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

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

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19 **404676)**

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

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

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

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

29 ABSTRACT

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

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

44 **Results:** Out of 1830 articles screened, 65 met the inclusion criteria ($n=23$ observational,
45 $n=42$ interventional); of these, 25 met the criteria for evidence evaluation using GRADE.
46 Overall, current evidence is insufficient for gene-diet associations related to omega-3
47 fatty acid intake on plasma apolipoproteins, total cholesterol, HDL-cholesterol, LDL-
48 cholesterol and LDL particle size. However, there is strong (GRADE rating: moderate
49 quality) evidence to suggest that male *APOE*-E4 carriers (rs429358, rs7412) exhibit
50 significant triglyceride reductions in response to omega-3-rich fish oil with a dose-
51 response effect. Moreover, strong (GRADE rating: high quality) evidence suggests that a
52 31-SNP nutrigenetic risk score can predict plasma triglyceride responsiveness to omega-
53 3-rich fish oil in adults with overweight/obesity from various ethnicities.

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

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

59 STRENGTHS AND LIMITATIONS

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

66 INTRODUCTION

67
68 Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research
69 demonstrates that there is significant inter-individual variability in cardiometabolic risk
70 factor levels, in part based on a combination of genetic and nutrition-related risk factors
71 (2,3). Consumers indicate great interest in personalized nutrition based on genetics (4,5),
72 however, a lack of industry oversight (6,7) has led to highly variable scientific validity of
73 nutrigenetic tests available to consumers. While recognizing that some groups question
74 whether genetic testing for personalized nutrition is ready for ‘prime time’, Gorman and
75 colleagues suggested that there are certain specific nutrigenetic interactions with strong
76 evidence that could be considered for implementation into clinical practice by expert
77 committees who are responsible for creating dietary guidelines (8). With this in mind,
78 systematic reviews that include an evaluation of levels of evidence are urgently needed in
79 order to determine if there are any nutrigenetic associations that may warrant potential
80 implementation into practice.

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

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3 89 suggests that long-chain omega-3s (EPA and DHA) reduce plasma TG by about 15%
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5 90 (13). There is also high-quality evidence suggesting that EPA and DHA can raise high-
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7 91 density lipoprotein (HDL) cholesterol (13). Some studies have further demonstrated an
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9 92 effect of omega-3 on HDL-cholesterol (14), low-density lipoprotein (LDL)-cholesterol
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11 93 (14), total cholesterol (15–17), apolipoproteins (18), and LDL particle size (19). Despite
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13 94 several studies with significant findings for these outcomes, when reviewing the
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15 95 evidence, studies have demonstrated conflicting results for the impact of omega-3 on
16
17 96 many lipid profile outcomes (13). Genetic variation could explain this heterogeneity.
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19 97 EPA and DHA have been shown to significantly impact the expression of thousands of
20
21 98 genes including those involved in inflammatory and atherogenic pathways (20,21).
22
23 99 Evidence now demonstrates that the health impacts of omega-3 intake could differ based
24
25 100 on genetic variation (22,23). Despite the potential for omega-3s to have a significant
26
27 101 positive impact on health outcomes, population intakes of omega-3s tend to be low (24).
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29 102 While the World Health Organization's Adequate Intake level for adults is 200-250 mg
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31 103 EPA+DHA daily (25,26), the mean reported intake of EPA+DHA in the United States is
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33 104 only approximately 100 mg daily (24). Nutrigenetic interventions have the potential to
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35 105 motivate improvements in dietary intake beyond population-based interventions (27).
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37 106 Additionally, evidence suggests that genetic variability affects health responses to
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39 107 omega-3s (22). Thus, critically appraising and grading the evidence for nutrigenetic
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41 108 interactions related to omega-3s and plasma lipids, lipoproteins and apolipoproteins is an
42
43 109 important research priority. The most recent systematic review on nutrigenetic
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45 110 interactions related to omega-3s and intermediate phenotypes of cardiovascular disease
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47 111 was conducted nearly a decade ago, and this study did not evaluate the quality of
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3 112 evidence using an established methodology (28). Therefore, we aimed to provide a
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5 113 comprehensive summary of current evidence related to inter-individual variability in
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7 114 plasma lipid, lipoprotein and apolipoprotein responses to omega-3 intake (plant and
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9 115 marine sources) based on genetic variations. Overall, the specific objective of this study
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11 116 was to: systematically search, identify (select), summarize, synthesize and assess the
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13 117 quality of evidence for gene-diet effects on cardiometabolic risk factors - more
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15 118 specifically, plasma lipid, lipoprotein and apolipoprotein responsiveness to omega-3s.
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20 119 **Methods**

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22 121 **Patient and Public Involvement:** No patient involvement.
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24 122 *Literature Search*

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28 123 The systematic review protocol was registered with PROSPERO (CRD42020185087).
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30 124 The review process was guided by previously established methods, including a
31
32 125 previously outlined five-step systematic review process (29,30). The search engines
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34 126 Embase, Web of Science and Medline OVID were used to conduct the search and screen
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36 127 for articles meeting inclusion criteria, using the comprehensive search terms outlined in
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38 128 Supplementary Table 1, properly combined by Boolean operators. The literature was
39
40 129 searched up until August 1, 2020. A PRISMA diagram (Figure 1) guided the article
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42 130 screening process (31).
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48 131 *Inclusion and Exclusion Criteria*

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51 132 Original studies were included if they were written in English or French. Inclusion
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53 133 criteria were developed using the Population, Intervention, Comparison, Outcomes,
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55 134 (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (32,33) for
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3 135 interventional and observational research, respectively. There were no limitations to the
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5 136 population characteristics (all populations/patient samples were included). Animal studies
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8 137 were excluded. Dietary interventions and observational studies involving omega-3s (total
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10 138 omega-3 or various types; supplemental and/or dietary intake) and comparing lipid and/or
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12 139 lipoprotein and/or apolipoprotein outcomes between different genetic variations based on
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15 140 omega-3 dietary or supplemental intake (and not blood fatty acid levels; e.g. EPA and
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17 141 DHA in red blood cells) were included. In included studies, samples had to be stratified
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19 142 on the basis of genetic variation. Specific lipid and lipoprotein outcomes of interest were:
20
21 143 HDL-cholesterol, LDL-cholesterol, LDL particle size, total cholesterol, apolipoproteins,
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23 144 and triglycerides (TG). Studies that reported ratios of the aforementioned lipid parameters
24
25 145 (e.g. HDL-cholesterol to total cholesterol ratio) were also included. Both observational
26
27 146 and interventional studies were included, as well as single-gene, polygenic and genome-
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29 147 wide association studies (GWAS). Differences in study designs and methods were
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31 148 considered when developing the overall evidence grades, as further detailed below.
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36 149 *Article Selection and Data Extraction*

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40 150 Two independent investigators (JH and VG) screened articles using the computer
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42 151 software *Covidence* (including title, abstract, and full-text screening) and extracted data
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44 152 from the included articles. Reference lists of included articles and of a systematic review
45
46 153 on a similar topic (34) were also screened for relevant articles. Data extraction templates
47
48 154 were piloted by two independent investigators (JH and VG) on ten included studies and
49
50 155 revised accordingly. The final data extraction templates included the following
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52 156 components for each study: first author name and year, study design, genetic approach,
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54 157 population and sample size, study duration (interventional studies only), genes and single
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3 158 nucleotide polymorphisms (SNPs) analyzed with rs numbers, quantity and type of
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5 159 omega-3, comparisons (e.g. a control group or different amount/type of omega-3s as well
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8 160 as genetic grouping), lipid/lipoprotein outcome(s), whether or not the study reported that
9
10 161 they followed STREGA guidelines and a summary of statistically significant study
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12 162 findings relevant to the research question. Corresponding authors of included studies
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14 163 were contacted as needed to provide clarity and/or additional information about the
15
16 164 included studies.

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20 165 *Evidence Grading*

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23 166 Upon reading all full-text articles included, and summarizing the body of evidence,
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25 167 SNPs/nutrigenetic risk scores (nutri-GRSs) and subsequent
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27 168 lipid/lipoprotein/apolipoprotein outcomes were systematically selected for evidence
28
29 169 grading based on the following predetermined replication criteria: statistically significant
30
31 170 nutrigenetic results for the same SNP(s)/nutri-GRS [or SNPs in strong linkage
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33 171 disequilibrium (LD)] and lipid/lipoprotein outcome in at least two studies. The Grading
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35 172 of Recommendations Assessment, Development and Evaluation (GRADE) approach
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37 173 indicates that a single study rarely (if ever) results in strong evidence, but two studies
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39 174 (typically RCTs) can indicate strong evidence if they are graded highly using the
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41 175 GRADE criteria (35). Prior to selecting the genetic variants and
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43 176 lipid/lipoprotein/apolipoprotein outcomes for evidence grading, LD was assessed using
44
45 177 the SNIPA SNP Annotator Software (36) for genes located on the same chromosome and
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47 178 arm (determined using the Online Mendelian Inheritance in Man® [OMIM] database) as
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49 179 outlined in the summary of results' tables in the column labelled 'Cytogenic Location of
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51 180 Gene(s)' (Tables 1 and 2). Strong LD was defined as $r^2 > 0.8$ and location < 250 kb away
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3 181 from the index SNP location. SNPs in strong LD were considered together for the
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5 182 purposes of evidencing grading.
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9 183 Based on our abovementioned predetermined criteria for study selection for evidence
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11 184 grading, SNPs that were not included in the evidence grading process likely have weak
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13 185 evidence (at minimum due to lack of replication). According to the GRADE guidelines,
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15 186 when only a single study exists indicating significant findings for an outcome of interest
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17 187 (especially when the study is observational), the overall quality of the evidence is
18
19 188 generally rated to be low or very low (37). Therefore, our study selection prioritization
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21 189 process aimed to filter out evidence that would be deemed low or very low quality. Two
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23 190 authors (JH and VG) critically appraised the selected nutrigenetic interactions using the
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25 191 GRADE methodology (37,38). Nutrigenetic interactions were grouped according to
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27 192 studies assessing the same SNP(s)/nutri-GRS and lipid/lipoprotein/apolipoprotein
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29 193 outcome, and the quality of the body of evidence was rated; this process was guided by
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31 194 the GRADE Evidence Profile, which included consideration of risk of bias,
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33 195 inconsistency, indirectness, imprecision, publication bias, plausible confounding, dose-
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35 196 response and other factors (37). For example, different sources of omega-3s (e.g.
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37 197 EPA+DHA vs. ALA; food sources vs. supplementation) were taken into consideration
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39 198 when grading the evidence through the analysis of indirectness within the GRADE
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41 199 approach (37,38). Risk of bias was assessed in each of the included interventional and
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43 200 observational studies using the National Institutes of Health Study Quality Assessment
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45 201 Tools, in line with recently published recommendations for risk of bias assessments (39).
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47 202 To assess measures of precision, coefficients of variation (CV) were calculated based on
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49 203 outcome means (mean change or absolute values – whichever was used for the analyses)
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3 204 and standard deviations. In cases where standard errors of the mean were reported, these
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5 205 were converted to standard deviation to calculate the CV. The nutrigenetic interactions
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8 206 were each given an evidence grade of high, moderate, low or very low.
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11 207 **Results**

