088

Supplementary Table 4: 31-SNP Nutri-GRS

***Gene,* rs Number**	**Alleles[1]**	**Associated Points**
IQCJ-SCHIP1, rs7639707	A/G	+1
IQCJ-SCHIP1, rs62270407	C/T	-1
NXPH1, rs61569932,	G/T	+1
NXPH1, rs1990554	A/C	+1
NXPH1, rs6463808	A/G	+1
NXPH1, rs6966968	A/G	+1
NXPH1, rs28473103	A/G	-1
NXPH1, rs28673635	A/G	+1
NXPH1, rs12702829	C/T	+1
NXPH1, rs78943417	A/T	-1
NXPH1, rs293180	G/T	+1
NXPH1, rs1837523	C/T	-1
PHF17, rs1216346	C/T	+1
PHF17, rs114348423	A/G	+1
PHF17, rs75007521	G/T	-1
MYB, rs72560788	C/T	-1
MYB, rs72974149	A/G	-1
MYB, rs210962	C/T	-1
MYB, rs6933462	C/G	+1
NELL1, rs79624996	A/G	+1
NELL1, rs1850875	C/T	+1
NELL1, rs78786240	C/T	-1
NELL1, rs117114492	G/T	+1
SLIT2, rs184945470	C/T	+1
SLIT2, rs143662727	A/G	-1
SLIT2, rs10009109	C/T	+1
SLIT2, rs10009535	A/G	+1
SLIT2, rs61790364	A/G	+1
SLIT2, rs73241936	C/T	+1
SLIT2, rs16869663	A/G	+1
SLIT2, rs76015249	A/G	+1

1. Minor alleles are underlined

For individuals carrying one or two minor alleles, provide the associated number of points (either +1 or -1). For individuals homozygous for the major allele, provide 0 points. Count the overall number of points. Individuals with lower nutri-GRS are more likely to respond to approximately 3.0 g/day EPA+DHA for TG lowering.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. T1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA (meta-analysis not appropriate)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12, Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Table 3, 34-39
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	45-46
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	40-47
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	47

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

A systematic review of nutrigenetics, omega-3 and plasma 2 lipids/lipoproteins/apolipoproteins with evidence evaluation using the GRADE approach

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Primary Subject Heading:	Nutrition and metabolism
Secondary Subject Heading:	Cardiovascular medicine, Genetics and genomics, Nutrition and metabolism
Keywords:	NUTRITION & DIETETICS, GENETICS, Lipid disorders < DIABETES & ENDOCRINOLOGY

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A systematic review of nutrigenetics, omega-3 and plasma lipids/lipoproteins/apolipoproteins with evidence evaluation using the GRADE approach

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Running Head: Nutrigenetics, omega-3 and lipids/lipoproteins

Data described in the manuscript will be made available upon request pending approval from the corresponding author.

Abbreviations: ALA (alpha-linolenic acid); CV (coefficient of variation); DHA (docosahexaenoic acid); EPA (eicosapentaenoic acid); FDA (Food and Drug Administration); GRADE (Grading of Recommendations Assessment, Development and Evaluation); HCP (healthcare professional); LD (linkage disequilibrium); nutri-GRS (nutrigenetic risk score); SNP (single nucleotide polymorphism)

ABSTRACT

Objectives: Despite the uptake of nutrigenetic testing through direct-to-consumer services and healthcare professionals, systematic reviews determining scientific validity are limited in this field. The objective of this review was to: retrieve, synthesize and assess the quality of evidence (confidence) for nutrigenetic approaches related to the effect of genetic variation on plasma lipid, lipo- and apolipoprotein responsiveness to omega-3 fatty acid intake.

Design: A systematic review was conducted using three search engines (Embase, Web of Science and Medline) for articles published up until August 1, 2020. Included studies for the narrative synthesis assessed any nutrigenetic associations/interactions for genetic variants influencing the plasma lipid, lipo- and/or apolipoprotein response to omega-3 fatty acid intake in humans (adult and pediatric). Specific nutrigenetic associations/interactions were then prioritized for evidence grading if they had been reported in at least two independent studies. Risk of bias was assessed in individual studies. Evidence was evaluated using the GRADE approach. This systematic review was registered with PROSPERO (CRD42020185087).

Results: Out of 1830 articles screened, 65 met the inclusion criteria for the narrative synthesis (*n*=23 observational, *n*=42 interventional); of these, 25 met the inclusion criteria for evidence evaluation using GRADE. Overall, current evidence is insufficient for gene-diet associations related to omega-3 fatty acid intake on plasma apolipoproteins, total cholesterol, HDL-cholesterol, LDL-cholesterol and LDL particle size. However, there is strong (GRADE rating: moderate quality) evidence to suggest that male *APOE*-E4 carriers (rs429358, rs7412) exhibit significant triglyceride reductions in response to omega-3-rich fish oil with a dose-response effect. Moreover, strong (GRADE rating: high quality) evidence suggests that a 31-SNP nutrigenetic risk score can predict plasma triglyceride responsiveness to omega-3-rich fish oil in adults with overweight/obesity from various ethnicities.

Conclusions: Most evidence in this area is weak, but two specific nutrigenetic interactions exhibited strong evidence, with limited generalizability to specific populations.

Keywords: nutrigenomics, nutrigenetics, nutritional genomics, genetic risk score, nutrigenetic risk score, triglycerides, lipids, lipoproteins, omega-3 fatty acid, *APOE*

STRENGTHS AND LIMITATIONS

- Strength: Comprehensive systematic review guided by PRISMA
- Strength: Critical appraisal of the evidence guided by GRADE
- Limitation: Inability to conduct a meta-analysis given the comprehensive overview of studies and thus heterogeneity
- Limitation: Several included studies without replication; most evidence was low or very low quality according to GRADE

INTRODUCTION

Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research demonstrates that there is significant inter-individual variability in cardiometabolic risk factor levels, in part based on a combination of genetic and nutrition-related risk factors (2,3). For example, protein intake has consistently been shown to influence measures of body weight and composition dependent on *FTO* genotype (rs9939609 or loci in strong linkage disequilibrium) (4,5). Consumers indicate great interest in personalized nutrition based on genetics (6,7), however, a lack of industry oversight (8,9) has led to highly variable scientific validity of nutrigenetic tests available to consumers. While recognizing that some groups question whether genetic testing for personalized nutrition is ready for 'prime time', Gorman and colleagues suggested that there are certain specific nutrigenetic interactions with strong evidence that could be considered for implementation into clinical practice by expert committees who are responsible for creating dietary guidelines (10). With this in mind, systematic reviews that include an evaluation of levels of evidence are urgently needed in order to determine if there are any nutrigenetic associations that may warrant potential implementation into practice.

The dominant omega-3 polyunsaturated fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which typically come from marine sources (e.g. fish oil), and alpha-linolenic acid (ALA), which are rich in plant sources (e.g., canola oil) (11,12). It is well established that higher intakes of omega-3 fatty acids from foods or supplements (herein after referred to collectively as "omega-3s"), particularly from long-chain EPA and DHA, tend to improve indicators of cardiometabolic health (12,13). In

terms of their lipid and lipoprotein lowering effects, omega-3s have consistently demonstrated an impact on triglycerides (TG) (14). High-quality evidence from population-based studies suggests that long-chain omega-3s (EPA and DHA) reduce plasma TG by about 15% (14). There is also high-quality evidence suggesting that EPA and DHA can raise high-density lipoprotein (HDL) cholesterol (14). Other studies have further demonstrated a relationship between omega-3 and HDL-cholesterol (15), low-density lipoprotein (LDL)-cholesterol (15), total cholesterol (16–18), apolipoproteins (19), and LDL particle size (20). Despite several studies with significant findings for these outcomes, when reviewing the evidence, studies have demonstrated conflicting results for the impact of omega-3 on many lipid profile outcomes (14). Genetic variation could explain this heterogeneity. EPA and DHA have been shown to significantly impact the expression of thousands of genes including those involved in inflammatory and atherogenic pathways (21,22). Evidence now demonstrates that the health impacts of omega-3 intake could differ based on genetic variation (23,24). Despite the potential for omega-3s to have a significant positive impact on health outcomes, population intakes of omega-3s tend to be low (25). While the World Health Organization's Adequate Intake level for adults is 200-250 mg EPA+DHA daily (26,27), the mean reported intake of EPA+DHA in the United States is only approximately 100 mg daily (25). Nutrigenetic interventions have the potential to motivate improvements in dietary intake beyond population-based interventions (28). Additionally, evidence suggests that genetic variability affects health responses to omega-3s (23). Thus, critically appraising and grading the evidence for nutrigenetic interactions related to omega-3s and plasma lipids, lipoproteins and apolipoproteins is an important research priority. The most recent

systematic review on nutrigenetic interactions related to omega-3s and intermediate phenotypes of cardiovascular disease was conducted nearly a decade ago, and this study did not evaluate the quality of evidence using an established methodology (29). Therefore, we aimed to provide a comprehensive summary of current evidence related to inter-individual variability in plasma lipid, lipoprotein and apolipoprotein responses to omega-3 intake (plant and marine sources) based on genetic variations. Overall, the specific objectives of this study were as follows:

Objective 1. Systematically search, identify (select), and provide a narrative synthesis of all studies that assessed nutrigenetic associations/interactions for genetic variants (comparators) influencing the plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population).

Objective 2. Assess the overall quality of evidence for specific priority nutrigenetic associations/interactions based on the following inclusion criteria: nutrigenetic associations/interactions reported for the same genetic variants (comparators) influencing the same plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population) in two independent studies, irrespective of the findings.

Methods

Patient and Public Involvement: No patient involvement.

Literature Search

The systematic review protocol was registered with PROSPERO (CRD42020185087). The review process was guided by previously established methods, including a previously outlined five-step systematic review process (30,31). The search engines Embase, Web of Science and Medline OVID were used to conduct the search starting in May 2020 and screen for articles meeting inclusion criteria, using the comprehensive search terms outlined in Supplementary Table 1, properly combined by Boolean operators. The literature was searched up until August 1, 2020. A PRISMA diagram (Figure 1) guided the article screening process (32).

Inclusion and Exclusion Criteria

Original studies were included if they were written in English or French. Inclusion criteria were developed using the Population, Intervention, Comparison, Outcomes, (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (33,34) for interventional and observational research, respectively. These are detailed in Table 1 for each study objective.

Table 1. PICO/PECO for Study Objectives

PICO/PECO for Objective 1:	
Population	Human studies (adult and pediatric)
Intervention/ Exposure	Omega-3s (total omega-3 or various types; supplemental and/or dietary intake)
Comparison	Genetic variation
Outcomes	HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and/or TG
PICO/PECO for Objective 2*:	
Population	Human studies (adult and pediatric)
Intervention/	Omega-3s (total omega-3 or various types; supplemental and/or dietary

Exposure	intake)
Comparison	Genetic variation in the same genetic location [gene(s) and SNP(s)]
Outcomes	The same outcome of interest among studies with the same genetic comparators: HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and/or TG

*Nutrigenetic associations/interactions were included in objective 2, **in the evidence grading process**, irrespective of the findings, provided that they had been reported in at least two independent studies on the same gene(s) and SNP(s), and the same plasma outcome.

There were no limitations to the population characteristics (all populations/patient samples were included). Animal studies were excluded. Dietary interventions and observational studies involving omega-3s (total omega-3 or various types; supplemental and/or dietary intake) and comparing lipid and/or lipoprotein and/or apolipoprotein outcomes between different genetic variations based on omega-3 dietary or supplemental intake (and not blood fatty acid levels; e.g. EPA and DHA in red blood cells) were included in the narrative synthesis. In included studies, samples had to be stratified on the basis of genetic variation. Specific lipid and lipoprotein outcomes of interest were: HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and triglycerides (TG). Studies that reported ratios of the aforementioned lipid parameters (e.g. HDL-cholesterol to total cholesterol ratio) were also included. Both observational and interventional studies were included, as well as single-gene, polygenic and genome-wide association studies (GWAS). Differences in study designs and methods were considered when developing the overall evidence grades, as further detailed below. Associations/interactions reported in two independent studies formed the basis of the inclusion criteria for objective 2, in which nutrigenetic associations/interactions were prioritized for evidence grading. This is further detailed in Table 1 and the section below entitled “Evidence Grading.”

Article Selection and Data Extraction

Two independent investigators (JK and VG) screened articles using the computer software *Covidence* (including title, abstract, and full-text screening) and extracted data from the included articles. Reference lists of included articles and of a systematic review on a similar topic (35) were also screened for relevant articles. Data extraction templates were piloted by two independent investigators (JK and VG) on ten included studies and revised accordingly. The final data extraction templates included the following components for each study: first author name and year, study design, genetic approach, population and sample size, study duration (interventional studies only), genes and single nucleotide polymorphisms (SNPs) analyzed with rs numbers, quantity and type of omega-3, comparisons (e.g. a control group or different amount/type of omega-3s as well as genetic grouping), lipid/lipoprotein outcome(s), whether or not the study reported that they followed STREGA guidelines and a summary of statistically significant study findings relevant to the research question. Corresponding authors of included studies were contacted as needed to provide clarity and/or additional information about the included studies.

Evidence Grading

Upon reading all full-text articles included, and summarizing the body of evidence (Tables 2 and 3), SNPs/nutrigenetic risk scores (nutri-GRSs) and subsequent lipid/lipoprotein/apolipoprotein outcomes were systematically prioritized and selected for evidence grading, if a specific nutrigenetic association/interaction was reported in at least two independent studies. To clarify, this refers to the same SNP(s)/nutri-GRS [or SNPs in strong linkage disequilibrium (LD)] being assessed and influencing the same lipid/lipoprotein outcome in at least two studies. For these nutrigenetic

associations/interactions, we proceeded with evidence grading, while including **all** studies relevant to the particular nutrigenetic association/interaction, irrespective of the findings. Consistency of results was then one of several factors considered when grading the body of evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach indicates that a single study rarely (if ever) results in strong evidence, but two studies (typically RCTs) can indicate strong evidence if they are graded highly using the GRADE criteria (36). Prior to selecting the nutrigenetic associations/interactions (genetic variants and lipid/lipoprotein/apolipoprotein outcomes) for evidence grading, LD was assessed using the SNIPA SNP Annotator Software (37) for genes located on the same chromosome and arm (determined using the Online Mendelian Inheritance in Man® [OMIM] database) as outlined in the summary of results' tables in the column labelled 'Cytogenic Location of Gene(s)' (Tables 1 and 2). Strong LD was defined as $r^2>0.8$ and location <250 kb away from the index SNP location. SNPs in strong LD were considered together for the purposes of evidencing grading.

Based on our abovementioned predetermined criteria for specific nutrigenetic topic selection for evidence grading, nutrigenetic associations/interactions that were not included in the evidence grading process likely have weak evidence (at minimum due to lack of replication, for example, *ZNT8* rs13266634 and HDL-c or TG responsiveness to omega-3, which has only been assessed in a single study (38)). According to the GRADE guidelines, when only a single study exists indicating significant findings for an outcome of interest (especially when the study is observational), the overall quality of the evidence is generally rated to be low or very low (39). Therefore, our process for prioritizing

nutrigenetic topics for evidence grading aimed to filter out specific nutrigenetic associations/interactions that would likely be deemed low or very low quality (based on, at minimum, lack of replication). Two authors (JK and VG) critically appraised the selected nutrigenetic interactions using the GRADE methodology (39,40). Nutrigenetic interactions were grouped according to studies assessing the same SNP(s)/nutri-GRS and lipid/lipoprotein/apolipoprotein outcome, and the quality of the body of evidence (studies with significant and non-significant results) was rated; this process was guided by the GRADE Evidence Profile, which included consideration of risk of bias, inconsistency, indirectness, imprecision, publication bias, plausible confounding, dose-response and other factors (39). For example, different sources of omega-3s (e.g. EPA+DHA vs. ALA; food sources vs. supplementation) were taken into consideration when grading the evidence through the analysis of indirectness within the GRADE approach (39,40). Risk of bias was assessed in each of the included interventional and observational studies using the National Institutes of Health Study Quality Assessment Tools, in line with recently published recommendations for risk of bias assessments (41). To assess measures of precision, coefficients of variation (CV) were calculated based on outcome means (mean change or absolute values – whichever was used for the analyses) and standard deviations. In cases where standard errors of the mean were reported, these were converted to standard deviations to calculate the CV. The nutrigenetic interactions were each given an evidence grade of high, moderate, low or very low.

Results

Figure 1 outlines the PRISMA Flow Diagram, which was used to guide the systematic review. Supplementary Tables 2 and 3 provide a summary of the 65 included studies. The

results columns of Supplementary Tables 2 and 3 (far right) indicate nutrigenetic findings that were statistically significant. Any results related to the studies' analyzed SNPs and outcomes of interest that were not statistically significant are not indicated in the results column. No studies explicitly reported that they followed STREGA guidelines. LD analysis of SNPs tested in different studies revealed strong LD in several SNPs from the *FADS* gene cluster (see Table 2 footnote). As such, LD was taken into consideration in the selection of nutrigenetic interactions selected for evidence grading.

Observational Studies

Of the 65 included studies, 23 were observational with the majority of these being cross-sectional, as outlined in Supplementary Table 2. A total of 62,221 participants were included in the observational studies. These studies assessed correlations among a number of different genetic variations and outcomes, with several studies assessing genetic variations in the *FADS* gene cluster (42–48), *TNFα* (49–51) and *PPARα* (52–54). Most studies (n=13) assessed total omega-3s (38,42,47–49,51,54–60). The intake and type of omega-3s, lipid/lipoprotein/apolipoprotein outcomes and associations revealed from these studies were variable as further detailed in Supplementary Table 2. In the observational studies assessing genetic variation in the *FADS* gene cluster, some studies indicated significant gene-diet findings related to HDL-cholesterol, LDL-cholesterol, TG, total-cholesterol while other studies demonstrated no significant gene-diet interactions for these outcomes thus indicating notable inconsistency among the results, while considering that SNPs differed by studies (42–48). In the observational studies focused on genetic variation in the *TNFα* gene, there was some evidence of a gene-diet relationship for omega-3 and LDL-cholesterol, total-cholesterol and total-

cholesterol:HDL-cholesterol ratio, but again, results differed between studies (49–51). For gene-diet relationships and *PPARα* genetic variation, individual studies indicated significant findings related to total-cholesterol, LDL-cholesterol, TG, apoC-III and LDL peak particle diameter (52–54). Comprehensive details of the observational studies are outlined in Supplementary Table 2.

Interventional Studies

Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-randomized studies included single arm clinical trials and sequential non-randomized cross-over interventions. For interventional studies, n=6,225 participants upon combining all sample sizes of the included studies. Again, these studies assessed relationships between a number of different genetic variants and study outcomes. In more recent years, several studies (n=8) used a nutri-GRS or polygenic approaches (61–68) given the plausibility that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are polygenic in nature. Numerous studies assessed genetic variations in the *FADS* gene cluster (61,62,69–71), *APOE* (61,71–80), *CD36* (67,81,82), *PPARγ2* (62,67,83–85) and *PPARα* (83,86,87). Among these studies, results related to significant gene-diet (omega-3) associations influencing lipid/lipoprotein outcomes were generally inconsistent except for *APOE* (rs429358 and rs7412), omega-3 and TG in males only (71–75,77–80), and for a 31-SNP nutri-GRS, omega-3 and TG (65,66). There was also consistent evidence to indicate a lack of association among *PPARγ2* (rs1801282) genetic variation, EPA+DHA and LDL cholesterol (62,67,84,85,88). Most studies (n=40) used supplemental EPA and/or DHA sources of omega-3s for the dietary intervention (see Supplementary Table 3). The dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages

ranging from 0.5-3.7 g/day across different studies, and one study with an ALA intervention dosage of 8.1 g/day, as further detailed in Table 3.

Levels of Evidence Using GRADE

A total of 25 articles were included in the evidence grading process, representing 11 unique nutrigenetic associations/interactions as outlined in Tables 2 and 3, and Supplementary Table 4. Through the GRADE process, it was determined that there is strong evidence (GRADE rating: moderate quality) for *APOE* genotypes (rs7412, rs429358), omega-3s and TG lowering in male adults only (71–75,77–80). This evidence suggests that adult males (but not females) with the APOE-E3/E4 or E4/E4 genotype (rs429358, rs7412) tend to experience significant reductions in TG in response to 0.7-3.7 g/day of EPA and/or DHA, with higher dosages demonstrating greater TG lowering effects (71–75,77–80). Furthermore, it was determined that there is strong evidence (GRADE rating: high quality) for using a 31-SNP nutri-GRS (detailed in Supplementary Tables 5 and 6) to assess the effectiveness of omega-3s for TG lowering in adults with overweight/obesity in various ethnicities (65,66). The evidence suggests that in adults with overweight/obesity, lower genetic risk scores demonstrate greater responsiveness to omega-3 supplementation (65,66).

All other evidence that was evaluated was determined to be weak (GRADE rating: low or very low quality), as further detailed in Table 2. Imprecision, indirectness, and inconsistency were common reasons for downgrading the evidence (refer to Table 2 footnote). There was evidence for a plausible mechanism of action for most of the nutrigenetic interactions that were graded; evidence of a dose response was less common.

Table 2. GRADE Evidence Profile: Genetic Variation, Omega-3 and Lipids

Nutrigenetic interactions for omega-3 and plasma lipid/lipoprotein outcomes **Patient or Population: adults** **Intervention/Exposure: dietary or supplemental omega-3 (EPA and/or DHA and/or ALA)** **Comparison/Control: genetic variation, different omega-3 intakes** **Outcomes: plasma lipids and lipoproteins**									
***Gene* rs Number and Lipid: Number and Type of Studies (total *n*)**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Dose Response**	**Biological Plausibility***	**Quality**	**Conclusion**
***CD36* rs1761667 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the AA genotype of *CD36* rs1761667 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1761667 and TG**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the GG genotype of *CD36* rs1761667 could lead to significant reductions in TG in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1049673 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	No serious imprecision	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or possibly the CC genotype of *CD36* rs1049673 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1527483 and TG**: 1 RCT and 1 single arm trial (*n*=250) (67,81)	Serious limitations[f]	No serious inconsistency	Serious indirectness[g]	Very serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GG genotype of *CD36* rs1527483 could lead to significant decreases in TG in response to approximately 2.0 g/day of EPA+DHA (but not ALA).
***APOE* rs429358, rs7412 and TG:** 4 RCTs and 5 single arm trials (1 single arm trial consisted of a	No serious limitations	No serious inconsistency	Serious indirectness[h]	No serious imprecision	Undetected	Evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that adult males (but not females) with the *APOE*-E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

subset sample of another single arm trial) (n=980) (71–75,77–80)									response to 0.7-3.7 g/day of EPA and/or DHA. Higher dosages may have greater TG lowering effects.
***APOE* rs429358, rs7412 and Total-c:** 4 RCTs, 5 single arm trials (1 single arm trial consisted of a subset sample of another single arm trial), 1 cross-sectional and longitudinal analysis within an RCT (*n*=2,446) (55,71–75,77–80)	No serious limitations	Serious inconsistency[i]	Serious indirectness[h]	No serious imprecision	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate: Males and Females) and ⊕⊕⊖⊖ (Low: Males)	In males and females combined, strong evidence suggests that there is no nutrigenetic interaction between EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, *APOE* (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c.
31-SNP Nutri-GRS and TG: 1 RCT, 1 single arm trial (*n*=330) (65,66)	No serious limitations	No serious inconsistency	Serious indirectness[j]	No serious imprecision	Undetected	Evidence of a gradient[k]	Some evidence of a mechanism of action[l]	⊕⊕⊕⊕ High	Strong evidence suggests that in adults with overweight/obesity, a 31-SNP genetic risk score can predict TG responsiveness to EPA+DHA supplementation. Individuals with lower genetic risk scores demonstrate greater responsiveness to EPA+DHA for TG lowering.
***PPARg2* rs1801282 and LDL-c:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	No serious inconsistency	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence LDL-c responses to omega-3s (EPA+DHA).
***PPARg2* rs1801282 and Total-c:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	Serious inconsistency[o]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or GG genotype of *PPARg2* (rs1801282) could lead to significant increases in total-c in response to approximately 3 g/day of omega-3s (EPA+DHA) in individuals with overweight or obesity, but not for individuals without overweight or obesity.
***PPARg2* rs1801282 and TG:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	Very serious inconsistency[p]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence total-c responses to omega-3s (EPA+DHA), but when dietary total fat and saturated fat intake are low, nutrigenetic interactions may exist.
***FADS* (rs174547**) and Total-c:** 2 RCTs, 1 single-arm trial, 4 cross-	Very serious risk of bias[q]	No serious inconsistency	Very serious indirectness[r]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊖⊖⊖ (Very Low)	Weak evidence suggests that genetic variation in *FADS* (rs174547**) does not influence total-c responses to omega-3.

sectional studies (*n*=9365) (44,45,47,48,61,69,71)									

*Direct mechanisms of action were considered

**FADS rs174547 was in strong LD with the following SNPs from other included studies and therefore these SNPs were also included in the selection of studies assessing FADS genetic variation, n-3 intake and LDL-c: rs174546, rs174599, rs174601, rs174583, rs1353, rs174561, rs174556, rs174545, rs174537 and rs174576.

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

a. Small sample sizes, especially among homozygous groups in the RCT (with a larger heterozygous group, potentially affecting the results)
b. Some variation in results by genotype
c. One study sample consisted of all males while the other sample consisted of both men and women; differences in age and n-3 dosages (with some overlap)
d. Coefficient of variation >1 for all significant values
e. Coefficient of variation substantially >1 for several values
f. Small sample size within genotype groups for minor allele homozygote and heterozygote groups in the RCT
g. One study sample consisted of all men while the other consisted of men and postmenopausal women with type 2 diabetes
h. Differences in age, omega-3 dosages, and types (with some overlap), and dietary interventions even when considering studies with male study samples separate from male + female study samples
i. Serious inconsistency for men subgroup only; men + women samples were consistent
j. EPA and DHA separate on one study and EPA+DHA in the other, sample stratified into two groups in one study (responders and non-responders) and separated into three groups (responders, non-responders and adverse responders)
k. Evidence of a gradient for GRS and TG responsiveness to omega-3 supplementation
l. Some evidence of a potential mechanism of action for *IQCJ-SCHIP1, NXPH1, PHF17, MYB and NELL1* as discussed by Rudkowska et al. (63), Vallée Marcotte et al. (64)
m. Differences in population (healthy adults, adults with chronic disease or obesity, infants), some variation in length of follow-up
n. Downgraded precision as it was not possible to assess precision in most studies due to lack of reporting of means and SD/SEM
o. Some variation in results even when considering differences in BMI and populations among studies
p. Major variability in results even when considering differences in BMI and populations among studies
q. Risk of bias detected in every study except one
r. Major differences in populations, types and amounts of omega-3 and follow-up for interventional studies

Table 3. Summary of Risk of Bias Across SNPs and Outcomes Following Omega-3 Exposure/Intervention

***CD36*, rs1761667 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1761667 and TG**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1049673 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1527483 and TG**	
Study	**Risk of Bias**
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
***ApoE*, rs429358, rs7412 and TG**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
***ApoE*, rs429358, rs7412 and Total-c**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Fallaize et al. 2016	⊖
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
31-SNP Nutri-GRS and TG	
Study	**Risk of Bias**
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

PPARg2, rs1801282 and LDL-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and Total-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and TG	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
FADS, rs174547 and Total-c	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Alsaleh et al. 2014	⊕
Lu et al. 2010	⊖
Standl et al. 2012	⊖
Dumont et al. 2011	⊖
Dumont et al. 2018	⊖
Roke and Mutch 2014	⊖

⊕ no serious risk of bias; ⊖ serious risk of bias; ⊖⊖ very serious risk of bias (for study design type using NIH Study Quality Assessment Tools)

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

DISCUSSION

Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and high quality evidence) for only a limited amount of evidence in this area: *APOE* (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity. Limited evidence exists for individual genetic-based responsiveness of omega-3s on apolipoprotein and/or LDL particle size, with no studies from the present comprehensive review meeting the criteria for evidence grading. This highlights the need for more replication studies in this area. While more research exists on omega-3 responsiveness for other lipid outcomes such as total-c, HDL-c and LDL-c, the level of evidence for nutrigenetic interactions related to these outcomes remains low. Again, more studies are needed related to these outcomes, including replication studies of previously identified nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the same type and amount of omega-3s as the original study), and recruit samples with similar characteristics to the original study. Once replication is established, research should then seek to expand the population studied to improve generalizability and explore the effectiveness of different interventions (i.e. different formulations and doses of omega-3s). The variability of the interventions and sample sizes in the studies conducted to date often resulted in the quality of evidence being downgraded (see Table 2). It should also be noted that study heterogeneity precluded the ability to conduct a meta-analysis. Thus, the GRADE approach worked well for evaluating the quality of the evidence given that this approach takes into consideration several factors when determining the quality of

evidence such as risk of bias, indirectness of evidence, inconsistency or results, imprecision and publication bias (39).

It is important to note that our results demonstrating strong evidence for interactions between *APOE* genotypes and lipid responses to omega-3s have notable ethical implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk of developing Alzheimer's disease (90). Moreover, *APOE* genotypes are significantly associated with CVD risk including risk of coronary artery disease and hyperlipidemia (91–93). Interestingly, the pathology of Alzheimer's disease has been linked to cardiovascular mechanisms (90). Future research should explore nutrigenetic interactions, with risk of developing Alzheimer's disease as the study endpoint/outcome of interest. Despite the current lack of knowledge about how diet may play a role in mitigating the genetic-based risk of Alzheimer's disease, several potentially modifiable risk factors account for around 40% of dementia and Alzheimer's disease globally (94), and the link between Alzheimer's disease risk and *APOE* is well-established (95). Therefore, despite the strong scientific validity identified in the present review, there are other factors that must be considered before this test can be recommended for implementation in a practice setting; this includes ethical, legal and social implications (96).

In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness to omega-3s in men but not women speaks to the importance of taking biological sex into account in nutrigenetics research. The importance of this has been further highlighted elsewhere, where it has been noted that the results of nutrition and nutrigenetic research

may differ in men and women (97). For example, UDP-glucuronidation isoenzyme expression profiles have been demonstrated to be regulated by sex hormones, and thus sex-specific differences in glucuronidation of resveratrol have been observed (98). As more studies are completed, researchers may find that certain nutrigenetic interactions differ depending on biological sex, ethnicity, age or other factors, similar to our findings on *APOE,* omega-3s and TG in which there was robust evidence of a nutrigenetic interaction in males only. Researchers may also find explanations for this, which are currently poorly understood. In general, it is becoming increasingly recognized that health-related responses to different interventions may vary based on biological sex; this is an important consideration of personalized nutrition (97). Nutrigenetic research often groups men and women together, but stratifying based on biological sex could provide further insights for specific nutrigenetic interactions and could also help explain why some replication studies have had conflicting findings (97). Moreover, biomedical research in general historically has been conducted more in men than women; yet such research findings are often generalized to women despite limited research conducted in samples of women, which is problematic for a number of reasons (99). In the present review, the evidence was strong for the *APOE* findings in men only, but not women in part because there were more studies conducted in men. Specifically, there were five studies conducted in men and women (combined) (71,73,74,100,101), and four studies conducted in samples of only men (75,78,79,102), yet no studies conducted in samples of only women. This brings to light important issues of equity and warrants further discussion and consideration.

As research continues to develop, it appears likely that lipid and lipoprotein responses are polygenic in nature. Therefore, future research should consider using nutri-GRSs or other polygenic methods of assessing responsiveness to nutrition interventions. This work should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs, such as establishing them from genetic-wide association studies. In addition to the two studies meeting the criteria for evidence grading (65,66), a modified version of the 31-SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs (65). While this did not meet our inclusion criteria for evidence grading given that a different GRS was used, the 23-SNP GRS was significantly associated with TG responsiveness to omega-3 supplementation in this population as well, providing further evidence for the scientific validity of this nutrigenetic interaction (65).

While we used the GRADE approach to evaluate the body of evidence, several tools are available for evaluating the quality of scientific evidence, though no generally accepted methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a set of guidelines to assess the scientific validity of genotype-based dietary advice (30). While we originally intended to use these guidelines for assessing the evidence, we came across some limitations that ultimately led us to use the GRADE guidelines. Specifically, Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines should be included in the assessment of scientific validity (30). However, limiting the evidence to only these studies could result in several important studies being missed. In the present review, none of the included studies explicitly indicated that they followed STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA

guidelines to assess risk of bias (30). However, the STREGA checklist is only intended for observational genetic association studies - not interventional research (103). In the present review, 42 of the 65 included studies were interventional (65%) (Supplementary Table 3). In addition, the STREGA guidelines are intended to improve the transparency and adequate reporting of genetic association studies, but it is not intended to be used as a study quality assessment tool (103). However, Grimaldi et al. nicely highlighted the importance of understanding the nature of the genetic variation, at a functional level, when assessing scientific validity (30). This is not included in the standard GRADE approach but is an important niche component of nutrigenetic research. As such, an analysis of functional SNPs (biological plausibility) was included as an additional component of the standard GRADE process, as indicated in the methods section above. Overall, we found that the methods used in this systematic review were effective and can be used to synthesize and evaluate nutrigenetic studies assessing other gene-nutrient-health outcome interactions.

The additional consideration of functional SNPs to the standard GRADE approach helped to strengthen this review, as biological mechanistic evidence can help ensure that study findings did not occur by chance alone, and this is a component of evidence evaluation frameworks in medical genetics (104,105). Transcriptomic and pathway analyses can help inform the direction of future nutrigenetic studies by generating hypotheses about the impact of specific genetic variations on varying responses to nutrition on health-related outcomes. For example, using transcriptomics and pathway analyses to identify changes in lipid metabolism following omega-3 supplementation, Rudkowska and

colleagues identified six genes expressed in opposite directions between responders and non-responders to omega-3 supplementation for TG lowering: *FADS2, PLA2G4A, ALOX15, PEMT, MGLL and GPAM* (106). Tremblay et al. then built on this knowledge and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a significant impact on the TG lowering effect of omega-3 supplementation (107). Others have built on this mechanistic knowledge as well (108). Future research should now seek to replicate this work given that we found that there have been no replication studies completed and thus, this research (107,108) did not meet the criteria for evidence grading.

In the current body of literature, there are some limitations that should be highlighted. Given the variability in allele frequencies for each SNP, it should be noted that study limitations can arise with small sample sizes whereby some genotype groups may not be adequately powered to detect significant differences. For example, Dawczynski et al. (2013) detected significant changes in TG among the GA genotype group of *CD36* rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA: n=8, GG: n=7) exhibited a significant difference, despite similar directions and magnitudes of effect among the GA and GG genotypes (82). It is thus possible that this study was not adequately powered. Some researchers aim to mitigate this issue of small numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for the minor allele) (69). However, such an approach precludes the possibility to detect an

allele-dosage effect. From a physiological perspective, an allele dosage effect would be expected whereby a significant change among a heterozygote group would likely be accompanied by a significant change in one of the homozygote groups but with an even greater magnitude of the effect. This consideration highlights the importance of having an adequately powered sample size, while factoring in the prevalence of each genotype.

While single SNP research provides important information about individual gene-nutrient interactions, the results of this review indicate that individual responses to omega-3s for altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus, we encourage researchers to further explore the use of nutri-GRSs to improve the accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et al., which obtained a high quality evidence grade in the present review (65,66). This is further exemplified in the analyses recently conducted by Chen et al. (42), which has yet to be replicated and thus was not selected for evidence grading.

The present analysis of scientific validity provides an important first step towards the eventual development of clinical practice guidelines for genetic-based responses to dietary intake. With questionable and variable scientific validity of existing consumer nutrigenetic tests, the development of clinical practice guidelines is an important next step as these can be used by HCPs and industry alike to help promote evidence-based practice in personalized nutrition. Ideally, industry should use future clinical practice guidelines to inform the nutrigenetic associations and related dietary recommendations included in their reports. Decision aids can also be useful to guide clinical practice for

HCPs (109), and future research should seek to develop a decision aid related to omega-3s and lipid/lipoprotein outcomes based on genetic variation.

Overall, we have provided a comprehensive overview the body of evidence related to nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing an overview of levels of evidence in this field. To our knowledge, this is the first systematic review with GRADE evidence evaluation in the broader field of nutrigenetics. The results of this work should be used in clinical practice guideline development, to ultimately guide evidence-based practice in personalized nutrition and move this emerging field forward.

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Data Sharing Statement: Data are available upon reasonable request.