12 208
13 209 Figure 1 outlines the PRISMA Flow Diagram, which was used to guide the systematic
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16 210 review. Tables 1 and 2 provide a summary of the 65 included studies. The results
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18 211 columns of Tables 1 and 2 (far right) indicate only nutrigenetic findings that were
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20 212 statistically significant. Any results related to the studies' analyzed SNPs and outcomes
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22 213 of interest that were not statistically significant are not indicated in the results column.
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24 214 No studies explicitly reported that they followed STREGA guidelines. LD analysis of
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26 215 SNPs tested in different studies revealed strong LD in several SNPs from the *FADS* gene
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28 216 cluster (see Table 3 footnote). As such, LD was taken into consideration in the selection
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30 217 of nutrigenetic interactions selected for evidence grading.
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35 218 *Observational Studies*

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38 219 Of the 65 included studies, 23 were observational with the majority of these being cross-
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40 220 sectional, as outlined in Table 1. A total of 62,221 participants were included in the
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42 221 observational studies. These studies assessed correlations among a number of different
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44 222 genetic variations and outcomes, with several studies assessing genetic variations in the
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46 223 *FADS* gene cluster (40–46), *TNF α* (47–49) and *PPAR α* (50–52). Most studies (n=13)
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48 224 assessed total omega-3s (40,45–47,49,52–59). The intake and type of omega-3s,
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51 225 lipid/lipoprotein/apolipoprotein outcomes and associations revealed from these studies
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54 226 were variable as further detailed in Table 1. In the observational studies assessing genetic
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3 227 variation in the *FADS* gene cluster, some studies indicated significant gene-diet findings
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5 228 related to HDL-cholesterol, LDL-cholesterol, TG, total-cholesterol while other studies
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8 229 demonstrated no significant gene-diet interactions for these outcomes thus indicating
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10 230 notable inconsistency among the results, while considering that SNPs differed by studies
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12 231 (40–46). In the observational studies focused on genetic variation in the *TNF α* gene, there
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15 232 was some evidence of a gene-diet relationship for omega-3 and LDL-cholesterol, total-
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17 233 cholesterol and total-cholesterol:HDL-cholesterol ratio, but again, results differed
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19 234 between studies (47–49). For gene-diet relationships and *PPAR α* genetic variation,
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21 235 individual studies indicated significant findings related to total-cholesterol, LDL-
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23 236 cholesterol, TG, apoC-III and LDL peak particle diameter (50–52). Comprehensive
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26 237 details of the observational studies are outlined in Table 1.
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29 238 *Interventional Studies*

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33 239 Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-
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35 240 randomized studies included single arm clinical trials and sequential non-randomized
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37 241 cross-over interventions. For interventional studies, n=6,225 upon combining all sample
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40 242 sizes of the included studies. Again, these studies assessed relationships between a
41
42 243 number of different genetic variants and study outcomes. In more recent years, several
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44 244 studies (n=8) used a nutri-GRS or polygenic approaches (60–67) given the plausibility
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46 245 that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are polygenic
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48 246 in nature. Numerous studies assessed genetic variations in the *FADS* gene cluster
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51 247 (60,61,68–70), *APOE* (60,70–79), *CD36* (66,80,81), *PPAR γ 2* (61,66,82–84) and *PPAR α*
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53 248 (82,85,86). Among these studies, results related to significant gene-diet (omega-3)
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56 249 associations influencing lipid/lipoprotein outcomes were generally inconsistent except for
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3 250 *APOE* (rs429358 and rs7412), omega-3 and TG in males only (70–74,76–79), and for a
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5 251 31-SNP nutri-GRS, omega-3 and TG (64,65). There was also consistent evidence to
6
7 252 indicate a lack of association among *PPAR* γ 2 (rs1801282) genetic variation, EPA+DHA
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9 253 and LDL cholesterol (61,66,83,84,87). Most studies (n=40) used supplemental EPA
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11 254 and/or DHA sources of omega-3s for the dietary intervention (see Table 2). The
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13 255 dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages
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15 256 ranging from 0.5-3.7 g/day across different studies, and one study with an ALA
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17 257 intervention dosage of 8.1 g/day, as further detailed in Table 2.

22 258 *Levels of Evidence Using GRADE*

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26 259 A total of 25 articles were included in the evidence grading process, representing 11
27
28 260 unique nutrigenetic interactions as outlined in Tables 3 and 4, and Supplementary Table
29
30 261 2. Through the GRADE process, it was determined that there is strong evidence (GRADE
31
32 262 rating: moderate quality) for *APOE* genotypes (rs7412, rs429358), omega-3s and TG
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34 263 lowering in male adults only (70–74,76–79). This evidence suggests that adult males (but
35
36 264 not females) with the *APOE*-E3/E4 or E4/E4 genotype (rs429358, rs7412) tend to
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38 265 experience significant reductions in TG in response to 0.7-3.7 g/day of EPA and/or DHA,
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40 266 with higher dosages demonstrating greater TG lowering effects (70–74,76–79).
41
42 267 Furthermore, it was determined that there is strong evidence (GRADE rating: high
43
44 268 quality) for using a 31-SNP nutri-GRS to assess the effectiveness of omega-3s for TG
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46 269 lowering in adults with overweight/obesity in various ethnicities (64,65). The evidence
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48 270 suggests that in adults with overweight/obesity, lower genetic risk scores demonstrate
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50 271 greater responsiveness to omega-3 supplementation (64,65).
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3 272 All other evidence that was evaluated was determined to be weak (GRADE rating: low or
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5 273 very low quality), as further detailed in Table 3. Imprecision, indirectness, and
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7 274 inconsistency were common reasons for downgrading the evidence (refer to Table 3
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10 275 footnote). There was evidence for a plausible mechanism of action for most of the
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12 276 nutrigenetic interactions that were graded; evidence of a dose response was less common.
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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)	<i>PPARα</i> , L162V (rs1800206) <i>PPARγ</i> , P12A (rs1801282) <i>PPARδ</i> , -87T→C (rs2016520)	<i>PPARα</i> : 22q13.31 <i>PPARγ</i> : 3p25.2 <i>PPARδ</i> : 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 <i>PPARα</i> L162V (rs1800206) polymorphism, the interaction of <i>PPARα</i> L162V 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)	<i>MC4R</i> , rs17782313 <i>TCF7L2</i> , rs12255372 <i>TCF7L2</i> , rs7903146	<i>MC4R</i> : 18q21.32 <i>TCF7L2</i> : 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 <i>TCF7L2</i> 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 <i>FADS1-FADS2-FADS3</i> gene cluster and variation within the 200kb upstream and downstream of the <i>FADS</i> region	<i>FADS1</i> : 11q12.2 <i>FADS2</i> : 11q12.2 <i>FADS3</i> : 11q12.2	High : >1.6 g/day Low : <1.6 g/day (food)	Entire <i>FADS</i> region gene-centric analysis and Variation in individual <i>FADS</i> 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 <i>FADS</i> 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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	<i>FADS1</i> ,	<i>FADS1</i> : 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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)	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E4- vs. <i>APOE</i> -E4+	Total-c	Total-c: Cross-sectional (baseline) analysis demonstrated a significant genotype effect for <i>APOE</i> , omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for <i>APOE</i> , 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)	<i>TNFα</i> , rs361525, rs1800629	<i>TNFα</i> : 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)	<i>NF-κB</i> -94Ins/Del ATTG (rs28362491)	<i>NF-κB</i> : 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 <i>NF-κB</i> 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)	<i>FADS</i> , rs174547	<i>FADS</i> : 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 <i>FADS</i> 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)	TNFA, rs1800629	TNFA: 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 TNFA, 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)	TNFA, rs361525	TNFA: 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 TNFA, 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 TNFA 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 TNFA 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: 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 <i>IL-6</i> rs1800795 CC genotypes and <i>IL-6</i> rs1554606 TT genotypes, increasing DHA intake in <i>IL-6</i> rs1800795 CC genotypes, and increasing ALA intake in <i>IL-6</i> rs1554606 TT genotypes.
Lai et al. 2006 (99)	Cross-Sectional	Single SNP	Men and women from the Framingham Heart Study (n=2148)	<i>APOA5</i> , rs662799, rs651821, rs3135506, rs2072560, rs2266788	<i>APOA5</i> : 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)	<i>FADS</i> , rs174546, rs482548, rs174570	<i>FADS</i> : 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)	<i>ANGPTL4</i> E40K (rs116843064)	<i>ANGPTL4</i> : 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)	<i>PLIN4</i> , rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	<i>PLIN4</i> : 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 <i>PLIN4</i> , 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)	<i>FADS1/FADS2</i> , rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	<i>FADS1/2</i> : 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)	<i>PPARα</i> , L162V (rs1800206)	<i>PPARα</i> : 22q13.31	High : >0.69 %kcal Low : <0.69 %kcal (food)	<i>PPARα</i> : 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)	<i>PPARα</i> , L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	<i>PPARα</i> : 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 <i>PPARα</i> (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)
Warodomwich et al. 2009 (105)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	<i>TCF7L2</i> rs7903146, rs12255372	<i>TCF7L2</i> : 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	<i>FADS1</i> , rs174561 <i>FADS2</i> , rs174583 <i>ELOVL2</i> , rs953413 <i>ELOVL5</i> , rs2397142 <i>CETP</i> , rs5882 <i>SCD1</i> , rs2234970, <i>PPARα</i> , rs6008259 <i>LIPF</i> , rs814628 and <i>APOE</i> , rs429358, rs7412	<i>FADS1/2</i> : 11q12.2 <i>ELOVL2</i> : 6p24.2 <i>ELOVL5</i> : 6p12.1 <i>CETP</i> : 16q13 <i>SCD1</i> : 10q24.31 <i>PPARα</i> : 22q13.31 <i>LIPF</i> : 10q23.31 <i>APOE</i> : 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except <i>PPARA</i> and <i>LIPF</i> whereby analyses were major allele homozygotes vs. minor allele carriers) and <i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -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	<i>CETP</i> , rs3764261, <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5/ABCG8</i> , rs4299376 <i>TIMD4/HAVCR1</i> , rs6882076 <i>GCKR</i> , rs1260326 <i>TRIB1</i> , rs2954029 <i>ANGPTL3/DOCK7</i> , rs2131925 <i>FADS1/2/3</i> , rs174546 <i>GALNT2</i> , rs4846914 <i>ABCA1</i> ,	<i>CETP</i> : 16q13 <i>LIPC</i> : 15q21.3 <i>APOB</i> : 2p24.1 <i>ABCG5/ABCG8</i> : 2p.21 <i>TIMD4/HAVCR1</i> : 5q33.3 <i>GCKR</i> : 2p23.3 <i>TRIB1</i> : 8q24.13 <i>ANGPTL3/DOCK7</i> : 7: 1p31.3 <i>FADS</i> : 11q12.2 <i>GALNT2</i> : 1q42.13 <i>ABCA1</i> : 9q31.1 <i>APOE/APOC1/APOC2</i> : 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 <i>FADS1</i> rs174546

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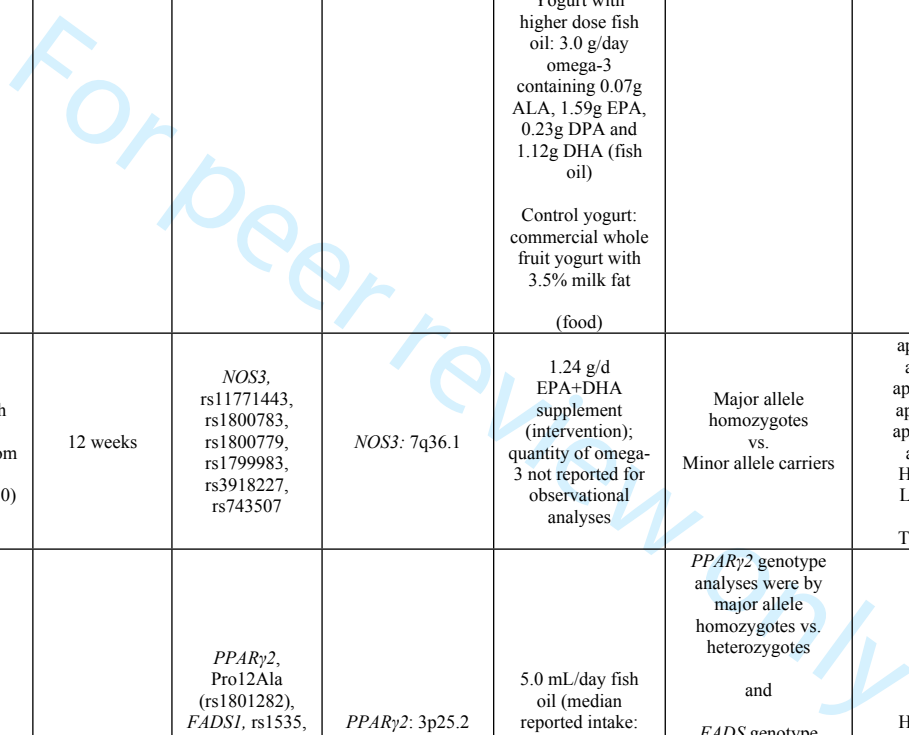
					rs4149268 <i>APOE/APOC1/</i> <i>APOC2,</i> rs439401					
Armstrong et al. 2012 (107)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	<i>ALOX5</i> , dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	<i>ALOX5</i> : 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	<i>PPARα</i> , L162V (rs1800206), <i>PPARγ2</i> , P12A (rs1801282)	<i>PPARα</i> : 22q13.31 <i>PPARγ2</i> : 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 (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> Pro12Pro genotypes only for individuals with BMI>25.0 kg/m ² Total-c : significant increase in total-c among minor allele carriers (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> 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	<i>SREBF1</i> , rs4925115, rs4925118, rs12953299 <i>ACLY</i> , rs8071753, rs8065502, rs2304497 <i>ACACA</i> rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	<i>SREBF1</i> : 17p11.2 <i>ACLY</i> : 17q21.2 <i>ACACA</i> : 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 <i>ACLY</i> rs8071753 and individuals with the GG or CG genotype of <i>ACACA</i> 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 <i>ACLY</i> 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	<i>RXRA</i> (12 SNPs), <i>CPT1A</i> (9 SNPs), <i>ACADVL</i> (1 SNP), <i>ACAA2</i> (6 SNPs), <i>ABCD2</i> (8 SNPs), <i>ACOX1</i> (8 SNPs), <i>ACAA1</i> (3 SNPs) [outlined in Supplementary	<i>RXRA</i> : 9q34.2 <i>CPT1A</i> : 11q13.3 <i>ACADVL</i> : 17p13.1 <i>ACAA2</i> : 18q21.1 <i>ABCD2</i> : 12q12 <i>ACOX1</i> : 17q25.1 <i>ACAA1</i> : 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 <i>RXRA</i> rs11185660 genotype dependent on total fat intake, <i>RXRA</i> rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and <i>ACOX1</i> rs17583163 dependent on total polyunsaturated fat intake

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Table 2]										
5	6	7	8	9	10	11	12	13	14	15
Bouchard-Mercier et al. 2014 (110)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	<i>GCK</i> (13 SNPs) [outlined in Supplementary Table 3]	<i>GCK</i> : 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 <i>GCK</i> 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.
13	14	15	16	17	18	19	20	21	22	23
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	<i>PPARA</i> , L162V (rs1800206)	<i>PPARA</i> : 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	--
21	22	23	24	25	26	27	28	29	30	31
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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -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 <i>APOE</i> -E3/4 carriers (compared to high-SFA diet alone)
30	31	32	33	34	35	36	37	38	39	40
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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E2/E2 + E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	TG: Significant interaction between treatment x sex x genotype whereby <i>APOE</i> -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
34	35	36	37	38	39	40	41	42	43	44
Cormier et al. 2012 (115)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	<i>FADS</i> gene cluster (19 SNPs) [outlined in Supplementary Table 3]	<i>FADS</i> : 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	--
37	38	39	40	41	42	43	44	45	46	47
Dang et al. 2015 (73)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	<i>APOE</i> -E4+ vs. <i>APOE</i> -E4-	HDL-c LDL-c TG Total-c	--
40	41	42	43	44	45	46	47	48	49	50
Dawczynski et	Randomized,	Single SNP	Men and	10 weeks	<i>CD36</i> ,	<i>CD36</i> : 7q21.11	Yogurt with lower	Comparison between	HDL-c	HDL-c: In response to omega-3 supplementation (0.8-3.0

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al. 2013 (81)	Placebo-Controlled, Double-Blind Intervention		women with TG \geq 1.7 mmol/L, otherwise healthy (n=47)		rs1761667, rs1049673		<p>dose fish oil: 0.8g/day omega-3 containing 0.01g ALA, 0.44g EPA, 0.06g DPA and 0.31g DHA (fish oil)</p> <p>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)</p> <p>Control yogurt: commercial whole fruit yogurt with 3.5% milk fat (food)</p>	three genotypes	TG	g/day), HDL-c increased in GA genotype of <i>CD36</i> rs1761667 and CG genotype of <i>CD36</i> rs1049673. TG: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of <i>CD36</i> 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 <i>NOS3</i> 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	<i>PPARγ2</i> , Pro12Ala (rs1801282), <i>FADS1</i> , rs1535, <i>FADS2</i> , rs174575, <i>FADS3</i> , rs174448 <i>COX2</i> , rs5275, rs689466	<i>PPARγ2</i> : 3p25.2 <i>FADS</i> : 11q12.2 <i>COX2</i> : 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)	<i>PPARγ2</i> genotype analyses were by major allele homozygotes vs. heterozygotes and <i>FADS</i> genotype analyses were by the number of DHA-increasing alleles and <i>COX2</i> genotype analyses were by major allele homozygotes vs.	HDL-c LDL-c TG Total-c	TG: <i>PPARγ2</i> heterozygotes exhibited reduced TG in response to omega-3 when compared to <i>PPARγ2</i> heterozygotes in the control (sunflower oil) group

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7	Itariu et al. 2012 (83)	Randomized, Controlled Intervention	Single SNP	Men and women without diabetes with a BMI \geq 40 kg/m ² aged 20-65 years (n=55)	8 weeks	<i>PPAR</i> γ 2, Pro12Ala (rs1801282)	<i>PPAR</i> γ 2: 3p25.2	Fish oil containing 3.4 g/day EPA + DHA (supplement)	<i>PPAR</i> γ 2, 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.
8	Jackson et al. 2012 (74)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	8 weeks and 480-min postprandial	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4	apoB apoC-III apoE HDL-c LDL-c TG Total-c	TG: <i>APOE</i> -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 <i>APOE</i> -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.
9	Jackson et al. 2017 (117)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	480-min postprandial	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4	apoB-48 apoB-100	--
10	Lindi et al. 2003 (84)	Randomized Intervention	Single SNP	Healthy men and women aged 30-65 years (n=150)	3 months	<i>PPAR</i> γ 2, Pro12Ala (rs1801282)	<i>PPAR</i> γ 2: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	<i>PPAR</i> γ 2, 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 \leq 37 %kcal or SFA intake was \leq 10 %kcal
11	Lindman et al. (118)	Randomized, Controlled Intervention	Single SNP	Men at high risk of cardiovascular disease aged 65-75 years (n=204)	6 months	<i>FVII</i> , rs6046	<i>FVII</i> : 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	--
12	Madden et al. 2008 (80)	Non-Randomized Intervention	Single SNP	Healthy men aged 43-84 years (n=111)	12 weeks	<i>CD36</i> , rs1527483, rs1049673, rs1761667, rs1984112	<i>CD36</i> : 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)
13	Markovic et	Single-Arm	Single SNP	Healthy men	12 weeks	<i>TNFA</i> , -308	<i>TNFA</i> : 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) <i>LT-α</i> , +252 (rs909253) <i>IL-1β</i> , -511 (rs16944) <i>IL-6</i> , -174 (rs1800795)	<i>LT-α</i> : 6p21.33 <i>IL-1β</i> : 2q14.1 <i>IL-6</i> : 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 <i>LT-α</i> rs909253 GG genotype and <i>IL-1β</i> rs16944 TT genotype. In <i>LT-α</i> rs909253 AA genotype and <i>TNFα</i> rs1800629 AA genotype, significant 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	<i>FABP2</i> , rs1799883	<i>FABP2</i> : 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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.0 g/d EPA and DHA, Control oil: 6.0 g/d olive oil capsule (supplement)	<i>APOE</i> -E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -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 <i>APOE</i> -E2/E3 relative to other <i>APOE</i> genotype categories Total-c: 6-week: <i>APOE</i> -E3/E4 + E4/E4 genotype group exhibited significantly different changes in total-c (increase), relative to other <i>APOE</i> genotypes, whereby reductions in total-c occurred
Olano-Martin et al. 2010 (77)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemi c men (n=38)	4 weeks per diet	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4 (carriers)	apoB apoE HDL-c LDL-c LDL-c TG TG:HDL-c Total-c	apoB, LDL-c: In <i>APOE</i> -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 <i>APOE</i> -E3/E3 group; significant reduction in TG in <i>APOE</i> -E4 carriers with EPA only. No significant interactions. Total-c: Significant genotype x treatment interaction whereby <i>APOE</i> -E4 carriers exhibit total-c reductions in response to EPA-rich oil.
Quellette et al. 2013 (122)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (n=210)	6 weeks	<i>GPAM</i> (3 SNPs), <i>AGPAT3</i> (13 SNPs), <i>AGPAT4</i> (35 SNPs) [outlined in Supplementary Table 3]	<i>GPAM</i> : 10q25.2 <i>AGPAT3</i> : 21q22.3 <i>AGPAT4</i> : 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 <i>GPAM</i> , rs2792751 genotype x supplementation interaction on LDL-c TG: Significant genotype x supplementation interaction on TG for <i>GPAM</i> , rs2792751 and rs17129561 as well as <i>AGPAT4</i> , rs9458172 and rs3798943
Quellette et al. 2014 (123)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18- 50 years (n=208)	6 weeks	<i>MGLL</i> (18 SNPs) [outlined in Supplementary Table 3]	<i>MGLL</i> : 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 <i>MGLL</i> 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

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								frequencies)		LDL particle size: Significant interactions for <i>MGLL</i> 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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	<i>APOE</i> -E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -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	<i>FABP2</i> , Ala54Thr (rs1799883)	<i>FABP2</i> : 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	<i>PPARα</i> , Leu162Val (rs1800206) <i>PPARα</i> , Intron 7 SNP	<i>PPARα</i> : 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)	<i>FADS1</i> , rs174537 <i>FADS2</i> , rs174576 (LD=1.0 therefore presented results for rs174537)	<i>FADS1/2</i> : 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	<i>SCD1</i> , rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	<i>SCD1</i> : 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 <i>SCD1</i> 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	<i>10CJ-SCHIP1</i> : 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.