Figure Legend:

Figure 1. PRISMA Flow Diagram

*The original PRISMA Flow Diagram indicated the number of studies included in meta-analysis in this box. This has been revised for the purposes of this research

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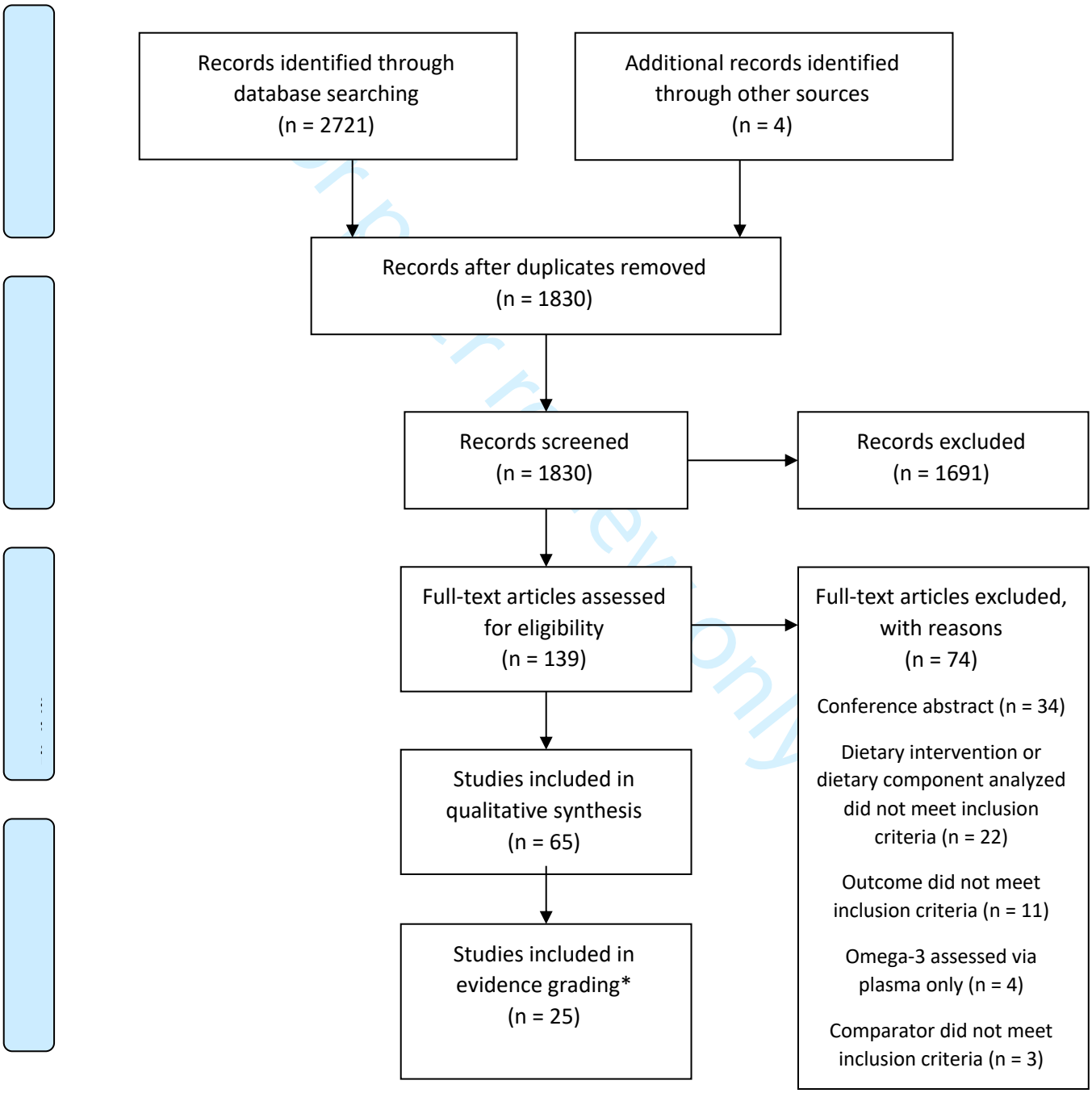
Figure 1: PRISMA 2009 Flow Diagram



Supplementary Tables

Supplementary Table 1: Search Strategy

Embase	
#	**Search Strategy**
1	omega-3':ti,ab,kw OR pufa$:ti,ab,kw OR ((acid* NEAR/5 ('n-3' OR polyunsaturated OR linolenic OR eicosapenta$noic OR timnodonic OR docosahexa$noic)):ti,ab,kw) OR docosahexaenoate:ti,ab,kw OR epa:ti,ab,kw OR dha:ti,ab,kw OR ala:ti,ab,kw
2	omega 3 fatty acid'/exp
3	**#1 OR #2**
4	cholesterol*:ti,ab,kw OR hdl:ti,ab,kw OR ldl:ti,ab,kw OR 'high density lipoprotein*':ti,ab,kw OR 'low density lipoprotein*':ti,ab,kw OR 'beta lipoprotein*':ti,ab,kw OR apo*protein*:ti,ab,kw OR apoa:ti,ab,kw OR apob:ti,ab,kw OR apoc:ti,ab,kw OR apod:ti,ab,kw OR apoe:ti,ab,kw OR apoh:ti,ab,kw OR ((apo NEXT/1 (a OR b OR c OR d OR e OR h)):ti,ab,kw) OR triglyceride*:ti,ab,kw OR triacylglycerol*:ti,ab,kw OR (((serum OR plasma) NEXT/1 (lipid* OR tg OR tag)):ti,ab,kw)
5	cholesterol'/exp OR 'lipoprotein'/exp OR 'triacylglycerol'/exp
6	**#4 OR #5**
7	nutrigenomic*:ti,ab,kw OR nutrigenetic*:ti,ab,kw OR (((nutritional OR expression* OR variation* OR variant*) NEAR/2 (genomic* OR genetic* OR gene OR genes)):ti,ab,kw) OR genotype:ti,ab,kw OR ((('nutrient-gene' OR 'gene-nutrient' OR 'gene-diet') NEXT/1 interaction*):ti,ab,kw) OR 'personali?ed nutrition':ti,ab,kw OR 'precision nutrition':ti,ab,kw
8	nutrigenomics'/exp OR 'nutrigenetics'/exp OR 'genetic variation'/exp OR 'genotype'/exp
9	**#7 OR #8**
10	**#3 AND #6 AND #9**
11	[animals]/lim NOT [humans]/lim
12	**#10 NOT #11**

Medline (Ovid)

#	Search Strategy
1	("omega-3" or PUFA? or (acid* adj5 ("n-3" or polyunsaturated or linolenic or eicosapenta?noic or timnodonic or docosahexa?noic)) or docosahexaenoate or EPA or DHA or ALA).ab,kf,ti.
2	exp Fatty Acids, Omega-3/
3	**1 or 2**
4	(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo adj (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) adj (lipid* or TG or TAG))).ab,kf,ti.
5	exp Cholesterol/ or exp Lipoproteins/ or exp Triglycerides/
6	**4 or 5**
7	(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) adj2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") adj interaction*) or "personali#ed nutrition" or "precision nutrition").ab,kf,ti.
8	Nutrigenomics/ or Genetic Variation/ or Genotype/
9	**7 or 8**
10	**3 and 6 and 9**
11	exp animals/ not humans.sh.
12	**10 not 11**

Web of Science

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan =All years

#	Search Strategy
1	TS=("omega-3" or PUFA$ or (acid* NEAR/5 ("n-3" or polyunsaturated or linolenic or eicosapenta$noic or timnodonic or docosahexa$noic)) or docosahexaenoate or EPA or DHA or ALA)
2	TS=(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo NEAR/0 (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) NEAR/0 (lipid* or TG or TAG)))
3	TS=(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) NEAR/2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") NEAR/0 interaction*) or "personali?ed nutrition" or "precision nutrition")
4	**#1 AND #2 AND #3**
5	TS=(animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)
6	**#4 not #5**

Supplementary Table 2: Summary of observational studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3[1]	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[2]
Bouchard-Mercier et al. 2011 (1)	Cross-Sectional	Single SNP	Healthy Caucasian men and women from INFOGENE study (n=674)	*PPARα*, L162V (rs1800206) *PPARγ*, P12A (rs1801282) *PPARδ*, –87T→ C (rs2016520)	*PPARα*: 22q13.31 *PPARγ:* 3p25.2 *PPARδ:* 6p21.31	Mean: L162: 2.8 g/day V162: 2.9 g/day (unclear if food and/or supplement sources)	Minor allele carriers vs. Non-carriers	LDL-PPD	**LDL-PPD:** In a model including age, sex, TG, BMI, energy and omega-3 intakes and PPAR*α* L162V (rs1800206) polymorphism, the interaction of PPAR*α*162V and omega-3 intakes explained 0.62% of the variance in LDL-PPD.
Bodhini et al. 2017 (2)	Cross-Sectional	Single SNP	Adults with normal glucose tolerance (n=821) and adults with type 2 diabetes (n=861)	*MC4R*, rs17782313 *TCF7L2*, rs12255372 *TCF7L2*, rs7903146	*MC4R:* 18q21.32 *TCF7L2:* 10q25.2-q25.3	**Low:** 0.38 g/day ALA **Moderate:** 0.58 g/day ALA **High:** 0.89 g/day ALA (means) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c	**HDL-c:** 'T' allele carriers of *TCF7L2* rs12255372 within the lowest tertile of ALA intake (mean=0.38 g/day) exhibited higher levels of HDL-c compared to GG homozygotes in the lowest tertile of ALA intake (mean=0.38 g/day)
Chen et al. 2019 (3)	Cross-Sectional Analysis within a Prospective Cohort	Single SNP, Haplotype and Gene-Centric	Adults of Swedish ancestry from the GLACIER cohort (n=5160)	All variations in the *FADS1-FADS2-FADS3* gene cluster and variation within 200kb upstream and downstream of the *FADS* region	*FADS1:* 11q12.2 *FADS2:* 11q12.2 *FADS3:* 11q12.2	**High:** >1.6 g/day **Low:** <1.6 g/day (food)	Entire FADS region gene-centric analysis and Variation in individual FADS cluster SNPs: rs174570, rs174602, rs74771917, rs3168072, rs12577276, rs7115739 and Haplotype analysis	HDL-c LDL-c TG Total-c	**HDL-c:** Significant interaction of rs174570 and omega-3 on HDL-c **LDL-c:** Significant interaction of rs174602 and omega-3 on LDL-c **TG:** Gene-centric analyses demonstrated a significant interaction between variation in the *FADS* gene cluster and omega-3 intake on TG **Total-c:** Significant interaction of rs174602 and omega-3 on total-c ('C' allele carriers exhibited lower total-c with low omega-3 intake, while no such relationship was observed with high omega-3 intake)
Ching et al. 2019 (4)	Cross-Sectional	Single SNP	Vegetarian adults of Malaysian ancestry (n=200)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low:** ≤0.45 g/day ALA **Moderate:** 0.46-0.64 g/day ALA **High:** >0.64 g/day ALA (means) (food)	Comparison between three genotypes	HDL-c TG	**HDL-c:** The TT genotype had significantly lower HDL-c when ALA intake was in the moderate intake range, but there were no significant gene-omega-3 interaction on lipid levels
Dumont et al. 2011 (5)	Cross-Sectional	Single SNP	Adolescents of European ancestry (n=573)	*FADS1*, rs174547	*FADS1:* 11q12.2	**High**: >1.4 g/day ALA **Low**: ≤1.4 g/day ALA (unclear if food and/or supplement sources)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c	**Total-c:** Significant interaction whereby the minor allele (CT+TT genotype) was associated with lower total-c when ALA intake is high as compared to when intake is low. This remained significant after assessing the interaction using ALA intake as a continuous variable.

Dumont et al. 2018 (6)	Cross-Sectional	Single SNP	Men and women aged 35 to 74 years from the MONA LISA Study of three French populations (n=3069)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low**: 0.6 g/day ALA (mean) **Median**: 0.8 g/day ALA (stratified by median for analyses) **High**: 1.3 g/day ALA (mean) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c	--
Fallaize et al. 2016 (7)	Cross-Sectional (Baseline) and Longitudinal Analyses within a Randomized Intervention	Single SNP*	Healthy adults enrolled in the Food4Me European trial (*n*=1466)	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**High**: >0.67 %kcal **Low**: <0.67 %kcal **Increased Intake:** reduced omega-3 intake from baseline **Decreased Intake:** decreased omega-3 intake from baseline (unclear if food and/or supplement sources)	*APOE*-E4- vs. *APOE*-E4+	Total-c	**Total-c:** Cross-sectional (baseline) analysis demonstrated a significant genotype effect for *APOE,* omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for *APOE,* change in omega-3 intake (increase or decrease) and total-c.
Fontaine-Bisson and El-Sohemy 2007 (8)	Cross-Sectional	Genetic Score	Men and women aged 20-29 years (n=595)	*TNFα,* rs361525, rs1800629	*TNFα:* 6p21.33	Intake range: 0.2-4.6 %kcal (mean intakes were 0.7 %kcal for 0/0, 0.7% kcal for 0/1 and 0.6%kcal for 1/0) (food)	No minor allele ('A') for both SNPs (0/0) vs. One minor allele for rs361525 (1/0) vs. One minor allele for rs1800625 (0/1)	HDL-c	--
Fontaine-Bisson et al. 2009 (9)	Cross-Sectional	Single SNP	Healthy men and women aged 20-29 years (n=593)	*NF-κB* -94Ins/Del ATTG (rs28362491)	*NF-κB:* 4q24	Mean intake: 0.7 %kcal (unclear if food and/or supplement sources)	Ins/Ins vs. Ins/Del vs. Del/Del	HDL-c	**HDL-c:** Significant interaction between *NF-κB* genotype and omega-3 intake on HDL-c
Hellstrand et al. 2012 (10)	Cross-Sectional	Single SNP	Healthy men and women aged 45-68 years from Sweden (n=4635)	*FADS,* rs174547	*FADS:* 11q12.2	**Low:** ≤0.14 %kcal long-chain omega-3 **Moderate:** 0.14-0.28 %kcal long-chain omega-3 **High:** >0.28 %kcal long-chain omega-3 (tertiles of intake reported only for certain significant findings) (food and supplement)	TT vs. TC vs. CC	HDL-c LDL-c TG	**LDL-c:** Significant interaction between *FADS* rs174547 genotype and long-chain omega-3 on LDL-c whereby the 'C' allele was significantly associated with lower LDL-c when long-chain omega-3 intake was in the lowest tertile (but not in the moderate or highest tertile). High long-chain omega-3 intake was associated with significantly higher LDL-c for CC and TC genotypes but not TT genotypes. Stratified analysis based on sex demonstrated that these significant interactions remained for men, but not women, however there was not a significant difference in interactions by sex.
Hosseini-Esfahani et al. 2017 (11)	Nested Case-Control	Single SNP	Healthy men and women aged ≥18 years from Iran	*ZNT8,* rs13266634	*ZNT8:* 8q24.11	**Tertiles for omega-3:** **Low:** <0.38 %kcal **Moderate:** 0.38-	CC vs. CT+TT	HDL-c TG	**HDL-c:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of low HDL-c whereby CC genotypes exhibited a decreased risk of low HDL-c with increasing intake of omega-3; this was not observed in

			(n=1634)			0.54 %kcal **High:** >0.54 %kcal (food)			the CT+TT genotype group. **TG:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of high TG whereby CC genotypes exhibited a decreased risk of high TG with increasing intake of omega-3; this was not exhibited in the CT+TT genotype group.
Jang et al. 2014 (12)	Cross-Sectional	Single SNP	Adult: Men and women aged 40-69 from Korea (n=4205) Children: Boys and girls aged 8-13 years from Korea (n=1548)	*PCSK5,* rs1029035	*PCSK5:* 9q21.13	Based on overall median intake (further detailed elsewhere (12)): **Low:** <0.4 %kcal **High:** >0.4 %kcal (food)	CC vs. CA vs. AA	HDL-c	**HDL-c:** Significant interaction between *PCSK5* rs1029035 and omega-3 on HDL-c in male children and male adults. 'C' allele carriers exhibit a tendency to decrease HDL-c with omega-3, while AA genotypes exhibit the opposite effect.
Joffe et al. 2010 (13)	Cross-Sectional	Single SNP	Black women from South Africa, normal weight or with obesity (n=138)	*TNFα,* rs1800629	*TNFα:* 6p21.33	ALA (amount not reported/cannot determine) (food)	GG vs. GA+AA	HDL-c LDL-c TG Total-c Total-c:HDL-c	**Total-c:HDL-c ratio:** Significant interaction between *TNFα,* rs1800629 genotypes and %kcal from ALA whereby increasing %kcal from ALA was associated with increases in Total-c:HDL-c for GG genotypes but decreases in Total-c:HDL-c ratio for GA+AA genotypes
Joffe et al. 2012 (14)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=263)	*TNFα,* rs361525	*TNFα:* 6p21.33	**Median Intakes:** omega-3: 0.28-0.36 % kcal ALA: 0.21-0.26 %kcal EPA: 0.02 %kcal DHA: 0.04-0.08 %kcal (food)	GG vs. GA(+AA for one participant: black, normal weight)	HDL-c LDL-c TG Total-c Total-c:HDL-c	**LDL-c:** Significant interaction for Caucasian women whereby LDL-c decreased with increasing %kcal from EPA in the GG genotype but not the GA genotype of *TNFα,* rs361525. **Total-c:** Significant interaction for white women whereby total-c decreased with increasing EPA and DHA intakes in the GG genotype group but not the GA genotype group of *TNFα* rs361525 but individual rates were not significant. **Total-c:HDL-c ratio:** Significant interaction for black women whereby Total-c:HDL-c decreased within increasing %kcal from omega-3 in the GA genotype group but not GG of *TNFα* rs361525.
Joffe et al. 2014 (15)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=268)	*IL-6,* −174 G>C, IVS3 (rs1800795), +281 G>T, IVS4 (rs1554606), +869 A>G (rs2069845)	*IL-6:* 7p15.3	Black Women (%kcal/day): 0.28 omega-3, 0.21 ALA, 0.02 EPA, 0.04 DHA (normal weight); 0.36 omega-3, 0.22 ALA, 0.04 EPA, 0.08 DHA (obesity) White Women (%kcal/day): 0.33 omega-3, 0.26 ALA, 0.01 EPA, 0.05 DHA (normal weight); 0.32 omega-3, 0.25 ALA, 0.02 EPA, 0.05 DHA (food)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	The following results were statistically significant only in white women, but not in black women[3]: **HDL-c:** Significant interaction whereby HDL-c increased with: increasing omega-3 and/or DHA and/or ALA intake in *IL-6* rs1800795 C allele carriers and increasing ALA intake in *IL-6* rs1554606 T allele carriers. HDL-c decreased with: increasing EPA and/or DHA intake in *IL-6* rs2069845 G allele carriers. **TG:** Significant interaction whereby TG reduced with increasing EPA intake in *IL-6* rs1800795 C allele carriers **Total-c:HDL-c:** Significant interaction whereby total-c:HDL-c ratio decreased with: increasing EPA intake in *IL-6* rs1800795 CC genotypes and *IL-6* rs1554606 TT genotypes, increasing DHA intake in *IL-6* rs1800795 CC genotypes, and increasing ALA intake in *IL-6* rs1554606 TT genotypes.
Lai et al. 2006 (16)	Cross-Sectional	Single SNP	Men and women from the Framingham	*APOA5,* rs662799, rs651821, rs3135506,	*APOA5:* 11q23.3	**Mean Intake:** 0.69 %kcal omega-3 **Tertiles for**	Major allele homozygotes vs. Minor allele carriers	TG	--

			Heart Study (n=2148)	rs2072560, rs2266788		**<u>omega-3:</u>** **Low:** <0.58 %kcal **Moderate:** 0.58-0.74 %kcal **High:** >0.74 %kcal (unclear if food and/or supplement sources)			
Lu et al. 2010 (17)	Cross-Sectional	Single SNP	Men and women of Doetinchem Cohort Study (n=3575)	*FADS,* rs174546, rs482548, rs174570	*FADS:* 11q12.2	Mean intake: 0.5 %kcal (food)	Comparison between three genotypes	HDL-c Total-c	**Total -c**: In high omega-3 intake group, total-c was significantly higher with each added minor 'C' allele of rs174546
Nettleton et al. 2009 (18)	Cross-Sectional	Single SNP	Men and women of Caucasian ancestry (n=8511)	*ANGPTL4* E40K (rs116843064)	*ANGPTL4:* 19p13.2	Not Reported/Cannot Determine (food)	Minor allele carriers vs. Non-allele carriers	HDL-c TG	--
Richardson et al. 2011 (19)	Meta-analysis of the Framingham Offspring Study (FOS) and the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	Single SNP	Men and women from FOS and GOLDN studies (*n*=3605)	*PLIN4*, rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	*PLIN4:* 19p13.3	Mean intakes: **FOS Men:** 1.43 g/d **FOS Women:** 1.37 g/d **GOLDN Men:** 1.83 g/d **GOLDN Women:** 1.48 g/d (food and supplement)	Minor allele carriers vs. Non-allele carriers	TG HDL-c	**TG:** Significant interactions for *PLIN4,* rs884164 whereby TG levels increased in minor allele carriers with higher omega-3 intake for males and females combined, and males individually.
Standl et al. 2012 (20)	Cross-Sectional Analysis (10-year time point) within a 10-year longitudinal cohort study	Single SNP	10 year-old children of the GINIplus and LISAplus birth cohort studies (n=1697)	*FADS1/FADS2,* rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	*FADS1/2:* 11q12.2	Median intake: 0.14 mg/MJ omega-3 (ALA+EPA+DPA +DHA) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c Total-c TG	--
Tai et al. 2005 (21)	Cross-Sectional	Single SNP	Framingham Cohort, men and women (*n*=2106)	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	**High**: >0.69 %kcal **Low**: <0.69 %kcal (food)	PPARα: 162V carriers vs. 162L/162L homozygotes	TG apoC-III	**TG:** 167V carriers had lower TG with high omega-3 intake compared to low omega-3 intake (gene-diet-interaction effects were NS) **apoC-III:** Significant gene-diet interactions; Higher apoC-III in 162V carriers with low omega-3 intake compared to 162V carriers with high omega-3 intake and 162L homozygotes with low omega-3 intake
Volcik et al. 2008 (22)	Cross-Sectional (Baseline) Analysis within a Prospective Cohort	Single SNP	African American (*n*=3480) and Caucasian (*n*=10 134) men and women (*N*=13,614)	*PPARα*, L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	*PPARα*: 22q13.31	African American: **High:** >0.32 g/d EPA+DHA **Low:** ≤0.32 g/d EPA+DHA Caucasian: **High:** >0.22 g/d EPA+DHA **Low:** ≤0.22 g/d EPA+DHA (food)	Comparison between three genotypes for each SNP	HDL-c LDL-c TG Total-c	**Total-c, LDL-c:** African Americans (but not Caucasians) homozygous for *PPARα* (rs3892755) TT genotype with high EPA+DHA intake had significantly lower total-c and LDL-c compared to CT and TT genotypes (both high and low EPA+DHA intake)

Warodomwichit et al. 2009 (23)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	*TCF7L2* rs7903146, rs12255372	*TCF7L2:* 10q25.2-25.3	N/A (Median omega-3: 0.67% of kcal) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c LDL-c particle size TG Total-c	--

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. Intakes are total omega-3 unless otherwise specified
2. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS

Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

3. These results were taken from the full-text manuscript's summary table of IL-6 results. Refer to Supplementary Tables S8-S13 in Joffe et al. 2014 (15) for several other significant results, stratified and un-stratified by ethnicity. Note: There were no corrections for multiple testing in the statistical analyses.

'--' indicates that all of the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε2, ε3 and ε4)

Supplementary Table 3: Summary of interventional studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Intervention Duration	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[1]
AbuMweis et al. 2018 (24)	Randomized, Crossover Controlled Intervention	Single SNP*	Adults with at least one cardiovascular risk factor (n=129)	4 weeks	*FADS1*, rs174561 *FADS2*, rs174583 *ELOVL2*, rs953413 *ELOVL5*, rs2397142 *CETP*, rs5882 *SCD1*, rs2234970, *PPARα*, rs6008259 *LIPF*, rs814628 and *APOE*, rs429358, rs7412	*FADS1/2:* 11q12.2 *ELOVL2:* 6p24.2 *ELOVL5:* 6p12.1 *CETP:* 16q13 *SCD1:* 10q24.31 *PPARα*: 22q13.31 *LIPF:* 10q23.31 *APOE:* 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except *PPARA* and *LIPF* whereby analyses were major allele homozygotes vs. minor allele carriers) and *APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoA1 apoB HDL-c LDL-c TG Total-c	--
Alsaleh et al. 2014 (25)	Randomized Controlled Intervention	Single SNP and Polygenic	Healthy men and women (n=310)	12 months	CETP, rs3764261, *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5/ABCG*, rs4299376 *TIMD4/HAVCR1*, rs6882076 *GCKR*, rs1260326 *TRIB1*, rs2954029 *ANGPTL3/DOCK7*, rs2131925 *FADS1/2/3*, rs174546 *GALNT2*, rs4846914 *ABCA1*, rs4149268 *APOE/APOC1/APOC2*, rs439401	*CETP:* 16q13 *LIPC:* 15q21.3 *APOB:* 2p24.1 *ABCG5/ABCG8:* 2p.21 *TIMD4/HAVCR1:* 5q33.3 *GCKR:* 2p23.3 *TRIB1:* 8q24.13 *ANGPTL3/DOCK7:* 1p31.3 *FADS:* 11q12.2 *GALNT2:* 1q42.13 *ABCA1:* 9q31.1 *APOE/APOC1/APOC2:* 19q13.32	**Low Dose:** 0.5 g/day EPA and DHA **Moderate Dose:** 0.9 g/day EPA and DHA **High Dose:** 1.8 g/day EPA and DHA (supplement)	Effect sizes per GRS risk allele after omega-3 treatment *and* Risk allele carriers vs. non-risk allele carriers	HDL-c LDL-c TG Total-c	**TG:** significant interaction whereby 1.8 g/day EPA and DHA significantly reduced TG in T allele carriers (21.6% reduction) vs. CC genotypes (3.5% reduction) of *FADS1* rs174546

Armstrong et al. 2012 (26)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	*ALOX5,* dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	*ALOX5:* 10q11.21	Fish oil: 5.0 g/day containing 2.0 g/day EPA and 1.0 g/day DHA Control oil: 5.0 g/day corn/soy oil (supplement)	dd vs. d5 vs. 55	TG Mean lipoprotein particle diameter, total number of particles and particle concentration for: HDL-c and LDL-c	**TG:** significant interaction whereby decreases in TG from omega-3 supplementation were specific to d5 genotype group **HDL-c particle concentration:** significant decrease with omega-3 intervention in the d5 and 55 genotype groups compared to placebo, but no decreases in the dd genotype group **Medium HDL-c particles and HDL-c (mmol/L):** significant gene-treatment interaction but no significant differences after post-hoc analysis for comparisons among genotypes
Binia et al. 2017 (27)	Single-Arm Clinical Trial	Single SNP	Mexican adults 18-40 years (n=191)	6 weeks	*PPARα*, L162V (rs1800206), *PPARγ2*, P12A (rs1801282)	*PPARα*: 22q13.31 *PPARγ2*: 3p25.2	Fish oil: 2.7 g/day containing 1.9 g/d EPA and 0.8 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c	**LDL-c:** significant increase in LDL-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2 **Total-c:** significant increase in total-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2
Bouchard Mercier et al. 2013 (28)	Single Arm Clinical Trial	Single SNP	Healthy adults aged 18-50 years (n=208)	6 weeks	*SREBF1,* rs4925115, rs4925118, rs12953299 *ACLY,* rs8071753, rs8065502, rs2304497 *ACACA* rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	*SREBF1:* 17p11.2 *ACLY:* 17q21.2 *ACACA:* 17q12	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** Significant gene-diet interaction whereby individuals with the GG genotype of *ACLY* rs8071753 and individuals with the GG or CG genotype of *ACACA* rs1714987 exhibited greater TG lower effects following omega-3 supplementation; these two SNPs explained approximately 8% of the variance in plasma TG responses to omega-3 supplementation. There were significant differences in genotype frequencies of *ACLY* rs8071753 for responders and non-responders to omega-3 for TG lowering.
Bouchard-Mercier et al. 2014 (29)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*RXRA* (12 SNPs), *CPT1A* (9 SNPs), *ACADVL* (1 SNP), *ACAA2* (6 SNPs), *ABCD2* (8 SNPs), *ACOX1* (8 SNPs), *ACAA1* (3 SNPs) [outlined in Supplementary Table 5]	*RXRA:* 9q34.2 *CPT1A:* 11q13.3 *ACADVL:* 17p13.1 *ACAA2:* 18q21.1 *ABCD2:* 12q12 *ACOX1:* 17q25.1 *ACAA1:* 3p22.2	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** There were significant gene-diet interaction effects on TG responses to omega-3 for RXRA rs11185660 genotype dependent on total fat intake, RXRA rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and ACOX1 rs17583163 dependent on total polyunsaturated fat intake
Bouchard-Mercier et al. 2014 (30)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*GCK* (13 SNPs) [outlined in Supplementary Table 5]	*GCK:* 7p13	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes	TG	**TG:** CC genotypes of *GCK* rs741038 exhibited significantly greater TG reduction in response to omega-3 when their carbohydrate intake was high (>48.6%kcal) compared to those with the CC genotype of rs741038 with low carbohydrate intake (≤48.6%kcal) and compared to CT or TT genotypes with either high or low carbohydrate intake.

								(when minor allele frequencies were >0.05)		
Caron-Dorval et al. 2008 (31)	Single Arm Clinical Trial	Single SNP	Healthy men of Caucasian ancestry aged 18-55 years (n=28)	6 weeks	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	V162 carriers vs. non-carriers	apoB-100 HDL-c LDL-c TG Total-c Total-C:HDL-c	--
Carvalho-Wells et al. 2012 (32)	Sequential Non-Randomized, Cross-Over Dietary Intervention	Single SNP*	Healthy men and women aged 35-70 years (*n*=88)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**Low-Fat**: 4.0 mg/day EPA, 10.6 mg/d DPA, 11.7 mg/d DHA **High-SFA**: 20.2 mg/d EPA, 27.1 mg/d DPA, 15.4 mg/d DHA **High-SFA+DHA**: 524.3 mg/d EPA, 215.5 mg/d DPA, 3017.3 mg/d DHA [actual intakes reported (33)] (supplemental DHA for High-SFA+DHA; others from food sources)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c sdLDL-c TG Total-c	**TG:** Significant diet x genotype interaction for TG; greater TG lowering response to high-SFA+DHA diet in *APOE*-E3/4 carriers (compared to high-SFA diet alone)
Caslake et al. 2008 (34)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men and women aged 20-70 years (*n*=312)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Control oil: 0.0 g/d EPA and DHA Fish oil: 0.7 g/d EPA and DHA Fish oil: 1.8 g/d EPA and DHA (supplement)	*APOE*-E2/E2 + E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	**TG:** Significant interaction between treatment x sex x genotype whereby *APOE*-E3/E4 + E4/E4 males exhibited the greatest TG reductions with both 0.7 g/d EPA and DHA as well as 1.8 g/d EPA and DHA compared to other genotypes
Cormier et al. 2012 (35)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*FADS* gene cluster (19 SNPs) [outlined in Supplementary Table 5]	*FADS:* 11q12.2	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	TG	--
Dang et al. 2015 (36)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	*APOE*-E4+ vs. *APOE*-E4-	HDL-c LDL-c TG Total-c	--
Dawczynski et al. 2013 (37)	Randomized, Placebo-Controlled, Double-Blind Intervention	Single SNP	Men and women with TG ≥ 1.7 mmol/L, otherwise healthy (n=47)	10 weeks	*CD36,* rs1761667, rs1049673	*CD36:* 7q21.11	Yogurt with lower dose fish oil: 0.8g/day omega-3 containing 0.01g ALA, 0.44g EPA, 0.06g DPA and 0.31g DHA (fish oil) Yogurt with higher dose fish oil: 3.0 g/day omega-3	Comparison between three genotypes	HDL-c TG	**HDL-c**: In response to omega-3 supplementation (0.8-3.0 g/day), HDL-c increased in GA genotype of *CD36* rs1761667 and CG genotype of *CD36* rs1049673. **TG**: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of *CD36* rs1761667.

							containing 0.07g ALA, 1.59g EPA, 0.23g DPA and 1.12g DHA (fish oil) Control yogurt: commercial whole fruit yogurt with 3.5% milk fat (food)			
Ferguson et al. 2010 (38)	Randomized Intervention and Cross-Sectional (Baseline) Analysis	Single SNP	Men and women with metabolic syndrome from LIPGENE cohort (*n*=450)	12 weeks	*NOS3,* rs11771443, rs1800783, rs1800779, rs1799983, rs3918227, rs743507	*NOS3:* 7q36.1	1.24 g/d EPA+DHA supplement (intervention); quantity of omega-3 not reported for observational analyses	Major allele homozygotes vs. Minor allele carriers	apoA-1 apoB apoB-48 apoC-II apoC-III apoE HDL-c LDL-c TG Total-c	**TG:** For *NOS3* rs1799983 minor-allele (A) carriers only, the observational analysis indicated higher TG with lower EPA+DHA intake (and lower TG with higher EPA+DHA intake). Post-intervention with omega-3 supplementation indicated that only minor-allele (A) carriers exhibited significant TG reduction (accompanied by increases in plasma omega-3).
Harsløf et al. 2014 (39)	Randomized, Controlled Intervention	Single SNP and Genetic Score	Infants of Danish ancestry (n=133)	9 months	*PPARγ2*, Pro12Ala (rs1801282), *FADS1,* rs1535, *FADS2,* rs174575, *FADS3,* rs174448 *COX2,* rs5275, rs689466	*PPARγ2*: 3p25.2 *FADS:* 11q12.2 *COX2:* 1q25.2-q25.3	5.0 mL/day fish oil (median reported intake: 3.8 g/day containing 630 mg/day EPA and 620 mg/day DHA) (supplement)	*PPARγ2* genotype analyses were by major allele homozygotes vs. heterozygotes and *FADS* genotype analyses were by the number of DHA-increasing alleles and *COX2* genotype analyses were by major allele homozygotes vs. heterozygotes vs. minor allele homozygotes	HDL-c LDL-c TG Total-c	**TG:** *PPARγ2* heterozygotes exhibited reduced TG in response to omega-3 when compared to *PPARγ2* heterozygotes in the control (sunflower oil) group
Itariu et al. 2012 (40)	Randomized, Controlled Intervention	Single SNP	Men and women without diabetes with a BMI ≥40 kg/m^2 aged 20-65 years (n=55)	8 weeks	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 3.4 g/day EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	apoB HDL-c LDL-c TG Total-c	**apoB:** Significant increases in apoB with omega-3 intervention in Ala12 carriers when compared to Pro12 carriers. **Total-c:** Significant interaction effect whereby increases in total-c were exhibited with omega-3 intervention in Ala12 carriers when compared to the Pro12Pro genotype.
Jackson et al. 2012 (41)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	8 weeks and 480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c TG	**TG:** *APOE*-E3/E4 exhibited reduced fasting TG in response to a high saturated fat + DHA intervention when compared to the high saturated fat diet alone. There was also a significant interaction (meal x time x genotype) for the postprandial TG lowering response whereby *APOE*-E3/4 consuming a high saturated fat + DHA intervention exhibited significantly lower

									Total-c	postprandial TG, TG area under the curve, and TG maximum concentration compared to those consuming the high saturated fat diet alone.
Jackson et al. 2017 (42)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB-48 apoB-100	--
Lindi et al. 2003 (43)	Randomized Intervention	Single SNP	Healthy men and women aged 30-65 years (*n*=150)	3 months	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	HDL-c LDL-c TG Total-c	**TG:** Compared to Pro12Pro, Ala12 carriers exhibited significantly greater TG reductions in response to omega-3 supplementation only when total fat intake was ≤37 %kcal or SFA intake was ≤10 %kcal
Lindman et al. (44)	Randomized, Controlled Intervention	Single SNP	Men at high risk of cardiovascular disease aged 65-75 years (n=204)	6 months	*FVII,* rs6046	*FVII:* 13q34	Fish oil containing 2.4 g/d EPA + DHA Dietary advice including recommendations to increase omega-3 (supplement and food)	Major allele homozygotes vs. Minor allele carriers	TG	--
Madden et al. 2008 (45)	Non-Randomized Intervention	Single SNP	Healthy men aged 43-84 years (*n*=111)	12 weeks	*CD36,* rs1527483, rs1049673, rs1761667, rs1984112	*CD36:* 7q21.11	Fish oil containing 1.02 g/d EPA and 0.69 g/d DHA (supplement)	For each SNP: AA vs. AG vs. GG	HDL-c LDL-c LDL-c:HDL-c TG	**TG:** In response to omega-3 supplementation, TG significantly reduced only in individuals with the GG genotype, for each SNP individually (i.e. for rs1527483, rs1049673, rs1761667 and rs1984112 individually) **LDL-c:** In response to omega-3 supplementation, LDL-c increased only in individuals with the rs1761667 AA genotype as well as for individuals with the rs1984112 AA genotype **HDL-c:** In response to omega-3 supplementation, HDL-c significantly increased in individuals with rs1761667 AA or AG as well as for individuals with the CC or CG genotype for either rs1984112, rs1527483 and/or rs1049673; NOTE: rs1527483 results should be interpreted with caution due to low sample sizes for AA and AG genotypes thus reducing statistical power)
Markovic et al. 2004 (46)	Single-Arm Clinical Trial	Single SNP	Healthy men (n=159)	12 weeks	*TNFα,* -308 (rs1800629) *LT-α,* +252 (rs909253) *IL-1β,* -511 (rs16944) *IL-6,* -174 (rs1800795)	*TNFα:* 6p21.33 *LT-α:* 6p21.33 *IL-1β:* 2q14.1 *IL-6:* 7p15.3	Fish oil containing 1.8 g/d EPA+DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	TG	**TG:** Significant negative correlation between pre-supplementation TG and change of TG during omega-3 supplementation for all genotypes of genes studied except for *LT-α* rs909253 GG genotype and *IL-1β* rs16944 TT genotype. In *LT-α* rs909253 AA genotype and *TNFα* rs1800629 AA genotype, signification association between BMI (divided in tertiles) and TG changes.
McColley et al. 2011 (47)	Crossover Intervention	Single SNP	Healthy post-menopausal women (n=16)	8 weeks per diet	*FABP2,* rs1799883	*FABP2:* 4q26	**High-Fat:** 50 %kcal from dietary fat **Low-Fat:** 20 %kcal from dietary fat **Low-Fat + omega-3:** 23% kcal from dietary fat with 3 %kcal from omega-3 (food)	Major allele homozygotes vs. Minor allele carriers	TG	--