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			aged 18-50 (n=141) + Replication of GRS in FINGEN study (n=310)		including: <i>IQCJ-SCHIP1</i> (4 SNPs), <i>SLIT2</i> (3 SNPs), <i>PHF17</i> (3 SNPs), <i>MYB</i> (1 SNP), <i>NXPH1</i> (1 SNP), <i>NELLI1</i> (1 SNP) [outlined in Supplementary Table 3]	<i>SLIT2</i> : 4p15.31 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 6q23.3 <i>NXPH1</i> : 7p21.3 <i>NELLI1</i> : 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	<i>PNPLA3</i> , <i>I148M</i> (rs738409) <i>TM6SF2</i> , <i>E167K</i> (rs58542926)	<i>PNPLA3</i> : 22q13.31 <i>TM6SF2</i> : 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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	<i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -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	<i>PLA2G2A</i> (5 SNPs), <i>PLA2G2C</i> (6 SNPs), <i>PLA2G2D</i> (8 SNPs), <i>PLA2G2F</i> (6 SNPs), <i>PLA2G4A</i> (22 SNPs), <i>PLA2G6</i> (5 SNPs), <i>PLA2G7</i> (9 SNPs) [outlined in Supplementary Table 3]	<i>PLA2G2A</i> : 1p36.13 <i>PLA2G2C</i> : 1p36.13 <i>PLA2G2D</i> : 1p36.12 <i>PLA2G2F</i> : 1p36.12 <i>PLA2G4A</i> : 1q31.1 <i>PLA2G6</i> : 22q13.1 <i>PLA2G7</i> : 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 <i>PLA2G7</i> rs1805018 as well as <i>PLA2G4A</i> rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, <i>PLA2G6</i> rs132989, <i>PLA2G7</i> rs679667, <i>PLA2G2D</i> rs12045689, <i>PLA2G4A</i> 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	<i>IQCJ</i> (16 SNPs), <i>NXPH1</i> (34 SNPs), <i>PHF17</i> (8 SNPs), <i>MYB</i> (9 SNPs) [outlined in	<i>IQCJ</i> : 3q25.32 <i>NXPH1</i> : 7p21.3 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 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: <i>IQCJ</i> (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), <i>NXPH1</i> (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), <i>MYB</i> (3 SNPs: rs9321493, rs11154794, rs210962). Four SNPs were still significant after applying the false discovery rate to account for multiple testing: rs1449009,

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5					Supplementary Table 3]					rs2621309, rs61332355 in <i>IQCJ</i> ; rs7805772 in <i>NXPPI</i> . There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in <i>IQCJ</i> , rs7805772 in <i>NXPPI</i> and rs11154794 in <i>MYB</i> . Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for <i>IQCJ</i> rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, <i>NXPPI</i> rs7806226, rs7805772, <i>MYB</i> rs11154794 and rs210936.	
11	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 (<i>NXPPI</i> rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and <i>IQCJ-SCHIP1</i> 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.
19	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).
26	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.
33	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	<i>eNOS</i> Glu298Asp (rs1799983)	<i>NOS3</i> : 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	-
37	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 postmenopausal	25 weeks	<i>CD36</i> , rs1527483 <i>NOS3</i> , rs1799983 <i>PPARγ2</i> , rs1801282	<i>CD36</i> : 7q21.11 <i>NOS3</i> : 7q36.1 <i>PPARγ2</i> : 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 <i>PPARγ2</i> rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of <i>PPARγ2</i> rs1801282 compared to CC genotype <i>only in the control</i> (corn oil) group TG: omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the <i>CD36</i> rs1527483 GG genotype (significant interaction); significant interaction

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			1 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
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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 ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$)

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 <i>CD36</i> 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 <i>CD36</i> 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 <i>CD36</i> 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 <i>CD36</i> 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 <i>APOE</i> -E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

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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, <i>APOE</i> (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, <i>APOE</i> (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, <i>APOE</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>FADS</i> (rs174547**) does not influence total-c responses to omega-3.

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sectional studies (n=9365) (42,43,45,46,60,68,70)									
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*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*, *NXP1*, *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

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For peer review only

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

<i>CD36, rs1761667 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1761667 and TG</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1049673 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1527483 and TG</i>	
Study	Risk of Bias
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
<i>ApoE, rs429358, rs7412 and TG</i>	
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	⊕
<i>ApoE, rs429358, rs7412 and Total-c</i>	
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	⊕
<i>31-SNP Nutri-GRS and TG</i>	
Study	Risk of Bias
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

<i>PPARG2, rs1801282 and LDL-c</i>	
Study	Risk of Bias
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
<i>PPARG2, rs1801282 and Total-c</i>	
Study	Risk of Bias
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
<i>PPARG2, rs1801282 and TG</i>	
Study	Risk of Bias
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
<i>FADS, rs174547 and Total-c</i>	
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

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5 273 Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and
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8 274 high quality evidence) for only a limited amount of evidence in this area: *APOE*
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10 275 (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-
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12 276 SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity.
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14 277 Limited evidence exists for individual genetic-based responsiveness of omega-3s on
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16 278 apolipoprotein and/or LDL particle size, with no studies from the present comprehensive
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18 279 review meeting the criteria for evidence. This highlights the need for more replication
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20 280 studies in this area. While more research exists on omega-3 responsiveness for other lipid
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22 281 outcomes such as total-c, HDL-c and LDL-c, the level of evidence for nutrigenetic
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24 282 interactions related to these outcomes remains low. Again, more studies are needed
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26 283 related to these outcomes, including replication studies of previously identified
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28 284 nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the
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30 285 same type and amount of omega-3s as the original study), and recruit samples with
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32 286 similar characteristics to the original study. Once replication is established, research
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34 287 should then seek to expand the population studied to improve generalizability and explore
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36 288 the effectiveness of different interventions (i.e. different formulations and doses of
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38 289 omega-3s). The variability of the interventions and sample sizes in the studies conducted
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40 290 to date often resulted in the quality of evidence being downgraded (see Table 3). It should
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42 291 also be noted that study heterogeneity precluded the ability to conduct a meta-analysis.
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44 292 Thus, the GRADE approach worked well for evaluating the quality of the evidence given
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46 293 that this approach takes into consideration several factors when determining the quality of
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3 294 evidence such as risk of bias, indirectness of evidence, inconsistency or results,
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5 295 imprecision and publication bias (37).
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10 297 It is important to note that our results demonstrating strong evidence for interactions
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12 298 between *APOE* genotypes and lipid responses to omega-3s have notable ethical
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14 299 implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk
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16 300 of developing Alzheimer's disease (136). Moreover, *APOE* genotypes are significantly
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18 301 associated with CVD risk including risk of coronary artery disease and hyperlipidemia
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20 302 (137–139). Interestingly, the pathology of Alzheimer's disease has been linked to
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22 303 cardiovascular mechanisms (136). Future research should explore nutrigenetic
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24 304 interactions, with risk of developing Alzheimer's disease as the study endpoint/outcome
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26 305 of interest. Despite the current lack of knowledge about how diet may play a role in
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28 306 mitigating the genetic-based risk of Alzheimer's disease, several potentially modifiable
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30 307 risk factors account for around 40% of dementia and Alzheimer's disease globally (140),
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32 308 and the link between Alzheimer's disease risk and *APOE* is well-established (141).
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34 309 Therefore, despite the strong scientific validity identified in the present review, there are
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36 310 other factors that must be considered before this test can be recommended for
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38 311 implementation in a practice setting; this includes ethical, legal and social implications
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40 312 (142).
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49 314 In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness
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51 315 to omega-3s in men but not women speaks to the importance of taking biological sex into
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53 316 account in nutrigenetics research. The importance of this has been further highlighted
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3 317 elsewhere, where it has been noted that the results of nutrigenetic research may differ in
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5 318 men and women (143). As more studies are completed, researchers may find that certain
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7 319 nutrigenetic interactions differ depending on biological sex, ethnicity, age or other
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10 320 factors, similar to our findings on *APOE*, omega-3s and TG in which there was evidence
11
12 321 of a nutrigenetic interaction in males only. Researchers may also find explanations for
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14 322 this, which are currently poorly understood. In general, it is becoming increasingly
15
16 323 recognized that health-related responses to different interventions may vary based on
17
18 324 biological sex; this is an important consideration of personalized nutrition (143).
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20 325 Nutrigenetic research often groups men and women together, but stratifying based on
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22 326 biological sex could provide further insights for specific nutrigenetic interactions and
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24 327 could also help explain why some replication studies have not demonstrated significant
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26 328 findings (143). Moreover, biomedical research in general historically has been conducted
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28 329 more in men than women; yet such research findings are often generalized to women
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30 330 despite limited research conducted in samples of women, which is problematic for a
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32 331 number of reasons (144). In the present review, the evidence was strong for the *APOE*
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34 332 findings in men only, but not women in part because there were more studies conducted
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36 333 in men. Specifically, there were five studies conducted in men and women (combined)
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38 334 (70,72,73,112,128), and four studies conducted in samples of only men (74,77,78,121),
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40 335 yet no studies conducted in samples of only women. This brings to light important issues
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42 336 of equity and warrants further discussion and consideration.
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52 338 As research continues to develop, it appears likely that lipid and lipoprotein responses are
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54 339 polygenic in nature. Therefore, future research should consider using nutri-GRSs or other
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3 340 polygenic methods of assessing responsiveness to nutrition interventions. This work
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5 341 should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs,
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7 342 such as establishing them from genetic-wide association studies. In addition to the two
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9 343 studies meeting the criteria for evidence grading (64,65), a modified version of the 31-
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11 344 SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs
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13 345 (64). While this did not meet our inclusion criteria for evidence grading given that a
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15 346 different GRS was used, the 23-SNP GRS was significantly associated with TG
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17 347 responsiveness to omega-3 supplementation in this population as well, providing further
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19 348 evidence for the scientific validity of this nutrigenetic interaction (64).
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26 350 While we used the GRADE approach to evaluate the body of evidence, several tools are
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28 351 available for evaluating the quality of scientific evidence, though no generally accepted
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30 352 methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a
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32 353 set of guidelines to assess the scientific validity of genotype-based dietary advice (29).
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34 354 While we originally intended to use these guidelines for assessing the evidence, we came
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36 355 across some limitations that ultimately led us to use the GRADE guidelines. Specifically,
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38 356 Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines
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40 357 should be included in the assessment of scientific validity (29). However, limiting the
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42 358 evidence to only these studies could result in several important studies being missed. In
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44 359 the present review, none of the included studies explicitly indicated that they followed
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46 360 STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA
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48 361 guidelines to assess risk of bias (29). However, the STREGA checklist is only intended
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50 362 for observational genetic association studies - not interventional research (145). In the
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3 363 present review, 42 of the 65 included studies were interventional (65%) (Table 2). In
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5 364 addition, the STREGA guidelines are intended to improve the transparency and adequate
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7 365 reporting of genetic association studies, but it is not intended to be used as a study quality
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10 366 assessment tool (145). However, Grimaldi et al. nicely highlighted the importance of
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12 367 understanding the nature of the genetic variation, at a functional level, when assessing
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14 368 scientific validity (29). This is not included in the standard GRADE approach but is an
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16 369 important niche component of nutrigenetic research. As such, an analysis of functional
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18 370 SNPs (biological plausibility) was included as an additional component of the standard
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20 371 GRADE process, as indicated in the methods section above. Overall, we found that the
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22 372 methods used in this systematic review were effective and can be used to synthesize and
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24 373 evaluate nutrigenetic studies assessing other gene-nutrient-health outcome interactions.
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30 375 The additional consideration of functional SNPs to the standard GRADE approach helped
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32 376 to strengthen this review, as biological mechanistic evidence can help ensure that study
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34 377 findings did not occur by chance alone, and this is a component of evidence evaluation
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36 378 frameworks in medical genetics (146,147). Transcriptomic and pathway analyses can
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38 379 help inform the direction of future nutrigenetic studies by generating hypotheses about
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40 380 the impact of specific genetic variations on varying responses to nutrition on health-
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42 381 related outcomes. For example, using transcriptomics and pathway analyses to identify
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44 382 changes in lipid metabolism following omega-3 supplementation, Rudkowska and
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46 383 colleagues identified six genes expressed in opposite directions between responders and
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48 384 non-responders to omega-3 supplementation for TG lowering: *FADS2*, *PLA2G4A*,
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50 385 *ALOX15*, *PEN1*, *MGLL* and *GPAM* (148). Tremblay et al. then built on this knowledge
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3 386 and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689,
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5 387 *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3
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7 388 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a
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9 389 significant impact on the TG lowering effect of omega-3 supplementation (129). Others
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11 390 have built on this mechanistic knowledge as well (122). Future research should now seek
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13 391 to replicate this work given that we found that there have been no replication studies
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15 392 completed and thus, this research (122,129) did not meet the criteria for evidence
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17 393 grading.
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24 395 In the current body of literature, there are some limitations that should be highlighted.
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26 396 Given the variability in allele frequencies for each SNP, it should be noted that study
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28 397 limitations can arise with small sample sizes whereby some genotype groups may not be
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30 398 adequately powered to detect significant differences. For example, Dawczynski et al.
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32 399 (2013) detected significant changes in TG among the GA genotype group of *CD36*
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34 400 rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA:
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36 401 n=8, GG: n=7) exhibited a significant difference, despite similar directions and
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38 402 magnitudes of effect among the GA and GG genotypes (81). It is thus possible that this
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40 403 study was not adequately powered. Some researchers aim to mitigate this issue of small
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42 404 numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for
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44 405 the minor allele) (68). However, such an approach precludes the possibility to detect an
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46 406 allele-dosage effect. From a physiological perspective, an allele dosage effect would be
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48 407 expected whereby a significant change among a heterozygote group would likely be
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50 408 accompanied by a significant change in one of the homozygote groups but with an even
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3 409 greater magnitude of the effect. This consideration highlights the importance of having an
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5 410 adequately powered sample size, while factoring in the prevalence of each genotype.
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10 412 While single SNP research provides important information about individual gene-nutrient
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12 413 interactions, the results of this review indicate that individual responses to omega-3s for
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14 414 altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus,
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16 415 we encourage researchers to further explore the use of nutri-GRSs to improve the
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18 416 accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et
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20 417 al., which obtained a high quality evidence grade in the present review (64,65). This is
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22 418 further exemplified in the analyses recently conducted by Chen et al. (40), which has yet
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24 419 to be replicated and thus was not selected for evidence grading.
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31 421 The present analysis of scientific validity provides an important first step towards the
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33 422 eventual development of clinical practice guidelines for genetic-based responses to
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35 423 dietary intake. With questionable and variable scientific validity of existing consumer
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37 424 nutrigenetic tests, the development of clinical practice guidelines is an important next
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39 425 step as these can be used by HCPs and industry alike to help promote evidence-based
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41 426 practice in personalized nutrition. Ideally, industry should use future clinical practice
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43 427 guidelines to inform the nutrigenetic associations and related dietary recommendations
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45 428 included in their reports. Decision aids can also be useful to guide clinical practice for
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47 429 HCPs (149), and future research should seek to develop a decision aid related to omega-
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49 430 3s and lipid/lipoprotein outcomes based on genetic variation.
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3 432 Overall, we have provided a comprehensive overview the body of evidence related to
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5 433 nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing
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7 434 an overview of levels of evidence in this field. To our knowledge, this is the first
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9 435 systematic review with evidence grading in the broader field of nutrigenetics. The results
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11 436 of this work should be used in clinical practice guideline development, to ultimately
12
13 437 guide evidence-based practice in personalized nutrition and move this emerging field
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15 438 forward.
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19 439
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27 447 responsible for article screening and selection, summarizing, evidence grading, and developing a
28 448 draft of the CPGs. The first CPG draft underwent revisions from S.D. and M-C.V. Following this,
29 449 all authors reviewed and revised the CPGs as well as the full-text manuscript. J.R.H. wrote the first
30 450 draft of the manuscript. All authors reviewed, revised and approved the final manuscript.
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41