Minihane et al. 2000 (48)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men aged 30-70 years at risk of atherogenic lipoprotein phenotype (*n*=50)	6 weeks per diet and 480 minute postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.0 g/d EPA and DHA, Control oil: 6.0 g/d olive oil capsule (supplement)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c Total-c:HDL	**TG:** Postprandial: Significantly greater reduction in TG incremental area under postprandial TG curve in *APOE*-E2/E3 relative to other *APOE* genotype categories **Total-c:** 6-week: *APOE*-E3/E4 + E4/E4 genotype group exhibited significantly different changes in total-c (increase), relative to other *APOE* genotypes, whereby reductions in total-c occurred
Olano-Martin et al. 2010 (49)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemic men (*n*=38)	4 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	EPA-rich fish oil: 3.3 g/d EPA DHA-rich fish oil: 3.7 g/d DHA Control oil: 80:20 palm olein:soyabean (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4 (carriers)	apoB apoE HDL-c LDL-c TG TG:HDL-c Total-c	**apoB, LDL-c:** In *APOE*-E4 carriers only, DHA-rich oil treatment resulted in significant increases in apoB and LDL-c **TG:** Significant reduction in TG in response to both EPA and DHA in *APOE*-E3/E3 group; significant reduction in TG in *APOE*-E4 carriers with EPA only. No significant interactions. **Total-c:** Significant genotype x treatment interaction whereby *APOE*-E4 carriers exhibit total-c reductions in response to EPA-rich oil.
Ouellette et al. 2013 (50)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*GPAM* (3 SNPs), *AGPAT3* (13 SNPs), *AGPAT4* (35 SNPs) [outlined in Supplementary Table 5]	*GPAM:* 10q25.2 *AGPAT3:* 21q22.3 *AGPAT4:* 6q26	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	HDL-c LDL-c TG Total-c	**LDL-c:** Significant *GPAM*, rs2792751 genotype x supplementation interaction on LDL-c **TG:** Significant genotype x supplementation interaction on TG for *GPAM,* rs2792751 and rs17129561 as well as *AGPAT4,* rs9458172 and rs3798943
Ouellette et al. 2014 (51)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18-50 years (*n*=208)	6 weeks	*MGLL* (18 SNPs) [outlined in Supplementary Table 5]	*MGLL:* 3q21.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	apoB HDL-c LDL-c LDL particle size TG Total-c	**LDL-c:** Significant interactions for *MGLL* rs6776142, rs555183, rs782444, rs6787155 and rs1466571 whereby omega-3 supplementation modulated LDL-c levels; rs782444 and rs555183 minor allele homozygotes more likely to be negative responders to omega-3 supplementation (i.e. exhibit reduced LDL-c); rs6780384, rs782444 and rs6787155 major allele homozygotes more likely to be negative responders to omega-3 supplementation **LDL particle size:** Significant interactions for *MGLL* rs782440, rs13076543 and rs9877819 whereby omega-3 supplementation modulated LDL particle size; rs549662 minor allele homozygotes more likely to be positive responders to omega-3 supplementation (i.e. exhibit increased LDL particle size)
Paschos et al. 2005 (52)	Single-Arm Clinical Trial	Single SNP*	Men with dyslipidemia, aged 35 to 67 years (n=50)	12 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4	ApoA-I ApoB HDL-c LDL-c TG Total-c	**ApoA-I:** Significant decrease in E3/E3 **HDL-c:** Significant decrease in E3/E3
Pishva et al. 2010 (53)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	*FABP2,* Ala54Thr (rs1799883)	*FABP2:* 4q26	2.0 g/day pure EPA (supplement)	Ala54Ala (GG) vs. Thr54 carriers (GT+TT)	ApoB ApoC-III HDL-c LDL-c TG Total-c	**ApoC-III:** In response to EPA supplementation, significantly greater reductions in ApoC-III in GT+TT genotypes of rs1799883 compared to GG genotype. **HDL-c:** In response to EPA supplementation, significantly greater increases in HDL-c in GT+TT genotypes of rs1799883 compared to GG genotype. **LDL-c:** In response to EPA supplementation, LDL-c significantly decreased in GG genotypes of rs1799883 but not GT+TT genotypes. **TG:** In response to EPA supplementation, significantly greater reductions in TG in GT+TT genotypes of rs1799883 compared to GG genotype.
Pishva et al.	Single-Arm	Single SNP	Adults with	8 weeks	*PPARα*,	*PPARα* : 22q13.31	2.0 g/day pure	Leu162	ApoB	--

2014 (54)	Clinical Trial		hypertriglyceridemia (n=46)		Leu162Val (rs1800206) *PPARα*, Intron 7 SNP		EPA (supplement)	vs. Val162 carriers *and* Intron 7 GG vs Intron 7 GC	ApoCIII HDL-c LDL-c TG Total-c	
Roke and Mutch, 2014 (55)	Single-Arm Clinical Trial	Single SNP	Men aged 18-25 years (n=12)	12 weeks (+8 week washout)	*FADS1,* rs174537 *FADS2,* rs174576 (LD=1.0 therefore presented results for rs174537)	*FADS1/2:* 11q12.2	Fish oil containing 1.8 g/d EPA+DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c Total-c:HDL-c	--
Rudkowska et al. 2014 (56)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*SCD1,* rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	*SCD1 :* 10q24.31	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	**TG:** For *SCD1* rs508384, AA genotype was associated with lower TG than CA and CC genotypes both pre- and post-supplementation.
Rudkowska et al. 2014 (57)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Healthy men and women aged 18-50 (*n*=141) + Replication of GRS in FINGEN study (n=310)	6 weeks	Genetic Risk Score including: *IQCJ-SCHIP1* (4 SNPs), *SLIT2* (3 SNPs), *PHF17* (3 SNPs), *MYB* (1 SNP), *NXPH1* (1SNP), *NELL1* (1SNP) [outlined in Supplementary Table 5]	*IQCJ-SCHIP1:* 3q25.32 *SLIT2:* 4p15.31 *PHF17:* 4q28.2 *MYB:* 6q23.3 *NXPH1:* 7p21.3 *NELL1:* 11p15.1	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Responders versus non-responders (i.e. TG response) to supplementation	TG	Thirteen SNPs were associated with TG response to omega-3 supplementation and 10 were used in the GRS calculation. The GRS was significantly associated with TG response. **TG**: The GRS explained 21.5% of the variation in TG response when adjusted for age, sex and BMI. Replication of this GRS in the FINGEN study: the GRS explained 2.0% of the TG change but the association as NS (adjusted for age, sex and BMI).
Scorletti et al. 2015 (58)	Randomized, Placebo-Controlled, Double-Blind Intervention	Single SNP	Men and women with non-alcoholic fatty liver disease (n=95)	15-18 months	*PNPLA3, I148M (rs738409) TM6SF2, E167K (rs58542926)*	*PNPLA3:* 22q13.31 *TM6SF2:* 19p13.11	1.8 g/day EPA+ 1.5 g/day DHA (supplement)	Comparison between three genotypes *and* Major allele homozygotes vs. Minor allele carriers	TG	--
Thifault et al. 2013 (59)	Single-Arm Clinical Trial	Single SNP*	Healthy men and women with overweight or obesity aged 18-50 (*n*=210)	6 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	*APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoB HDL-c LDL-c TG Total-c	--
Tremblay et	Single-Arm	Single SNP	Healthy men	6 weeks	*PLA2G2A* (5	*PLA2G2A:*	Fish oil containing	Major allele	apoB-100	**TG:** omega-3 supplementation significantly reduced TG in

al. 2015 (60)	Clinical Trial		and women aged 18-50 years (*n*=208)		SNPs), *PLA2G2C* (6 SNPs), *PLA2G2D* (8 SNPs), *PLA2G2F* (6 SNPs), *PLA2G4A* (22 SNPs), *PLA2G6* (5 SNPs), *PLA2G7* (9 SNPs) [outlined in Supplementary Table 5]	1p36.13 *PLA2G2C*: 1p36.13 *PLA2G2D*: 1p36.12 *PLA2G2F*: 1p36.12 *PLA2G4A:* 1q31.1 *PLA2G6:* 22q13.1 *PLA2G7:* 6p12.3	1.9 g/d EPA + 1.1 g/d DHA (supplement)	homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	HDL-c LDL-c TG Total-c	*PLA2G7* rs1805018 as well as *PLA2G4A* rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs 10752979 and rs1160719 together explained 5.9% of post-supplementation TG levels
Vallée Marcotte et al. 2016 (61)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Men and woman aged 18-50 years (*n*=208)	6 weeks	*IQCJ* (16 SNPs), *NXPH1* (34 SNPs), *PHF17* (8 SNPs), *MYB* (9 SNPs) [outlined in Supplementary Table 5]	*IQCJ:* 3q25.32 *NXPH1:* 7p21.3 *PHF17:* 4q28.2 *MYB:* 6q23.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	TG	**TG:** Significant gene-diet interaction on TG levels pre- vs. post-supplementation for the following SNPs: *IQCJ* (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), *NXPH1* (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), *MYB* (3 SNPs: rs9321493, rs11154794, rs210962). Four SNPs were still significant after applying the false discovery rate to account for multiple testing: rs1449009, rs2621309, rs61332355 in *IQCJ*; rs7805772 in *NXPH1*. There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in *IQCJ*, rs7805772 in *NXPH1* and rs11154794 in *MYB*. Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for *IQCJ* rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, *NXPH1* rs7806226, rs7805772, *MYB* rs11154794 and rs210936.
Vallée Marcotte et al. 2019 (62)	Single-Arm Clinical Trial (replication of GRS in a novel cohort)	Nutrigenomic GWAS	Healthy adults of Mexican descent aged 18-40 years (n=191)	6 weeks	Genetic Risk Score including 103 SNPs: [outlined in Supplementary Table 5]	NA	Fish oil containing 1.9 g/day EPA + 0.8 g/day DHA (supplement)	Responders versus non-responders (i.e. TG response) to supplementation	TG	**TG:** A first 7-SNP GRS [SNPs selected based on previously developed GRS (57,61)] did not explain TG variation. A second GRS calculated from 103 SNPs significantly explained 4.4% of TG variation. A third GRS including the 5 most relevant SNPs significantly explained 11.0% of TG variation (*NXPH1* rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and *IQCJ-SCHIP1* rs2595241). When subjects with the lowest TG change were not included, this third GRS explained more TG variation. Including only the 28 responders and 28 non-responders with the greatest TG variation, this third GRS explained 29.1% of TG variation.
Vallée Marcotte et al. 2019 (63)	Single-Arm Clinical Trial	Nutrigenomics GWAS (polygenic)	Men and woman aged 18-50 years with overweight or obesity (*n*=208)	6 weeks	GWAS; GRS included 31 SNPs [outlined in Supplementary Table 5]	NA	Fish oil containing 1.9-2.2g/d EPA + 1.1g/d DHA (supplement)	Responders to omega-3 supplementation for TG reduction vs. Non-Responders	TG	**TG:** 31 SNPs associated with TG response to omega-3 supplementation and used in GRS calculation; Lower GRSs were significantly more responsive to omega-3 supplementation for TG reduction compared to higher GRS (GRS accounted for 49.7% of TG responses); These findings were replicated in the FINGEN study with 23 SNPs (GRS accounted for 3.7% of TG responses).
Vallée Marcotte et al. 2020 (64)	Double-Blind, Randomized, Controlled, Crossover Intervention	Nutrigenomics GWAS (polygenic)	Men and women with abdominal obesity and elevated CRP aged 18-70	10 weeks per diet	GRS included 30 SNPs [outlined in Supplementary Table 5]	NA	Control oil: 3 g/d corn oil Pure EPA: 2.7 g/d Pure DHA: 2.7 g/d (supplement)	Responders to different types of omega-3 supplementation for TG reduction vs.	TG	**TG:** The GRS was significantly associated with responsiveness to EPA for TG reduction when comparing responders vs. non-responders vs. adverse responders (trend, p=0.08, for DHA). The GRS was significantly associated with responsiveness to both EPA and DHA for TG reduction when comparing responders vs. adverse responders.

			years (n=122)					Non-Responders vs. Adverse Responders *and* Responders vs. Adverse Responders		
Wu et al. 2014 (65)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP	Men and women with moderate risk of CVD (n=84)	8 weeks	*eNOS* Glu298Asp (rs1799983)	*NOS3:* 7q36.1	Fish oil containing 0.9 g/day EPA + 0.6 g/day DHA (supplement)	Major allele homozygotes (GG) vs. Minor allele carriers (GT+TT)	LDL-c HDL-c TG Total-c	--
Zheng et al. 2018 (66)	Double-Blind, Randomized, Controlled Intervention	Single SNP and Polygenic	Men and women with type 2 diabetes aged 35-80 years for men or postmenopausal and 80 years for women (*n*=139)	25 weeks	*CD36,* rs1527483 NOS3, rs1799983 *PPARγ2*, rs1801282	*CD36:* 7q21.11 *NOS3:* 7q36.1 *PPARγ2*: 3p25.2	Fish oil: 2.0 g/d EPA and DHA Flaxseed oil: 2.5 g/d ALA Control oil: corn oil (supplement)	Major allele homozygotes vs. Minor allele carriers and High vs. low genetic score calculated based on three SNPs	HDL-c LDL-c TG Total-c:HDL-c Total-c	**LDL-c:** significant interaction for *PPARγ2* rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of *PPARγ2* rs1801282 compared to CC genotype *only in the control* (corn oil) group **TG:** omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the *CD36* rs1527483 GG genotype (significant interaction); significant interaction between genetic score and omega-3 on TG levels whereby omega-3 (fish oil and flaxseed oil) supplementation significantly reduced TG levels compared to control only in individuals with high genetic scores

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, omega-3: omega-3, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS

Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

'--' indicates that all the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε 2, ε 3 and ε 4)

Supplementary Table 4: Genes, SNPs, lipid/lipoprotein outcomes and studies included in evidence grading process and guideline development

Gene, SNP(s)	Outcome	Studies
APOE: rs429358, rs7412 (Genotype)	TG	AbuMweis et al. 2018 (24) Carvalho-Wells et al. 2012 (32) Caslake et al. 2008 (34) Dang et al. 2015 (36) Jackson et al. 2012 (41) Olano-Martin et al. 2010 (49) Minihane et al. 2000 (48) Paschos et al. 2005 (52) Thifault et al. 2013 (59)
APOE: rs429358, rs7412	Total-c	Fallaize et al. 2016 (7) AbuMweis et al. 2018 (24) Carvalho-Wells et al. 2012 (32) Caslake et al. 2008 (34) Dang et al. 2015 (36) Jackson et al. 2012 (41) Olano-Martin et al. 2010 (49) Paschos et al. 2005 (52) Thifault et al. 2013 (59)
PPARγ2: rs1801282	LDL-c	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
PPARγ2: rs1801282	Total-c	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
PPARγ2: rs1801282	TG	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
CD36: rs1761667	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1761667	TG	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1049673	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1527483	TG	Madden et al. 2008 (45) Zheng et al. 2018 (66)
FADS: rs174547*	Total-c	Dumont et al. 2011 (5) Dumont et al. 2018 (6) Lu et al. 2010 (17) Standl et al. 2012 (20) Alsaleh et al. 2014 (25) AbuMweis et al. 2018 (24) Roke et al. 2014 (55)
31-SNP Genetic Risk Score	TG	Vallée Marcotte et al. 2019 (67) Vallée Marcotte et al. 2020 (64)

Supplementary Table 5: Additional list of gene(s) and SNP(s) tested in studies

Study	*Gene(s)*, SNP(s)
Chen et al. Int J Obes;43:808-820 (2019)	*FADS2,* rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276 *FADS3,* rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285 *RAB3IL1,* rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252
Cormier et al. 2012	*FADS* gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567
Vallée Marcotte et al. Am J Clin Nutr;109:176–185 (2019)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Tremblay et al. Lipids in Health and Disease (2015) 14:12	*PLA2G2A*, rs876018, rs955587, rs3753827, rs11573156, rs11573142 *PLA2G2C*, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718 *PLA2G2D*, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671 *PLA2G2F*, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904

	PLA2G4A, rs979924, rs2076075, rs3736741, rs10911949, rs10752979, rs1160719, rs10737277, rs12720702, rs7522213, rs7540602, rs10157410, rs12720497, rs4651331, rs1569480, rs10911935, rs12353944, rs11576330, rs10489410, rs10911946, rs3820185, rs12746200, rs11587539 *PLA2G6*, rs5750546, rs132989, rs133016, rs2235346, rs2284060 *PLA2G7*, rs12195701, rs12528807, rs1421368, rs1421378, rs17288905, rs1805017, rs1805018, rs6929105, rs7756935
Ouellette et al. J Nutrigenet Nutrigenomics;6:268–280 (2013)	*GPAM*, rs17129561, rs10787428, rs2792751 *AGPAT3*, rs999519, rs2838440, rs2838445, rs2838458, rs4818873, rs9978441, rs9982600, rs11700575, rs17004619, rs2838452, rs2838456, rs3788086, rs2838429 *AGPAT4*, rs746731, rs747866, rs1125640, rs2277092, rs2293286, rs3757025, rs3798225, rs3798920, rs3798924, rs3798929, rs3798943, rs3798945, rs3822853, rs3823058, rs4709501, rs6906489, rs6923835, rs7750302, rs7769321, rs9458172, rs10945713, rs10945719, rs11965825, rs12202278, rs17627837, rs12524665, rs1001422, rs6455711, rs9456642, rs2064721, rs3778227, rs3798922, rs11967514, rs7768457, rs12662114
Ouellette et al. Lipids in Health and Disease, 13:86 (2014)	*MGLL,* rs782440, rs16826716, rs6776142, rs9877819, rs555183, rs6780384, rs13076593, rs605188, rs6765071, rs782444, rs549662, rs3773155, rs541855, rs6439081, rs6439082, rs6787155, rs1466571, rs893294
Bouchard-Mercier et al. Genes Nutr 9:395 (2014)	*GCK,* rs2268573, rs2908297, rs2971676, rs758989, rs12673242, rs2908290, rs2284777, rs2300584, rs1990458, rs741038, rs1799884, rs2908277, rs3757838
Bouchard-Mercier et al. Nutrients, 6, 1145-1163 (2014)	*RXRA*, rs10881576, rs7871655, rs12339187, rs11185660, rs11103473, rs10776909, rs12004589, rs3132301, rs1805352, rs3132294, rs1805343, rs1045570 *CPT1A*, rs3019598, rs897048, rs7942147, rs4930248, rs11228364, rs11228368, rs10896371, rs1017640, rs613084 *ACADVL*, rs2017365 *ACAA2*, rs529556, rs10502901, rs631536, rs1942421, rs2276168, rs7237253 *ABCD2*, rs4072006, rs10877201, rs12582802, rs4294600, rs11172696, rs10877173, rs7133376, rs7968837 *ACOX1*, rs10852766, rs3744033, rs12430, rs8065144,

	rs11651351, rs3643, rs7213998, rs17583163 *ACAA1*, rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	*CETP*, rs3764261, rs247616, rs7205804 *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5, ABCG8*, rs4299376 *TIMD4, HAVCR1*, rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 *ANGPTL3, DOCK7*, rs3850634, rs1167998, rs2131925 *FADS1, FADS2, FADS3*, rs174550, rs174547, rs174546, rs174583 *GALNT2*, rs4846914, rs1321257 *ABCA1,* rs4149268 *APOE, APOC1, APOC2,* rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	*IQCJ-SCHIP1, MYB, NELL1, NXPH1, PHF17, SLIT2,* rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	*IQCJ*, rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	NXPH1, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs12537067, rs4318981, rs17153997, rs7801099, rs4725120, rs1859275, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862 PHF17, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308
Vallée Marcotte et al. Nutrients; 11, 737 (2019)	*IQCJ-SCHIP1*, rs12497650, rs4501157, rs13091349, rs2044704, rs1962071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs1449009, rs61332355, rs12485627, rs2595242, rs7639937, rs9820807, rs1375409, rs1967363, rs9824310, rs11915303, rs9835214, rs11921343, rs13066560, rs1675497, rs9839862, rs16829875, rs17795566, rs9860588, rs16830408, rs17798579, rs2364930, rs9865997, rs2595241, rs7632574, rs2621308 *NXPH1*, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs4318981, rs17153997, rs7801099, rs4725120, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862, rs6463808 *PHF17*, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, *SLIT2,* rs2952724 *NELL1*, rs752088

Supplementary Table 6: 31-SNP Nutri-GRS

***Gene,* rs Number**	**Alleles[1]**	**Associated Points**
IQCJ-SCHIP1, rs7639707	A/G	+1
IQCJ-SCHIP1, rs62270407	C/T	-1
NXPH1, rs61569932,	G/T	+1
NXPH1, rs1990554	A/C	+1
NXPH1, rs6463808	A/G	+1
NXPH1, rs6966968	A/G	+1
NXPH1, rs28473103	A/G	-1
NXPH1, rs28673635	A/G	+1
NXPH1, rs12702829	C/T	+1
NXPH1, rs78943417	A/T	-1
NXPH1, rs293180	G/T	+1
NXPH1, rs1837523	C/T	-1
PHF17, rs1216346	C/T	+1
PHF17, rs114348423	A/G	+1
PHF17, rs75007521	G/T	-1
MYB, rs72560788	C/T	-1
MYB, rs72974149	A/G	-1
MYB, rs210962	C/T	-1
MYB, rs6933462	C/G	+1
NELL1, rs79624996	A/G	+1
NELL1, rs1850875	C/T	+1
NELL1, rs78786240	C/T	-1
NELL1, rs117114492	G/T	+1
SLIT2, rs184945470	C/T	+1
SLIT2, rs143662727	A/G	-1
SLIT2, rs10009109	C/T	+1
SLIT2, rs10009535	A/G	+1
SLIT2, rs61790364	A/G	+1
SLIT2, rs73241936	C/T	+1
SLIT2, rs16869663	A/G	+1
SLIT2, rs76015249	A/G	+1

1. Minor alleles are underlined

For individuals carrying one or two minor alleles, provide the associated number of points (either +1 or -1). For individuals homozygous for the major allele, provide 0 points. Count the overall number of points. Individuals with lower nutri-GRS are more likely to respond to approximately 3.0 g/day EPA+DHA for TG lowering.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. T1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA (meta-analysis not appropriate)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12, Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Table 3, 34-39
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	45-46
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	40-47
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	47

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BMJ Open

A systematic review of nutrigenetics, omega-3 and plasma lipids/lipoproteins/apolipoproteins with evidence evaluation using the GRADE approach

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A systematic review of nutrigenetics, omega-3 and plasma lipids/lipoproteins/apolipoproteins with evidence evaluation using the GRADE approach

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Ethics Approval Statement: No ethics approval was required for a systematic review.

Running Head: Nutrigenetics, omega-3 and lipids/lipoproteins

Data described in the manuscript will be made available upon request pending approval from the corresponding author.

Abbreviations: ALA (alpha-linolenic acid); CV (coefficient of variation); DHA (docosahexaenoic acid); EPA (eicosapentaenoic acid); FDA (Food and Drug Administration); GRADE (Grading of Recommendations Assessment, Development and Evaluation); HCP (healthcare professional); LD (linkage disequilibrium); nutri-GRS (nutrigenetic risk score); SNP (single nucleotide polymorphism)

ABSTRACT

Objectives: Despite the uptake of nutrigenetic testing through direct-to-consumer services and healthcare professionals, systematic reviews determining scientific validity are limited in this field. The objective of this review was to: retrieve, synthesize and assess the quality of evidence (confidence) for nutrigenetic approaches related to the effect of genetic variation on plasma lipid, lipo- and apolipoprotein responsiveness to omega-3 fatty acid intake.

Design: A systematic review was conducted using three search engines (Embase, Web of Science and Medline) for articles published up until August 1, 2020. We aimed to systematically search, identify (select), and provide a narrative synthesis of all studies that assessed nutrigenetic associations/interactions for genetic variants (comparators) influencing the plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population). We further aimed to assess the overall quality of evidence for specific priority nutrigenetic associations/interactions based on the following inclusion criteria: nutrigenetic associations/interactions reported for the same genetic variants (comparators) influencing the same plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population) in two independent studies, irrespective of the findings. Risk of bias was assessed in individual studies. Evidence was evaluated using the GRADE approach. This systematic review was registered with PROSPERO (CRD42020185087).

Results: Out of 1830 articles screened, 65 met the inclusion criteria for the narrative synthesis (*n*=23 observational, *n*=42 interventional); of these, 25 met the inclusion criteria for evidence evaluation using GRADE. Overall, current evidence is insufficient for gene-diet associations related to omega-3 fatty acid intake on plasma apolipoproteins, total cholesterol, HDL-cholesterol, LDL-cholesterol and LDL particle size. However, there is strong (GRADE rating: moderate quality) evidence to suggest that male *APOE*-E4 carriers (rs429358, rs7412) exhibit significant triglyceride reductions in response to omega-3-rich fish oil with a dose-response effect. Moreover, strong (GRADE rating: high quality) evidence suggests that a 31-SNP nutrigenetic risk score can predict plasma triglyceride responsiveness to omega-3-rich fish oil in adults with overweight/obesity from various ethnicities.

Conclusions: Most evidence in this area is weak, but two specific nutrigenetic interactions exhibited strong evidence, with limited generalizability to specific populations.

Keywords: nutrigenomics, nutrigenetics, nutritional genomics, genetic risk score, nutrigenetic risk score, triglycerides, lipids, lipoproteins, omega-3 fatty acid, *APOE*

STRENGTHS AND LIMITATIONS

- Strength: Comprehensive systematic review guided by PRISMA

- Strength: Critical appraisal of the evidence guided by GRADE
- Limitation: Inability to conduct a meta-analysis given the comprehensive overview of studies and thus heterogeneity
- Limitation: Several included studies without replication; most evidence was low or very low quality according to GRADE

INTRODUCTION

Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research demonstrates that there is significant inter-individual variability in cardiometabolic risk factor levels, in part based on a combination of genetic and nutrition-related risk factors (2,3). For example, protein intake has consistently been shown to influence measures of body weight and composition dependent on *FTO* genotype (rs9939609 or loci in strong linkage disequilibrium) (4,5). Consumers indicate great interest in personalized nutrition based on genetics (6,7), however, a lack of industry oversight (8,9) has led to highly variable scientific validity of nutrigenetic tests available to consumers. While recognizing that some groups question whether genetic testing for personalized nutrition is ready for 'prime time', Gorman and colleagues suggested that there are certain specific nutrigenetic interactions with strong evidence that could be considered for implementation into clinical practice by expert committees who are responsible for creating dietary guidelines (10). With this in mind, systematic reviews that include an evaluation of levels of evidence are urgently needed in order to determine if there are any nutrigenetic associations that may warrant potential implementation into practice.

The dominant omega-3 polyunsaturated fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which typically come from marine sources (e.g. fish oil), and alpha-linolenic acid (ALA), which are rich in plant sources (e.g., canola oil) (11,12). It is well established that higher intakes of omega-3 fatty acids from foods or supplements (herein after referred to collectively as "omega-3s"), particularly from long-chain EPA and DHA, tend to improve indicators of cardiometabolic health (12,13). In

terms of their lipid and lipoprotein lowering effects, omega-3s have consistently demonstrated an impact on triglycerides (TG) (14). High-quality evidence from population-based studies suggests that long-chain omega-3s (EPA and DHA) reduce plasma TG by about 15% (14). There is also high-quality evidence suggesting that EPA and DHA can raise high-density lipoprotein (HDL) cholesterol (14). Other studies have further demonstrated a relationship between omega-3 and HDL-cholesterol (15), low-density lipoprotein (LDL)-cholesterol (15), total cholesterol (16–18), apolipoproteins (19), and LDL particle size (20). Despite several studies with significant findings for these outcomes, when reviewing the evidence, studies have demonstrated conflicting results for the impact of omega-3 on many lipid profile outcomes (14). Genetic variation could explain this heterogeneity. EPA and DHA have been shown to significantly impact the expression of thousands of genes including those involved in inflammatory and atherogenic pathways (21,22). Evidence now demonstrates that the health impacts of omega-3 intake could differ based on genetic variation (23,24). Despite the potential for omega-3s to have a significant positive impact on health outcomes, population intakes of omega-3s tend to be low (25). While the World Health Organization's Adequate Intake level for adults is 200-250 mg EPA+DHA daily (26,27), the mean reported intake of EPA+DHA in the United States is only approximately 100 mg daily (25). Nutrigenetic interventions have the potential to motivate improvements in dietary intake beyond population-based interventions (28). Additionally, evidence suggests that genetic variability affects health responses to omega-3s (23). Thus, critically appraising and grading the evidence for nutrigenetic interactions related to omega-3s and plasma lipids, lipoproteins and apolipoproteins is an important research priority. The most recent

systematic review on nutrigenetic interactions related to omega-3s and intermediate phenotypes of cardiovascular disease was conducted nearly a decade ago, and this study did not evaluate the quality of evidence using an established methodology (29). Therefore, we aimed to provide a comprehensive summary of current evidence related to inter-individual variability in plasma lipid, lipoprotein and apolipoprotein responses to omega-3 intake (plant and marine sources) based on genetic variations. Overall, the specific objectives of this study were as follows:

Objective 1. Systematically search, identify (select), and provide a narrative synthesis of all studies that assessed nutrigenetic associations/interactions for genetic variants (comparators; i.e. outcomes in those with a specific genotype for a genetic variant compared to a different genotype) influencing the plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population).

Objective 2. Assess the overall quality of evidence for specific priority nutrigenetic associations/interactions based on the following inclusion criteria: nutrigenetic associations/interactions reported for the same genetic variants (comparators) influencing the same plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population) in two independent studies, irrespective of the findings.

Methods

Patient and Public Involvement: No patient involvement.

Literature Search

The systematic review protocol was registered with PROSPERO (CRD42020185087). The review process was guided by previously established methods, including a previously outlined five-step systematic review process (30,31). The search engines Embase, Web of Science and Medline OVID were used to conduct the search starting in May 2020 and screen for articles meeting inclusion criteria, using the comprehensive search terms outlined in Supplementary Table 1, properly combined by Boolean operators. The literature was searched up until August 1, 2020 (there was no minimum start date; any article published prior to this date was included in the search). A PRISMA diagram (Figure 1) guided the article screening process (32).

Inclusion and Exclusion Criteria

Original studies were included if they were written in English or French. Inclusion criteria were developed using the Population, Intervention, Comparison, Outcomes, (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (33,34) for interventional and observational research, respectively. These are detailed in Table 1 for each study objective.

Table 1. PICO/PECO for Study Objectives

PICO/PECO for Objective 1:	
Population	Human studies (adult and pediatric)
Intervention/ Exposure	Omega-3s (total omega-3 or various types; supplemental and/or dietary intake)

Comparison	Genetic variation
Outcomes	HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and/or TG
PICO/PECO for Objective 2*:	
Population	Human studies (adult and pediatric)
Intervention/ Exposure	Omega-3s (total omega-3 or various types; supplemental and/or dietary intake)
Comparison	Genetic variation in the same genetic location [gene(s) and SNP(s)]
Outcomes	The same outcome of interest among studies with the same genetic comparators: HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and/or TG

*Nutrigenetic associations/interactions were included in objective 2, **in the evidence grading process**, irrespective of the findings, provided that they had been reported in at least two independent studies on the same gene(s) and SNP(s), and the same plasma outcome.

There were no limitations to the population characteristics (all populations/patient samples were included). Animal studies were excluded. Dietary interventions and observational studies involving omega-3s (total omega-3 or various types; supplemental and/or dietary intake) and comparing lipid and/or lipoprotein and/or apolipoprotein outcomes between different genetic variations based on omega-3 dietary or supplemental intake (and not blood fatty acid levels; e.g. EPA and DHA in red blood cells) were included in the narrative synthesis. In included studies, samples had to be stratified on the basis of genetic variation. Specific lipid and lipoprotein outcomes of interest were: HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and triglycerides (TG). Studies that reported ratios of the aforementioned lipid parameters (e.g. HDL-cholesterol to total cholesterol ratio) were also included. Both observational and interventional studies were included, as well as single-gene, polygenic and genome-wide association studies (GWAS). Differences in study designs and methods were considered when developing the overall evidence grades, as further detailed below. Associations/interactions reported in two independent studies formed the basis of the inclusion criteria for objective 2, in which nutrigenetic associations/interactions were

prioritized for evidence grading. This is further detailed in Table 1 and the section below entitled "Evidence Grading."

Article Selection and Data Extraction

Two independent investigators (JK and VG) screened articles using the computer software *Covidence* (including title, abstract, and full-text screening) and extracted data from the included articles. Reference lists of included articles and of a systematic review on a similar topic (35) were also screened for relevant articles. Data extraction templates were piloted by two independent investigators (JK and VG) on ten included studies and revised accordingly. The final data extraction templates included the following components for each study: first author name and year, study design, genetic approach, population and sample size, study duration (interventional studies only), genes and single nucleotide polymorphisms (SNPs) analyzed with rs numbers, quantity and type of omega-3, comparisons (e.g. a control group or different amount/type of omega-3s as well as genetic grouping), lipid/lipoprotein outcome(s), whether or not the study reported that they followed STREGA guidelines and a summary of statistically significant study findings relevant to the research question. Corresponding authors of included studies were contacted as needed to provide clarity and/or additional information about the included studies.

Evidence Grading

Upon reading all full-text articles included, and summarizing the body of evidence (Tables 2 and 3), SNPs/nutrigenetic risk scores (nutri-GRSs) and subsequent lipid/lipoprotein/apolipoprotein outcomes were systematically prioritized and selected for

evidence grading, if a specific nutrigenetic association/interaction was reported in at least two independent studies. To clarify, this refers to the same SNP(s)/nutri-GRS [or SNPs in strong linkage disequilibrium (LD)] being assessed and influencing the same lipid/lipoprotein outcome in at least two studies. For these nutrigenetic associations/interactions, we proceeded with evidence grading, while including **all** studies relevant to the particular nutrigenetic association/interaction, irrespective of the findings. Consistency of results was then one of several factors considered when grading the body of evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach indicates that a single study rarely (if ever) results in strong evidence, but two studies (typically RCTs) can indicate strong evidence if they are graded highly using the GRADE criteria (36). Prior to selecting the nutrigenetic associations/interactions (genetic variants and lipid/lipoprotein/apolipoprotein outcomes) for evidence grading, LD was assessed using the SNIPA SNP Annotator Software (37) for genes located on the same chromosome and arm (determined using the Online Mendelian Inheritance in Man® [OMIM] database) as outlined in the summary of results' tables in the column labelled 'Cytogenic Location of Gene(s)' (Tables 1 and 2). Strong LD was defined as $r^2>0.8$ and location <250 kb away from the index SNP location. SNPs in strong LD were considered together for the purposes of evidencing grading.

Based on our abovementioned predetermined criteria for specific nutrigenetic topic selection for evidence grading, nutrigenetic associations/interactions that were not included in the evidence grading process likely have weak evidence (at minimum due to lack of replication, for example, *ZNT8* rs13266634 and HDL-c or TG responsiveness to

omega-3, which has only been assessed in a single study (38)). According to the GRADE guidelines, when only a single study exists indicating significant findings for an outcome of interest (especially when the study is observational), the overall quality of the evidence is generally rated to be low or very low (39). Therefore, our process for prioritizing nutrigenetic topics for evidence grading aimed to filter out specific nutrigenetic associations/interactions that would likely be deemed low or very low quality (based on, at minimum, lack of replication). Two authors (JK and VG) critically appraised the selected nutrigenetic interactions using the GRADE methodology (39,40). Nutrigenetic interactions were grouped according to studies assessing the same SNP(s)/nutri-GRS and lipid/lipoprotein/apolipoprotein outcome, and the quality of the body of evidence (studies with significant and non-significant results) was rated; this process was guided by the GRADE Evidence Profile, which included consideration of risk of bias, inconsistency, indirectness, imprecision, publication bias, plausible confounding, dose-response and other factors (39). For example, different sources of omega-3s (e.g. EPA+DHA vs. ALA; food sources vs. supplementation) were taken into consideration when grading the evidence through the analysis of indirectness within the GRADE approach (39,40). Risk of bias was assessed in each of the included interventional and observational studies using the National Institutes of Health Study Quality Assessment Tools, in line with recently published recommendations for risk of bias assessments (41). To assess measures of precision, coefficients of variation (CV) were calculated based on outcome means (mean change or absolute values – whichever was used for the analyses) and standard deviations. In cases where standard errors of the mean were reported, these were converted to standard deviations to calculate the CV. The nutrigenetic interactions were

each given an evidence grade of high, moderate, low or very low.

Results

Figure 1 outlines the PRISMA Flow Diagram, which was used to guide the systematic review. Supplementary Tables 2 and 3 provide a summary of the 65 included studies. The results columns of Supplementary Tables 2 and 3 (far right) indicate nutrigenetic findings that were statistically significant. Any results related to the studies' analyzed SNPs and outcomes of interest that were not statistically significant are not indicated in the results column. No studies explicitly reported that they followed STREGA guidelines. LD analysis of SNPs tested in different studies revealed strong LD in several SNPs from the *FADS* gene cluster (see Table 2 footnote). As such, LD was taken into consideration in the selection of nutrigenetic interactions selected for evidence grading.