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49 455 **Data Sharing Statement:** Data are available upon reasonable request.
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458 **Figure Legend:**

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460 **Figure 1. PRISMA Flow Diagram**

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

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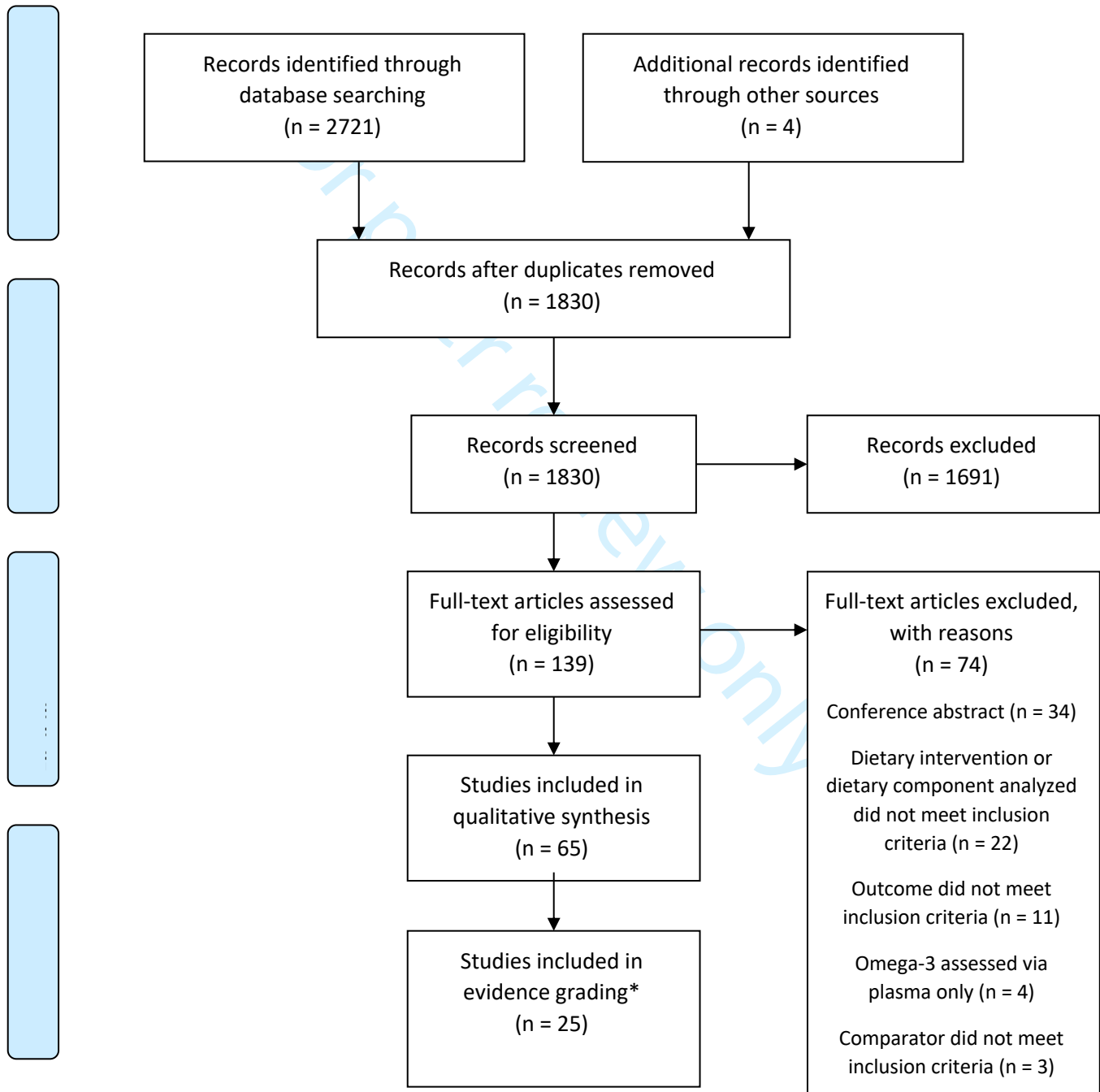
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Figure 1: PRISMA 2009 Flow Diagram



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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 'personalized 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 "personalized 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

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#	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 "personalized 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 drosophila 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
<i>APOE</i> : 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)
<i>APOE</i> : 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>CD36</i> : rs1761667	HDL-c	Dawczynski et al. 2013 (76) Madden et al. 2008 (75)
<i>CD36</i> : rs1761667	TG	Dawczynski et al. 2013 (76) Madden et al. 2008 (75)
<i>CD36</i> : rs1049673	HDL-c	Dawczynski et al. 2013 (76) Madden et al. 2008 (75)
<i>CD36</i> : rs1527483	TG	Madden et al. 2008 (75) Zheng et al. 2018 (128)
<i>FADS</i> : 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)	<p><i>FADS2</i>, rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276</p> <p><i>FADS3</i>, rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285</p> <p><i>RAB31L1</i>, rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252</p>
Cormier et al. 2012	<p><i>FADS</i> gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567</p>
Vallée Marcotte et al. Am J Clin Nutr;109:176–185 (2019)	<p><i>IQCJ-SCHIP1</i>, rs7639707, rs62270407</p> <p><i>NXPH1</i>, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523</p> <p><i>PHF17</i>, rs1216346, rs114348423, rs75007521</p> <p><i>MYB</i>, rs72560788, rs72974149, rs210962, rs6933462</p> <p><i>NELL1</i>, rs79624996, rs1850875, rs78786240, rs117114492</p> <p><i>SLIT2</i>, rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249</p>
Tremblay et al. Lipids in Health and Disease (2015) 14:12	<p><i>PLA2G2A</i>, rs876018, rs955587, rs3753827, rs11573156, rs11573142</p> <p><i>PLA2G2C</i>, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718</p> <p><i>PLA2G2D</i>, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671</p> <p><i>PLA2G2F</i>, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904</p>

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

	rs11651351, rs3643, rs7213998, rs17583163 <i>ACAA1</i> , rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	<i>CETP</i> , rs3764261, rs247616, rs7205804 <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5</i> , <i>ABCG8</i> , rs4299376 <i>TIMD4</i> , <i>HAVCR1</i> , rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 <i>ANGPTL3</i> , <i>DOCK7</i> , rs3850634, rs1167998, rs2131925 <i>FADS1</i> , <i>FADS2</i> , <i>FADS3</i> , rs174550, rs174547, rs174546, rs174583 <i>GALNT2</i> , rs4846914, rs1321257 <i>ABCA1</i> , rs4149268 <i>APOE</i> , <i>APOC1</i> , <i>APOC2</i> , rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	<i>IQCJ-SCHIP1</i> , rs7639707, rs62270407 NXP1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 <i>PHF17</i> , rs1216346, rs114348423, rs75007521 <i>MYB</i> , rs72560788, rs72974149, rs210962, rs6933462 <i>NELL1</i> , rs79624996, rs1850875, rs78786240, rs117114492 <i>SLIT2</i> , rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	<i>IQCJ-SCHIP1</i> , <i>MYB</i> , <i>NELL1</i> , <i>NXP1</i> , <i>PHF17</i> , <i>SLIT2</i> , rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	<i>IQCJ</i> , rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	<p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308</p>
<p>Vallée Marcotte et al. Nutrients; 11, 737 (2019)</p>	<p><i>IQCJ-SCHIP1</i>, 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</p> <p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, <i>SLIT2</i>, rs2952724</p> <p><i>NELLI</i>, rs752088</p>

Supplementary Table 4: 31-SNP Nutri-GRS

Gene, rs Number	Alleles ¹	Associated Points
<i>IQCJ-SCHIP1</i> , rs7639707	<u>A</u> /G	+1
<i>IQCJ-SCHIP1</i> , rs62270407	C/ <u>T</u>	-1
<i>NXPH1</i> , rs61569932,	<u>G</u> /T	+1
<i>NXPH1</i> , rs1990554	<u>A</u> /C	+1
<i>NXPH1</i> , rs6463808	<u>A</u> /G	+1
<i>NXPH1</i> , rs6966968	<u>A</u> /G	+1
<i>NXPH1</i> , rs28473103	<u>A</u> / <u>G</u>	-1
<i>NXPH1</i> , rs28673635	<u>A</u> /G	+1
<i>NXPH1</i> , rs12702829	<u>C</u> /T	+1
<i>NXPH1</i> , rs78943417	A/ <u>T</u>	-1
<i>NXPH1</i> , rs293180	G/ <u>T</u>	+1
<i>NXPH1</i> , rs1837523	<u>C</u> /T	-1
<i>PHF17</i> , rs1216346	<u>C</u> /T	+1
<i>PHF17</i> , rs114348423	<u>A</u> /G	+1
<i>PHF17</i> , rs75007521	<u>G</u> /T	-1
<i>MYB</i> , rs72560788	<u>C</u> / <u>T</u>	-1
<i>MYB</i> , rs72974149	<u>A</u> / <u>G</u>	-1
<i>MYB</i> , rs210962	<u>C</u> / <u>T</u>	-1
<i>MYB</i> , rs6933462	<u>C</u> / <u>G</u>	+1
<i>NELL1</i> , rs79624996	<u>A</u> /G	+1
<i>NELL1</i> , rs1850875	<u>C</u> /T	+1
<i>NELL1</i> , rs78786240	<u>C</u> / <u>T</u>	-1
<i>NELL1</i> , rs117114492	<u>G</u> /T	+1
<i>SLIT2</i> , rs184945470	<u>C</u> / <u>T</u>	+1
<i>SLIT2</i> , rs143662727	<u>A</u> / <u>G</u>	-1
<i>SLIT2</i> , rs10009109	<u>C</u> /T	+1
<i>SLIT2</i> , rs10009535	<u>A</u> / <u>G</u>	+1
<i>SLIT2</i> , rs61790364	<u>A</u> / <u>G</u>	+1
<i>SLIT2</i> , rs73241936	<u>C</u> / <u>T</u>	+1
<i>SLIT2</i> , rs16869663	<u>A</u> / <u>G</u>	+1
<i>SLIT2</i> , rs76015249	<u>A</u> / <u>G</u>	+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)
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Page 1 of 2

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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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
For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only

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

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

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

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

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

29 ABSTRACT

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

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

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

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

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

61 STRENGTHS AND LIMITATIONS

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

68 INTRODUCTION

69
70 Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research
71 demonstrates that there is significant inter-individual variability in cardiometabolic risk
72 factor levels, in part based on a combination of genetic and nutrition-related risk factors
73 (2,3). For example, protein intake has consistently been shown to influence measures of
74 body weight and composition dependent on *FTO* genotype (rs9939609 or loci in strong
75 linkage disequilibrium) (4,5). Consumers indicate great interest in personalized nutrition
76 based on genetics (6,7), however, a lack of industry oversight (8,9) has led to highly
77 variable scientific validity of nutrigenetic tests available to consumers. While recognizing
78 that some groups question whether genetic testing for personalized nutrition is ready for
79 ‘prime time’, Gorman and colleagues suggested that there are certain specific nutrigenetic
80 interactions with strong evidence that could be considered for implementation into
81 clinical practice by expert committees who are responsible for creating dietary guidelines
82 (10). With this in mind, systematic reviews that include an evaluation of levels of
83 evidence are urgently needed in order to determine if there are any nutrigenetic
84 associations that may warrant potential implementation into practice.

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

1
2
3 91 terms of their lipid and lipoprotein lowering effects, omega-3s have consistently
4
5 92 demonstrated an impact on triglycerides (TG) (14). High-quality evidence from
6
7 93 population-based studies suggests that long-chain omega-3s (EPA and DHA) reduce
8
9 94 plasma TG by about 15% (14). There is also high-quality evidence suggesting that EPA
10
11 95 and DHA can raise high-density lipoprotein (HDL) cholesterol (14). Other studies have
12
13 96 further demonstrated a relationship between omega-3 and HDL-cholesterol (15), low-
14
15 97 density lipoprotein (LDL)-cholesterol (15), total cholesterol (16–18), apolipoproteins
16
17 98 (19), and LDL particle size (20). Despite several studies with significant findings for
18
19 99 these outcomes, when reviewing the evidence, studies have demonstrated conflicting
20
21 100 results for the impact of omega-3 on many lipid profile outcomes (14). Genetic variation
22
23 101 could explain this heterogeneity. EPA and DHA have been shown to significantly impact
24
25 102 the expression of thousands of genes including those involved in inflammatory and
26
27 103 atherogenic pathways (21,22). Evidence now demonstrates that the health impacts of
28
29 104 omega-3 intake could differ based on genetic variation (23,24). Despite the potential for
30
31 105 omega-3s to have a significant positive impact on health outcomes, population intakes of
32
33 106 omega-3s tend to be low (25). While the World Health Organization's Adequate Intake
34
35 107 level for adults is 200-250 mg EPA+DHA daily (26,27), the mean reported intake of
36
37 108 EPA+DHA in the United States is only approximately 100 mg daily (25). Nutrigenetic
38
39 109 interventions have the potential to motivate improvements in dietary intake beyond
40
41 110 population-based interventions (28). Additionally, evidence suggests that genetic
42
43 111 variability affects health responses to omega-3s (23). Thus, critically appraising and
44
45 112 grading the evidence for nutrigenetic interactions related to omega-3s and plasma lipids,
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47 113 lipoproteins and apolipoproteins is an important research priority. The most recent
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1
2
3 114 systematic review on nutrigenetic interactions related to omega-3s and intermediate
4
5 115 phenotypes of cardiovascular disease was conducted nearly a decade ago, and this study
6
7
8 116 did not evaluate the quality of evidence using an established methodology (29).
9
10 117 Therefore, we aimed to provide a comprehensive summary of current evidence related to
11
12 118 inter-individual variability in plasma lipid, lipoprotein and apolipoprotein responses to
13
14
15 119 omega-3 intake (plant and marine sources) based on genetic variations. Overall, the
16
17 120 specific objectives of this study were as follows:

18
19
20 121 **Objective 1.** Systematically search, identify (select), and provide a narrative
21
22 122 synthesis of all studies that assessed nutrigenetic associations/interactions for genetic
23
24 123 variants (comparators) influencing the plasma lipid, lipoprotein and/or apolipoprotein
25
26 124 response (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans –
27
28
29 125 both pediatric and adult populations (population).

30
31
32
33 126 **Objective 2.** Assess the overall quality of evidence for specific priority nutrigenetic
34
35 127 associations/interactions based on the following inclusion criteria: nutrigenetic
36
37 128 associations/interactions reported for the same genetic variants (comparators)
38
39 129 influencing the same plasma lipid, lipoprotein and/or apolipoprotein response
40
41 130 (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both
42
43 131 pediatric and adult populations (population) in two independent studies, irrespective
44
45
46 132 of the findings.

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50 133

51 52 53 134 **Methods**

54 135

55 136 **Patient and Public Involvement:** No patient involvement.
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1
2
3 137 *Literature Search*
4
5

6 138 The systematic review protocol was registered with PROSPERO (CRD42020185087).
7
8
9 139 The review process was guided by previously established methods, including a
10
11 140 previously outlined five-step systematic review process (30,31). The search engines
12
13 141 Embase, Web of Science and Medline OVID were used to conduct the search starting in
14
15 142 May 2020 and screen for articles meeting inclusion criteria, using the comprehensive
16
17 143 search terms outlined in Supplementary Table 1, properly combined by Boolean
18
19 144 operators. The literature was searched up until August 1, 2020. A PRISMA diagram
20
21 145 (Figure 1) guided the article screening process (32).
22
23
24
25

26 146 *Inclusion and Exclusion Criteria*
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28

29 147 Original studies were included if they were written in English or French. Inclusion
30
31 148 criteria were developed using the Population, Intervention, Comparison, Outcomes,
32
33 149 (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (33,34) for
34
35 150 interventional and observational research, respectively. These are detailed in Table 1 for
36
37 151 each study objective.
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41

42 152 **Table 1. PICO/PECO for Study Objectives**
43
44

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

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

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

170 Associations/interactions reported in two independent studies formed the basis of the
 171 inclusion criteria for objective 2, in which nutrigenetic associations/interactions were
 172 prioritized for evidence grading. This is further detailed in Table 1 and the section below
 173 entitled “Evidence Grading.”