Observational Studies

Of the 65 included studies, 23 were observational with the majority of these being cross-sectional, as outlined in Supplementary Table 2. A total of 62,221 participants were included in the observational studies. These studies assessed correlations among a number of different genetic variations and outcomes, with several studies assessing genetic variations in the *FADS* gene cluster (42–48), *TNFα* (49–51) and *PPARα* (52–54). Most studies (n=13) assessed total omega-3s (38,42,47–49,51,54–60). The intake and type of omega-3s, lipid/lipoprotein/apolipoprotein outcomes and associations revealed from these studies were variable as further detailed in Supplementary Table 2. In the observational studies assessing genetic variation in the *FADS* gene cluster, some studies indicated significant gene-diet findings related to HDL-cholesterol, LDL-cholesterol, TG,

total-cholesterol while other studies demonstrated no significant gene-diet interactions for these outcomes thus indicating notable inconsistency among the results, while considering that SNPs differed by studies (42–48). In the observational studies focused on genetic variation in the *TNFα* gene, there was some evidence of a gene-diet relationship for omega-3 and LDL-cholesterol, total-cholesterol and total-cholesterol:HDL-cholesterol ratio, but again, results differed between studies (49–51). For gene-diet relationships and *PPARα* genetic variation, individual studies indicated significant findings related to total-cholesterol, LDL-cholesterol, TG, apoC-III and LDL peak particle diameter (52–54). Comprehensive details of the observational studies are outlined in Supplementary Table 2.

Interventional Studies

Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-randomized studies included single arm clinical trials and sequential non-randomized cross-over interventions. For interventional studies, n=6,225 participants upon combining all sample sizes of the included studies. Again, these studies assessed relationships between a number of different genetic variants and study outcomes. In more recent years, several studies (n=8) used a nutri-GRS or polygenic approaches (61–68) given the plausibility that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are polygenic in nature. Numerous studies assessed genetic variations in the *FADS* gene cluster (61,62,69–71), *APOE* (61,71–80), *CD36* (67,81,82), *PPARγ2* (62,67,83–85) and *PPARα* (83,86,87). Among these studies, results related to significant gene-diet (omega-3) associations influencing lipid/lipoprotein outcomes were generally inconsistent except for *APOE* (rs429358 and rs7412), omega-3 and TG in males only (71–75,77–80), and for

a 31-SNP nutri-GRS, omega-3 and TG (65,66). There was also consistent evidence to indicate a lack of association among *PPARγ2* (rs1801282) genetic variation, EPA+DHA and LDL cholesterol (62,67,84,85,88). Most studies (n=40) used supplemental EPA and/or DHA sources of omega-3s for the dietary intervention (see Supplementary Table 3). The dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages ranging from 0.5-3.7 g/day across different studies, and one study with an ALA intervention dosage of 8.1 g/day, as further detailed in Table 3.

Levels of Evidence Using GRADE

A total of 25 articles were included in the evidence grading process, representing 11 unique nutrigenetic associations/interactions as outlined in Tables 2 and 3, and Supplementary Table 4. Through the GRADE process, it was determined that there is strong evidence (GRADE rating: moderate quality) for *APOE* genotypes (rs7412, rs429358), omega-3s and TG lowering in male adults only (71–75,77–80). This evidence suggests that adult males (but not females) with the APOE-E3/E4 or E4/E4 genotype (rs429358, rs7412) tend to experience significant reductions in TG in response to 0.7-3.7 g/day of EPA and/or DHA, with higher dosages demonstrating greater TG lowering effects (71–75,77–80). Furthermore, it was determined that there is strong evidence (GRADE rating: high quality) for using a 31-SNP nutri-GRS (detailed in Supplementary Tables 5 and 6) to assess the effectiveness of omega-3s for TG lowering in adults with overweight/obesity in various ethnicities (65,66). The evidence suggests that in adults with overweight/obesity, lower genetic risk scores demonstrate greater responsiveness to omega-3 supplementation (65,66).

All other evidence that was evaluated was determined to be weak (GRADE rating: low or very low quality), as further detailed in Table 2. Imprecision, indirectness, and inconsistency were common reasons for downgrading the evidence (refer to Table 2 footnote). There was evidence for a plausible mechanism of action for most of the nutrigenetic interactions that were graded; evidence of a dose response was less common.

Table 2. GRADE Evidence Profile: Genetic Variation, Omega-3 and Lipids

Nutrigenetic interactions for omega-3 and plasma lipid/lipoprotein outcomes									
Patient or Population: adults **Intervention/Exposure: dietary or supplemental omega-3 (EPA and/or DHA and/or ALA)** **Comparison/Control: genetic variation, different omega-3 intakes** **Outcomes: plasma lipids and lipoproteins**									
***Gene* rs Number and Lipid: Number and Type of Studies (total *n*)**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Dose Response**	**Biological Plausibility***	**Quality**	**Conclusion**
***CD36* rs1761667 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the AA genotype of *CD36* rs1761667 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1761667 and TG**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the GG genotype of *CD36* rs1761667 could lead to significant reductions in TG in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1049673 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	No serious imprecision	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or possibly the CC genotype of *CD36* rs1049673 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1527483 and TG**: 1 RCT and 1 single arm trial (*n*=250) (67,81)	Serious limitations[f]	No serious inconsistency	Serious indirectness[g]	Very serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GG genotype of *CD36* rs1527483 could lead to significant decreases in TG in response to approximately 2.0 g/day of EPA+DHA (but not ALA).
***APOE* rs429358, rs7412 and TG:** 4 RCTs and 5 single arm trials (1 single arm trial consisted of a	No serious limitations	No serious inconsistency	Serious indirectness[h]	No serious imprecision	Undetected	Evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that adult males (but not females) with the *APOE*-E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

subset sample of another single arm trial) (n=980) (71–75,77–80)									response to 0.7-3.7 g/day of EPA and/or DHA. Higher dosages may have greater TG lowering effects.
***APOE* rs429358, rs7412 and Total-c:** 4 RCTs, 5 single arm trials (1 single arm trial consisted of a subset sample of another single arm trial), 1 cross-sectional and longitudinal analysis within an RCT (*n*=2,446) (55,71–75,77–80)	No serious limitations	Serious inconsistency[i]	Serious indirectness[h]	No serious imprecision	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate: Males and Females) and ⊕⊕⊖⊖ (Low: Males)	In males and females combined, strong evidence suggests that there is no nutrigenetic interaction between EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, *APOE* (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c.
31-SNP Nutri-GRS and TG: 1 RCT, 1 single arm trial (*n*=330) (65,66)	No serious limitations	No serious inconsistency	Serious indirectness[j]	No serious imprecision	Undetected	Evidence of a gradient[k]	Some evidence of a mechanism of action[l]	⊕⊕⊕⊕ High	Strong evidence suggests that in adults with overweight/obesity, a 31-SNP genetic risk score can predict TG responsiveness to EPA+DHA supplementation. Individuals with lower genetic risk scores demonstrate greater responsiveness to EPA+DHA for TG lowering.
***PPARg2* rs1801282 and LDL-c:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	No serious inconsistency	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence LDL-c responses to omega-3s (EPA+DHA).
***PPARg2* rs1801282 and Total-c:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	Serious inconsistency[o]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or GG genotype of *PPARg2* (rs1801282) could lead to significant increases in total-c in response to approximately 3 g/day of omega-3s (EPA+DHA) in individuals with overweight or obesity, but not for individuals without overweight or obesity.
***PPARg2* rs1801282 and TG:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	Very serious inconsistency[p]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence total-c responses to omega-3s (EPA+DHA), but when dietary total fat and saturated fat intake are low, nutrigenetic interactions may exist.
***FADS* (rs174547**) and Total-c:** 2 RCTs, 1 single-arm trial, 4 cross-	Very serious risk of bias[q]	No serious inconsistency	Very serious indirectness[r]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊖⊖⊖ (Very Low)	Weak evidence suggests that genetic variation in *FADS* (rs174547**) does not influence total-c responses to omega-3.

sectional studies (*n*=9365) (44,45,47,48,61,69,71)									

*Direct mechanisms of action were considered

**FADS rs174547 was in strong LD with the following SNPs from other included studies and therefore these SNPs were also included in the selection of studies assessing FADS genetic variation, n-3 intake and LDL-c: rs174546, rs174599, rs174601, rs174583, rs1353, rs174561, rs174556, rs174545, rs174537 and rs174576.

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

a. Small sample sizes, especially among homozygous groups in the RCT (with a larger heterozygous group, potentially affecting the results)
b. Some variation in results by genotype
c. One study sample consisted of all males while the other sample consisted of both men and women; differences in age and n-3 dosages (with some overlap)
d. Coefficient of variation >1 for all significant values
e. Coefficient of variation substantially >1 for several values
f. Small sample size within genotype groups for minor allele homozygote and heterozygote groups in the RCT
g. One study sample consisted of all men while the other consisted of men and postmenopausal women with type 2 diabetes
h. Differences in age, omega-3 dosages, and types (with some overlap), and dietary interventions even when considering studies with male study samples separate from male + female study samples
i. Serious inconsistency for men subgroup only; men + women samples were consistent
j. EPA and DHA separate on one study and EPA+DHA in the other, sample stratified into two groups in one study (responders and non-responders) and separated into three groups (responders, non-responders and adverse responders)
k. Evidence of a gradient for GRS and TG responsiveness to omega-3 supplementation
l. Some evidence of a potential mechanism of action for *IQCJ-SCHIP1, NXPH1, PHF17, MYB and NELL1* as discussed by Rudkowska et al. (63), Vallée Marcotte et al. (64)
m. Differences in population (healthy adults, adults with chronic disease or obesity, infants), some variation in length of follow-up
n. Downgraded precision as it was not possible to assess precision in most studies due to lack of reporting of means and SD/SEM
o. Some variation in results even when considering differences in BMI and populations among studies
p. Major variability in results even when considering differences in BMI and populations among studies
q. Risk of bias detected in every study except one
r. Major differences in populations, types and amounts of omega-3 and follow-up for interventional studies

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Table 3. Summary of Risk of Bias Across SNPs and Outcomes Following Omega-3 Exposure/Intervention

***CD36*, rs1761667 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1761667 and TG**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1049673 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1527483 and TG**	
Study	**Risk of Bias**
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
***ApoE*, rs429358, rs7412 and TG**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
***ApoE*, rs429358, rs7412 and Total-c**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Fallaize et al. 2016	⊖
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
31-SNP Nutri-GRS and TG	
Study	**Risk of Bias**
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

PPARg2, rs1801282 and LDL-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and Total-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and TG	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
FADS, rs174547 and Total-c	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Alsaleh et al. 2014	⊕
Lu et al. 2010	⊖
Standl et al. 2012	⊖
Dumont et al. 2011	⊖
Dumont et al. 2018	⊖
Roke and Mutch 2014	⊖

⊕ no serious risk of bias; ⊖ serious risk of bias; ⊖⊖ very serious risk of bias (for study design type using NIH Study Quality Assessment Tools)

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

DISCUSSION

Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and high quality evidence) for only a limited amount of evidence in this area: *APOE* (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity. Limited evidence exists for individual genetic-based responsiveness of omega-3s on apolipoprotein and/or LDL particle size, with no studies from the present comprehensive review meeting the criteria for evidence grading. This highlights the need for more replication studies in this area. While more research exists on omega-3 responsiveness for other lipid outcomes such as total-c, HDL-c and LDL-c, the level of evidence for nutrigenetic interactions related to these outcomes remains low. Again, more studies are needed related to these outcomes, including replication studies of previously identified nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the same type and amount of omega-3s as the original study), and recruit samples with similar characteristics to the original study. Once replication is established, research should then seek to expand the population studied to improve generalizability and explore the effectiveness of different interventions (i.e. different formulations and doses of omega-3s). The variability of the interventions and sample sizes in the studies conducted to date often resulted in the quality of evidence being downgraded (see Table 2). It should also be noted that study heterogeneity precluded the ability to conduct a meta-analysis. Thus, the GRADE approach worked well for evaluating the quality of the evidence given that this approach takes into consideration several factors when determining the quality of

evidence such as risk of bias, indirectness of evidence, inconsistency or results, imprecision and publication bias (39).

It is important to note that our results demonstrating strong evidence for interactions between *APOE* genotypes and lipid responses to omega-3s have notable ethical implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk of developing Alzheimer's disease (90). Moreover, *APOE* genotypes are significantly associated with CVD risk including risk of coronary artery disease and hyperlipidemia (91–93). Interestingly, the pathology of Alzheimer's disease has been linked to cardiovascular mechanisms (90). Future research should explore nutrigenetic interactions, with risk of developing Alzheimer's disease as the study endpoint/outcome of interest. Despite the current lack of knowledge about how diet may play a role in mitigating the genetic-based risk of Alzheimer's disease, several potentially modifiable risk factors account for around 40% of dementia and Alzheimer's disease globally (94), and the link between Alzheimer's disease risk and *APOE* is well-established (95). Therefore, despite the strong scientific validity identified in the present review, there are other factors that must be considered before this test can be recommended for implementation in a practice setting; this includes ethical, legal and social implications (96).

In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness to omega-3s in men but not women speaks to the importance of taking biological sex into account in nutrigenetics research. The importance of this has been further highlighted elsewhere, where it has been noted that the results of nutrition and nutrigenetic research

may differ in men and women (97). For example, UDP-glucuronidation isoenzyme expression profiles have been demonstrated to be regulated by sex hormones, and thus sex-specific differences in glucuronidation of resveratrol have been observed (98). As more studies are completed, researchers may find that certain nutrigenetic interactions differ depending on biological sex, ethnicity, age or other factors, similar to our findings on *APOE,* omega-3s and TG in which there was robust evidence of a nutrigenetic interaction in males only. Researchers may also find explanations for this, which are currently poorly understood. In general, it is becoming increasingly recognized that health-related responses to different interventions may vary based on biological sex; this is an important consideration of personalized nutrition (97). Nutrigenetic research often groups men and women together, but stratifying based on biological sex could provide further insights for specific nutrigenetic interactions and could also help explain why some replication studies have had conflicting findings (97). Moreover, biomedical research in general historically has been conducted more in men than women; yet such research findings are often generalized to women despite limited research conducted in samples of women, which is problematic for a number of reasons (99). In the present review, the evidence was strong for the *APOE* findings in men only, but not women in part because there were more studies conducted in men. Specifically, there were five studies conducted in men and women (combined) (71,73,74,100,101), and four studies conducted in samples of only men (75,78,79,102), yet no studies conducted in samples of only women. This brings to light important issues of equity and warrants further discussion and consideration.

As research continues to develop, it appears likely that lipid and lipoprotein responses are polygenic in nature. Therefore, future research should consider using nutri-GRSs or other polygenic methods of assessing responsiveness to nutrition interventions. This work should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs, such as establishing them from genetic-wide association studies. In addition to the two studies meeting the criteria for evidence grading (65,66), a modified version of the 31-SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs (65). While this did not meet our inclusion criteria for evidence grading given that a different GRS was used, the 23-SNP GRS was significantly associated with TG responsiveness to omega-3 supplementation in this population as well, providing further evidence for the scientific validity of this nutrigenetic interaction (65).

While we used the GRADE approach to evaluate the body of evidence, several tools are available for evaluating the quality of scientific evidence, though no generally accepted methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a set of guidelines to assess the scientific validity of genotype-based dietary advice (30). While we originally intended to use these guidelines for assessing the evidence, we came across some limitations that ultimately led us to use the GRADE guidelines. Specifically, Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines should be included in the assessment of scientific validity (30). However, limiting the evidence to only these studies could result in several important studies being missed. In the present review, none of the included studies explicitly indicated that they followed STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA

guidelines to assess risk of bias (30). However, the STREGA checklist is only intended for observational genetic association studies - not interventional research (103). In the present review, 42 of the 65 included studies were interventional (65%) (Supplementary Table 3). In addition, the STREGA guidelines are intended to improve the transparency and adequate reporting of genetic association studies, but it is not intended to be used as a study quality assessment tool (103). However, Grimaldi et al. nicely highlighted the importance of understanding the nature of the genetic variation, at a functional level, when assessing scientific validity (30). This is not included in the standard GRADE approach but is an important niche component of nutrigenetic research. As such, an analysis of functional SNPs (biological plausibility) was included as an additional component of the standard GRADE process, as indicated in the methods section above. Overall, we found that the methods used in this systematic review were effective and can be used to synthesize and evaluate nutrigenetic studies assessing other gene-nutrient-health outcome interactions.

The additional consideration of functional SNPs to the standard GRADE approach helped to strengthen this review, as biological mechanistic evidence can help ensure that study findings did not occur by chance alone, and this is a component of evidence evaluation frameworks in medical genetics (104,105). Transcriptomic and pathway analyses can help inform the direction of future nutrigenetic studies by generating hypotheses about the impact of specific genetic variations on varying responses to nutrition on health-related outcomes. For example, using transcriptomics and pathway analyses to identify changes in lipid metabolism following omega-3 supplementation, Rudkowska and

colleagues identified six genes expressed in opposite directions between responders and non-responders to omega-3 supplementation for TG lowering: *FADS2, PLA2G4A, ALOX15, PEMT, MGLL and GPAM* (106). Tremblay et al. then built on this knowledge and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a significant impact on the TG lowering effect of omega-3 supplementation (107). Others have built on this mechanistic knowledge as well (108). Future research should now seek to replicate this work given that we found that there have been no replication studies completed and thus, this research (107,108) did not meet the criteria for evidence grading.

In the current body of literature, there are some limitations that should be highlighted. Given the variability in allele frequencies for each SNP, it should be noted that study limitations can arise with small sample sizes whereby some genotype groups may not be adequately powered to detect significant differences. For example, Dawczynski et al. (2013) detected significant changes in TG among the GA genotype group of *CD36* rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA: n=8, GG: n=7) exhibited a significant difference, despite similar directions and magnitudes of effect among the GA and GG genotypes (82). It is thus possible that this study was not adequately powered. Some researchers aim to mitigate this issue of small numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for the minor allele) (69). However, such an approach precludes the possibility to detect an

allele-dosage effect. From a physiological perspective, an allele dosage effect would be expected whereby a significant change among a heterozygote group would likely be accompanied by a significant change in one of the homozygote groups but with an even greater magnitude of the effect. This consideration highlights the importance of having an adequately powered sample size, while factoring in the prevalence of each genotype.

While single SNP research provides important information about individual gene-nutrient interactions, the results of this review indicate that individual responses to omega-3s for altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus, we encourage researchers to further explore the use of nutri-GRSs to improve the accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et al., which obtained a high quality evidence grade in the present review (65,66). This is further exemplified in the analyses recently conducted by Chen et al. (42), which has yet to be replicated and thus was not selected for evidence grading.

The present analysis of scientific validity provides an important first step towards the eventual development of clinical practice guidelines for genetic-based responses to dietary intake. With questionable and variable scientific validity of existing consumer nutrigenetic tests, the development of clinical practice guidelines is an important next step as these can be used by HCPs and industry alike to help promote evidence-based practice in personalized nutrition. Ideally, industry should use future clinical practice guidelines to inform the nutrigenetic associations and related dietary recommendations included in their reports. Decision aids can also be useful to guide clinical practice for

HCPs (109), and future research should seek to develop a decision aid related to omega-3s and lipid/lipoprotein outcomes based on genetic variation.

It should be noted that there are some limitations to the present systematic review. First, the literature was searched up until August 2020; as such, any articles published after this date were not included. Furthermore, certain nutrigenetic associations/interactions were prioritized for evidence grading therefore evidence grades remain unknown for numerous associations/interactions included in the narrative synthesis. However, evidence from a single study typically results in an evidence grade of low or very low using the GRADE approach (39), therefore it is unlikely that any/many nutrigenetic associations/interactions with strong scientific validity (which could be considered for use in clinical practice) were missed. Future research groups may choose to instead select a specific SNP or nutri-GRS as the focus of future systematic reviews. The specific SNP or nutri-GRS chosen may be selected based on the results of a preliminary scoping review. This would allow for all articles included in the systematic review to undergo evidence grading. The approach taken in the present review was more comprehensive, but has its limitations as stated above.

Overall, we have provided a comprehensive overview the body of evidence related to nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing an overview of levels of evidence in this field. To our knowledge, this is the first systematic review with GRADE evidence evaluation in the broader field of nutrigenetics. The results of this work should be used in clinical practice guideline development, to

ultimately guide evidence-based practice in personalized nutrition and move this emerging field forward.

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Contributorship Statements: M-C.V. and J.K. conceptualized the review. G.S. was responsible for the search strategy, in collaboration with J.K., M-C.V., S.D. and V.G. J.K. and V.G. were responsible for article screening and selection, summarizing, evidence grading, and developing a draft of the systematic review. The first systematic review draft underwent revisions from S.D. and M-C.V., who provided overall supervision for the project. Following this, J.K., V.G., V.M., D.M.M., J.R., I.R., G.S., S.D., and M-C.V. served as scientific advisors and reviewed and revised the full-text manuscript. J.K. wrote the first draft of the manuscript. J.K., V.G., V.M., D.M.M., J.R., I.R., G.S., S.D., and M-C.V., reviewed, revised and approved the final manuscript.

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Data Sharing Statement: Data are available upon reasonable request.

Figure Legend:

Figure 1. PRISMA Flow Diagram

*The original PRISMA Flow Diagram indicated the number of studies included in meta-analysis in this box. This has been revised for the purposes of this research

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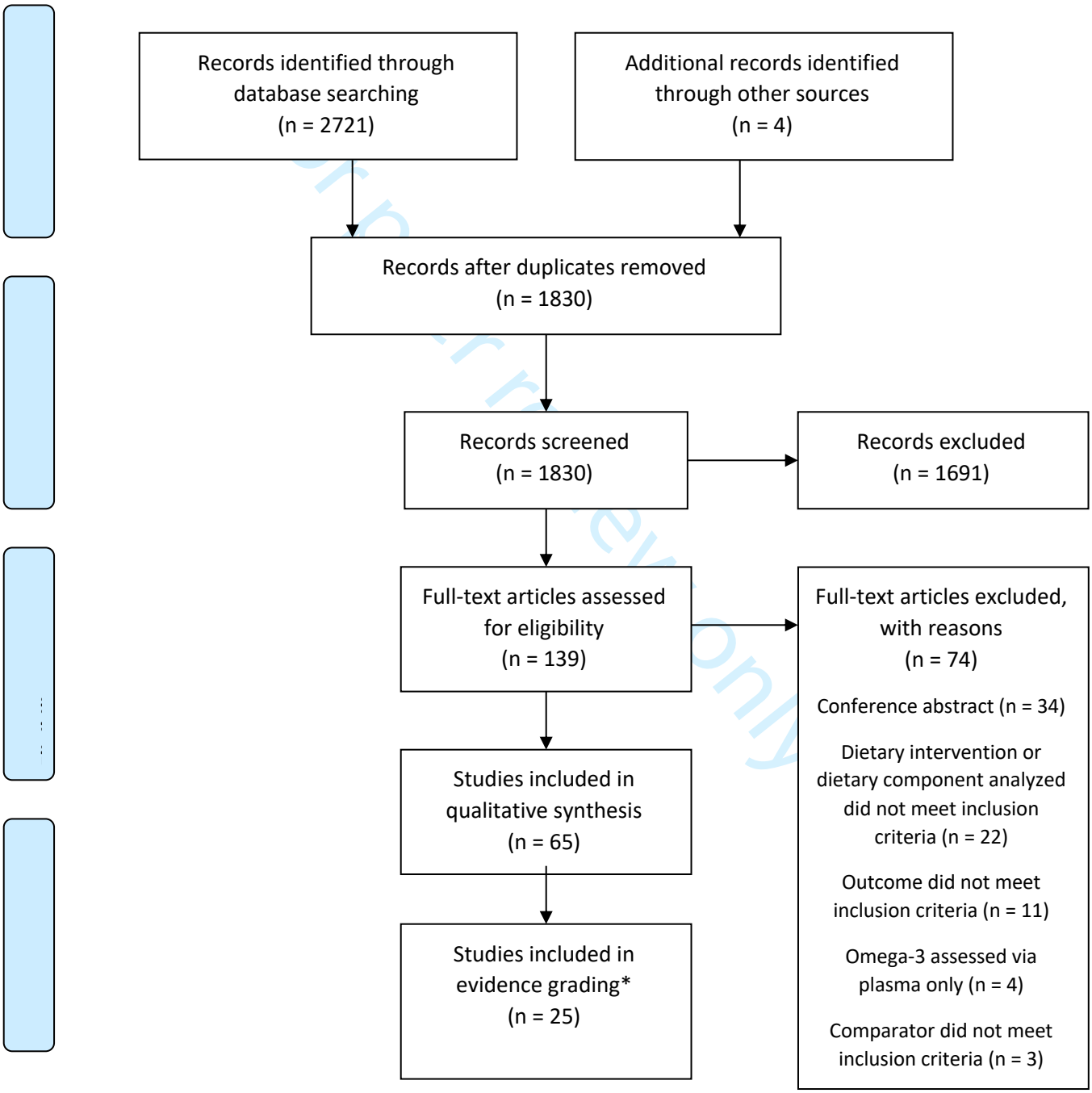
Figure 1: PRISMA 2009 Flow Diagram



Supplementary Tables

Supplementary Table 1: Search Strategy

Embase	
#	**Search Strategy**
1	omega-3':ti,ab,kw OR pufa$:ti,ab,kw OR ((acid* NEAR/5 ('n-3' OR polyunsaturated OR linolenic OR eicosapenta$noic OR timnodonic OR docosahexa$noic)):ti,ab,kw) OR docosahexaenoate:ti,ab,kw OR epa:ti,ab,kw OR dha:ti,ab,kw OR ala:ti,ab,kw
2	omega 3 fatty acid'/exp
3	**#1 OR #2**
4	cholesterol*:ti,ab,kw OR hdl:ti,ab,kw OR ldl:ti,ab,kw OR 'high density lipoprotein*':ti,ab,kw OR 'low density lipoprotein*':ti,ab,kw OR 'beta lipoprotein*':ti,ab,kw OR apo*protein*:ti,ab,kw OR apoa:ti,ab,kw OR apob:ti,ab,kw OR apoc:ti,ab,kw OR apod:ti,ab,kw OR apoe:ti,ab,kw OR apoh:ti,ab,kw OR ((apo NEXT/1 (a OR b OR c OR d OR e OR h)):ti,ab,kw) OR triglyceride*:ti,ab,kw OR triacylglycerol*:ti,ab,kw OR (((serum OR plasma) NEXT/1 (lipid* OR tg OR tag)):ti,ab,kw)
5	cholesterol'/exp OR 'lipoprotein'/exp OR 'triacylglycerol'/exp
6	**#4 OR #5**
7	nutrigenomic*:ti,ab,kw OR nutrigenetic*:ti,ab,kw OR (((nutritional OR expression* OR variation* OR variant*) NEAR/2 (genomic* OR genetic* OR gene OR genes)):ti,ab,kw) OR genotype:ti,ab,kw OR ((('nutrient-gene' OR 'gene-nutrient' OR 'gene-diet') NEXT/1 interaction*):ti,ab,kw) OR 'personali?ed nutrition':ti,ab,kw OR 'precision nutrition':ti,ab,kw
8	nutrigenomics'/exp OR 'nutrigenetics'/exp OR 'genetic variation'/exp OR 'genotype'/exp
9	**#7 OR #8**
10	**#3 AND #6 AND #9**
11	[animals]/lim NOT [humans]/lim
12	**#10 NOT #11**

Medline (Ovid)

#	Search Strategy
1	("omega-3" or PUFA? or (acid* adj5 ("n-3" or polyunsaturated or linolenic or eicosapenta?noic or timnodonic or docosahexa?noic)) or docosahexaenoate or EPA or DHA or ALA).ab,kf,ti.
2	exp Fatty Acids, Omega-3/
3	**1 or 2**
4	(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo adj (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) adj (lipid* or TG or TAG))).ab,kf,ti.
5	exp Cholesterol/ or exp Lipoproteins/ or exp Triglycerides/
6	**4 or 5**
7	(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) adj2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") adj interaction*) or "personali#ed nutrition" or "precision nutrition").ab,kf,ti.
8	Nutrigenomics/ or Genetic Variation/ or Genotype/
9	**7 or 8**
10	**3 and 6 and 9**
11	exp animals/ not humans.sh.
12	**10 not 11**

Web of Science

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan =All years

#	Search Strategy
1	TS=("omega-3" or PUFA$ or (acid* NEAR/5 ("n-3" or polyunsaturated or linolenic or eicosapenta$noic or timnodonic or docosahexa$noic)) or docosahexaenoate or EPA or DHA or ALA)
2	TS=(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo NEAR/0 (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) NEAR/0 (lipid* or TG or TAG)))
3	TS=(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) NEAR/2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") NEAR/0 interaction*) or "personali?ed nutrition" or "precision nutrition")
4	**#1 AND #2 AND #3**
5	TS=(animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)
6	**#4 not #5**

Supplementary Table 2: Summary of observational studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3[1]	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[2]
Bouchard-Mercier et al. 2011 (1)	Cross-Sectional	Single SNP	Healthy Caucasian men and women from INFOGENE study (n=674)	*PPARα*, L162V (rs1800206) *PPARγ*, P12A (rs1801282) *PPARδ*, –87T→ C (rs2016520)	*PPARα*: 22q13.31 *PPARγ:* 3p25.2 *PPARδ:* 6p21.31	Mean: L162: 2.8 g/day V162: 2.9 g/day (unclear if food and/or supplement sources)	Minor allele carriers vs. Non-carriers	LDL-PPD	**LDL-PPD:** In a model including age, sex, TG, BMI, energy and omega-3 intakes and PPAR*α* L162V (rs1800206) polymorphism, the interaction of PPAR*α*162V and omega-3 intakes explained 0.62% of the variance in LDL-PPD.
Bodhini et al. 2017 (2)	Cross-Sectional	Single SNP	Adults with normal glucose tolerance (n=821) and adults with type 2 diabetes (n=861)	*MC4R*, rs17782313 *TCF7L2*, rs12255372 *TCF7L2*, rs7903146	*MC4R:* 18q21.32 *TCF7L2:* 10q25.2-q25.3	**Low:** 0.38 g/day ALA **Moderate:** 0.58 g/day ALA **High:** 0.89 g/day ALA (means) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c	**HDL-c:** 'T' allele carriers of *TCF7L2* rs12255372 within the lowest tertile of ALA intake (mean=0.38 g/day) exhibited higher levels of HDL-c compared to GG homozygotes in the lowest tertile of ALA intake (mean=0.38 g/day)
Chen et al. 2019 (3)	Cross-Sectional Analysis within a Prospective Cohort	Single SNP, Haplotype and Gene-Centric	Adults of Swedish ancestry from the GLACIER cohort (n=5160)	All variations in the *FADS1-FADS2-FADS3* gene cluster and variation within 200kb upstream and downstream of the *FADS* region	*FADS1:* 11q12.2 *FADS2:* 11q12.2 *FADS3:* 11q12.2	**High:** >1.6 g/day **Low:** <1.6 g/day (food)	Entire FADS region gene-centric analysis and Variation in individual FADS cluster SNPs: rs174570, rs174602, rs74771917, rs3168072, rs12577276, rs7115739 and Haplotype analysis	HDL-c LDL-c TG Total-c	**HDL-c:** Significant interaction of rs174570 and omega-3 on HDL-c **LDL-c:** Significant interaction of rs174602 and omega-3 on LDL-c **TG:** Gene-centric analyses demonstrated a significant interaction between variation in the *FADS* gene cluster and omega-3 intake on TG **Total-c:** Significant interaction of rs174602 and omega-3 on total-c ('C' allele carriers exhibited lower total-c with low omega-3 intake, while no such relationship was observed with high omega-3 intake)
Ching et al. 2019 (4)	Cross-Sectional	Single SNP	Vegetarian adults of Malaysian ancestry (n=200)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low:** ≤0.45 g/day ALA **Moderate:** 0.46-0.64 g/day ALA **High:** >0.64 g/day ALA (means) (food)	Comparison between three genotypes	HDL-c TG	**HDL-c:** The TT genotype had significantly lower HDL-c when ALA intake was in the moderate intake range, but there were no significant gene-omega-3 interaction on lipid levels
Dumont et al. 2011 (5)	Cross-Sectional	Single SNP	Adolescents of European ancestry (n=573)	*FADS1*, rs174547	*FADS1:* 11q12.2	**High**: >1.4 g/day ALA **Low**: ≤1.4 g/day ALA (unclear if food and/or supplement sources)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c	**Total-c:** Significant interaction whereby the minor allele (CT+TT genotype) was associated with lower total-c when ALA intake is high as compared to when intake is low. This remained significant after assessing the interaction using ALA intake as a continuous variable.

Dumont et al. 2018 (6)	Cross-Sectional	Single SNP	Men and women aged 35 to 74 years from the MONA LISA Study of three French populations (n=3069)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low**: 0.6 g/day ALA (mean) **Median**: 0.8 g/day ALA (stratified by median for analyses) **High**: 1.3 g/day ALA (mean) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c	--
Fallaize et al. 2016 (7)	Cross-Sectional (Baseline) and Longitudinal Analyses within a Randomized Intervention	Single SNP*	Healthy adults enrolled in the Food4Me European trial (*n*=1466)	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**High**: >0.67 %kcal **Low**: <0.67 %kcal **Increased Intake:** reduced omega-3 intake from baseline **Decreased Intake:** decreased omega-3 intake from baseline (unclear if food and/or supplement sources)	*APOE*-E4- vs. *APOE*-E4+	Total-c	**Total-c:** Cross-sectional (baseline) analysis demonstrated a significant genotype effect for *APOE,* omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for *APOE,* change in omega-3 intake (increase or decrease) and total-c.
Fontaine-Bisson and El-Sohemy 2007 (8)	Cross-Sectional	Genetic Score	Men and women aged 20-29 years (n=595)	*TNFα,* rs361525, rs1800629	*TNFα:* 6p21.33	Intake range: 0.2-4.6 %kcal (mean intakes were 0.7 %kcal for 0/0, 0.7% kcal for 0/1 and 0.6%kcal for 1/0) (food)	No minor allele ('A') for both SNPs (0/0) vs. One minor allele for rs361525 (1/0) vs. One minor allele for rs1800625 (0/1)	HDL-c	--
Fontaine-Bisson et al. 2009 (9)	Cross-Sectional	Single SNP	Healthy men and women aged 20-29 years (n=593)	*NF-κB* -94Ins/Del ATTG (rs28362491)	*NF-κB:* 4q24	Mean intake: 0.7 %kcal (unclear if food and/or supplement sources)	Ins/Ins vs. Ins/Del vs. Del/Del	HDL-c	**HDL-c:** Significant interaction between *NF-κB* genotype and omega-3 intake on HDL-c
Hellstrand et al. 2012 (10)	Cross-Sectional	Single SNP	Healthy men and women aged 45-68 years from Sweden (n=4635)	*FADS,* rs174547	*FADS:* 11q12.2	**Low:** ≤0.14 %kcal long-chain omega-3 **Moderate:** 0.14-0.28 %kcal long-chain omega-3 **High:** >0.28 %kcal long-chain omega-3 (tertiles of intake reported only for certain significant findings) (food and supplement)	TT vs. TC vs. CC	HDL-c LDL-c TG	**LDL-c:** Significant interaction between *FADS* rs174547 genotype and long-chain omega-3 on LDL-c whereby the 'C' allele was significantly associated with lower LDL-c when long-chain omega-3 intake was in the lowest tertile (but not in the moderate or highest tertile). High long-chain omega-3 intake was associated with significantly higher LDL-c for CC and TC genotypes but not TT genotypes. Stratified analysis based on sex demonstrated that these significant interactions remained for men, but not women, however there was not a significant difference in interactions by sex.
Hosseini-Esfahani et al. 2017 (11)	Nested Case-Control	Single SNP	Healthy men and women aged ≥18 years from Iran	*ZNT8,* rs13266634	*ZNT8:* 8q24.11	**Tertiles for omega-3:** **Low:** <0.38 %kcal **Moderate:** 0.38-	CC vs. CT+TT	HDL-c TG	**HDL-c:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of low HDL-c whereby CC genotypes exhibited a decreased risk of low HDL-c with increasing intake of omega-3; this was not observed in