174 *Article Selection and Data Extraction*

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3 175 Two independent investigators (JK and VG) screened articles using the computer
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5 176 software *Covidence* (including title, abstract, and full-text screening) and extracted data
6
7 177 from the included articles. Reference lists of included articles and of a systematic review
8
9 178 on a similar topic (35) were also screened for relevant articles. Data extraction templates
10
11 179 were piloted by two independent investigators (JK and VG) on ten included studies and
12
13 180 revised accordingly. The final data extraction templates included the following
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15 181 components for each study: first author name and year, study design, genetic approach,
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17 182 population and sample size, study duration (interventional studies only), genes and single
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19 183 nucleotide polymorphisms (SNPs) analyzed with rs numbers, quantity and type of
20
21 184 omega-3, comparisons (e.g. a control group or different amount/type of omega-3s as well
22
23 185 as genetic grouping), lipid/lipoprotein outcome(s), whether or not the study reported that
24
25 186 they followed STREGA guidelines and a summary of statistically significant study
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27 187 findings relevant to the research question. Corresponding authors of included studies
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29 188 were contacted as needed to provide clarity and/or additional information about the
30
31 189 included studies.
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38 190 *Evidence Grading*

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42 191 Upon reading all full-text articles included, and summarizing the body of evidence
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44 192 (Tables 2 and 3), SNPs/nutrigenetic risk scores (nutri-GRSs) and subsequent
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46 193 lipid/lipoprotein/apolipoprotein outcomes were systematically prioritized and selected for
47
48 194 evidence grading, if a specific nutrigenetic association/interaction was reported in at least
49
50 195 two independent studies. To clarify, this refers to the same SNP(s)/nutri-GRS [or SNPs
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52 196 in strong linkage disequilibrium (LD)] being assessed and influencing the same
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54 197 lipid/lipoprotein outcome in at least two studies. For these nutrigenetic
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3 198 associations/interactions, we proceeded with evidence grading, while including **all**
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5 199 studies relevant to the particular nutrigenetic association/interaction, irrespective of the
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7 200 findings. Consistency of results was then one of several factors considered when grading
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9 201 the body of evidence. The Grading of Recommendations Assessment, Development and
10
11 202 Evaluation (GRADE) approach indicates that a single study rarely (if ever) results in
12
13 203 strong evidence, but two studies (typically RCTs) can indicate strong evidence if they are
14
15 204 graded highly using the GRADE criteria (36). Prior to selecting the nutrigenetic
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17 205 associations/interactions (genetic variants and lipid/lipoprotein/apolipoprotein outcomes)
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19 206 for evidence grading, LD was assessed using the SNIPA SNP Annotator Software (37)
20
21 207 for genes located on the same chromosome and arm (determined using the Online
22
23 208 Mendelian Inheritance in Man® [OMIM] database) as outlined in the summary of
24
25 209 results' tables in the column labelled 'Cytogenic Location of Gene(s)' (Tables 1 and 2).
26
27 210 Strong LD was defined as $r^2 > 0.8$ and location < 250 kb away from the index SNP
28
29 211 location. SNPs in strong LD were considered together for the purposes of evidencing
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31 212 grading.

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33 213 Based on our abovementioned predetermined criteria for specific nutrigenetic topic
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35 214 selection for evidence grading, nutrigenetic associations/interactions that were not
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37 215 included in the evidence grading process likely have weak evidence (at minimum due to
38
39 216 lack of replication, for example, *ZNT8* rs13266634 and HDL-c or TG responsiveness to
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41 217 omega-3, which has only been assessed in a single study (38)). According to the GRADE
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43 218 guidelines, when only a single study exists indicating significant findings for an outcome
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45 219 of interest (especially when the study is observational), the overall quality of the evidence
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47 220 is generally rated to be low or very low (39). Therefore, our process for prioritizing
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221 nutrigenetic topics for evidence grading aimed to filter out specific nutrigenetic
222 associations/interactions that would likely be deemed low or very low quality (based on,
223 at minimum, lack of replication). Two authors (JK and VG) critically appraised the
224 selected nutrigenetic interactions using the GRADE methodology (39,40). Nutrigenetic
225 interactions were grouped according to studies assessing the same SNP(s)/nutri-GRS and
226 lipid/lipoprotein/apolipoprotein outcome, and the quality of the body of evidence (studies
227 with significant and non-significant results) was rated; this process was guided by the
228 GRADE Evidence Profile, which included consideration of risk of bias, inconsistency,
229 indirectness, imprecision, publication bias, plausible confounding, dose-response and
230 other factors (39). For example, different sources of omega-3s (e.g. EPA+DHA vs. ALA;
231 food sources vs. supplementation) were taken into consideration when grading the
232 evidence through the analysis of indirectness within the GRADE approach (39,40). Risk
233 of bias was assessed in each of the included interventional and observational studies
234 using the National Institutes of Health Study Quality Assessment Tools, in line with
235 recently published recommendations for risk of bias assessments (41). To assess
236 measures of precision, coefficients of variation (CV) were calculated based on outcome
237 means (mean change or absolute values – whichever was used for the analyses) and
238 standard deviations. In cases where standard errors of the mean were reported, these were
239 converted to standard deviations to calculate the CV. The nutrigenetic interactions were
240 each given an evidence grade of high, moderate, low or very low.

241 **Results**

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

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3 245 results columns of Supplementary Tables 2 and 3 (far right) indicate nutrigenetic findings
4
5 246 that were statistically significant. Any results related to the studies' analyzed SNPs and
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7
8 247 outcomes of interest that were not statistically significant are not indicated in the results
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10 248 column. No studies explicitly reported that they followed STREGA guidelines. LD
11
12 249 analysis of SNPs tested in different studies revealed strong LD in several SNPs from the
13
14 250 *FADS* gene cluster (see Table 2 footnote). As such, LD was taken into consideration in
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16
17 251 the selection of nutrigenetic interactions selected for evidence grading.

20 252 *Observational Studies*

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23 253 Of the 65 included studies, 23 were observational with the majority of these being cross-
24
25 254 sectional, as outlined in Supplementary Table 2. A total of 62,221 participants were
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28 255 included in the observational studies. These studies assessed correlations among a
29
30 256 number of different genetic variations and outcomes, with several studies assessing
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32 257 genetic variations in the *FADS* gene cluster (42–48), *TNF α* (49–51) and *PPAR α* (52–54).
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34 258 Most studies (n=13) assessed total omega-3s (38,42,47–49,51,54–60). The intake and
35
36
37 259 type of omega-3s, lipid/lipoprotein/apolipoprotein outcomes and associations revealed
38
39 260 from these studies were variable as further detailed in Supplementary Table 2. In the
40
41 261 observational studies assessing genetic variation in the *FADS* gene cluster, some studies
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43 262 indicated significant gene-diet findings related to HDL-cholesterol, LDL-cholesterol, TG,
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45 263 total-cholesterol while other studies demonstrated no significant gene-diet interactions for
46
47 264 these outcomes thus indicating notable inconsistency among the results, while
48
49 265 considering that SNPs differed by studies (42–48). In the observational studies focused
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51 266 on genetic variation in the *TNF α* gene, there was some evidence of a gene-diet
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54 267 relationship for omega-3 and LDL-cholesterol, total-cholesterol and total-
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3 268 cholesterol:HDL-cholesterol ratio, but again, results differed between studies (49–51).
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5 269 For gene-diet relationships and *PPARα* genetic variation, individual studies indicated
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7 270 significant findings related to total-cholesterol, LDL-cholesterol, TG, apoC-III and LDL
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10 271 peak particle diameter (52–54). Comprehensive details of the observational studies are
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12 272 outlined in Supplementary Table 2.
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15 273 *Interventional Studies*

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18 274 Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-
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20 275 randomized studies included single arm clinical trials and sequential non-randomized
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22 276 cross-over interventions. For interventional studies, n=6,225 participants upon combining
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24 277 all sample sizes of the included studies. Again, these studies assessed relationships
25
26 278 between a number of different genetic variants and study outcomes. In more recent years,
27
28 279 several studies (n=8) used a nutri-GRS or polygenic approaches (61–68) given the
29
30 280 plausibility that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are
31
32 281 polygenic in nature. Numerous studies assessed genetic variations in the *FADS* gene
33
34 282 cluster (61,62,69–71), *APOE* (61,71–80), *CD36* (67,81,82), *PPARγ2* (62,67,83–85) and
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36 283 *PPARα* (83,86,87). Among these studies, results related to significant gene-diet (omega-
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38 284 3) associations influencing lipid/lipoprotein outcomes were generally inconsistent except
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40 285 for *APOE* (rs429358 and rs7412), omega-3 and TG in males only (71–75,77–80), and for
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42 286 a 31-SNP nutri-GRS, omega-3 and TG (65,66). There was also consistent evidence to
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44 287 indicate a lack of association among *PPARγ2* (rs1801282) genetic variation, EPA+DHA
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46 288 and LDL cholesterol (62,67,84,85,88). Most studies (n=40) used supplemental EPA
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48 289 and/or DHA sources of omega-3s for the dietary intervention (see Supplementary Table
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50 290 3). The dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages
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291 ranging from 0.5-3.7 g/day across different studies, and one study with an ALA
292 intervention dosage of 8.1 g/day, as further detailed in Table 3.

293 *Levels of Evidence Using GRADE*

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

308 All other evidence that was evaluated was determined to be weak (GRADE rating: low or
309 very low quality), as further detailed in Table 2. Imprecision, indirectness, and
310 inconsistency were common reasons for downgrading the evidence (refer to Table 2
311 footnote). There was evidence for a plausible mechanism of action for most of the
312 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									
1 Patient or Population: adults 2 Intervention/Exposure: dietary or supplemental omega-3 (EPA and/or DHA and/or ALA) 3 Comparison/Control: genetic variation, different omega-3 intakes 4 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
5 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 <i>CD36</i> rs1761667 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
6 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 <i>CD36</i> rs1761667 could lead to significant reductions in TG in response to 0.8-3.0 g/day of omega-3s.
7 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 <i>CD36</i> rs1049673 could lead to significant increases in HDL-c in response to 0.8-3.0 g/day of omega-3s.
8 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 <i>CD36</i> rs1527483 could lead to significant decreases in TG in response to approximately 2.0 g/day of EPA+DHA (but not ALA).
9 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 <i>APOE</i> -E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

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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, <i>APOE</i> (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, <i>APOE</i> (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, <i>APOE</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>FADS</i> (rs174547**) does not influence total-c responses to omega-3.