			(n=1634)			0.54 %kcal **High:** >0.54 %kcal (food)			the CT+TT genotype group. **TG:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of high TG whereby CC genotypes exhibited a decreased risk of high TG with increasing intake of omega-3; this was not exhibited in the CT+TT genotype group.
Jang et al. 2014 (12)	Cross-Sectional	Single SNP	Adult: Men and women aged 40-69 from Korea (n=4205) Children: Boys and girls aged 8-13 years from Korea (n=1548)	*PCSK5,* rs1029035	*PCSK5:* 9q21.13	Based on overall median intake (further detailed elsewhere (12)): **Low:** <0.4 %kcal **High:** >0.4 %kcal (food)	CC vs. CA vs. AA	HDL-c	**HDL-c:** Significant interaction between *PCSK5* rs1029035 and omega-3 on HDL-c in male children and male adults. 'C' allele carriers exhibit a tendency to decrease HDL-c with omega-3, while AA genotypes exhibit the opposite effect.
Joffe et al. 2010 (13)	Cross-Sectional	Single SNP	Black women from South Africa, normal weight or with obesity (n=138)	*TNFα,* rs1800629	*TNFα:* 6p21.33	ALA (amount not reported/cannot determine) (food)	GG vs. GA+AA	HDL-c LDL-c TG Total-c Total-c:HDL-c	**Total-c:HDL-c ratio:** Significant interaction between *TNFα,* rs1800629 genotypes and %kcal from ALA whereby increasing %kcal from ALA was associated with increases in Total-c:HDL-c for GG genotypes but decreases in Total-c:HDL-c ratio for GA+AA genotypes
Joffe et al. 2012 (14)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=263)	*TNFα,* rs361525	*TNFα:* 6p21.33	**Median Intakes:** omega-3: 0.28-0.36 % kcal ALA: 0.21-0.26 %kcal EPA: 0.02 %kcal DHA: 0.04-0.08 %kcal (food)	GG vs. GA(+AA for one participant: black, normal weight)	HDL-c LDL-c TG Total-c Total-c:HDL-c	**LDL-c:** Significant interaction for Caucasian women whereby LDL-c decreased with increasing %kcal from EPA in the GG genotype but not the GA genotype of *TNFα,* rs361525. **Total-c:** Significant interaction for white women whereby total-c decreased with increasing EPA and DHA intakes in the GG genotype group but not the GA genotype group of *TNFα* rs361525 but individual rates were not significant. **Total-c:HDL-c ratio:** Significant interaction for black women whereby Total-c:HDL-c decreased within increasing %kcal from omega-3 in the GA genotype group but not GG of *TNFα* rs361525.
Joffe et al. 2014 (15)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=268)	*IL-6,* −174 G>C, IVS3 (rs1800795), +281 G>T, IVS4 (rs1554606), +869 A>G (rs2069845)	*IL-6:* 7p15.3	Black Women (%kcal/day): 0.28 omega-3, 0.21 ALA, 0.02 EPA, 0.04 DHA (normal weight); 0.36 omega-3, 0.22 ALA, 0.04 EPA, 0.08 DHA (obesity) White Women (%kcal/day): 0.33 omega-3, 0.26 ALA, 0.01 EPA, 0.05 DHA (normal weight); 0.32 omega-3, 0.25 ALA, 0.02 EPA, 0.05 DHA (food)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	The following results were statistically significant only in white women, but not in black women[3]: **HDL-c:** Significant interaction whereby HDL-c increased with: increasing omega-3 and/or DHA and/or ALA intake in *IL-6* rs1800795 C allele carriers and increasing ALA intake in *IL-6* rs1554606 T allele carriers. HDL-c decreased with: increasing EPA and/or DHA intake in *IL-6* rs2069845 G allele carriers. **TG:** Significant interaction whereby TG reduced with increasing EPA intake in *IL-6* rs1800795 C allele carriers **Total-c:HDL-c:** Significant interaction whereby total-c:HDL-c ratio decreased with: increasing EPA intake in *IL-6* rs1800795 CC genotypes and *IL-6* rs1554606 TT genotypes, increasing DHA intake in *IL-6* rs1800795 CC genotypes, and increasing ALA intake in *IL-6* rs1554606 TT genotypes.
Lai et al. 2006 (16)	Cross-Sectional	Single SNP	Men and women from the Framingham	*APOA5,* rs662799, rs651821, rs3135506,	*APOA5:* 11q23.3	**Mean Intake:** 0.69 %kcal omega-3 **Tertiles for**	Major allele homozygotes vs. Minor allele carriers	TG	--

			Heart Study (n=2148)	rs2072560, rs2266788		**<u>omega-3:</u>** **Low:** <0.58 %kcal **Moderate:** 0.58-0.74 %kcal **High:** >0.74 %kcal (unclear if food and/or supplement sources)			
Lu et al. 2010 (17)	Cross-Sectional	Single SNP	Men and women of Doetinchem Cohort Study (n=3575)	*FADS,* rs174546, rs482548, rs174570	*FADS:* 11q12.2	Mean intake: 0.5 %kcal (food)	Comparison between three genotypes	HDL-c Total-c	**Total -c**: In high omega-3 intake group, total-c was significantly higher with each added minor 'C' allele of rs174546
Nettleton et al. 2009 (18)	Cross-Sectional	Single SNP	Men and women of Caucasian ancestry (n=8511)	*ANGPTL4* E40K (rs116843064)	*ANGPTL4:* 19p13.2	Not Reported/Cannot Determine (food)	Minor allele carriers vs. Non-allele carriers	HDL-c TG	--
Richardson et al. 2011 (19)	Meta-analysis of the Framingham Offspring Study (FOS) and the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	Single SNP	Men and women from FOS and GOLDN studies (*n*=3605)	*PLIN4*, rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	*PLIN4:* 19p13.3	Mean intakes: **FOS Men:** 1.43 g/d **FOS Women:** 1.37 g/d **GOLDN Men:** 1.83 g/d **GOLDN Women:** 1.48 g/d (food and supplement)	Minor allele carriers vs. Non-allele carriers	TG HDL-c	**TG:** Significant interactions for *PLIN4,* rs884164 whereby TG levels increased in minor allele carriers with higher omega-3 intake for males and females combined, and males individually.
Standl et al. 2012 (20)	Cross-Sectional Analysis (10-year time point) within a 10-year longitudinal cohort study	Single SNP	10 year-old children of the GINIplus and LISAplus birth cohort studies (n=1697)	*FADS1/FADS2,* rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	*FADS1/2:* 11q12.2	Median intake: 0.14 mg/MJ omega-3 (ALA+EPA+DPA +DHA) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c Total-c TG	--
Tai et al. 2005 (21)	Cross-Sectional	Single SNP	Framingham Cohort, men and women (*n*=2106)	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	**High**: >0.69 %kcal **Low**: <0.69 %kcal (food)	PPARα: 162V carriers vs. 162L/162L homozygotes	TG apoC-III	**TG:** 167V carriers had lower TG with high omega-3 intake compared to low omega-3 intake (gene-diet-interaction effects were NS) **apoC-III:** Significant gene-diet interactions; Higher apoC-III in 162V carriers with low omega-3 intake compared to 162V carriers with high omega-3 intake and 162L homozygotes with low omega-3 intake
Volcik et al. 2008 (22)	Cross-Sectional (Baseline) Analysis within a Prospective Cohort	Single SNP	African American (*n*=3480) and Caucasian (*n*=10 134) men and women (*N*=13,614)	*PPARα*, L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	*PPARα*: 22q13.31	African American: **High:** >0.32 g/d EPA+DHA **Low:** ≤0.32 g/d EPA+DHA Caucasian: **High:** >0.22 g/d EPA+DHA **Low:** ≤0.22 g/d EPA+DHA (food)	Comparison between three genotypes for each SNP	HDL-c LDL-c TG Total-c	**Total-c, LDL-c:** African Americans (but not Caucasians) homozygous for *PPARα* (rs3892755) TT genotype with high EPA+DHA intake had significantly lower total-c and LDL-c compared to CT and TT genotypes (both high and low EPA+DHA intake)

Warodomwichit et al. 2009 (23)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	*TCF7L2* rs7903146, rs12255372	*TCF7L2:* 10q25.2-25.3	N/A (Median omega-3: 0.67% of kcal) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c LDL-c particle size TG Total-c	--

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. Intakes are total omega-3 unless otherwise specified
2. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS

Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

3. These results were taken from the full-text manuscript's summary table of IL-6 results. Refer to Supplementary Tables S8-S13 in Joffe et al. 2014 (15) for several other significant results, stratified and un-stratified by ethnicity. Note: There were no corrections for multiple testing in the statistical analyses.

'--' indicates that all of the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε2, ε3 and ε4)

Supplementary Table 3: Summary of interventional studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Intervention Duration	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[1]
AbuMweis et al. 2018 (24)	Randomized, Crossover Controlled Intervention	Single SNP*	Adults with at least one cardiovascular risk factor (n=129)	4 weeks	*FADS1*, rs174561 *FADS2*, rs174583 *ELOVL2*, rs953413 *ELOVL5*, rs2397142 *CETP*, rs5882 *SCD1*, rs2234970, *PPARα*, rs6008259 *LIPF*, rs814628 and *APOE*, rs429358, rs7412	*FADS1/2:* 11q12.2 *ELOVL2:* 6p24.2 *ELOVL5:* 6p12.1 *CETP:* 16q13 *SCD1:* 10q24.31 *PPARα*: 22q13.31 *LIPF:* 10q23.31 *APOE:* 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except *PPARA* and *LIPF* whereby analyses were major allele homozygotes vs. minor allele carriers) and *APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoA1 apoB HDL-c LDL-c TG Total-c	--
Alsaleh et al. 2014 (25)	Randomized Controlled Intervention	Single SNP and Polygenic	Healthy men and women (n=310)	12 months	CETP, rs3764261, *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5/ABCG*, rs4299376 *TIMD4/HAVCR1*, rs6882076 *GCKR*, rs1260326 *TRIB1*, rs2954029 *ANGPTL3/DOCK7*, rs2131925 *FADS1/2/3*, rs174546 *GALNT2*, rs4846914 *ABCA1*, rs4149268 *APOE/APOC1/APOC2*, rs439401	*CETP:* 16q13 *LIPC:* 15q21.3 *APOB:* 2p24.1 *ABCG5/ABCG8:* 2p.21 *TIMD4/HAVCR1:* 5q33.3 *GCKR:* 2p23.3 *TRIB1:* 8q24.13 *ANGPTL3/DOCK7:* 1p31.3 *FADS:* 11q12.2 *GALNT2:* 1q42.13 *ABCA1:* 9q31.1 *APOE/APOC1/APOC2:* 19q13.32	**Low Dose:** 0.5 g/day EPA and DHA **Moderate Dose:** 0.9 g/day EPA and DHA **High Dose:** 1.8 g/day EPA and DHA (supplement)	Effect sizes per GRS risk allele after omega-3 treatment *and* Risk allele carriers vs. non-risk allele carriers	HDL-c LDL-c TG Total-c	**TG:** significant interaction whereby 1.8 g/day EPA and DHA significantly reduced TG in T allele carriers (21.6% reduction) vs. CC genotypes (3.5% reduction) of *FADS1* rs174546

Armstrong et al. 2012 (26)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	*ALOX5,* dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	*ALOX5:* 10q11.21	Fish oil: 5.0 g/day containing 2.0 g/day EPA and 1.0 g/day DHA Control oil: 5.0 g/day corn/soy oil (supplement)	dd vs. d5 vs. 55	TG Mean lipoprotein particle diameter, total number of particles and particle concentration for: HDL-c and LDL-c	**TG:** significant interaction whereby decreases in TG from omega-3 supplementation were specific to d5 genotype group **HDL-c particle concentration:** significant decrease with omega-3 intervention in the d5 and 55 genotype groups compared to placebo, but no decreases in the dd genotype group **Medium HDL-c particles and HDL-c (mmol/L):** significant gene-treatment interaction but no significant differences after post-hoc analysis for comparisons among genotypes
Binia et al. 2017 (27)	Single-Arm Clinical Trial	Single SNP	Mexican adults 18-40 years (n=191)	6 weeks	*PPARα*, L162V (rs1800206), *PPARγ2*, P12A (rs1801282)	*PPARα*: 22q13.31 *PPARγ2*: 3p25.2	Fish oil: 2.7 g/day containing 1.9 g/d EPA and 0.8 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c	**LDL-c:** significant increase in LDL-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2 **Total-c:** significant increase in total-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2
Bouchard Mercier et al. 2013 (28)	Single Arm Clinical Trial	Single SNP	Healthy adults aged 18-50 years (n=208)	6 weeks	*SREBF1,* rs4925115, rs4925118, rs12953299 *ACLY,* rs8071753, rs8065502, rs2304497 *ACACA* rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	*SREBF1:* 17p11.2 *ACLY:* 17q21.2 *ACACA:* 17q12	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** Significant gene-diet interaction whereby individuals with the GG genotype of *ACLY* rs8071753 and individuals with the GG or CG genotype of *ACACA* rs1714987 exhibited greater TG lower effects following omega-3 supplementation; these two SNPs explained approximately 8% of the variance in plasma TG responses to omega-3 supplementation. There were significant differences in genotype frequencies of *ACLY* rs8071753 for responders and non-responders to omega-3 for TG lowering.
Bouchard-Mercier et al. 2014 (29)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*RXRA* (12 SNPs), *CPT1A* (9 SNPs), *ACADVL* (1 SNP), *ACAA2* (6 SNPs), *ABCD2* (8 SNPs), *ACOX1* (8 SNPs), *ACAA1* (3 SNPs) [outlined in Supplementary Table 5]	*RXRA:* 9q34.2 *CPT1A:* 11q13.3 *ACADVL:* 17p13.1 *ACAA2:* 18q21.1 *ABCD2:* 12q12 *ACOX1:* 17q25.1 *ACAA1:* 3p22.2	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** There were significant gene-diet interaction effects on TG responses to omega-3 for RXRA rs11185660 genotype dependent on total fat intake, RXRA rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and ACOX1 rs17583163 dependent on total polyunsaturated fat intake
Bouchard-Mercier et al. 2014 (30)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*GCK* (13 SNPs) [outlined in Supplementary Table 5]	*GCK:* 7p13	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes	TG	**TG:** CC genotypes of *GCK* rs741038 exhibited significantly greater TG reduction in response to omega-3 when their carbohydrate intake was high (>48.6%kcal) compared to those with the CC genotype of rs741038 with low carbohydrate intake (≤48.6%kcal) and compared to CT or TT genotypes with either high or low carbohydrate intake.

								(when minor allele frequencies were >0.05)		
Caron-Dorval et al. 2008 (31)	Single Arm Clinical Trial	Single SNP	Healthy men of Caucasian ancestry aged 18-55 years (n=28)	6 weeks	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	V162 carriers vs. non-carriers	apoB-100 HDL-c LDL-c TG Total-c Total-C:HDL-c	--
Carvalho-Wells et al. 2012 (32)	Sequential Non-Randomized, Cross-Over Dietary Intervention	Single SNP*	Healthy men and women aged 35-70 years (*n*=88)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**Low-Fat**: 4.0 mg/day EPA, 10.6 mg/d DPA, 11.7 mg/d DHA **High-SFA**: 20.2 mg/d EPA, 27.1 mg/d DPA, 15.4 mg/d DHA **High-SFA+DHA**: 524.3 mg/d EPA, 215.5 mg/d DPA, 3017.3 mg/d DHA [actual intakes reported (33)] (supplemental DHA for High-SFA+DHA; others from food sources)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c sdLDL-c TG Total-c	**TG:** Significant diet x genotype interaction for TG; greater TG lowering response to high-SFA+DHA diet in *APOE*-E3/4 carriers (compared to high-SFA diet alone)
Caslake et al. 2008 (34)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men and women aged 20-70 years (*n*=312)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Control oil: 0.0 g/d EPA and DHA Fish oil: 0.7 g/d EPA and DHA Fish oil: 1.8 g/d EPA and DHA (supplement)	*APOE*-E2/E2 + E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	**TG:** Significant interaction between treatment x sex x genotype whereby *APOE*-E3/E4 + E4/E4 males exhibited the greatest TG reductions with both 0.7 g/d EPA and DHA as well as 1.8 g/d EPA and DHA compared to other genotypes
Cormier et al. 2012 (35)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*FADS* gene cluster (19 SNPs) [outlined in Supplementary Table 5]	*FADS:* 11q12.2	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	TG	--
Dang et al. 2015 (36)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	*APOE*-E4+ vs. *APOE*-E4-	HDL-c LDL-c TG Total-c	--
Dawczynski et al. 2013 (37)	Randomized, Placebo-Controlled, Double-Blind Intervention	Single SNP	Men and women with TG ≥ 1.7 mmol/L, otherwise healthy (n=47)	10 weeks	*CD36,* rs1761667, rs1049673	*CD36:* 7q21.11	Yogurt with lower dose fish oil: 0.8g/day omega-3 containing 0.01g ALA, 0.44g EPA, 0.06g DPA and 0.31g DHA (fish oil) Yogurt with higher dose fish oil: 3.0 g/day omega-3	Comparison between three genotypes	HDL-c TG	**HDL-c**: In response to omega-3 supplementation (0.8-3.0 g/day), HDL-c increased in GA genotype of *CD36* rs1761667 and CG genotype of *CD36* rs1049673. **TG**: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of *CD36* rs1761667.

							containing 0.07g ALA, 1.59g EPA, 0.23g DPA and 1.12g DHA (fish oil) Control yogurt: commercial whole fruit yogurt with 3.5% milk fat (food)			
Ferguson et al. 2010 (38)	Randomized Intervention and Cross-Sectional (Baseline) Analysis	Single SNP	Men and women with metabolic syndrome from LIPGENE cohort (*n*=450)	12 weeks	*NOS3,* rs11771443, rs1800783, rs1800779, rs1799983, rs3918227, rs743507	*NOS3:* 7q36.1	1.24 g/d EPA+DHA supplement (intervention); quantity of omega-3 not reported for observational analyses	Major allele homozygotes vs. Minor allele carriers	apoA-1 apoB apoB-48 apoC-II apoC-III apoE HDL-c LDL-c TG Total-c	**TG:** For *NOS3* rs1799983 minor-allele (A) carriers only, the observational analysis indicated higher TG with lower EPA+DHA intake (and lower TG with higher EPA+DHA intake). Post-intervention with omega-3 supplementation indicated that only minor-allele (A) carriers exhibited significant TG reduction (accompanied by increases in plasma omega-3).
Harsløf et al. 2014 (39)	Randomized, Controlled Intervention	Single SNP and Genetic Score	Infants of Danish ancestry (n=133)	9 months	*PPARγ2*, Pro12Ala (rs1801282), *FADS1,* rs1535, *FADS2,* rs174575, *FADS3,* rs174448 *COX2,* rs5275, rs689466	*PPARγ2*: 3p25.2 *FADS:* 11q12.2 *COX2:* 1q25.2-q25.3	5.0 mL/day fish oil (median reported intake: 3.8 g/day containing 630 mg/day EPA and 620 mg/day DHA) (supplement)	*PPARγ2* genotype analyses were by major allele homozygotes vs. heterozygotes and *FADS* genotype analyses were by the number of DHA-increasing alleles and *COX2* genotype analyses were by major allele homozygotes vs. heterozygotes vs. minor allele homozygotes	HDL-c LDL-c TG Total-c	**TG:** *PPARγ2* heterozygotes exhibited reduced TG in response to omega-3 when compared to *PPARγ2* heterozygotes in the control (sunflower oil) group
Itariu et al. 2012 (40)	Randomized, Controlled Intervention	Single SNP	Men and women without diabetes with a BMI ≥40 kg/m^2 aged 20-65 years (n=55)	8 weeks	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 3.4 g/day EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	apoB HDL-c LDL-c TG Total-c	**apoB:** Significant increases in apoB with omega-3 intervention in Ala12 carriers when compared to Pro12 carriers. **Total-c:** Significant interaction effect whereby increases in total-c were exhibited with omega-3 intervention in Ala12 carriers when compared to the Pro12Pro genotype.
Jackson et al. 2012 (41)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	8 weeks and 480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c TG	**TG:** *APOE*-E3/E4 exhibited reduced fasting TG in response to a high saturated fat + DHA intervention when compared to the high saturated fat diet alone. There was also a significant interaction (meal x time x genotype) for the postprandial TG lowering response whereby *APOE*-E3/4 consuming a high saturated fat + DHA intervention exhibited significantly lower

									Total-c	postprandial TG, TG area under the curve, and TG maximum concentration compared to those consuming the high saturated fat diet alone.
Jackson et al. 2017 (42)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB-48 apoB-100	--
Lindi et al. 2003 (43)	Randomized Intervention	Single SNP	Healthy men and women aged 30-65 years (*n*=150)	3 months	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	HDL-c LDL-c TG Total-c	**TG:** Compared to Pro12Pro, Ala12 carriers exhibited significantly greater TG reductions in response to omega-3 supplementation only when total fat intake was ≤37 %kcal or SFA intake was ≤10 %kcal
Lindman et al. (44)	Randomized, Controlled Intervention	Single SNP	Men at high risk of cardiovascular disease aged 65-75 years (n=204)	6 months	*FVII,* rs6046	*FVII:* 13q34	Fish oil containing 2.4 g/d EPA + DHA Dietary advice including recommendations to increase omega-3 (supplement and food)	Major allele homozygotes vs. Minor allele carriers	TG	--
Madden et al. 2008 (45)	Non-Randomized Intervention	Single SNP	Healthy men aged 43-84 years (*n*=111)	12 weeks	*CD36,* rs1527483, rs1049673, rs1761667, rs1984112	*CD36:* 7q21.11	Fish oil containing 1.02 g/d EPA and 0.69 g/d DHA (supplement)	For each SNP: AA vs. AG vs. GG	HDL-c LDL-c LDL-c:HDL-c TG	**TG:** In response to omega-3 supplementation, TG significantly reduced only in individuals with the GG genotype, for each SNP individually (i.e. for rs1527483, rs1049673, rs1761667 and rs1984112 individually) **LDL-c:** In response to omega-3 supplementation, LDL-c increased only in individuals with the rs1761667 AA genotype as well as for individuals with the rs1984112 AA genotype **HDL-c:** In response to omega-3 supplementation, HDL-c significantly increased in individuals with rs1761667 AA or AG as well as for individuals with the CC or CG genotype for either rs1984112, rs1527483 and/or rs1049673; NOTE: rs1527483 results should be interpreted with caution due to low sample sizes for AA and AG genotypes thus reducing statistical power)
Markovic et al. 2004 (46)	Single-Arm Clinical Trial	Single SNP	Healthy men (n=159)	12 weeks	*TNFα,* -308 (rs1800629) *LT-α,* +252 (rs909253) *IL-1β,* -511 (rs16944) *IL-6,* -174 (rs1800795)	*TNFα:* 6p21.33 *LT-α:* 6p21.33 *IL-1β:* 2q14.1 *IL-6:* 7p15.3	Fish oil containing 1.8 g/d EPA+DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	TG	**TG:** Significant negative correlation between pre-supplementation TG and change of TG during omega-3 supplementation for all genotypes of genes studied except for *LT-α* rs909253 GG genotype and *IL-1β* rs16944 TT genotype. In *LT-α* rs909253 AA genotype and *TNFα* rs1800629 AA genotype, signification association between BMI (divided in tertiles) and TG changes.
McColley et al. 2011 (47)	Crossover Intervention	Single SNP	Healthy post-menopausal women (n=16)	8 weeks per diet	*FABP2,* rs1799883	*FABP2:* 4q26	**High-Fat:** 50 %kcal from dietary fat **Low-Fat:** 20 %kcal from dietary fat **Low-Fat + omega-3:** 23% kcal from dietary fat with 3 %kcal from omega-3 (food)	Major allele homozygotes vs. Minor allele carriers	TG	--

Minihane et al. 2000 (48)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men aged 30-70 years at risk of atherogenic lipoprotein phenotype (*n*=50)	6 weeks per diet and 480 minute postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.0 g/d EPA and DHA, Control oil: 6.0 g/d olive oil capsule (supplement)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c Total-c:HDL	**TG:** Postprandial: Significantly greater reduction in TG incremental area under postprandial TG curve in *APOE*-E2/E3 relative to other *APOE* genotype categories **Total-c:** 6-week: *APOE*-E3/E4 + E4/E4 genotype group exhibited significantly different changes in total-c (increase), relative to other *APOE* genotypes, whereby reductions in total-c occurred
Olano-Martin et al. 2010 (49)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemic men (*n*=38)	4 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	EPA-rich fish oil: 3.3 g/d EPA DHA-rich fish oil: 3.7 g/d DHA Control oil: 80:20 palm olein:soyabean (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4 (carriers)	apoB apoE HDL-c LDL-c TG TG:HDL-c Total-c	**apoB, LDL-c:** In *APOE*-E4 carriers only, DHA-rich oil treatment resulted in significant increases in apoB and LDL-c **TG:** Significant reduction in TG in response to both EPA and DHA in *APOE*-E3/E3 group; significant reduction in TG in *APOE*-E4 carriers with EPA only. No significant interactions. **Total-c:** Significant genotype x treatment interaction whereby *APOE*-E4 carriers exhibit total-c reductions in response to EPA-rich oil.
Ouellette et al. 2013 (50)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*GPAM* (3 SNPs), *AGPAT3* (13 SNPs), *AGPAT4* (35 SNPs) [outlined in Supplementary Table 5]	*GPAM:* 10q25.2 *AGPAT3:* 21q22.3 *AGPAT4:* 6q26	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	HDL-c LDL-c TG Total-c	**LDL-c:** Significant *GPAM*, rs2792751 genotype x supplementation interaction on LDL-c **TG:** Significant genotype x supplementation interaction on TG for *GPAM,* rs2792751 and rs17129561 as well as *AGPAT4,* rs9458172 and rs3798943
Ouellette et al. 2014 (51)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18-50 years (*n*=208)	6 weeks	*MGLL* (18 SNPs) [outlined in Supplementary Table 5]	*MGLL:* 3q21.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	apoB HDL-c LDL-c LDL particle size TG Total-c	**LDL-c:** Significant interactions for *MGLL* rs6776142, rs555183, rs782444, rs6787155 and rs1466571 whereby omega-3 supplementation modulated LDL-c levels; rs782444 and rs555183 minor allele homozygotes more likely to be negative responders to omega-3 supplementation (i.e. exhibit reduced LDL-c); rs6780384, rs782444 and rs6787155 major allele homozygotes more likely to be negative responders to omega-3 supplementation **LDL particle size:** Significant interactions for *MGLL* rs782440, rs13076543 and rs9877819 whereby omega-3 supplementation modulated LDL particle size; rs549662 minor allele homozygotes more likely to be positive responders to omega-3 supplementation (i.e. exhibit increased LDL particle size)
Paschos et al. 2005 (52)	Single-Arm Clinical Trial	Single SNP*	Men with dyslipidemia, aged 35 to 67 years (n=50)	12 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4	ApoA-I ApoB HDL-c LDL-c TG Total-c	**ApoA-I:** Significant decrease in E3/E3 **HDL-c:** Significant decrease in E3/E3
Pishva et al. 2010 (53)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	*FABP2,* Ala54Thr (rs1799883)	*FABP2:* 4q26	2.0 g/day pure EPA (supplement)	Ala54Ala (GG) vs. Thr54 carriers (GT+TT)	ApoB ApoC-III HDL-c LDL-c TG Total-c	**ApoC-III:** In response to EPA supplementation, significantly greater reductions in ApoC-III in GT+TT genotypes of rs1799883 compared to GG genotype. **HDL-c:** In response to EPA supplementation, significantly greater increases in HDL-c in GT+TT genotypes of rs1799883 compared to GG genotype. **LDL-c:** In response to EPA supplementation, LDL-c significantly decreased in GG genotypes of rs1799883 but not GT+TT genotypes. **TG:** In response to EPA supplementation, significantly greater reductions in TG in GT+TT genotypes of rs1799883 compared to GG genotype.
Pishva et al.	Single-Arm	Single SNP	Adults with	8 weeks	*PPARα*,	*PPARα* : 22q13.31	2.0 g/day pure	Leu162	ApoB	--

2014 (54)	Clinical Trial		hypertriglyceridemia (n=46)		Leu162Val (rs1800206) *PPARα*, Intron 7 SNP		EPA (supplement)	vs. Val162 carriers *and* Intron 7 GG vs Intron 7 GC	ApoCIII HDL-c LDL-c TG Total-c	
Roke and Mutch, 2014 (55)	Single-Arm Clinical Trial	Single SNP	Men aged 18-25 years (n=12)	12 weeks (+8 week washout)	*FADS1,* rs174537 *FADS2,* rs174576 (LD=1.0 therefore presented results for rs174537)	*FADS1/2:* 11q12.2	Fish oil containing 1.8 g/d EPA+DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c Total-c:HDL-c	--
Rudkowska et al. 2014 (56)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*SCD1,* rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	*SCD1 :* 10q24.31	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	**TG:** For *SCD1* rs508384, AA genotype was associated with lower TG than CA and CC genotypes both pre- and post-supplementation.
Rudkowska et al. 2014 (57)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Healthy men and women aged 18-50 (*n*=141) + Replication of GRS in FINGEN study (n=310)	6 weeks	Genetic Risk Score including: *IQCJ-SCHIP1* (4 SNPs), *SLIT2* (3 SNPs), *PHF17* (3 SNPs), *MYB* (1 SNP), *NXPH1* (1SNP), *NELL1* (1SNP) [outlined in Supplementary Table 5]	*IQCJ-SCHIP1:* 3q25.32 *SLIT2:* 4p15.31 *PHF17:* 4q28.2 *MYB:* 6q23.3 *NXPH1:* 7p21.3 *NELL1:* 11p15.1	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Responders versus non-responders (i.e. TG response) to supplementation	TG	Thirteen SNPs were associated with TG response to omega-3 supplementation and 10 were used in the GRS calculation. The GRS was significantly associated with TG response. **TG**: The GRS explained 21.5% of the variation in TG response when adjusted for age, sex and BMI. Replication of this GRS in the FINGEN study: the GRS explained 2.0% of the TG change but the association as NS (adjusted for age, sex and BMI).
Scorletti et al. 2015 (58)	Randomized, Placebo-Controlled, Double-Blind Intervention	Single SNP	Men and women with non-alcoholic fatty liver disease (n=95)	15-18 months	*PNPLA3, I148M (rs738409) TM6SF2, E167K (rs58542926)*	*PNPLA3:* 22q13.31 *TM6SF2:* 19p13.11	1.8 g/day EPA+ 1.5 g/day DHA (supplement)	Comparison between three genotypes *and* Major allele homozygotes vs. Minor allele carriers	TG	--
Thifault et al. 2013 (59)	Single-Arm Clinical Trial	Single SNP*	Healthy men and women with overweight or obesity aged 18-50 (*n*=210)	6 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	*APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoB HDL-c LDL-c TG Total-c	--
Tremblay et	Single-Arm	Single SNP	Healthy men	6 weeks	*PLA2G2A* (5	*PLA2G2A:*	Fish oil containing	Major allele	apoB-100	**TG:** omega-3 supplementation significantly reduced TG in

al. 2015 (60)	Clinical Trial		and women aged 18-50 years (*n*=208)		SNPs), *PLA2G2C* (6 SNPs), *PLA2G2D* (8 SNPs), *PLA2G2F* (6 SNPs), *PLA2G4A* (22 SNPs), *PLA2G6* (5 SNPs), *PLA2G7* (9 SNPs) [outlined in Supplementary Table 5]	1p36.13 *PLA2G2C*: 1p36.13 *PLA2G2D*: 1p36.12 *PLA2G2F*: 1p36.12 *PLA2G4A:* 1q31.1 *PLA2G6:* 22q13.1 *PLA2G7:* 6p12.3	1.9 g/d EPA + 1.1 g/d DHA (supplement)	homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	HDL-c LDL-c TG Total-c	*PLA2G7* rs1805018 as well as *PLA2G4A* rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs 10752979 and rs1160719 together explained 5.9% of post-supplementation TG levels
Vallée Marcotte et al. 2016 (61)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Men and woman aged 18-50 years (*n*=208)	6 weeks	*IQCJ* (16 SNPs), *NXPH1* (34 SNPs), *PHF17* (8 SNPs), *MYB* (9 SNPs) [outlined in Supplementary Table 5]	*IQCJ:* 3q25.32 *NXPH1:* 7p21.3 *PHF17:* 4q28.2 *MYB:* 6q23.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	TG	**TG:** Significant gene-diet interaction on TG levels pre- vs. post-supplementation for the following SNPs: *IQCJ* (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), *NXPH1* (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), *MYB* (3 SNPs: rs9321493, rs11154794, rs210962). Four SNPs were still significant after applying the false discovery rate to account for multiple testing: rs1449009, rs2621309, rs61332355 in *IQCJ*; rs7805772 in *NXPH1*. There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in *IQCJ*, rs7805772 in *NXPH1* and rs11154794 in *MYB*. Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for *IQCJ* rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, *NXPH1* rs7806226, rs7805772, *MYB* rs11154794 and rs210936.
Vallée Marcotte et al. 2019 (62)	Single-Arm Clinical Trial (replication of GRS in a novel cohort)	Nutrigenomic GWAS	Healthy adults of Mexican descent aged 18-40 years (n=191)	6 weeks	Genetic Risk Score including 103 SNPs: [outlined in Supplementary Table 5]	NA	Fish oil containing 1.9 g/day EPA + 0.8 g/day DHA (supplement)	Responders versus non-responders (i.e. TG response) to supplementation	TG	**TG:** A first 7-SNP GRS [SNPs selected based on previously developed GRS (57,61)] did not explain TG variation. A second GRS calculated from 103 SNPs significantly explained 4.4% of TG variation. A third GRS including the 5 most relevant SNPs significantly explained 11.0% of TG variation (*NXPH1* rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and *IQCJ-SCHIP1* rs2595241). When subjects with the lowest TG change were not included, this third GRS explained more TG variation. Including only the 28 responders and 28 non-responders with the greatest TG variation, this third GRS explained 29.1% of TG variation.
Vallée Marcotte et al. 2019 (63)	Single-Arm Clinical Trial	Nutrigenomics GWAS (polygenic)	Men and woman aged 18-50 years with overweight or obesity (*n*=208)	6 weeks	GWAS; GRS included 31 SNPs [outlined in Supplementary Table 5]	NA	Fish oil containing 1.9-2.2g/d EPA + 1.1g/d DHA (supplement)	Responders to omega-3 supplementation for TG reduction vs. Non-Responders	TG	**TG:** 31 SNPs associated with TG response to omega-3 supplementation and used in GRS calculation; Lower GRSs were significantly more responsive to omega-3 supplementation for TG reduction compared to higher GRS (GRS accounted for 49.7% of TG responses); These findings were replicated in the FINGEN study with 23 SNPs (GRS accounted for 3.7% of TG responses).
Vallée Marcotte et al. 2020 (64)	Double-Blind, Randomized, Controlled, Crossover Intervention	Nutrigenomics GWAS (polygenic)	Men and women with abdominal obesity and elevated CRP aged 18-70	10 weeks per diet	GRS included 30 SNPs [outlined in Supplementary Table 5]	NA	Control oil: 3 g/d corn oil Pure EPA: 2.7 g/d Pure DHA: 2.7 g/d (supplement)	Responders to different types of omega-3 supplementation for TG reduction vs.	TG	**TG:** The GRS was significantly associated with responsiveness to EPA for TG reduction when comparing responders vs. non-responders vs. adverse responders (trend, p=0.08, for DHA). The GRS was significantly associated with responsiveness to both EPA and DHA for TG reduction when comparing responders vs. adverse responders.

			years (n=122)					Non-Responders vs. Adverse Responders *and* Responders vs. Adverse Responders		
Wu et al. 2014 (65)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP	Men and women with moderate risk of CVD (n=84)	8 weeks	*eNOS* Glu298Asp (rs1799983)	*NOS3:* 7q36.1	Fish oil containing 0.9 g/day EPA + 0.6 g/day DHA (supplement)	Major allele homozygotes (GG) vs. Minor allele carriers (GT+TT)	LDL-c HDL-c TG Total-c	--
Zheng et al. 2018 (66)	Double-Blind, Randomized, Controlled Intervention	Single SNP and Polygenic	Men and women with type 2 diabetes aged 35-80 years for men or postmenopausal and 80 years for women (*n*=139)	25 weeks	*CD36,* rs1527483 NOS3, rs1799983 *PPARγ2*, rs1801282	*CD36:* 7q21.11 *NOS3:* 7q36.1 *PPARγ2*: 3p25.2	Fish oil: 2.0 g/d EPA and DHA Flaxseed oil: 2.5 g/d ALA Control oil: corn oil (supplement)	Major allele homozygotes vs. Minor allele carriers and High vs. low genetic score calculated based on three SNPs	HDL-c LDL-c TG Total-c:HDL-c Total-c	**LDL-c:** significant interaction for *PPARγ2* rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of *PPARγ2* rs1801282 compared to CC genotype *only in the control* (corn oil) group **TG:** omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the *CD36* rs1527483 GG genotype (significant interaction); significant interaction between genetic score and omega-3 on TG levels whereby omega-3 (fish oil and flaxseed oil) supplementation significantly reduced TG levels compared to control only in individuals with high genetic scores

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, omega-3: omega-3, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS

Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

'--' indicates that all the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε 2, ε 3 and ε 4)

Supplementary Table 4: Genes, SNPs, lipid/lipoprotein outcomes and studies included in evidence grading process and guideline development

Gene, SNP(s)	Outcome	Studies
APOE: rs429358, rs7412 (Genotype)	TG	AbuMweis et al. 2018 (24) Carvalho-Wells et al. 2012 (32) Caslake et al. 2008 (34) Dang et al. 2015 (36) Jackson et al. 2012 (41) Olano-Martin et al. 2010 (49) Minihane et al. 2000 (48) Paschos et al. 2005 (52) Thifault et al. 2013 (59)
APOE: rs429358, rs7412	Total-c	Fallaize et al. 2016 (7) AbuMweis et al. 2018 (24) Carvalho-Wells et al. 2012 (32) Caslake et al. 2008 (34) Dang et al. 2015 (36) Jackson et al. 2012 (41) Olano-Martin et al. 2010 (49) Paschos et al. 2005 (52) Thifault et al. 2013 (59)
PPARγ2: rs1801282	LDL-c	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
PPARγ2: rs1801282	Total-c	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
PPARγ2: rs1801282	TG	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
CD36: rs1761667	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1761667	TG	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1049673	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1527483	TG	Madden et al. 2008 (45) Zheng et al. 2018 (66)
FADS: rs174547*	Total-c	Dumont et al. 2011 (5) Dumont et al. 2018 (6) Lu et al. 2010 (17) Standl et al. 2012 (20) Alsaleh et al. 2014 (25) AbuMweis et al. 2018 (24) Roke et al. 2014 (55)
31-SNP Genetic Risk Score	TG	Vallée Marcotte et al. 2019 (67) Vallée Marcotte et al. 2020 (64)

Supplementary Table 5: Additional list of gene(s) and SNP(s) tested in studies

Study	*Gene(s)*, SNP(s)
Chen et al. Int J Obes;43:808-820 (2019)	*FADS2,* rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276 *FADS3,* rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285 *RAB3IL1,* rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252
Cormier et al. 2012	*FADS* gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567
Vallée Marcotte et al. Am J Clin Nutr;109:176–185 (2019)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Tremblay et al. Lipids in Health and Disease (2015) 14:12	*PLA2G2A*, rs876018, rs955587, rs3753827, rs11573156, rs11573142 *PLA2G2C*, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718 *PLA2G2D*, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671 *PLA2G2F*, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904

	PLA2G4A, rs979924, rs2076075, rs3736741, rs10911949, rs10752979, rs1160719, rs10737277, rs12720702, rs7522213, rs7540602, rs10157410, rs12720497, rs4651331, rs1569480, rs10911935, rs12353944, rs11576330, rs10489410, rs10911946, rs3820185, rs12746200, rs11587539 *PLA2G6*, rs5750546, rs132989, rs133016, rs2235346, rs2284060 *PLA2G7*, rs12195701, rs12528807, rs1421368, rs1421378, rs17288905, rs1805017, rs1805018, rs6929105, rs7756935
Ouellette et al. J Nutrigenet Nutrigenomics;6:268–280 (2013)	*GPAM*, rs17129561, rs10787428, rs2792751 *AGPAT3*, rs999519, rs2838440, rs2838445, rs2838458, rs4818873, rs9978441, rs9982600, rs11700575, rs17004619, rs2838452, rs2838456, rs3788086, rs2838429 *AGPAT4*, rs746731, rs747866, rs1125640, rs2277092, rs2293286, rs3757025, rs3798225, rs3798920, rs3798924, rs3798929, rs3798943, rs3798945, rs3822853, rs3823058, rs4709501, rs6906489, rs6923835, rs7750302, rs7769321, rs9458172, rs10945713, rs10945719, rs11965825, rs12202278, rs17627837, rs12524665, rs1001422, rs6455711, rs9456642, rs2064721, rs3778227, rs3798922, rs11967514, rs7768457, rs12662114
Ouellette et al. Lipids in Health and Disease, 13:86 (2014)	*MGLL,* rs782440, rs16826716, rs6776142, rs9877819, rs555183, rs6780384, rs13076593, rs605188, rs6765071, rs782444, rs549662, rs3773155, rs541855, rs6439081, rs6439082, rs6787155, rs1466571, rs893294
Bouchard-Mercier et al. Genes Nutr 9:395 (2014)	*GCK,* rs2268573, rs2908297, rs2971676, rs758989, rs12673242, rs2908290, rs2284777, rs2300584, rs1990458, rs741038, rs1799884, rs2908277, rs3757838
Bouchard-Mercier et al. Nutrients, 6, 1145-1163 (2014)	*RXRA*, rs10881576, rs7871655, rs12339187, rs11185660, rs11103473, rs10776909, rs12004589, rs3132301, rs1805352, rs3132294, rs1805343, rs1045570 *CPT1A*, rs3019598, rs897048, rs7942147, rs4930248, rs11228364, rs11228368, rs10896371, rs1017640, rs613084 *ACADVL*, rs2017365 *ACAA2*, rs529556, rs10502901, rs631536, rs1942421, rs2276168, rs7237253 *ABCD2*, rs4072006, rs10877201, rs12582802, rs4294600, rs11172696, rs10877173, rs7133376, rs7968837 *ACOX1*, rs10852766, rs3744033, rs12430, rs8065144,

	rs11651351, rs3643, rs7213998, rs17583163 *ACAA1*, rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	*CETP*, rs3764261, rs247616, rs7205804 *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5, ABCG8*, rs4299376 *TIMD4, HAVCR1*, rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 *ANGPTL3, DOCK7*, rs3850634, rs1167998, rs2131925 *FADS1, FADS2, FADS3*, rs174550, rs174547, rs174546, rs174583 *GALNT2*, rs4846914, rs1321257 *ABCA1,* rs4149268 *APOE, APOC1, APOC2,* rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	*IQCJ-SCHIP1, MYB, NELL1, NXPH1, PHF17, SLIT2,* rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	*IQCJ*, rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	NXPH1, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs12537067, rs4318981, rs17153997, rs7801099, rs4725120, rs1859275, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862 PHF17, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308
Vallée Marcotte et al. Nutrients; 11, 737 (2019)	*IQCJ-SCHIP1*, rs12497650, rs4501157, rs13091349, rs2044704, rs1962071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs1449009, rs61332355, rs12485627, rs2595242, rs7639937, rs9820807, rs1375409, rs1967363, rs9824310, rs11915303, rs9835214, rs11921343, rs13066560, rs1675497, rs9839862, rs16829875, rs17795566, rs9860588, rs16830408, rs17798579, rs2364930, rs9865997, rs2595241, rs7632574, rs2621308 *NXPH1*, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs4318981, rs17153997, rs7801099, rs4725120, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862, rs6463808 *PHF17*, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, *SLIT2,* rs2952724 *NELL1*, rs752088

Supplementary Table 6: 31-SNP Nutri-GRS

***Gene,* rs Number**	**Alleles[1]**	**Associated Points**
IQCJ-SCHIP1, rs7639707	A/G	+1
IQCJ-SCHIP1, rs62270407	C/T	-1
NXPH1, rs61569932,	G/T	+1
NXPH1, rs1990554	A/C	+1
NXPH1, rs6463808	A/G	+1
NXPH1, rs6966968	A/G	+1
NXPH1, rs28473103	A/G	-1
NXPH1, rs28673635	A/G	+1
NXPH1, rs12702829	C/T	+1
NXPH1, rs78943417	A/T	-1
NXPH1, rs293180	G/T	+1
NXPH1, rs1837523	C/T	-1
PHF17, rs1216346	C/T	+1
PHF17, rs114348423	A/G	+1
PHF17, rs75007521	G/T	-1
MYB, rs72560788	C/T	-1
MYB, rs72974149	A/G	-1
MYB, rs210962	C/T	-1
MYB, rs6933462	C/G	+1
NELL1, rs79624996	A/G	+1
NELL1, rs1850875	C/T	+1
NELL1, rs78786240	C/T	-1
NELL1, rs117114492	G/T	+1
SLIT2, rs184945470	C/T	+1
SLIT2, rs143662727	A/G	-1
SLIT2, rs10009109	C/T	+1
SLIT2, rs10009535	A/G	+1
SLIT2, rs61790364	A/G	+1
SLIT2, rs73241936	C/T	+1
SLIT2, rs16869663	A/G	+1
SLIT2, rs76015249	A/G	+1

1. Minor alleles are underlined

For individuals carrying one or two minor alleles, provide the associated number of points (either +1 or -1). For individuals homozygous for the major allele, provide 0 points. Count the overall number of points. Individuals with lower nutri-GRS are more likely to respond to approximately 3.0 g/day EPA+DHA for TG lowering.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. T1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA (meta-analysis not appropriate)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12, Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Table 3, 34-39
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	45-46
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	40-47
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	47

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

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BMJ Open

A systematic review of nutrigenetics, omega-3 and plasma lipids/lipoproteins/apolipoproteins with evidence evaluation using the GRADE approach

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A systematic review of nutrigenetics, omega-3 and plasma lipids/lipoproteins/apolipoproteins with evidence evaluation using the GRADE approach

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Ethics Approval Statement: No ethics approval was required for a systematic review.

Running Head: Nutrigenetics, omega-3 and lipids/lipoproteins

Data described in the manuscript will be made available upon request pending approval from the corresponding author.

Abbreviations: ALA (alpha-linolenic acid); CV (coefficient of variation); DHA (docosahexaenoic acid); EPA (eicosapentaenoic acid); FDA (Food and Drug Administration); GRADE (Grading of Recommendations Assessment, Development and Evaluation); HCP (healthcare professional); LD (linkage disequilibrium); nutri-GRS (nutrigenetic risk score); SNP (single nucleotide polymorphism)

ABSTRACT

Objectives: Despite the uptake of nutrigenetic testing through direct-to-consumer services and healthcare professionals, systematic reviews determining scientific validity are limited in this field. The objective of this review was to: retrieve, synthesize and assess the quality of evidence (confidence) for nutrigenetic approaches related to the effect of genetic variation on plasma lipid, lipo- and apolipoprotein responsiveness to omega-3 fatty acid intake.

Design: A systematic review was conducted using three search engines (Embase, Web of Science and Medline) for articles published up until August 1, 2020. We aimed to systematically search, identify (select), and provide a narrative synthesis of all studies that assessed nutrigenetic associations/interactions for genetic variants (comparators) influencing the plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population). We further aimed to assess the overall quality of evidence for specific priority nutrigenetic associations/interactions based on the following inclusion criteria: nutrigenetic associations/interactions reported for the same genetic variants (comparators) influencing the same plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population) in two independent studies, irrespective of the findings. Risk of bias was assessed in individual studies. Evidence was evaluated using the GRADE approach with a modification to further consider biological plausibility. This systematic review was registered with PROSPERO (CRD42020185087).

Results: Out of 1830 articles screened, 65 met the inclusion criteria for the narrative synthesis (*n*=23 observational, *n*=42 interventional); of these, 25 met the inclusion criteria for GRADE evidence evaluation. Overall, current evidence is insufficient for gene-diet associations related to omega-3 fatty acid intake on plasma apolipoproteins, total cholesterol, HDL-cholesterol, LDL-cholesterol and LDL particle size. However, there is strong (GRADE rating: moderate quality) evidence to suggest that male *APOE*-E4 carriers (rs429358, rs7412) exhibit significant triglyceride reductions in response to omega-3-rich fish oil with a dose-response effect. Moreover, strong (GRADE rating: high quality) evidence suggests that a 31-SNP nutrigenetic risk score can predict plasma triglyceride responsiveness to omega-3-rich fish oil in adults with overweight/obesity from various ethnicities.

Conclusions: Most evidence in this area is weak, but two specific nutrigenetic interactions exhibited strong evidence, with limited generalizability to specific populations.

Keywords: nutrigenomics, nutrigenetics, nutritional genomics, genetic risk score, nutrigenetic risk score, triglycerides, lipids, lipoproteins, omega-3 fatty acid, *APOE*

STRENGTHS AND LIMITATIONS

- Strength: Comprehensive systematic review guided by PRISMA
- Strength: Critical appraisal of the evidence guided by GRADE with a modification to further consider biological plausibility in addition to the standard components of the GRADE approach
- Limitation: Inability to conduct a meta-analysis given the comprehensive overview of studies and thus heterogeneity
- Limitation: Several included studies without replication; most evidence was low or very low quality according to GRADE

INTRODUCTION

Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research demonstrates that there is significant inter-individual variability in cardiometabolic risk factor levels, in part based on a combination of genetic and nutrition-related risk factors (2,3). For example, protein intake has consistently been shown to influence measures of body weight and composition dependent on *FTO* genotype (rs9939609 or loci in strong linkage disequilibrium) (4,5). Consumers indicate great interest in personalized nutrition based on genetics (6,7), however, a lack of industry oversight (8,9) has led to highly variable scientific validity of nutrigenetic tests available to consumers. While recognizing that some groups question whether genetic testing for personalized nutrition is ready for 'prime time', Gorman and colleagues suggested that there are certain specific nutrigenetic interactions with strong evidence that could be considered for implementation into clinical practice by expert committees who are responsible for creating dietary guidelines (10). With this in mind, systematic reviews that include an evaluation of levels of evidence are urgently needed in order to determine if there are any nutrigenetic associations that may warrant potential implementation into practice.

The dominant omega-3 polyunsaturated fatty acids are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), which typically come from marine sources (e.g. fish oil), and alpha-linolenic acid (ALA), which are rich in plant sources (e.g., canola oil) (11,12). It is well established that higher intakes of omega-3 fatty acids from foods or supplements (herein after referred to collectively as "omega-3s"), particularly from long-chain EPA and DHA, tend to improve indicators of cardiometabolic health (12,13). In

terms of their lipid and lipoprotein lowering effects, omega-3s have consistently demonstrated an impact on triglycerides (TG) (14). High-quality evidence from population-based studies suggests that long-chain omega-3s (EPA and DHA) reduce plasma TG by about 15% (14). There is also high-quality evidence suggesting that EPA and DHA can raise high-density lipoprotein (HDL) cholesterol (14). Other studies have further demonstrated a relationship between omega-3 and HDL-cholesterol (15), low-density lipoprotein (LDL)-cholesterol (15), total cholesterol (16–18), apolipoproteins (19), and LDL particle size (20). Despite several studies with significant findings for these outcomes, when reviewing the evidence, studies have demonstrated conflicting results for the impact of omega-3 on many lipid profile outcomes (14). Genetic variation could explain this heterogeneity. EPA and DHA have been shown to significantly impact the expression of thousands of genes including those involved in inflammatory and atherogenic pathways (21,22). Evidence now demonstrates that the health impacts of omega-3 intake could differ based on genetic variation (23,24). Despite the potential for omega-3s to have a significant positive impact on health outcomes, population intakes of omega-3s tend to be low (25). While the World Health Organization's Adequate Intake level for adults is 200-250 mg EPA+DHA daily (26,27), the mean reported intake of EPA+DHA in the United States is only approximately 100 mg daily (25). Nutrigenetic interventions have the potential to motivate improvements in dietary intake beyond population-based interventions (28). Additionally, evidence suggests that genetic variability affects health responses to omega-3s (23). Thus, critically appraising and grading the evidence for nutrigenetic interactions related to omega-3s and plasma lipids, lipoproteins and apolipoproteins is an important research priority. The most recent

systematic review on nutrigenetic interactions related to omega-3s and intermediate phenotypes of cardiovascular disease was conducted nearly a decade ago, and this study did not evaluate the quality of evidence using an established methodology (29). Therefore, we aimed to provide a comprehensive summary of current evidence related to inter-individual variability in plasma lipid, lipoprotein and apolipoprotein responses to omega-3 intake (plant and marine sources) based on genetic variations. Overall, the specific objectives of this study were as follows:

Objective 1. Systematically search, identify (select), and provide a narrative synthesis of all studies that assessed nutrigenetic associations/interactions for genetic variants (comparators; i.e. outcomes in those with a specific genotype for a genetic variant compared to a different genotype) influencing the plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population).

Objective 2. Assess the overall quality of evidence for specific priority nutrigenetic associations/interactions based on the following inclusion criteria: nutrigenetic associations/interactions reported for the same genetic variants (comparators) influencing the same plasma lipid, lipoprotein and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both pediatric and adult populations (population) in two independent studies, irrespective of the findings.

Methods

Patient and Public Involvement: No patient involvement.

Literature Search

The systematic review protocol was registered with PROSPERO (CRD42020185087). The review process was guided by previously established methods, including a previously outlined five-step systematic review process (30,31). The search engines Embase, Web of Science and Medline OVID were used to conduct the search starting in May 2020 and screen for articles meeting inclusion criteria, using the comprehensive search terms outlined in Supplementary Table 1, properly combined by Boolean operators. The literature was searched up until August 1, 2020 (there was no minimum start date; any article published prior to this date was included in the search). A PRISMA diagram (Figure 1) guided the article screening process (32).

Inclusion and Exclusion Criteria

Original studies were included if they were written in English or French. Inclusion criteria were developed using the Population, Intervention, Comparison, Outcomes, (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (33,34) for interventional and observational research, respectively. These are detailed in Table 1 for each study objective.

Table 1. PICO/PECO for Study Objectives

PICO/PECO for Objective 1:	
Population	Human studies (adult and pediatric)
Intervention/ Exposure	Omega-3s (total omega-3 or various types; supplemental and/or dietary intake)

Comparison	Genetic variation
Outcomes	HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and/or TG
PICO/PECO for Objective 2*:	
Population	Human studies (adult and pediatric)
Intervention/ Exposure	Omega-3s (total omega-3 or various types; supplemental and/or dietary intake)
Comparison	Genetic variation in the same genetic location [gene(s) and SNP(s)]
Outcomes	The same outcome of interest among studies with the same genetic comparators: HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and/or TG

*Nutrigenetic associations/interactions were included in objective 2, **in the evidence grading process**, irrespective of the findings, provided that they had been reported in at least two independent studies on the same gene(s) and SNP(s), and the same plasma outcome.

There were no limitations to the population characteristics (all populations/patient samples were included). Animal studies were excluded. Dietary interventions and observational studies involving omega-3s (total omega-3 or various types; supplemental and/or dietary intake) and comparing lipid and/or lipoprotein and/or apolipoprotein outcomes between different genetic variations based on omega-3 dietary or supplemental intake (and not blood fatty acid levels; e.g. EPA and DHA in red blood cells) were included in the narrative synthesis. In included studies, samples had to be stratified on the basis of genetic variation. Specific lipid and lipoprotein outcomes of interest were: HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins, and triglycerides (TG). Studies that reported ratios of the aforementioned lipid parameters (e.g. HDL-cholesterol to total cholesterol ratio) were also included. Both observational and interventional studies were included, as well as single-gene, polygenic and genome-wide association studies (GWAS). Differences in study designs and methods were considered when developing the overall evidence grades, as further detailed below. Associations/interactions reported in two independent studies formed the basis of the inclusion criteria for objective 2, in which nutrigenetic associations/interactions were

prioritized for evidence grading. This is further detailed in Table 1 and the section below entitled "Evidence Grading."

Article Selection and Data Extraction

Two independent investigators (JK and VG) screened articles using the computer software *Covidence* (including title, abstract, and full-text screening) and extracted data from the included articles. Reference lists of included articles and of a systematic review on a similar topic (35) were also screened for relevant articles. Data extraction templates were piloted by two independent investigators (JK and VG) on ten included studies and revised accordingly. The final data extraction templates included the following components for each study: first author name and year, study design, genetic approach, population and sample size, study duration (interventional studies only), genes and single nucleotide polymorphisms (SNPs) analyzed with rs numbers, quantity and type of omega-3, comparisons (e.g. a control group or different amount/type of omega-3s as well as genetic grouping), lipid/lipoprotein outcome(s), whether or not the study reported that they followed STREGA guidelines and a summary of statistically significant study findings relevant to the research question. Corresponding authors of included studies were contacted as needed to provide clarity and/or additional information about the included studies.

Evidence Grading

Upon reading all full-text articles included, and summarizing the body of evidence (Tables 2 and 3), SNPs/nutrigenetic risk scores (nutri-GRSs) and subsequent lipid/lipoprotein/apolipoprotein outcomes were systematically prioritized and selected for

evidence grading, if a specific nutrigenetic association/interaction was reported in at least two independent studies. To clarify, this refers to the same SNP(s)/nutri-GRS [or SNPs in strong linkage disequilibrium (LD)] being assessed and influencing the same lipid/lipoprotein outcome in at least two studies. For these nutrigenetic associations/interactions, we proceeded with evidence grading, while including **all** studies relevant to the particular nutrigenetic association/interaction, irrespective of the findings. Consistency of results was then one of several factors considered when grading the body of evidence. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach indicates that a single study rarely (if ever) results in strong evidence, but two studies (typically RCTs) can indicate strong evidence if they are graded highly using the GRADE criteria (36). Prior to selecting the nutrigenetic associations/interactions (genetic variants and lipid/lipoprotein/apolipoprotein outcomes) for evidence grading, LD was assessed using the SNIPA SNP Annotator Software (37) for genes located on the same chromosome and arm (determined using the Online Mendelian Inheritance in Man® [OMIM] database) as outlined in the summary of results' tables in the column labelled 'Cytogenic Location of Gene(s)' (Tables 1 and 2). Strong LD was defined as $r^2>0.8$ and location <250 kb away from the index SNP location. SNPs in strong LD were considered together for the purposes of evidencing grading.

Based on our abovementioned predetermined criteria for specific nutrigenetic topic selection for evidence grading, nutrigenetic associations/interactions that were not included in the evidence grading process likely have weak evidence (at minimum due to lack of replication, for example, *ZNT8* rs13266634 and HDL-c or TG responsiveness to

omega-3, which has only been assessed in a single study (38)). According to the GRADE guidelines, when only a single study exists indicating significant findings for an outcome of interest (especially when the study is observational), the overall quality of the evidence is generally rated to be low or very low (39). Therefore, our process for prioritizing nutrigenetic topics for evidence grading aimed to filter out specific nutrigenetic associations/interactions that would likely be deemed low or very low quality (based on, at minimum, lack of replication). Two authors (JK and VG) critically appraised the selected nutrigenetic interactions using the GRADE methodology, with one modification (39,40). The modified GRADE approach consisted of the additional consideration of biological plausibility whereby evidence was considered for upgrading if there was evidence of biological plausibility for the nutrigenetic interaction. Nutrigenetic interactions were grouped according to studies assessing the same SNP(s)/nutri-GRS and lipid/lipoprotein/apolipoprotein outcome, and the quality of the body of evidence (studies with significant and non-significant results) was rated; this process was guided by the GRADE Evidence Profile, which included consideration of risk of bias, inconsistency, indirectness, imprecision, publication bias, plausible confounding, dose-response and other factors (39). For example, different sources of omega-3s (e.g. EPA+DHA vs. ALA; food sources vs. supplementation) were taken into consideration when grading the evidence through the analysis of indirectness within the modified GRADE approach (39,40). Risk of bias was assessed in each of the included interventional and observational studies using the National Institutes of Health Study Quality Assessment Tools, in line with recently published recommendations for risk of bias assessments (41). To assess measures of precision, coefficients of variation (CV) were calculated based on

outcome means (mean change or absolute values – whichever was used for the analyses) and standard deviations. In cases where standard errors of the mean were reported, these were converted to standard deviations to calculate the CV. The nutrigenetic interactions were each given an evidence grade of high, moderate, low or very low.

Results

Figure 1 outlines the PRISMA Flow Diagram, which was used to guide the systematic review. Supplementary Tables 2 and 3 provide a summary of the 65 included studies. The results columns of Supplementary Tables 2 and 3 (far right) indicate nutrigenetic findings that were statistically significant. There were many results from the included studies that were not statistically significant. It is important to highlight that any results related to the studies' analyzed SNPs and outcomes of interest that were not statistically significant are not indicated in the results column. No studies explicitly reported that they followed STREGA guidelines. LD analysis of SNPs tested in different studies revealed strong LD in several SNPs from the *FADS* gene cluster (see Table 2 footnote). As such, LD was taken into consideration in the selection of nutrigenetic interactions selected for evidence grading.

Observational Studies

Of the 65 included studies, 23 were observational with the majority of these being cross-sectional, as outlined in Supplementary Table 2. A total of 62,221 participants were included in the observational studies. These studies assessed correlations among a number of different genetic variations and outcomes, with several studies assessing genetic variations in the *FADS* gene cluster (42–48), *TNFα* (49–51) and *PPARα* (52–54).

Most studies (n=13) assessed total omega-3s (38,42,47–49,51,54–60). The intake and type of omega-3s, lipid/lipoprotein/apolipoprotein outcomes and associations revealed from these studies were variable as further detailed in Supplementary Table 2. In the observational studies assessing genetic variation in the *FADS* gene cluster, some studies indicated significant gene-diet findings related to HDL-cholesterol, LDL-cholesterol, TG, total-cholesterol while other studies demonstrated no significant gene-diet interactions for these outcomes thus indicating notable inconsistency among the results, while considering that SNPs differed by studies (42–48). In the observational studies focused on genetic variation in the *TNFα* gene, there was some evidence of a gene-diet relationship for omega-3 and LDL-cholesterol, total-cholesterol and total-cholesterol:HDL-cholesterol ratio, but again, results differed between studies (49–51). For gene-diet relationships and *PPARα* genetic variation, individual studies indicated significant findings related to total-cholesterol, LDL-cholesterol, TG, apoC-III and LDL peak particle diameter (52–54). Comprehensive details of the observational studies are outlined in Supplementary Table 2.

Interventional Studies

Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-randomized studies included single arm clinical trials and sequential non-randomized cross-over interventions. For interventional studies, n=6,225 participants upon combining all sample sizes of the included studies. Again, these studies assessed relationships between a number of different genetic variants and study outcomes. In more recent years, several studies (n=8) used a nutri-GRS or polygenic approaches (61–68) given the plausibility that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are

polygenic in nature. Numerous studies assessed genetic variations in the *FADS* gene cluster (61,62,69–71), *APOE* (61,71–80), *CD36* (67,81,82), *PPARγ2* (62,67,83–85) and *PPARα* (83,86,87). Among these studies, results related to significant gene-diet (omega-3) associations influencing lipid/lipoprotein outcomes were generally inconsistent except for *APOE* (rs429358 and rs7412), omega-3 and TG in males only (71–75,77–80), and for a 31-SNP nutri-GRS, omega-3 and TG (65,66). There was also consistent evidence to indicate a lack of association among *PPARγ2* (rs1801282) genetic variation, EPA+DHA and LDL cholesterol (62,67,84,85,88). Most studies (n=40) used supplemental EPA and/or DHA sources of omega-3s for the dietary intervention (see Supplementary Table 3). The dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages ranging from 0.5-3.7 g/day across different studies, and one study with an ALA intervention dosage of 8.1 g/day, as further detailed in Table 3.

Levels of Evidence Using GRADE

A total of 25 articles were included in the evidence grading process, representing 11 unique nutrigenetic associations/interactions as outlined in Tables 2 and 3, and Supplementary Table 4. Through the modified GRADE process, it was determined that there is strong evidence (GRADE rating: moderate quality) for *APOE* genotypes (rs7412, rs429358), omega-3s and TG lowering in male adults only (71–75,77–80). This evidence suggests that adult males (but not females) with the APOE-E3/E4 or E4/E4 genotype (rs429358, rs7412) tend to experience significant reductions in TG in response to 0.7-3.7 g/day of EPA and/or DHA, with higher dosages demonstrating greater TG lowering effects (71–75,77–80). Furthermore, it was determined that there is strong evidence (GRADE rating: high quality) for using a 31-SNP nutri-GRS (detailed in Supplementary

Tables 5 and 6) to assess the effectiveness of omega-3s for TG lowering in adults with overweight/obesity in various ethnicities (65,66). The evidence suggests that in adults with overweight/obesity, lower genetic risk scores demonstrate greater responsiveness to omega-3 supplementation (65,66).

All other evidence that was evaluated was determined to be weak (GRADE rating: low or very low quality), as further detailed in Table 2. Imprecision, indirectness, and inconsistency were common reasons for downgrading the evidence (refer to Table 2 footnote). There was evidence for a plausible mechanism of action for most of the nutrigenetic interactions that were graded; evidence of a dose response was less common.

Table 2. GRADE Evidence Profile: Genetic Variation, Omega-3 and Lipids

Nutrigenetic interactions for omega-3 and plasma lipid/lipoprotein outcomes									
Patient or Population: adults **Intervention/Exposure: dietary or supplemental omega-3 (EPA and/or DHA and/or ALA)** **Comparison/Control: genetic variation, different omega-3 intakes** **Outcomes: plasma lipids and lipoproteins**									
***Gene* rs Number and Lipid: Number and Type of Studies (total *n*)**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication Bias**	**Dose Response**	**Biological Plausibility***	**Quality**	**Conclusion**
***CD36* rs1761667 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[d]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the AA genotype of *CD36* rs1761667 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1761667 and TG**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	Serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GA or possibly the GG genotype of *CD36* rs1761667 could lead to significant reductions in TG in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1049673 and HDL-c**: 1 RCT and 1 single arm trial (*n*=115) (81,89)	Serious limitations[a]	Serious inconsistency[b]	Serious indirectness[c]	No serious imprecision	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or possibly the CC genotype of *CD36* rs1049673 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
***CD36* rs1527483 and TG**: 1 RCT and 1 single arm trial (*n*=250) (67,81)	Serious limitations[f]	No serious inconsistency	Serious indirectness[g]	Very serious imprecision[e]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the GG genotype of *CD36* rs1527483 could lead to significant decreases in TG in response to approximately 2.0 g/day of EPA+DHA (but not ALA).
***APOE* rs429358, rs7412 and TG:** 4 RCTs and 5 single arm trials (1 single arm trial consisted of a	No serious limitations	No serious inconsistency	Serious indirectness[h]	No serious imprecision	Undetected	Evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that adult males (but not females) with the *APOE*-E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

subset sample of another single arm trial) (n=980) (71–75,77–80)									response to 0.7-3.7 g/day of EPA and/or DHA. Higher dosages may have greater TG lowering effects.
***APOE* rs429358, rs7412 and Total-c:** 4 RCTs, 5 single arm trials (1 single arm trial consisted of a subset sample of another single arm trial), 1 cross-sectional and longitudinal analysis within an RCT (*n*=2,446) (55,71–75,77–80)	No serious limitations	Serious inconsistency[i]	Serious indirectness[h]	No serious imprecision	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate: Males and Females) and ⊕⊕⊖⊖ (Low: Males)	In males and females combined, strong evidence suggests that there is no nutrigenetic interaction between EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, *APOE* (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, *APOE* (rs429358, rs7412) and total-c.
31-SNP Nutri-GRS and TG: 1 RCT, 1 single arm trial (*n*=330) (65,66)	No serious limitations	No serious inconsistency	Serious indirectness[j]	No serious imprecision	Undetected	Evidence of a gradient[k]	Some evidence of a mechanism of action[l]	⊕⊕⊕⊕ High	Strong evidence suggests that in adults with overweight/obesity, a 31-SNP genetic risk score can predict TG responsiveness to EPA+DHA supplementation. Individuals with lower genetic risk scores demonstrate greater responsiveness to EPA+DHA for TG lowering.
***PPARg2* rs1801282 and LDL-c:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	No serious inconsistency	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊕⊖ (Moderate)	Strong evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence LDL-c responses to omega-3s (EPA+DHA).
***PPARg2* rs1801282 and Total-c:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	Serious inconsistency[o]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Lack of evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that possessing the CG or GG genotype of *PPARg2* (rs1801282) could lead to significant increases in total-c in response to approximately 3 g/day of omega-3s (EPA+DHA) in individuals with overweight or obesity, but not for individuals without overweight or obesity.
***PPARg2* rs1801282 and TG:** 4 RCTs, 1 single arm trial (*n*=670) (62,67,84,85,88)	No serious limitations	Very serious inconsistency[p]	Serious indirectness[m]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊕⊖⊖ (Low)	Weak evidence suggests that genetic variation in *PPARg2* (rs1801282) does not influence total-c responses to omega-3s (EPA+DHA), but when dietary total fat and saturated fat intake are low, nutrigenetic interactions may exist.
***FADS* (rs174547**) and Total-c:** 2 RCTs, 1 single-arm trial, 4 cross-	Very serious risk of bias[q]	No serious inconsistency	Very serious indirectness[r]	Serious imprecision[n]	Undetected	No evidence of a gradient	Evidence of a mechanism of action	⊕⊖⊖⊖ (Very Low)	Weak evidence suggests that genetic variation in *FADS* (rs174547**) does not influence total-c responses to omega-3.

sectional studies (*n*=9365) (44,45,47,48,61,69,71)									

*Direct mechanisms of action were considered

**FADS rs174547 was in strong LD with the following SNPs from other included studies and therefore these SNPs were also included in the selection of studies assessing FADS genetic variation, n-3 intake and LDL-c: rs174546, rs174599, rs174601, rs174583, rs1353, rs174561, rs174556, rs174545, rs174537 and rs174576.

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

a. Small sample sizes, especially among homozygous groups in the RCT (with a larger heterozygous group, potentially affecting the results)
b. Some variation in results by genotype
c. One study sample consisted of all males while the other sample consisted of both men and women; differences in age and n-3 dosages (with some overlap)
d. Coefficient of variation >1 for all significant values
e. Coefficient of variation substantially >1 for several values
f. Small sample size within genotype groups for minor allele homozygote and heterozygote groups in the RCT
g. One study sample consisted of all men while the other consisted of men and postmenopausal women with type 2 diabetes
h. Differences in age, omega-3 dosages, and types (with some overlap), and dietary interventions even when considering studies with male study samples separate from male + female study samples
i. Serious inconsistency for men subgroup only; men + women samples were consistent
j. EPA and DHA separate on one study and EPA+DHA in the other, sample stratified into two groups in one study (responders and non-responders) and separated into three groups (responders, non-responders and adverse responders)
k. Evidence of a gradient for GRS and TG responsiveness to omega-3 supplementation
l. Some evidence of a potential mechanism of action for *IQCJ-SCHIP1, NXPH1, PHF17, MYB and NELL1* as discussed by Rudkowska et al. (63), Vallée Marcotte et al. (64)
m. Differences in population (healthy adults, adults with chronic disease or obesity, infants), some variation in length of follow-up
n. Downgraded precision as it was not possible to assess precision in most studies due to lack of reporting of means and SD/SEM
o. Some variation in results even when considering differences in BMI and populations among studies
p. Major variability in results even when considering differences in BMI and populations among studies
q. Risk of bias detected in every study except one
r. Major differences in populations, types and amounts of omega-3 and follow-up for interventional studies

1

Table 3. Summary of Risk of Bias Across SNPs and Outcomes Following Omega-3 Exposure/Intervention

***CD36*, rs1761667 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1761667 and TG**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1049673 and HDL-c**	
Study	**Risk of Bias**
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
***CD36*, rs1527483 and TG**	
Study	**Risk of Bias**
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
***ApoE*, rs429358, rs7412 and TG**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
***ApoE*, rs429358, rs7412 and Total-c**	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Carvalho-Wells et al. 2012	⊕
Caslake et al. 2008	⊕
Dang et al. 2015	⊕
Fallaize et al. 2016	⊖
Jackson et al. 2012	⊖
Minihane et al. 2000	⊕
Olano-Martin et al. 2010	⊕
Paschos et al. 2005	⊖
Thifault et al. 2013	⊕
31-SNP Nutri-GRS and TG	
Study	**Risk of Bias**
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

PPARg2, rs1801282 and LDL-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and Total-c	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
PPARg2, rs1801282 and TG	
Study	**Risk of Bias**
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
FADS, rs174547 and Total-c	
Study	**Risk of Bias**
AbuMweis et al. 2018	⊖
Alsaleh et al. 2014	⊕
Lu et al. 2010	⊖
Standl et al. 2012	⊖
Dumont et al. 2011	⊖
Dumont et al. 2018	⊖
Roke and Mutch 2014	⊖

⊕ no serious risk of bias; ⊖ serious risk of bias; ⊖⊖ very serious risk of bias (for study design type using NIH Study Quality Assessment Tools)

HDL-c: high-density lipoprotein cholesterol, LDL-c: low-density lipoprotein cholesterol, TG: triglycerides, total-c: total cholesterol

DISCUSSION

Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and high quality evidence) for only a limited amount of evidence in this area: *APOE* (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity. Limited evidence exists for individual genetic-based responsiveness of omega-3s on apolipoprotein and/or LDL particle size, with no studies from the present comprehensive review meeting the criteria for evidence grading. This highlights the need for more replication studies in this area. While more research exists on omega-3 responsiveness for other lipid outcomes such as total-c, HDL-c and LDL-c, the level of evidence for nutrigenetic interactions related to these outcomes remains low. Again, more studies are needed related to these outcomes, including replication studies of previously identified nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the same type and amount of omega-3s as the original study), and recruit samples with similar characteristics to the original study. Once replication is established, research should then seek to expand the population studied to improve generalizability and explore the effectiveness of different interventions (i.e. different formulations and doses of omega-3s). The variability of the interventions and sample sizes in the studies conducted to date often resulted in the quality of evidence being downgraded (see Table 2). It should also be noted that study heterogeneity precluded the ability to conduct a meta-analysis. Thus, the GRADE approach worked well for evaluating the quality of the evidence given that this approach takes into consideration several factors when determining the quality of

evidence such as risk of bias, indirectness of evidence, inconsistency or results, imprecision and publication bias (39).

It is important to note that our results demonstrating strong evidence for interactions between *APOE* genotypes and lipid responses to omega-3s have notable ethical implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk of developing Alzheimer's disease (90). Moreover, *APOE* genotypes are significantly associated with CVD risk including risk of coronary artery disease and hyperlipidemia (91–93). Interestingly, the pathology of Alzheimer's disease has been linked to cardiovascular mechanisms (90). Future research should explore nutrigenetic interactions, with risk of developing Alzheimer's disease as the study endpoint/outcome of interest. Despite the current lack of knowledge about how diet may play a role in mitigating the genetic-based risk of Alzheimer's disease, several potentially modifiable risk factors account for around 40% of dementia and Alzheimer's disease globally (94), and the link between Alzheimer's disease risk and *APOE* is well-established (95). Therefore, despite the strong scientific validity identified in the present review, there are other factors that must be considered before this test can be recommended for implementation in a practice setting; this includes ethical, legal and social implications (96).

In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness to omega-3s in men but not women speaks to the importance of taking biological sex into account in nutrigenetics research. The importance of this has been further highlighted elsewhere, where it has been noted that the results of nutrition and nutrigenetic research

may differ in men and women (97). For example, UDP-glucuronidation isoenzyme expression profiles have been demonstrated to be regulated by sex hormones, and thus sex-specific differences in glucuronidation of resveratrol have been observed (98). As more studies are completed, researchers may find that certain nutrigenetic interactions differ depending on biological sex, ethnicity, age or other factors, similar to our findings on *APOE,* omega-3s and TG in which there was robust evidence of a nutrigenetic interaction in males only. Researchers may also find explanations for this, which are currently poorly understood. In general, it is becoming increasingly recognized that health-related responses to different interventions may vary based on biological sex; this is an important consideration of personalized nutrition (97). Nutrigenetic research often groups men and women together, but stratifying based on biological sex could provide further insights for specific nutrigenetic interactions and could also help explain why some replication studies have had conflicting findings (97). Moreover, biomedical research in general historically has been conducted more in men than women; yet such research findings are often generalized to women despite limited research conducted in samples of women, which is problematic for a number of reasons (99). In the present review, the evidence was strong for the *APOE* findings in men only, but not women in part because there were more studies conducted in men. Specifically, there were five studies conducted in men and women (combined) (71,73,74,100,101), and four studies conducted in samples of only men (75,78,79,102), yet no studies conducted in samples of only women. This brings to light important issues of equity and warrants further discussion and consideration.

As research continues to develop, it appears likely that lipid and lipoprotein responses are polygenic in nature. Therefore, future research should consider using nutri-GRSs or other polygenic methods of assessing responsiveness to nutrition interventions. This work should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs, such as establishing them from genetic-wide association studies. In addition to the two studies meeting the criteria for evidence grading (65,66), a modified version of the 31-SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs (65). While this did not meet our inclusion criteria for evidence grading given that a different GRS was used, the 23-SNP GRS was significantly associated with TG responsiveness to omega-3 supplementation in this population as well, providing further evidence for the scientific validity of this nutrigenetic interaction (65).

While we used a modified version of the GRADE approach (with the additional consideration of biological plausibility) to evaluate the body of evidence, several tools are available for evaluating the quality of scientific evidence, though no generally accepted methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a set of guidelines to assess the scientific validity of genotype-based dietary advice (30). While we originally intended to use these guidelines for assessing the evidence, we came across some limitations that ultimately led us to use the GRADE guidelines. Specifically, Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines should be included in the assessment of scientific validity (30). However, limiting the evidence to only these studies could result in several important studies being missed. In the present review, none of the included studies explicitly indicated that they followed

STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA guidelines to assess risk of bias (30). However, the STREGA checklist is only intended for observational genetic association studies - not interventional research (103). In the present review, 42 of the 65 included studies were interventional (65%) (Supplementary Table 3). In addition, the STREGA guidelines are intended to improve the transparency and adequate reporting of genetic association studies, but it is not intended to be used as a study quality assessment tool (103). However, Grimaldi et al. nicely highlighted the importance of understanding the nature of the genetic variation, at a functional level, when assessing scientific validity (30). This is not included in the standard GRADE approach but is an important niche component of nutrigenetic research. As such, an analysis of functional SNPs (biological plausibility) was included as an additional component of the standard GRADE process, as indicated in the methods section above. Overall, we found that the methods used in this systematic review were effective and can be used to synthesize and evaluate nutrigenetic studies assessing other gene-nutrient-health outcome interactions.

The additional consideration of functional SNPs to the standard GRADE approach helped to strengthen this review, as biological mechanistic evidence can help ensure that study findings did not occur by chance alone, and this is a component of evidence evaluation frameworks in medical genetics (104,105). Transcriptomic and pathway analyses can help inform the direction of future nutrigenetic studies by generating hypotheses about the impact of specific genetic variations on varying responses to nutrition on health-related outcomes. For example, using transcriptomics and pathway analyses to identify

changes in lipid metabolism following omega-3 supplementation, Rudkowska and colleagues identified six genes expressed in opposite directions between responders and non-responders to omega-3 supplementation for TG lowering: *FADS2, PLA2G4A, ALOX15, PEMT, MGLL and GPAM* (106). Tremblay et al. then built on this knowledge and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a significant impact on the TG lowering effect of omega-3 supplementation (107). Others have built on this mechanistic knowledge as well (108). Future research should now seek to replicate this work given that we found that there have been no replication studies completed and thus, this research (107,108) did not meet the criteria for evidence grading.

In the current body of literature, there are some limitations that should be highlighted. Given the variability in allele frequencies for each SNP, it should be noted that study limitations can arise with small sample sizes whereby some genotype groups may not be adequately powered to detect significant differences. For example, Dawczynski et al. (2013) detected significant changes in TG among the GA genotype group of *CD36* rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA: n=8, GG: n=7) exhibited a significant difference, despite similar directions and magnitudes of effect among the GA and GG genotypes (82). It is thus possible that this study was not adequately powered. Some researchers aim to mitigate this issue of small numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for

the minor allele) (69). However, such an approach precludes the possibility to detect an allele-dosage effect. From a physiological perspective, an allele dosage effect would be expected whereby a significant change among a heterozygote group would likely be accompanied by a significant change in one of the homozygote groups but with an even greater magnitude of the effect. This consideration highlights the importance of having an adequately powered sample size, while factoring in the prevalence of each genotype.

While single SNP research provides important information about individual gene-nutrient interactions, the results of this review indicate that individual responses to omega-3s for altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus, we encourage researchers to further explore the use of nutri-GRSs to improve the accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et al., which obtained a high quality evidence grade in the present review (65,66). This is further exemplified in the analyses recently conducted by Chen et al. (42), which has yet to be replicated and thus was not selected for evidence grading.

The present analysis of scientific validity provides an important first step towards the eventual development of clinical practice guidelines for genetic-based responses to dietary intake. With questionable and variable scientific validity of existing consumer nutrigenetic tests, the development of clinical practice guidelines is an important next step as these can be used by HCPs and industry alike to help promote evidence-based practice in personalized nutrition. Ideally, industry should use future clinical practice guidelines to inform the nutrigenetic associations and related dietary recommendations

included in their reports. Decision aids can also be useful to guide clinical practice for HCPs (109), and future research should seek to develop a decision aid related to omega-3s and lipid/lipoprotein outcomes based on genetic variation.

It should be noted that there are some limitations to the present systematic review. First, the literature was searched up until August 2020; as such, any articles published after this date were not included. Furthermore, certain nutrigenetic associations/interactions were prioritized for evidence grading therefore evidence grades remain unknown for numerous associations/interactions included in the narrative synthesis. However, evidence from a single study typically results in an evidence grade of low or very low using the GRADE approach (39), therefore it is unlikely that any/many nutrigenetic associations/interactions with strong scientific validity (which could be considered for use in clinical practice) were missed. Future research groups may choose to instead select a specific SNP or nutri-GRS as the focus of future systematic reviews. The specific SNP or nutri-GRS chosen may be selected based on the results of a preliminary scoping review. This would allow for all articles included in the systematic review to undergo evidence grading. The approach taken in the present review was more comprehensive, but has its limitations as stated above.

Overall, we have provided a comprehensive overview the body of evidence related to nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing an overview of levels of evidence in this field. To our knowledge, this is the first systematic review with GRADE evidence evaluation in the broader field of nutrigenetics.

The results of this work should be used in clinical practice guideline development, to ultimately guide evidence-based practice in personalized nutrition and move this emerging field forward.

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Contributorship Statements: M-C.V. and J.K. conceptualized the review. G.S. was responsible for the search strategy, in collaboration with J.K., M-C.V., S.D. and V.G. J.K. and V.G. were responsible for article screening and selection, summarizing, evidence grading, and developing a draft of the systematic review. The first systematic review draft underwent revisions from S.D. and M-C.V., who provided overall supervision for the project. Following this, J.K., V.G., V.M., D.M.M., J.R., I.R., G.S., S.D., and M-C.V. served as scientific advisors and reviewed and revised the full-text manuscript. J.K. wrote the first draft of the manuscript. J.K., V.G., V.M., D.M.M., J.R., I.R., G.S., S.D., and M-C.V., reviewed, revised and approved the final manuscript.

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Figure Legend:

Figure 1. PRISMA Flow Diagram

*The original PRISMA Flow Diagram indicated the number of studies included in meta-analysis in this box. This has been revised for the purposes of this research

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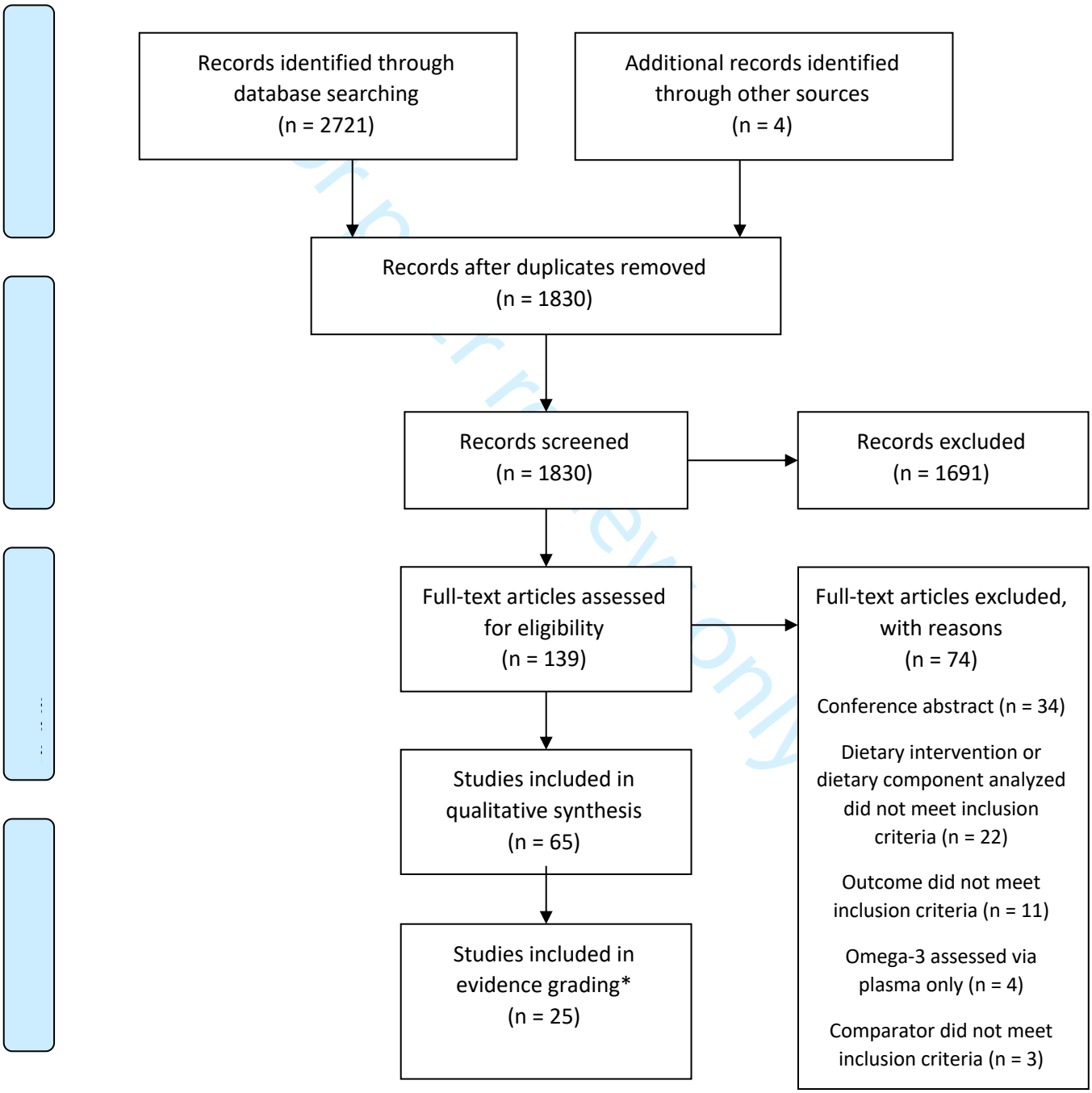
Figure 1: PRISMA 2009 Flow Diagram



Supplementary Tables

Supplementary Table 1: Search Strategy

Embase	
#	**Search Strategy**
1	omega-3':ti,ab,kw OR pufa$:ti,ab,kw OR ((acid* NEAR/5 ('n-3' OR polyunsaturated OR linolenic OR eicosapenta$noic OR timnodonic OR docosahexa$noic)):ti,ab,kw) OR docosahexaenoate:ti,ab,kw OR epa:ti,ab,kw OR dha:ti,ab,kw OR ala:ti,ab,kw
2	omega 3 fatty acid'/exp
3	**#1 OR #2**
4	cholesterol*:ti,ab,kw OR hdl:ti,ab,kw OR ldl:ti,ab,kw OR 'high density lipoprotein*':ti,ab,kw OR 'low density lipoprotein*':ti,ab,kw OR 'beta lipoprotein*':ti,ab,kw OR apo*protein*:ti,ab,kw OR apoa:ti,ab,kw OR apob:ti,ab,kw OR apoc:ti,ab,kw OR apod:ti,ab,kw OR apoe:ti,ab,kw OR apoh:ti,ab,kw OR ((apo NEXT/1 (a OR b OR c OR d OR e OR h)):ti,ab,kw) OR triglyceride*:ti,ab,kw OR triacylglycerol*:ti,ab,kw OR (((serum OR plasma) NEXT/1 (lipid* OR tg OR tag)):ti,ab,kw)
5	cholesterol'/exp OR 'lipoprotein'/exp OR 'triacylglycerol'/exp
6	**#4 OR #5**
7	nutrigenomic*:ti,ab,kw OR nutrigenetic*:ti,ab,kw OR (((nutritional OR expression* OR variation* OR variant*) NEAR/2 (genomic* OR genetic* OR gene OR genes)):ti,ab,kw) OR genotype:ti,ab,kw OR ((('nutrient-gene' OR 'gene-nutrient' OR 'gene-diet') NEXT/1 interaction*):ti,ab,kw) OR 'personali?ed nutrition':ti,ab,kw OR 'precision nutrition':ti,ab,kw
8	nutrigenomics'/exp OR 'nutrigenetics'/exp OR 'genetic variation'/exp OR 'genotype'/exp
9	**#7 OR #8**
10	**#3 AND #6 AND #9**
11	[animals]/lim NOT [humans]/lim
12	**#10 NOT #11**

Medline (Ovid)

#	Search Strategy
1	("omega-3" or PUFA? or (acid* adj5 ("n-3" or polyunsaturated or linolenic or eicosapenta?noic or timnodonic or docosahexa?noic)) or docosahexaenoate or EPA or DHA or ALA).ab,kf,ti.
2	exp Fatty Acids, Omega-3/
3	**1 or 2**
4	(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo adj (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) adj (lipid* or TG or TAG))).ab,kf,ti.
5	exp Cholesterol/ or exp Lipoproteins/ or exp Triglycerides/
6	**4 or 5**
7	(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) adj2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") adj interaction*) or "personali#ed nutrition" or "precision nutrition").ab,kf,ti.
8	Nutrigenomics/ or Genetic Variation/ or Genotype/
9	**7 or 8**
10	**3 and 6 and 9**
11	exp animals/ not humans.sh.
12	**10 not 11**

Web of Science

Indexes = SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Timespan =All years

#	Search Strategy
1	TS=("omega-3" or PUFA$ or (acid* NEAR/5 ("n-3" or polyunsaturated or linolenic or eicosapenta$noic or timnodonic or docosahexa$noic)) or docosahexaenoate or EPA or DHA or ALA)
2	TS=(cholesterol* or HDL or LDL or "high density lipoprotein*" or "low density lipoprotein*" or "beta lipoprotein*" or apo*protein* or apoA or apoB or apoC or apoD or apoE or apoH or (apo NEAR/0 (A or B or C or D or E or H)) or triglyceride* or triacylglycerol* or ((serum or plasma) NEAR/0 (lipid* or TG or TAG)))
3	TS=(nutrigenomic* or nutrigenetic* or ((nutritional or expression* or variation* or variant*) NEAR/2 (genomic* or genetic* or gene or genes)) or genotype or (("nutrient-gene" or "gene-nutrient" or "gene-diet") NEAR/0 interaction*) or "personali?ed nutrition" or "precision nutrition")
4	**#1 AND #2 AND #3**
5	TS=(animals OR animal OR mice OR mus OR mouse OR murine OR woodmouse OR rats OR rat OR murinae OR muridae OR cottonrat OR cottonrats OR hamster OR hamsters OR cricetinae OR rodentia OR rodent OR rodents OR pigs OR pig OR swine OR swines OR piglets OR piglet OR boar OR boars OR "sus scrofa" OR ferrets OR ferret OR polecat OR polecats OR "mustela putorius" OR "guinea pigs" OR "guinea pig" OR cavia OR callithrix OR marmoset OR marmosets OR cebuella OR hapale OR octodon OR chinchilla OR chinchillas OR gerbillinae OR gerbil OR gerbils OR jird OR jirds OR merione OR meriones OR rabbits OR rabbit OR hares OR hare OR diptera OR flies OR fly OR dipteral OR drosphila OR drosophilidae OR cats OR cat OR carus OR felis OR nematoda OR nematode OR nematoda OR nematode OR nematodes OR sipunculida OR dogs OR dog OR canine OR canines OR canis OR sheep OR sheeps OR mouflon OR mouflons OR ovis OR goats OR goat OR capra OR capras OR rupicapra OR chamois OR haplorhini OR monkey OR monkeys OR anthropoidea OR anthropoids OR saguinus OR tamarin OR tamarins OR leontopithecus OR hominidae OR ape OR apes OR pan OR paniscus OR "pan paniscus" OR bonobo OR bonobos OR troglodytes OR "pan troglodytes" OR gibbon OR gibbons OR siamang OR siamangs OR nomascus OR symphalangus OR chimpanzee OR chimpanzees OR prosimians OR "bush baby" OR prosimian OR bush babies OR galagos OR galago OR pongidae OR gorilla OR gorillas OR pongo OR pygmaeus OR "pongo pygmaeus" OR orangutans OR pygmaeus OR lemur OR lemurs OR lemuridae OR horse OR horses OR pongo OR equus OR cow OR calf OR bull OR chicken OR chickens OR gallus OR quail OR bird OR birds OR quails OR poultry OR poultries OR fowl OR fowls OR reptile OR reptilia OR reptiles OR snakes OR snake OR lizard OR lizards OR alligator OR alligators OR crocodile OR crocodiles OR turtle OR turtles OR amphibian OR amphibians OR amphibia OR frog OR frogs OR bombina OR salientia OR toad OR toads OR "epidalea calamita" OR salamander OR salamanders OR eel OR eels OR sciuridae OR squirrel OR squirrels OR chipmunk OR chipmunks OR suslik OR susliks OR vole OR voles OR lemming OR lemmings OR muskrat OR muskrats OR lemmus OR otter OR otters OR marten OR martens OR martes OR weasel OR badger OR badgers OR ermine OR mink OR minks OR sable OR sables OR gulo OR gulos OR wolverine OR wolverines OR minks OR mustela OR llama OR llamas OR alpaca OR alpacas OR camelid OR camelids OR guanaco OR guanacos OR chiroptera OR chiropteras OR bat OR bats OR fox OR foxes OR iguana OR iguanas OR xenopus laevis OR parakeet OR parakeets OR parrot OR parrots OR donkey OR donkeys OR mule OR mules OR zebra OR zebras OR shrew OR shrews OR bison OR bisons OR buffalo OR buffaloes OR deer OR deers OR bear OR bears OR panda OR pandas OR "wild hog" OR "wild boar" OR fitchew OR fitch OR beaver OR beavers OR jerboa OR jerboas OR capybara OR capybaras)
6	**#4 not #5**

Supplementary Table 2: Summary of observational studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3[1]	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[2]
Bouchard-Mercier et al. 2011 (1)	Cross-Sectional	Single SNP	Healthy Caucasian men and women from INFOGENE study (n=674)	*PPARα*, L162V (rs1800206) *PPARγ*, P12A (rs1801282) *PPARδ*, –87T→ C (rs2016520)	*PPARα*: 22q13.31 *PPARγ:* 3p25.2 *PPARδ:* 6p21.31	Mean: L162: 2.8 g/day V162: 2.9 g/day (unclear if food and/or supplement sources)	Minor allele carriers vs. Non-carriers	LDL-PPD	**LDL-PPD:** In a model including age, sex, TG, BMI, energy and omega-3 intakes and PPAR*α* L162V (rs1800206) polymorphism, the interaction of PPAR*α*162V and omega-3 intakes explained 0.62% of the variance in LDL-PPD.
Bodhini et al. 2017 (2)	Cross-Sectional	Single SNP	Adults with normal glucose tolerance (n=821) and adults with type 2 diabetes (n=861)	*MC4R*, rs17782313 *TCF7L2*, rs12255372 *TCF7L2*, rs7903146	*MC4R:* 18q21.32 *TCF7L2:* 10q25.2-q25.3	**Low:** 0.38 g/day ALA **Moderate:** 0.58 g/day ALA **High:** 0.89 g/day ALA (means) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c	**HDL-c:** 'T' allele carriers of *TCF7L2* rs12255372 within the lowest tertile of ALA intake (mean=0.38 g/day) exhibited higher levels of HDL-c compared to GG homozygotes in the lowest tertile of ALA intake (mean=0.38 g/day)
Chen et al. 2019 (3)	Cross-Sectional Analysis within a Prospective Cohort	Single SNP, Haplotype and Gene-Centric	Adults of Swedish ancestry from the GLACIER cohort (n=5160)	All variations in the *FADS1-FADS2-FADS3* gene cluster and variation within 200kb upstream and downstream of the *FADS* region	*FADS1:* 11q12.2 *FADS2:* 11q12.2 *FADS3:* 11q12.2	**High:** >1.6 g/day **Low:** <1.6 g/day (food)	Entire FADS region gene-centric analysis and Variation in individual FADS cluster SNPs: rs174570, rs174602, rs74771917, rs3168072, rs12577276, rs7115739 and Haplotype analysis	HDL-c LDL-c TG Total-c	**HDL-c:** Significant interaction of rs174570 and omega-3 on HDL-c **LDL-c:** Significant interaction of rs174602 and omega-3 on LDL-c **TG:** Gene-centric analyses demonstrated a significant interaction between variation in the *FADS* gene cluster and omega-3 intake on TG **Total-c:** Significant interaction of rs174602 and omega-3 on total-c ('C' allele carriers exhibited lower total-c with low omega-3 intake, while no such relationship was observed with high omega-3 intake)
Ching et al. 2019 (4)	Cross-Sectional	Single SNP	Vegetarian adults of Malaysian ancestry (n=200)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low:** ≤0.45 g/day ALA **Moderate:** 0.46-0.64 g/day ALA **High:** >0.64 g/day ALA (means) (food)	Comparison between three genotypes	HDL-c TG	**HDL-c:** The TT genotype had significantly lower HDL-c when ALA intake was in the moderate intake range, but there were no significant gene-omega-3 interaction on lipid levels
Dumont et al. 2011 (5)	Cross-Sectional	Single SNP	Adolescents of European ancestry (n=573)	*FADS1*, rs174547	*FADS1:* 11q12.2	**High**: >1.4 g/day ALA **Low**: ≤1.4 g/day ALA (unclear if food and/or supplement sources)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c	**Total-c:** Significant interaction whereby the minor allele (CT+TT genotype) was associated with lower total-c when ALA intake is high as compared to when intake is low. This remained significant after assessing the interaction using ALA intake as a continuous variable.

Dumont et al. 2018 (6)	Cross-Sectional	Single SNP	Men and women aged 35 to 74 years from the MONA LISA Study of three French populations (n=3069)	*FADS1*, rs174547	*FADS1:* 11q12.2	**Low**: 0.6 g/day ALA (mean) **Median**: 0.8 g/day ALA (stratified by median for analyses) **High**: 1.3 g/day ALA (mean) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c	--
Fallaize et al. 2016 (7)	Cross-Sectional (Baseline) and Longitudinal Analyses within a Randomized Intervention	Single SNP*	Healthy adults enrolled in the Food4Me European trial (*n*=1466)	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**High**: >0.67 %kcal **Low**: <0.67 %kcal **Increased Intake:** reduced omega-3 intake from baseline **Decreased Intake:** decreased omega-3 intake from baseline (unclear if food and/or supplement sources)	*APOE*-E4- vs. *APOE*-E4+	Total-c	**Total-c:** Cross-sectional (baseline) analysis demonstrated a significant genotype effect for *APOE,* omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for *APOE,* change in omega-3 intake (increase or decrease) and total-c.
Fontaine-Bisson and El-Sohemy 2007 (8)	Cross-Sectional	Genetic Score	Men and women aged 20-29 years (n=595)	*TNFα,* rs361525, rs1800629	*TNFα:* 6p21.33	Intake range: 0.2-4.6 %kcal (mean intakes were 0.7 %kcal for 0/0, 0.7% kcal for 0/1 and 0.6%kcal for 1/0) (food)	No minor allele ('A') for both SNPs (0/0) vs. One minor allele for rs361525 (1/0) vs. One minor allele for rs1800625 (0/1)	HDL-c	--
Fontaine-Bisson et al. 2009 (9)	Cross-Sectional	Single SNP	Healthy men and women aged 20-29 years (n=593)	*NF-κB* -94Ins/Del ATTG (rs28362491)	*NF-κB:* 4q24	Mean intake: 0.7 %kcal (unclear if food and/or supplement sources)	Ins/Ins vs. Ins/Del vs. Del/Del	HDL-c	**HDL-c:** Significant interaction between *NF-κB* genotype and omega-3 intake on HDL-c
Hellstrand et al. 2012 (10)	Cross-Sectional	Single SNP	Healthy men and women aged 45-68 years from Sweden (n=4635)	*FADS,* rs174547	*FADS:* 11q12.2	**Low:** ≤0.14 %kcal long-chain omega-3 **Moderate:** 0.14-0.28 %kcal long-chain omega-3 **High:** >0.28 %kcal long-chain omega-3 (tertiles of intake reported only for certain significant findings) (food and supplement)	TT vs. TC vs. CC	HDL-c LDL-c TG	**LDL-c:** Significant interaction between *FADS* rs174547 genotype and long-chain omega-3 on LDL-c whereby the 'C' allele was significantly associated with lower LDL-c when long-chain omega-3 intake was in the lowest tertile (but not in the moderate or highest tertile). High long-chain omega-3 intake was associated with significantly higher LDL-c for CC and TC genotypes but not TT genotypes. Stratified analysis based on sex demonstrated that these significant interactions remained for men, but not women, however there was not a significant difference in interactions by sex.
Hosseini-Esfahani et al. 2017 (11)	Nested Case-Control	Single SNP	Healthy men and women aged ≥18 years from Iran	*ZNT8,* rs13266634	*ZNT8:* 8q24.11	**Tertiles for omega-3:** **Low:** <0.38 %kcal **Moderate:** 0.38-	CC vs. CT+TT	HDL-c TG	**HDL-c:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of low HDL-c whereby CC genotypes exhibited a decreased risk of low HDL-c with increasing intake of omega-3; this was not observed in

			(n=1634)			0.54 %kcal **High:** >0.54 %kcal (food)			the CT+TT genotype group. **TG:** Significant interaction between *ZNT8* rs13266634 genotype and omega-3 intake on the risk of high TG whereby CC genotypes exhibited a decreased risk of high TG with increasing intake of omega-3; this was not exhibited in the CT+TT genotype group.
Jang et al. 2014 (12)	Cross-Sectional	Single SNP	Adult: Men and women aged 40-69 from Korea (n=4205) Children: Boys and girls aged 8-13 years from Korea (n=1548)	*PCSK5,* rs1029035	*PCSK5:* 9q21.13	Based on overall median intake (further detailed elsewhere (12)): **Low:** <0.4 %kcal **High:** >0.4 %kcal (food)	CC vs. CA vs. AA	HDL-c	**HDL-c:** Significant interaction between *PCSK5* rs1029035 and omega-3 on HDL-c in male children and male adults. 'C' allele carriers exhibit a tendency to decrease HDL-c with omega-3, while AA genotypes exhibit the opposite effect.
Joffe et al. 2010 (13)	Cross-Sectional	Single SNP	Black women from South Africa, normal weight or with obesity (n=138)	*TNFα,* rs1800629	*TNFα:* 6p21.33	ALA (amount not reported/cannot determine) (food)	GG vs. GA+AA	HDL-c LDL-c TG Total-c Total-c:HDL-c	**Total-c:HDL-c ratio:** Significant interaction between *TNFα,* rs1800629 genotypes and %kcal from ALA whereby increasing %kcal from ALA was associated with increases in Total-c:HDL-c for GG genotypes but decreases in Total-c:HDL-c ratio for GA+AA genotypes
Joffe et al. 2012 (14)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=263)	*TNFα,* rs361525	*TNFα:* 6p21.33	**Median Intakes:** omega-3: 0.28-0.36 % kcal ALA: 0.21-0.26 %kcal EPA: 0.02 %kcal DHA: 0.04-0.08 %kcal (food)	GG vs. GA(+AA for one participant: black, normal weight)	HDL-c LDL-c TG Total-c Total-c:HDL-c	**LDL-c:** Significant interaction for Caucasian women whereby LDL-c decreased with increasing %kcal from EPA in the GG genotype but not the GA genotype of *TNFα,* rs361525. **Total-c:** Significant interaction for white women whereby total-c decreased with increasing EPA and DHA intakes in the GG genotype group but not the GA genotype group of *TNFα* rs361525 but individual rates were not significant. **Total-c:HDL-c ratio:** Significant interaction for black women whereby Total-c:HDL-c decreased within increasing %kcal from omega-3 in the GA genotype group but not GG of *TNFα* rs361525.
Joffe et al. 2014 (15)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=268)	*IL-6,* −174 G>C, IVS3 (rs1800795), +281 G>T, IVS4 (rs1554606), +869 A>G (rs2069845)	*IL-6:* 7p15.3	Black Women (%kcal/day): 0.28 omega-3, 0.21 ALA, 0.02 EPA, 0.04 DHA (normal weight); 0.36 omega-3, 0.22 ALA, 0.04 EPA, 0.08 DHA (obesity) White Women (%kcal/day): 0.33 omega-3, 0.26 ALA, 0.01 EPA, 0.05 DHA (normal weight); 0.32 omega-3, 0.25 ALA, 0.02 EPA, 0.05 DHA (food)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	The following results were statistically significant only in white women, but not in black women[3]: **HDL-c:** Significant interaction whereby HDL-c increased with: increasing omega-3 and/or DHA and/or ALA intake in *IL-6* rs1800795 C allele carriers and increasing ALA intake in *IL-6* rs1554606 T allele carriers. HDL-c decreased with: increasing EPA and/or DHA intake in *IL-6* rs2069845 G allele carriers. **TG:** Significant interaction whereby TG reduced with increasing EPA intake in *IL-6* rs1800795 C allele carriers **Total-c:HDL-c:** Significant interaction whereby total-c:HDL-c ratio decreased with: increasing EPA intake in *IL-6* rs1800795 CC genotypes and *IL-6* rs1554606 TT genotypes, increasing DHA intake in *IL-6* rs1800795 CC genotypes, and increasing ALA intake in *IL-6* rs1554606 TT genotypes.
Lai et al. 2006 (16)	Cross-Sectional	Single SNP	Men and women from the Framingham	*APOA5,* rs662799, rs651821, rs3135506,	*APOA5:* 11q23.3	**Mean Intake:** 0.69 %kcal omega-3 **Tertiles for**	Major allele homozygotes vs. Minor allele carriers	TG	--

			Heart Study (n=2148)	rs2072560, rs2266788		**<u>omega-3:</u>** **Low:** <0.58 %kcal **Moderate:** 0.58-0.74 %kcal **High:** >0.74 %kcal (unclear if food and/or supplement sources)			
Lu et al. 2010 (17)	Cross-Sectional	Single SNP	Men and women of Doetinchem Cohort Study (n=3575)	*FADS,* rs174546, rs482548, rs174570	*FADS:* 11q12.2	Mean intake: 0.5 %kcal (food)	Comparison between three genotypes	HDL-c Total-c	**Total -c**: In high omega-3 intake group, total-c was significantly higher with each added minor 'C' allele of rs174546
Nettleton et al. 2009 (18)	Cross-Sectional	Single SNP	Men and women of Caucasian ancestry (n=8511)	*ANGPTL4* E40K (rs116843064)	*ANGPTL4:* 19p13.2	Not Reported/Cannot Determine (food)	Minor allele carriers vs. Non-allele carriers	HDL-c TG	--
Richardson et al. 2011 (19)	Meta-analysis of the Framingham Offspring Study (FOS) and the Genetics of Lipid Lowering Drugs and Diet Network (GOLDN)	Single SNP	Men and women from FOS and GOLDN studies (*n*=3605)	*PLIN4*, rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	*PLIN4:* 19p13.3	Mean intakes: **FOS Men:** 1.43 g/d **FOS Women:** 1.37 g/d **GOLDN Men:** 1.83 g/d **GOLDN Women:** 1.48 g/d (food and supplement)	Minor allele carriers vs. Non-allele carriers	TG HDL-c	**TG:** Significant interactions for *PLIN4,* rs884164 whereby TG levels increased in minor allele carriers with higher omega-3 intake for males and females combined, and males individually.
Standl et al. 2012 (20)	Cross-Sectional Analysis (10-year time point) within a 10-year longitudinal cohort study	Single SNP	10 year-old children of the GINIplus and LISAplus birth cohort studies (n=1697)	*FADS1/FADS2,* rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	*FADS1/2:* 11q12.2	Median intake: 0.14 mg/MJ omega-3 (ALA+EPA+DPA +DHA) (food and supplement)	Comparison between three genotypes	HDL-c LDL-c Total-c TG	--
Tai et al. 2005 (21)	Cross-Sectional	Single SNP	Framingham Cohort, men and women (*n*=2106)	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	**High**: >0.69 %kcal **Low**: <0.69 %kcal (food)	PPARα: 162V carriers vs. 162L/162L homozygotes	TG apoC-III	**TG:** 167V carriers had lower TG with high omega-3 intake compared to low omega-3 intake (gene-diet-interaction effects were NS) **apoC-III:** Significant gene-diet interactions; Higher apoC-III in 162V carriers with low omega-3 intake compared to 162V carriers with high omega-3 intake and 162L homozygotes with low omega-3 intake
Volcik et al. 2008 (22)	Cross-Sectional (Baseline) Analysis within a Prospective Cohort	Single SNP	African American (*n*=3480) and Caucasian (*n*=10 134) men and women (*N*=13,614)	*PPARα*, L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	*PPARα*: 22q13.31	African American: **High:** >0.32 g/d EPA+DHA **Low:** ≤0.32 g/d EPA+DHA Caucasian: **High:** >0.22 g/d EPA+DHA **Low:** ≤0.22 g/d EPA+DHA (food)	Comparison between three genotypes for each SNP	HDL-c LDL-c TG Total-c	**Total-c, LDL-c:** African Americans (but not Caucasians) homozygous for *PPARα* (rs3892755) TT genotype with high EPA+DHA intake had significantly lower total-c and LDL-c compared to CT and TT genotypes (both high and low EPA+DHA intake)

Warodomwichit et al. 2009 (23)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	*TCF7L2* rs7903146, rs12255372	*TCF7L2:* 10q25.2-25.3	N/A (Median omega-3: 0.67% of kcal) (food)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c LDL-c particle size TG Total-c	--

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. Intakes are total omega-3 unless otherwise specified
2. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS

Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

3. These results were taken from the full-text manuscript's summary table of IL-6 results. Refer to Supplementary Tables S8-S13 in Joffe et al. 2014 (15) for several other significant results, stratified and un-stratified by ethnicity. Note: There were no corrections for multiple testing in the statistical analyses.

'--' indicates that all of the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε2, ε3 and ε4)

Supplementary Table 3: Summary of interventional studies

Author, Year	Study Design	Genetic Approach	Population (sample size included in analyses)	Intervention Duration	Gene(s), SNP(s)	Cytogenic Location of Gene(s)	Quantity, Source and Type of Omega-3	Comparators	Plasma Lipid/ Lipoprotein Outcome(s)	Summary of Statistically Significant Study Findings Relevant to the Research Question[1]
AbuMweis et al. 2018 (24)	Randomized, Crossover Controlled Intervention	Single SNP*	Adults with at least one cardiovascular risk factor (n=129)	4 weeks	*FADS1*, rs174561 *FADS2*, rs174583 *ELOVL2*, rs953413 *ELOVL5*, rs2397142 *CETP*, rs5882 *SCD1*, rs2234970, *PPARα*, rs6008259 *LIPF*, rs814628 and *APOE*, rs429358, rs7412	*FADS1/2:* 11q12.2 *ELOVL2:* 6p24.2 *ELOVL5:* 6p12.1 *CETP:* 16q13 *SCD1:* 10q24.31 *PPARα*: 22q13.31 *LIPF:* 10q23.31 *APOE:* 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except *PPARA* and *LIPF* whereby analyses were major allele homozygotes vs. minor allele carriers) and *APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoA1 apoB HDL-c LDL-c TG Total-c	--
Alsaleh et al. 2014 (25)	Randomized Controlled Intervention	Single SNP and Polygenic	Healthy men and women (n=310)	12 months	CETP, rs3764261, *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5/ABCG*, rs4299376 *TIMD4/HAVCR1*, rs6882076 *GCKR*, rs1260326 *TRIB1*, rs2954029 *ANGPTL3/DOCK7*, rs2131925 *FADS1/2/3*, rs174546 *GALNT2*, rs4846914 *ABCA1*, rs4149268 *APOE/APOC1/APOC2*, rs439401	*CETP:* 16q13 *LIPC:* 15q21.3 *APOB:* 2p24.1 *ABCG5/ABCG8:* 2p.21 *TIMD4/HAVCR1:* 5q33.3 *GCKR:* 2p23.3 *TRIB1:* 8q24.13 *ANGPTL3/DOCK7:* 1p31.3 *FADS:* 11q12.2 *GALNT2:* 1q42.13 *ABCA1:* 9q31.1 *APOE/APOC1/APOC2:* 19q13.32	**Low Dose:** 0.5 g/day EPA and DHA **Moderate Dose:** 0.9 g/day EPA and DHA **High Dose:** 1.8 g/day EPA and DHA (supplement)	Effect sizes per GRS risk allele after omega-3 treatment *and* Risk allele carriers vs. non-risk allele carriers	HDL-c LDL-c TG Total-c	**TG:** significant interaction whereby 1.8 g/day EPA and DHA significantly reduced TG in T allele carriers (21.6% reduction) vs. CC genotypes (3.5% reduction) of *FADS1* rs174546

Armstrong et al. 2012 (26)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	*ALOX5,* dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	*ALOX5:* 10q11.21	Fish oil: 5.0 g/day containing 2.0 g/day EPA and 1.0 g/day DHA Control oil: 5.0 g/day corn/soy oil (supplement)	dd vs. d5 vs. 55	TG Mean lipoprotein particle diameter, total number of particles and particle concentration for: HDL-c and LDL-c	**TG:** significant interaction whereby decreases in TG from omega-3 supplementation were specific to d5 genotype group **HDL-c particle concentration:** significant decrease with omega-3 intervention in the d5 and 55 genotype groups compared to placebo, but no decreases in the dd genotype group **Medium HDL-c particles and HDL-c (mmol/L):** significant gene-treatment interaction but no significant differences after post-hoc analysis for comparisons among genotypes
Binia et al. 2017 (27)	Single-Arm Clinical Trial	Single SNP	Mexican adults 18-40 years (n=191)	6 weeks	*PPARα*, L162V (rs1800206), *PPARγ2*, P12A (rs1801282)	*PPARα*: 22q13.31 *PPARγ2*: 3p25.2	Fish oil: 2.7 g/day containing 1.9 g/d EPA and 0.8 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c	**LDL-c:** significant increase in LDL-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2 **Total-c:** significant increase in total-c among minor allele carriers (PPARγ2 Pro12Ala and Ala12Ala) only vs. PPARγ2 Pro12Pro genotypes only for individuals with BMI>25.0 kg/m^2
Bouchard Mercier et al. 2013 (28)	Single Arm Clinical Trial	Single SNP	Healthy adults aged 18-50 years (n=208)	6 weeks	*SREBF1,* rs4925115, rs4925118, rs12953299 *ACLY,* rs8071753, rs8065502, rs2304497 *ACACA* rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	*SREBF1:* 17p11.2 *ACLY:* 17q21.2 *ACACA:* 17q12	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** Significant gene-diet interaction whereby individuals with the GG genotype of *ACLY* rs8071753 and individuals with the GG or CG genotype of *ACACA* rs1714987 exhibited greater TG lower effects following omega-3 supplementation; these two SNPs explained approximately 8% of the variance in plasma TG responses to omega-3 supplementation. There were significant differences in genotype frequencies of *ACLY* rs8071753 for responders and non-responders to omega-3 for TG lowering.
Bouchard-Mercier et al. 2014 (29)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*RXRA* (12 SNPs), *CPT1A* (9 SNPs), *ACADVL* (1 SNP), *ACAA2* (6 SNPs), *ABCD2* (8 SNPs), *ACOX1* (8 SNPs), *ACAA1* (3 SNPs) [outlined in Supplementary Table 5]	*RXRA:* 9q34.2 *CPT1A:* 11q13.3 *ACADVL:* 17p13.1 *ACAA2:* 18q21.1 *ABCD2:* 12q12 *ACOX1:* 17q25.1 *ACAA1:* 3p22.2	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (when minor allele frequencies were >0.05)	TG	**TG:** There were significant gene-diet interaction effects on TG responses to omega-3 for RXRA rs11185660 genotype dependent on total fat intake, RXRA rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and ACOX1 rs17583163 dependent on total polyunsaturated fat intake
Bouchard-Mercier et al. 2014 (30)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*GCK* (13 SNPs) [outlined in Supplementary Table 5]	*GCK:* 7p13	Fish oil: 5.0 g/day containing 1.9-2.2 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes	TG	**TG:** CC genotypes of *GCK* rs741038 exhibited significantly greater TG reduction in response to omega-3 when their carbohydrate intake was high (>48.6%kcal) compared to those with the CC genotype of rs741038 with low carbohydrate intake (≤48.6%kcal) and compared to CT or TT genotypes with either high or low carbohydrate intake.

								(when minor allele frequencies were >0.05)		
Caron-Dorval et al. 2008 (31)	Single Arm Clinical Trial	Single SNP	Healthy men of Caucasian ancestry aged 18-55 years (n=28)	6 weeks	*PPARα*, L162V (rs1800206)	*PPARα*: 22q13.31	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	V162 carriers vs. non-carriers	apoB-100 HDL-c LDL-c TG Total-c Total-C:HDL-c	--
Carvalho-Wells et al. 2012 (32)	Sequential Non-Randomized, Cross-Over Dietary Intervention	Single SNP*	Healthy men and women aged 35-70 years (*n*=88)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	**Low-Fat**: 4.0 mg/day EPA, 10.6 mg/d DPA, 11.7 mg/d DHA **High-SFA**: 20.2 mg/d EPA, 27.1 mg/d DPA, 15.4 mg/d DHA **High-SFA+DHA**: 524.3 mg/d EPA, 215.5 mg/d DPA, 3017.3 mg/d DHA [actual intakes reported (33)] (supplemental DHA for High-SFA+DHA; others from food sources)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c sdLDL-c TG Total-c	**TG:** Significant diet x genotype interaction for TG; greater TG lowering response to high-SFA+DHA diet in *APOE*-E3/4 carriers (compared to high-SFA diet alone)
Caslake et al. 2008 (34)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men and women aged 20-70 years (*n*=312)	8 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Control oil: 0.0 g/d EPA and DHA Fish oil: 0.7 g/d EPA and DHA Fish oil: 1.8 g/d EPA and DHA (supplement)	*APOE*-E2/E2 + E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	**TG:** Significant interaction between treatment x sex x genotype whereby *APOE*-E3/E4 + E4/E4 males exhibited the greatest TG reductions with both 0.7 g/d EPA and DHA as well as 1.8 g/d EPA and DHA compared to other genotypes
Cormier et al. 2012 (35)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	*FADS* gene cluster (19 SNPs) [outlined in Supplementary Table 5]	*FADS:* 11q12.2	Fish oil: 5.0 g/day containing 1.9 g/day EPA and 1.1 g/day DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	TG	--
Dang et al. 2015 (36)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	*APOE*-E4+ vs. *APOE*-E4-	HDL-c LDL-c TG Total-c	--
Dawczynski et al. 2013 (37)	Randomized, Placebo-Controlled, Double-Blind Intervention	Single SNP	Men and women with TG ≥ 1.7 mmol/L, otherwise healthy (n=47)	10 weeks	*CD36,* rs1761667, rs1049673	*CD36:* 7q21.11	Yogurt with lower dose fish oil: 0.8g/day omega-3 containing 0.01g ALA, 0.44g EPA, 0.06g DPA and 0.31g DHA (fish oil) Yogurt with higher dose fish oil: 3.0 g/day omega-3	Comparison between three genotypes	HDL-c TG	**HDL-c**: In response to omega-3 supplementation (0.8-3.0 g/day), HDL-c increased in GA genotype of *CD36* rs1761667 and CG genotype of *CD36* rs1049673. **TG**: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of *CD36* rs1761667.

							containing 0.07g ALA, 1.59g EPA, 0.23g DPA and 1.12g DHA (fish oil) Control yogurt: commercial whole fruit yogurt with 3.5% milk fat (food)			
Ferguson et al. 2010 (38)	Randomized Intervention and Cross-Sectional (Baseline) Analysis	Single SNP	Men and women with metabolic syndrome from LIPGENE cohort (*n*=450)	12 weeks	*NOS3,* rs11771443, rs1800783, rs1800779, rs1799983, rs3918227, rs743507	*NOS3:* 7q36.1	1.24 g/d EPA+DHA supplement (intervention); quantity of omega-3 not reported for observational analyses	Major allele homozygotes vs. Minor allele carriers	apoA-1 apoB apoB-48 apoC-II apoC-III apoE HDL-c LDL-c TG Total-c	**TG:** For *NOS3* rs1799983 minor-allele (A) carriers only, the observational analysis indicated higher TG with lower EPA+DHA intake (and lower TG with higher EPA+DHA intake). Post-intervention with omega-3 supplementation indicated that only minor-allele (A) carriers exhibited significant TG reduction (accompanied by increases in plasma omega-3).
Harsløf et al. 2014 (39)	Randomized, Controlled Intervention	Single SNP and Genetic Score	Infants of Danish ancestry (n=133)	9 months	*PPARγ2*, Pro12Ala (rs1801282), *FADS1,* rs1535, *FADS2,* rs174575, *FADS3,* rs174448 *COX2,* rs5275, rs689466	*PPARγ2*: 3p25.2 *FADS:* 11q12.2 *COX2:* 1q25.2-q25.3	5.0 mL/day fish oil (median reported intake: 3.8 g/day containing 630 mg/day EPA and 620 mg/day DHA) (supplement)	*PPARγ2* genotype analyses were by major allele homozygotes vs. heterozygotes and *FADS* genotype analyses were by the number of DHA-increasing alleles and *COX2* genotype analyses were by major allele homozygotes vs. heterozygotes vs. minor allele homozygotes	HDL-c LDL-c TG Total-c	**TG:** *PPARγ2* heterozygotes exhibited reduced TG in response to omega-3 when compared to *PPARγ2* heterozygotes in the control (sunflower oil) group
Itariu et al. 2012 (40)	Randomized, Controlled Intervention	Single SNP	Men and women without diabetes with a BMI ≥40 kg/m^2 aged 20-65 years (n=55)	8 weeks	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 3.4 g/day EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	apoB HDL-c LDL-c TG Total-c	**apoB:** Significant increases in apoB with omega-3 intervention in Ala12 carriers when compared to Pro12 carriers. **Total-c:** Significant interaction effect whereby increases in total-c were exhibited with omega-3 intervention in Ala12 carriers when compared to the Pro12Pro genotype.
Jackson et al. 2012 (41)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	8 weeks and 480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB apoC-III apoE HDL-c LDL-c TG	**TG:** *APOE*-E3/E4 exhibited reduced fasting TG in response to a high saturated fat + DHA intervention when compared to the high saturated fat diet alone. There was also a significant interaction (meal x time x genotype) for the postprandial TG lowering response whereby *APOE*-E3/4 consuming a high saturated fat + DHA intervention exhibited significantly lower

									Total-c	postprandial TG, TG area under the curve, and TG maximum concentration compared to those consuming the high saturated fat diet alone.
Jackson et al. 2017 (42)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	480-min postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4	apoB-48 apoB-100	--
Lindi et al. 2003 (43)	Randomized Intervention	Single SNP	Healthy men and women aged 30-65 years (*n*=150)	3 months	*PPARγ2*, Pro12Ala (rs1801282)	*PPARγ2*: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	*PPARγ2*, Ala12 carriers vs. Pro12Pro	HDL-c LDL-c TG Total-c	**TG:** Compared to Pro12Pro, Ala12 carriers exhibited significantly greater TG reductions in response to omega-3 supplementation only when total fat intake was ≤37 %kcal or SFA intake was ≤10 %kcal
Lindman et al. (44)	Randomized, Controlled Intervention	Single SNP	Men at high risk of cardiovascular disease aged 65-75 years (n=204)	6 months	*FVII,* rs6046	*FVII:* 13q34	Fish oil containing 2.4 g/d EPA + DHA Dietary advice including recommendations to increase omega-3 (supplement and food)	Major allele homozygotes vs. Minor allele carriers	TG	--
Madden et al. 2008 (45)	Non-Randomized Intervention	Single SNP	Healthy men aged 43-84 years (*n*=111)	12 weeks	*CD36,* rs1527483, rs1049673, rs1761667, rs1984112	*CD36:* 7q21.11	Fish oil containing 1.02 g/d EPA and 0.69 g/d DHA (supplement)	For each SNP: AA vs. AG vs. GG	HDL-c LDL-c LDL-c:HDL-c TG	**TG:** In response to omega-3 supplementation, TG significantly reduced only in individuals with the GG genotype, for each SNP individually (i.e. for rs1527483, rs1049673, rs1761667 and rs1984112 individually) **LDL-c:** In response to omega-3 supplementation, LDL-c increased only in individuals with the rs1761667 AA genotype as well as for individuals with the rs1984112 AA genotype **HDL-c:** In response to omega-3 supplementation, HDL-c significantly increased in individuals with rs1761667 AA or AG as well as for individuals with the CC or CG genotype for either rs1984112, rs1527483 and/or rs1049673; NOTE: rs1527483 results should be interpreted with caution due to low sample sizes for AA and AG genotypes thus reducing statistical power)
Markovic et al. 2004 (46)	Single-Arm Clinical Trial	Single SNP	Healthy men (n=159)	12 weeks	*TNFα,* -308 (rs1800629) *LT-α,* +252 (rs909253) *IL-1β,* -511 (rs16944) *IL-6,* -174 (rs1800795)	*TNFα:* 6p21.33 *LT-α:* 6p21.33 *IL-1β:* 2q14.1 *IL-6:* 7p15.3	Fish oil containing 1.8 g/d EPA+DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	TG	**TG:** Significant negative correlation between pre-supplementation TG and change of TG during omega-3 supplementation for all genotypes of genes studied except for *LT-α* rs909253 GG genotype and *IL-1β* rs16944 TT genotype. In *LT-α* rs909253 AA genotype and *TNFα* rs1800629 AA genotype, signification association between BMI (divided in tertiles) and TG changes.
McColley et al. 2011 (47)	Crossover Intervention	Single SNP	Healthy post-menopausal women (n=16)	8 weeks per diet	*FABP2,* rs1799883	*FABP2:* 4q26	**High-Fat:** 50 %kcal from dietary fat **Low-Fat:** 20 %kcal from dietary fat **Low-Fat + omega-3:** 23% kcal from dietary fat with 3 %kcal from omega-3 (food)	Major allele homozygotes vs. Minor allele carriers	TG	--

Minihane et al. 2000 (48)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP*	Healthy men aged 30-70 years at risk of atherogenic lipoprotein phenotype (*n*=50)	6 weeks per diet and 480 minute postprandial	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 3.0 g/d EPA and DHA, Control oil: 6.0 g/d olive oil capsule (supplement)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4 + E4/E4	HDL-c LDL-c TG Total-c Total-c:HDL	**TG:** Postprandial: Significantly greater reduction in TG incremental area under postprandial TG curve in *APOE*-E2/E3 relative to other *APOE* genotype categories **Total-c:** 6-week: *APOE*-E3/E4 + E4/E4 genotype group exhibited significantly different changes in total-c (increase), relative to other *APOE* genotypes, whereby reductions in total-c occurred
Olano-Martin et al. 2010 (49)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemic men (*n*=38)	4 weeks per diet	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	EPA-rich fish oil: 3.3 g/d EPA DHA-rich fish oil: 3.7 g/d DHA Control oil: 80:20 palm olein:soyabean (supplement)	*APOE*-E3/3 vs. *APOE*-E3/4 (carriers)	apoB apoE HDL-c LDL-c TG TG:HDL-c Total-c	**apoB, LDL-c:** In *APOE*-E4 carriers only, DHA-rich oil treatment resulted in significant increases in apoB and LDL-c **TG:** Significant reduction in TG in response to both EPA and DHA in *APOE*-E3/E3 group; significant reduction in TG in *APOE*-E4 carriers with EPA only. No significant interactions. **Total-c:** Significant genotype x treatment interaction whereby *APOE*-E4 carriers exhibit total-c reductions in response to EPA-rich oil.
Ouellette et al. 2013 (50)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*GPAM* (3 SNPs), *AGPAT3* (13 SNPs), *AGPAT4* (35 SNPs) [outlined in Supplementary Table 5]	*GPAM:* 10q25.2 *AGPAT3:* 21q22.3 *AGPAT4:* 6q26	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	HDL-c LDL-c TG Total-c	**LDL-c:** Significant *GPAM*, rs2792751 genotype x supplementation interaction on LDL-c **TG:** Significant genotype x supplementation interaction on TG for *GPAM,* rs2792751 and rs17129561 as well as *AGPAT4,* rs9458172 and rs3798943
Ouellette et al. 2014 (51)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18-50 years (*n*=208)	6 weeks	*MGLL* (18 SNPs) [outlined in Supplementary Table 5]	*MGLL:* 3q21.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Major allele homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	apoB HDL-c LDL-c LDL particle size TG Total-c	**LDL-c:** Significant interactions for *MGLL* rs6776142, rs555183, rs782444, rs6787155 and rs1466571 whereby omega-3 supplementation modulated LDL-c levels; rs782444 and rs555183 minor allele homozygotes more likely to be negative responders to omega-3 supplementation (i.e. exhibit reduced LDL-c); rs6780384, rs782444 and rs6787155 major allele homozygotes more likely to be negative responders to omega-3 supplementation **LDL particle size:** Significant interactions for *MGLL* rs782440, rs13076543 and rs9877819 whereby omega-3 supplementation modulated LDL particle size; rs549662 minor allele homozygotes more likely to be positive responders to omega-3 supplementation (i.e. exhibit increased LDL particle size)
Paschos et al. 2005 (52)	Single-Arm Clinical Trial	Single SNP*	Men with dyslipidemia, aged 35 to 67 years (n=50)	12 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	*APOE*-E2/E3 vs. *APOE*-E3/E3 vs. *APOE*-E3/E4	ApoA-I ApoB HDL-c LDL-c TG Total-c	**ApoA-I:** Significant decrease in E3/E3 **HDL-c:** Significant decrease in E3/E3
Pishva et al. 2010 (53)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	*FABP2,* Ala54Thr (rs1799883)	*FABP2:* 4q26	2.0 g/day pure EPA (supplement)	Ala54Ala (GG) vs. Thr54 carriers (GT+TT)	ApoB ApoC-III HDL-c LDL-c TG Total-c	**ApoC-III:** In response to EPA supplementation, significantly greater reductions in ApoC-III in GT+TT genotypes of rs1799883 compared to GG genotype. **HDL-c:** In response to EPA supplementation, significantly greater increases in HDL-c in GT+TT genotypes of rs1799883 compared to GG genotype. **LDL-c:** In response to EPA supplementation, LDL-c significantly decreased in GG genotypes of rs1799883 but not GT+TT genotypes. **TG:** In response to EPA supplementation, significantly greater reductions in TG in GT+TT genotypes of rs1799883 compared to GG genotype.
Pishva et al.	Single-Arm	Single SNP	Adults with	8 weeks	*PPARα*,	*PPARα* : 22q13.31	2.0 g/day pure	Leu162	ApoB	--

2014 (54)	Clinical Trial		hypertriglyceridemia (n=46)		Leu162Val (rs1800206) *PPARα*, Intron 7 SNP		EPA (supplement)	vs. Val162 carriers *and* Intron 7 GG vs Intron 7 GC	ApoCIII HDL-c LDL-c TG Total-c	
Roke and Mutch, 2014 (55)	Single-Arm Clinical Trial	Single SNP	Men aged 18-25 years (n=12)	12 weeks (+8 week washout)	*FADS1,* rs174537 *FADS2,* rs174576 (LD=1.0 therefore presented results for rs174537)	*FADS1/2:* 11q12.2	Fish oil containing 1.8 g/d EPA+DHA (supplement)	Major allele homozygotes vs. Minor allele carriers	HDL-c LDL-c TG Total-c Total-c:HDL-c	--
Rudkowska et al. 2014 (56)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (*n*=210)	6 weeks	*SCD1,* rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	*SCD1 :* 10q24.31	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	HDL-c LDL-c TG Total-c Total-c:HDL-c	**TG:** For *SCD1* rs508384, AA genotype was associated with lower TG than CA and CC genotypes both pre- and post-supplementation.
Rudkowska et al. 2014 (57)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Healthy men and women aged 18-50 (*n*=141) + Replication of GRS in FINGEN study (n=310)	6 weeks	Genetic Risk Score including: *IQCJ-SCHIP1* (4 SNPs), *SLIT2* (3 SNPs), *PHF17* (3 SNPs), *MYB* (1 SNP), *NXPH1* (1SNP), *NELL1* (1SNP) [outlined in Supplementary Table 5]	*IQCJ-SCHIP1:* 3q25.32 *SLIT2:* 4p15.31 *PHF17:* 4q28.2 *MYB:* 6q23.3 *NXPH1:* 7p21.3 *NELL1:* 11p15.1	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Responders versus non-responders (i.e. TG response) to supplementation	TG	Thirteen SNPs were associated with TG response to omega-3 supplementation and 10 were used in the GRS calculation. The GRS was significantly associated with TG response. **TG**: The GRS explained 21.5% of the variation in TG response when adjusted for age, sex and BMI. Replication of this GRS in the FINGEN study: the GRS explained 2.0% of the TG change but the association as NS (adjusted for age, sex and BMI).
Scorletti et al. 2015 (58)	Randomized, Placebo-Controlled, Double-Blind Intervention	Single SNP	Men and women with non-alcoholic fatty liver disease (n=95)	15-18 months	*PNPLA3, I148M (rs738409) TM6SF2, E167K (rs58542926)*	*PNPLA3:* 22q13.31 *TM6SF2:* 19p13.11	1.8 g/day EPA+ 1.5 g/day DHA (supplement)	Comparison between three genotypes *and* Major allele homozygotes vs. Minor allele carriers	TG	--
Thifault et al. 2013 (59)	Single-Arm Clinical Trial	Single SNP*	Healthy men and women with overweight or obesity aged 18-50 (*n*=210)	6 weeks	*APOE*, rs429358, rs7412	*APOE:* 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	*APOE*-E2 vs. *APOE*-E3 vs. *APOE*-E4	apoB HDL-c LDL-c TG Total-c	--
Tremblay et	Single-Arm	Single SNP	Healthy men	6 weeks	*PLA2G2A* (5	*PLA2G2A:*	Fish oil containing	Major allele	apoB-100	**TG:** omega-3 supplementation significantly reduced TG in

al. 2015 (60)	Clinical Trial		and women aged 18-50 years (*n*=208)		SNPs), *PLA2G2C* (6 SNPs), *PLA2G2D* (8 SNPs), *PLA2G2F* (6 SNPs), *PLA2G4A* (22 SNPs), *PLA2G6* (5 SNPs), *PLA2G7* (9 SNPs) [outlined in Supplementary Table 5]	1p36.13 *PLA2G2C*: 1p36.13 *PLA2G2D*: 1p36.12 *PLA2G2F*: 1p36.12 *PLA2G4A:* 1q31.1 *PLA2G6:* 22q13.1 *PLA2G7:* 6p12.3	1.9 g/d EPA + 1.1 g/d DHA (supplement)	homozygotes vs. Minor allele carriers *or* Comparison between three genotypes (depending on allele frequencies)	HDL-c LDL-c TG Total-c	*PLA2G7* rs1805018 as well as *PLA2G4A* rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689, *PLA2G4A* rs 10752979 and rs1160719 together explained 5.9% of post-supplementation TG levels
Vallée Marcotte et al. 2016 (61)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Men and woman aged 18-50 years (*n*=208)	6 weeks	*IQCJ* (16 SNPs), *NXPH1* (34 SNPs), *PHF17* (8 SNPs), *MYB* (9 SNPs) [outlined in Supplementary Table 5]	*IQCJ:* 3q25.32 *NXPH1:* 7p21.3 *PHF17:* 4q28.2 *MYB:* 6q23.3	Fish oil containing 1.9-2.2 g/d EPA + 1.1 g/d DHA (supplement)	Comparison between three genotypes	TG	**TG:** Significant gene-diet interaction on TG levels pre- vs. post-supplementation for the following SNPs: *IQCJ* (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), *NXPH1* (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), *MYB* (3 SNPs: rs9321493, rs11154794, rs210962). Four SNPs were still significant after applying the false discovery rate to account for multiple testing: rs1449009, rs2621309, rs61332355 in *IQCJ*; rs7805772 in *NXPH1*. There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in *IQCJ*, rs7805772 in *NXPH1* and rs11154794 in *MYB*. Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for *IQCJ* rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, *NXPH1* rs7806226, rs7805772, *MYB* rs11154794 and rs210936.
Vallée Marcotte et al. 2019 (62)	Single-Arm Clinical Trial (replication of GRS in a novel cohort)	Nutrigenomic GWAS	Healthy adults of Mexican descent aged 18-40 years (n=191)	6 weeks	Genetic Risk Score including 103 SNPs: [outlined in Supplementary Table 5]	NA	Fish oil containing 1.9 g/day EPA + 0.8 g/day DHA (supplement)	Responders versus non-responders (i.e. TG response) to supplementation	TG	**TG:** A first 7-SNP GRS [SNPs selected based on previously developed GRS (57,61)] did not explain TG variation. A second GRS calculated from 103 SNPs significantly explained 4.4% of TG variation. A third GRS including the 5 most relevant SNPs significantly explained 11.0% of TG variation (*NXPH1* rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and *IQCJ-SCHIP1* rs2595241). When subjects with the lowest TG change were not included, this third GRS explained more TG variation. Including only the 28 responders and 28 non-responders with the greatest TG variation, this third GRS explained 29.1% of TG variation.
Vallée Marcotte et al. 2019 (63)	Single-Arm Clinical Trial	Nutrigenomics GWAS (polygenic)	Men and woman aged 18-50 years with overweight or obesity (*n*=208)	6 weeks	GWAS; GRS included 31 SNPs [outlined in Supplementary Table 5]	NA	Fish oil containing 1.9-2.2g/d EPA + 1.1g/d DHA (supplement)	Responders to omega-3 supplementation for TG reduction vs. Non-Responders	TG	**TG:** 31 SNPs associated with TG response to omega-3 supplementation and used in GRS calculation; Lower GRSs were significantly more responsive to omega-3 supplementation for TG reduction compared to higher GRS (GRS accounted for 49.7% of TG responses); These findings were replicated in the FINGEN study with 23 SNPs (GRS accounted for 3.7% of TG responses).
Vallée Marcotte et al. 2020 (64)	Double-Blind, Randomized, Controlled, Crossover Intervention	Nutrigenomics GWAS (polygenic)	Men and women with abdominal obesity and elevated CRP aged 18-70	10 weeks per diet	GRS included 30 SNPs [outlined in Supplementary Table 5]	NA	Control oil: 3 g/d corn oil Pure EPA: 2.7 g/d Pure DHA: 2.7 g/d (supplement)	Responders to different types of omega-3 supplementation for TG reduction vs.	TG	**TG:** The GRS was significantly associated with responsiveness to EPA for TG reduction when comparing responders vs. non-responders vs. adverse responders (trend, p=0.08, for DHA). The GRS was significantly associated with responsiveness to both EPA and DHA for TG reduction when comparing responders vs. adverse responders.

			years (n=122)					Non-Responders vs. Adverse Responders *and* Responders vs. Adverse Responders		
Wu et al. 2014 (65)	Double-Blind, Randomized, Placebo-Controlled, Crossover Intervention	Single SNP	Men and women with moderate risk of CVD (n=84)	8 weeks	*eNOS* Glu298Asp (rs1799983)	*NOS3:* 7q36.1	Fish oil containing 0.9 g/day EPA + 0.6 g/day DHA (supplement)	Major allele homozygotes (GG) vs. Minor allele carriers (GT+TT)	LDL-c HDL-c TG Total-c	--
Zheng et al. 2018 (66)	Double-Blind, Randomized, Controlled Intervention	Single SNP and Polygenic	Men and women with type 2 diabetes aged 35-80 years for men or postmenopausal and 80 years for women (*n*=139)	25 weeks	*CD36,* rs1527483 NOS3, rs1799983 *PPARγ2*, rs1801282	*CD36:* 7q21.11 *NOS3:* 7q36.1 *PPARγ2*: 3p25.2	Fish oil: 2.0 g/d EPA and DHA Flaxseed oil: 2.5 g/d ALA Control oil: corn oil (supplement)	Major allele homozygotes vs. Minor allele carriers and High vs. low genetic score calculated based on three SNPs	HDL-c LDL-c TG Total-c:HDL-c Total-c	**LDL-c:** significant interaction for *PPARγ2* rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of *PPARγ2* rs1801282 compared to CC genotype *only in the control* (corn oil) group **TG:** omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the *CD36* rs1527483 GG genotype (significant interaction); significant interaction between genetic score and omega-3 on TG levels whereby omega-3 (fish oil and flaxseed oil) supplementation significantly reduced TG levels compared to control only in individuals with high genetic scores

ALA: alpha-linolenic acid, Apo: apolipoprotein, DHA: docosahexaenoic acid, EPA: eicosapentaenoic acid, HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, omega-3: omega-3, N/A: not applicable, NS: Non-significant, sdLDL-c: small, dense, low-density lipoprotein cholesterol, SNP: single nucleotide polymorphism, TG: triglycerides

1. All other (not listed) gene/omega-3/lipid/lipoprotein results of interest to the present review were NS

Participants are described as "healthy" for studies that incorporated exclusion criteria for certain conditions, blood lipid levels, etc. and when studies described the population as "healthy."

'--' indicates that all the completed gene/omega-3/lipid/lipoprotein analyses were NS

*Human *APOE* is polymorphic at two single nucleotides (rs429358 and rs7412) resulting in three different alleles (ε 2, ε 3 and ε 4)

Supplementary Table 4: Genes, SNPs, lipid/lipoprotein outcomes and studies included in evidence grading process and guideline development

Gene, SNP(s)	Outcome	Studies
APOE: rs429358, rs7412 (Genotype)	TG	AbuMweis et al. 2018 (24) Carvalho-Wells et al. 2012 (32) Caslake et al. 2008 (34) Dang et al. 2015 (36) Jackson et al. 2012 (41) Olano-Martin et al. 2010 (49) Minihane et al. 2000 (48) Paschos et al. 2005 (52) Thifault et al. 2013 (59)
APOE: rs429358, rs7412	Total-c	Fallaize et al. 2016 (7) AbuMweis et al. 2018 (24) Carvalho-Wells et al. 2012 (32) Caslake et al. 2008 (34) Dang et al. 2015 (36) Jackson et al. 2012 (41) Olano-Martin et al. 2010 (49) Paschos et al. 2005 (52) Thifault et al. 2013 (59)
PPARγ2: rs1801282	LDL-c	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
PPARγ2: rs1801282	Total-c	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
PPARγ2: rs1801282	TG	Binia et al. 2017 (27) Harsløf et al. 2014 (39) Itariu et al. 2012 (40) Lindi et al. 2003 (43) Zheng et al. 2018 (66)
CD36: rs1761667	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1761667	TG	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1049673	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
CD36: rs1527483	TG	Madden et al. 2008 (45) Zheng et al. 2018 (66)
FADS: rs174547*	Total-c	Dumont et al. 2011 (5) Dumont et al. 2018 (6) Lu et al. 2010 (17) Standl et al. 2012 (20) Alsaleh et al. 2014 (25) AbuMweis et al. 2018 (24) Roke et al. 2014 (55)
31-SNP Genetic Risk Score	TG	Vallée Marcotte et al. 2019 (67) Vallée Marcotte et al. 2020 (64)

Supplementary Table 5: Additional list of gene(s) and SNP(s) tested in studies

Study	*Gene(s)*, SNP(s)
Chen et al. Int J Obes;43:808-820 (2019)	*FADS2,* rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276 *FADS3,* rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285 *RAB3IL1,* rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252
Cormier et al. 2012	*FADS* gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567
Vallée Marcotte et al. Am J Clin Nutr;109:176–185 (2019)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Tremblay et al. Lipids in Health and Disease (2015) 14:12	*PLA2G2A*, rs876018, rs955587, rs3753827, rs11573156, rs11573142 *PLA2G2C*, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718 *PLA2G2D*, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671 *PLA2G2F*, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904

	PLA2G4A, rs979924, rs2076075, rs3736741, rs10911949, rs10752979, rs1160719, rs10737277, rs12720702, rs7522213, rs7540602, rs10157410, rs12720497, rs4651331, rs1569480, rs10911935, rs12353944, rs11576330, rs10489410, rs10911946, rs3820185, rs12746200, rs11587539 *PLA2G6*, rs5750546, rs132989, rs133016, rs2235346, rs2284060 *PLA2G7*, rs12195701, rs12528807, rs1421368, rs1421378, rs17288905, rs1805017, rs1805018, rs6929105, rs7756935
Ouellette et al. J Nutrigenet Nutrigenomics;6:268–280 (2013)	*GPAM*, rs17129561, rs10787428, rs2792751 *AGPAT3*, rs999519, rs2838440, rs2838445, rs2838458, rs4818873, rs9978441, rs9982600, rs11700575, rs17004619, rs2838452, rs2838456, rs3788086, rs2838429 *AGPAT4*, rs746731, rs747866, rs1125640, rs2277092, rs2293286, rs3757025, rs3798225, rs3798920, rs3798924, rs3798929, rs3798943, rs3798945, rs3822853, rs3823058, rs4709501, rs6906489, rs6923835, rs7750302, rs7769321, rs9458172, rs10945713, rs10945719, rs11965825, rs12202278, rs17627837, rs12524665, rs1001422, rs6455711, rs9456642, rs2064721, rs3778227, rs3798922, rs11967514, rs7768457, rs12662114
Ouellette et al. Lipids in Health and Disease, 13:86 (2014)	*MGLL,* rs782440, rs16826716, rs6776142, rs9877819, rs555183, rs6780384, rs13076593, rs605188, rs6765071, rs782444, rs549662, rs3773155, rs541855, rs6439081, rs6439082, rs6787155, rs1466571, rs893294
Bouchard-Mercier et al. Genes Nutr 9:395 (2014)	*GCK,* rs2268573, rs2908297, rs2971676, rs758989, rs12673242, rs2908290, rs2284777, rs2300584, rs1990458, rs741038, rs1799884, rs2908277, rs3757838
Bouchard-Mercier et al. Nutrients, 6, 1145-1163 (2014)	*RXRA*, rs10881576, rs7871655, rs12339187, rs11185660, rs11103473, rs10776909, rs12004589, rs3132301, rs1805352, rs3132294, rs1805343, rs1045570 *CPT1A*, rs3019598, rs897048, rs7942147, rs4930248, rs11228364, rs11228368, rs10896371, rs1017640, rs613084 *ACADVL*, rs2017365 *ACAA2*, rs529556, rs10502901, rs631536, rs1942421, rs2276168, rs7237253 *ABCD2*, rs4072006, rs10877201, rs12582802, rs4294600, rs11172696, rs10877173, rs7133376, rs7968837 *ACOX1*, rs10852766, rs3744033, rs12430, rs8065144,

	rs11651351, rs3643, rs7213998, rs17583163 *ACAA1*, rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	*CETP*, rs3764261, rs247616, rs7205804 *LIPC*, rs1532085 *APOB*, rs1367117 *ABCG5, ABCG8*, rs4299376 *TIMD4, HAVCR1*, rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 *ANGPTL3, DOCK7*, rs3850634, rs1167998, rs2131925 *FADS1, FADS2, FADS3*, rs174550, rs174547, rs174546, rs174583 *GALNT2*, rs4846914, rs1321257 *ABCA1,* rs4149268 *APOE, APOC1, APOC2,* rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	*IQCJ-SCHIP1*, rs7639707, rs62270407 NXPH1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 *PHF17*, rs1216346, rs114348423, rs75007521 *MYB,* rs72560788, rs72974149, rs210962, rs6933462 *NELL1*, rs79624996, rs1850875, rs78786240, rs117114492 *SLIT2,* rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	*IQCJ-SCHIP1, MYB, NELL1, NXPH1, PHF17, SLIT2,* rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	*IQCJ*, rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	NXPH1, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs12537067, rs4318981, rs17153997, rs7801099, rs4725120, rs1859275, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862 PHF17, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308
Vallée Marcotte et al. Nutrients; 11, 737 (2019)	*IQCJ-SCHIP1*, rs12497650, rs4501157, rs13091349, rs2044704, rs1962071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs1449009, rs61332355, rs12485627, rs2595242, rs7639937, rs9820807, rs1375409, rs1967363, rs9824310, rs11915303, rs9835214, rs11921343, rs13066560, rs1675497, rs9839862, rs16829875, rs17795566, rs9860588, rs16830408, rs17798579, rs2364930, rs9865997, rs2595241, rs7632574, rs2621308 *NXPH1*, rs6956210, rs2107779, rs10273195, rs12216689, rs6963644, rs17150341, rs1013868, rs4318981, rs17153997, rs7801099, rs4725120, rs10238726, rs1012960, rs11767429, rs4333500, rs7793115, rs7799856, rs7806226, rs13221144, rs17406479, rs10486228, rs17154569, rs4141002, rs7805772, rs2349780, rs2107474, rs11769942, rs6952383, rs6974252, rs10265408, rs2189904, rs2057862, rs6463808 *PHF17*, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365 *MYB*, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, *SLIT2,* rs2952724 *NELL1*, rs752088

Supplementary Table 6: 31-SNP Nutri-GRS

***Gene,* rs Number**	**Alleles[1]**	**Associated Points**
IQCJ-SCHIP1, rs7639707	A/G	+1
IQCJ-SCHIP1, rs62270407	C/T	-1
NXPH1, rs61569932,	G/T	+1
NXPH1, rs1990554	A/C	+1
NXPH1, rs6463808	A/G	+1
NXPH1, rs6966968	A/G	+1
NXPH1, rs28473103	A/G	-1
NXPH1, rs28673635	A/G	+1
NXPH1, rs12702829	C/T	+1
NXPH1, rs78943417	A/T	-1
NXPH1, rs293180	G/T	+1
NXPH1, rs1837523	C/T	-1
PHF17, rs1216346	C/T	+1
PHF17, rs114348423	A/G	+1
PHF17, rs75007521	G/T	-1
MYB, rs72560788	C/T	-1
MYB, rs72974149	A/G	-1
MYB, rs210962	C/T	-1
MYB, rs6933462	C/G	+1
NELL1, rs79624996	A/G	+1
NELL1, rs1850875	C/T	+1
NELL1, rs78786240	C/T	-1
NELL1, rs117114492	G/T	+1
SLIT2, rs184945470	C/T	+1
SLIT2, rs143662727	A/G	-1
SLIT2, rs10009109	C/T	+1
SLIT2, rs10009535	A/G	+1
SLIT2, rs61790364	A/G	+1
SLIT2, rs73241936	C/T	+1
SLIT2, rs16869663	A/G	+1
SLIT2, rs76015249	A/G	+1

1. Minor alleles are underlined

For individuals carrying one or two minor alleles, provide the associated number of points (either +1 or -1). For individuals homozygous for the major allele, provide 0 points. Count the overall number of points. Individuals with lower nutri-GRS are more likely to respond to approximately 3.0 g/day EPA+DHA for TG lowering.

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Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5, 7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. T1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8-9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

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Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	NA (meta-analysis not appropriate)

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Table 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	11-12
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Tables 1 and 2
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 4
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Tables 1 and 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	NA
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	11-12, Table 3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Table 3, 34-39
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	45-46
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	40-47
FUNDING			

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Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	47

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