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sectional studies (n=9365) (44,45,47,48,61,69,71)									
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*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*, *NXP1*, *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

<i>CD36, rs1761667 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1761667 and TG</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1049673 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1527483 and TG</i>	
Study	Risk of Bias
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
<i>ApoE, rs429358, rs7412 and TG</i>	
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	⊕
<i>ApoE, rs429358, rs7412 and Total-c</i>	
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	⊕
<i>31-SNP Nutri-GRS and TG</i>	
Study	Risk of Bias
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

<i>PPARG2</i> , 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	⊕
<i>PPARG2</i> , 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	⊕
<i>PPARG2</i> , 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	⊕
<i>FADS</i> , 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

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3 271 **DISCUSSION**

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5 273 Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and
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7
8 274 high quality evidence) for only a limited amount of evidence in this area: *APOE*
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10 275 (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-
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12 276 SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity.
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14 277 Limited evidence exists for individual genetic-based responsiveness of omega-3s on
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16 278 apolipoprotein and/or LDL particle size, with no studies from the present comprehensive
17
18 279 review meeting the criteria for evidence grading. This highlights the need for more
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20 280 replication studies in this area. While more research exists on omega-3 responsiveness for
21
22 281 other lipid outcomes such as total-c, HDL-c and LDL-c, the level of evidence for
23
24 282 nutrigenetic interactions related to these outcomes remains low. Again, more studies are
25
26 283 needed related to these outcomes, including replication studies of previously identified
27
28 284 nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the
29
30 285 same type and amount of omega-3s as the original study), and recruit samples with
31
32 286 similar characteristics to the original study. Once replication is established, research
33
34 287 should then seek to expand the population studied to improve generalizability and explore
35
36 288 the effectiveness of different interventions (i.e. different formulations and doses of
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38 289 omega-3s). The variability of the interventions and sample sizes in the studies conducted
39
40 290 to date often resulted in the quality of evidence being downgraded (see Table 2). It should
41
42 291 also be noted that study heterogeneity precluded the ability to conduct a meta-analysis.
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44 292 Thus, the GRADE approach worked well for evaluating the quality of the evidence given
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46 293 that this approach takes into consideration several factors when determining the quality of
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3 294 evidence such as risk of bias, indirectness of evidence, inconsistency or results,
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5 295 imprecision and publication bias (39).
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9
10 297 It is important to note that our results demonstrating strong evidence for interactions
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12 298 between *APOE* genotypes and lipid responses to omega-3s have notable ethical
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14 299 implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk
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16 300 of developing Alzheimer's disease (90). Moreover, *APOE* genotypes are significantly
17
18 301 associated with CVD risk including risk of coronary artery disease and hyperlipidemia
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20 302 (91–93). Interestingly, the pathology of Alzheimer's disease has been linked to
21
22 303 cardiovascular mechanisms (90). Future research should explore nutrigenetic interactions,
23
24 304 with risk of developing Alzheimer's disease as the study endpoint/outcome of interest.
25
26 305 Despite the current lack of knowledge about how diet may play a role in mitigating the
27
28 306 genetic-based risk of Alzheimer's disease, several potentially modifiable risk factors
29
30 307 account for around 40% of dementia and Alzheimer's disease globally (94), and the link
31
32 308 between Alzheimer's disease risk and *APOE* is well-established (95). Therefore, despite
33
34 309 the strong scientific validity identified in the present review, there are other factors that
35
36 310 must be considered before this test can be recommended for implementation in a practice
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38 311 setting; this includes ethical, legal and social implications (96).
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42 313 In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness
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44 314 to omega-3s in men but not women speaks to the importance of taking biological sex into
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46 315 account in nutrigenetics research. The importance of this has been further highlighted
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48 316 elsewhere, where it has been noted that the results of nutrition and nutrigenetic research
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3 317 may differ in men and women (97). For example, UDP-glucuronidation isoenzyme
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5 318 expression profiles have been demonstrated to be regulated by sex hormones, and thus
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7 319 sex-specific differences in glucuronidation of resveratrol have been observed (98). As
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10 320 more studies are completed, researchers may find that certain nutrigenetic interactions
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12 321 differ depending on biological sex, ethnicity, age or other factors, similar to our findings
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14 322 on *APOE*, omega-3s and TG in which there was robust evidence of a nutrigenetic
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16 323 interaction in males only. Researchers may also find explanations for this, which are
17
18 324 currently poorly understood. In general, it is becoming increasingly recognized that
19
20 325 health-related responses to different interventions may vary based on biological sex; this
21
22 326 is an important consideration of personalized nutrition (97). Nutrigenetic research often
23
24 327 groups men and women together, but stratifying based on biological sex could provide
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26 328 further insights for specific nutrigenetic interactions and could also help explain why
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28 329 some replication studies have had conflicting findings (97). Moreover, biomedical
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30 330 research in general historically has been conducted more in men than women; yet such
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32 331 research findings are often generalized to women despite limited research conducted in
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34 332 samples of women, which is problematic for a number of reasons (99). In the present
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36 333 review, the evidence was strong for the *APOE* findings in men only, but not women in
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38 334 part because there were more studies conducted in men. Specifically, there were five
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40 335 studies conducted in men and women (combined) (71,73,74,100,101), and four studies
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42 336 conducted in samples of only men (75,78,79,102), yet no studies conducted in samples of
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44 337 only women. This brings to light important issues of equity and warrants further
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46 338 discussion and consideration.
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3 340 As research continues to develop, it appears likely that lipid and lipoprotein responses are
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5 341 polygenic in nature. Therefore, future research should consider using nutri-GRSs or other
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8 342 polygenic methods of assessing responsiveness to nutrition interventions. This work
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10 343 should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs,
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12 344 such as establishing them from genetic-wide association studies. In addition to the two
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14 345 studies meeting the criteria for evidence grading (65,66), a modified version of the 31-
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16 346 SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs
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18 347 (65). While this did not meet our inclusion criteria for evidence grading given that a
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20 348 different GRS was used, the 23-SNP GRS was significantly associated with TG
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22 349 responsiveness to omega-3 supplementation in this population as well, providing further
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24 350 evidence for the scientific validity of this nutrigenetic interaction (65).
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30 352 While we used the GRADE approach to evaluate the body of evidence, several tools are
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32 353 available for evaluating the quality of scientific evidence, though no generally accepted
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34 354 methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a
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36 355 set of guidelines to assess the scientific validity of genotype-based dietary advice (30).
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38 356 While we originally intended to use these guidelines for assessing the evidence, we came
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40 357 across some limitations that ultimately led us to use the GRADE guidelines. Specifically,
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42 358 Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines
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44 359 should be included in the assessment of scientific validity (30). However, limiting the
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46 360 evidence to only these studies could result in several important studies being missed. In
47
48 361 the present review, none of the included studies explicitly indicated that they followed
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50 362 STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA
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3 363 guidelines to assess risk of bias (30). However, the STREGA checklist is only intended
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5 364 for observational genetic association studies - not interventional research (103). In the
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8 365 present review, 42 of the 65 included studies were interventional (65%) (Supplementary
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10 366 Table 3). In addition, the STREGA guidelines are intended to improve the transparency
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12 367 and adequate reporting of genetic association studies, but it is not intended to be used as a
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15 368 study quality assessment tool (103). However, Grimaldi et al. nicely highlighted the
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17 369 importance of understanding the nature of the genetic variation, at a functional level,
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19 370 when assessing scientific validity (30). This is not included in the standard GRADE
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21 371 approach but is an important niche component of nutrigenetic research. As such, an
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23 372 analysis of functional SNPs (biological plausibility) was included as an additional
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25 373 component of the standard GRADE process, as indicated in the methods section above.
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28 374 Overall, we found that the methods used in this systematic review were effective and can
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31 375 be used to synthesize and evaluate nutrigenetic studies assessing other gene-nutrient-
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33 376 health outcome interactions.

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38 378 The additional consideration of functional SNPs to the standard GRADE approach helped
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40 379 to strengthen this review, as biological mechanistic evidence can help ensure that study
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42 380 findings did not occur by chance alone, and this is a component of evidence evaluation
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44 381 frameworks in medical genetics (104,105). Transcriptomic and pathway analyses can
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46 382 help inform the direction of future nutrigenetic studies by generating hypotheses about
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48 383 the impact of specific genetic variations on varying responses to nutrition on health-
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50 384 related outcomes. For example, using transcriptomics and pathway analyses to identify
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52 385 changes in lipid metabolism following omega-3 supplementation, Rudkowska and
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3 386 colleagues identified six genes expressed in opposite directions between responders and
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5 387 non-responders to omega-3 supplementation for TG lowering: *FADS2*, *PLA2G4A*,
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7 388 *ALOX15*, *PEMT*, *MGLL* and *GPAM* (106). Tremblay et al. then built on this knowledge
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10 389 and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689,
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12 390 *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3
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14 391 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a
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16 392 significant impact on the TG lowering effect of omega-3 supplementation (107). Others
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18 393 have built on this mechanistic knowledge as well (108). Future research should now seek
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20 394 to replicate this work given that we found that there have been no replication studies
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22 395 completed and thus, this research (107,108) did not meet the criteria for evidence
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24 396 grading.

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30 398 In the current body of literature, there are some limitations that should be highlighted.
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32 399 Given the variability in allele frequencies for each SNP, it should be noted that study
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34 400 limitations can arise with small sample sizes whereby some genotype groups may not be
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36 401 adequately powered to detect significant differences. For example, Dawczynski et al.
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38 402 (2013) detected significant changes in TG among the GA genotype group of *CD36*
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40 403 rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA:
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42 404 n=8, GG: n=7) exhibited a significant difference, despite similar directions and
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44 405 magnitudes of effect among the GA and GG genotypes (82). It is thus possible that this
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46 406 study was not adequately powered. Some researchers aim to mitigate this issue of small
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48 407 numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for
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50 408 the minor allele) (69). However, such an approach precludes the possibility to detect an
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3 409 allele-dosage effect. From a physiological perspective, an allele dosage effect would be
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5 410 expected whereby a significant change among a heterozygote group would likely be
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7 411 accompanied by a significant change in one of the homozygote groups but with an even
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9 412 greater magnitude of the effect. This consideration highlights the importance of having an
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11 413 adequately powered sample size, while factoring in the prevalence of each genotype.
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17 415 While single SNP research provides important information about individual gene-nutrient
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19 416 interactions, the results of this review indicate that individual responses to omega-3s for
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21 417 altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus,
22
23 418 we encourage researchers to further explore the use of nutri-GRSs to improve the
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25 419 accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et
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27 420 al., which obtained a high quality evidence grade in the present review (65,66). This is
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29 421 further exemplified in the analyses recently conducted by Chen et al. (42), which has yet
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31 422 to be replicated and thus was not selected for evidence grading.
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37 424 The present analysis of scientific validity provides an important first step towards the
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39 425 eventual development of clinical practice guidelines for genetic-based responses to
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41 426 dietary intake. With questionable and variable scientific validity of existing consumer
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43 427 nutrigenetic tests, the development of clinical practice guidelines is an important next
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45 428 step as these can be used by HCPs and industry alike to help promote evidence-based
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47 429 practice in personalized nutrition. Ideally, industry should use future clinical practice
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49 430 guidelines to inform the nutrigenetic associations and related dietary recommendations
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51 431 included in their reports. Decision aids can also be useful to guide clinical practice for
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3 432 HCPs (109), and future research should seek to develop a decision aid related to omega-
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5 433 3s and lipid/lipoprotein outcomes based on genetic variation.
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10 435 Overall, we have provided a comprehensive overview the body of evidence related to
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12 436 nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing
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14 437 an overview of levels of evidence in this field. To our knowledge, this is the first
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16 438 systematic review with GRADE evidence evaluation in the broader field of nutrigenetics.
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19 439 The results of this work should be used in clinical practice guideline development, to
20
21 440 ultimately guide evidence-based practice in personalized nutrition and move this
22
23 441 emerging field forward.
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26 442

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30 446 Nutrition Applied to Genetics and Metabolic Health.
31
32 447

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34
35 449 for the search strategy, in collaboration with J.K., M-C.V., S.D. and V.G. J.K. and V.G. were
36
37 450 responsible for article screening and selection, summarizing, evidence grading, and developing a
38
39 451 draft of the systematic review. The first systematic review draft underwent revisions from S.D. and
40
41 452 M-C.V., who provided overall supervision for the project. Following this, J.K., V.G., V.M.,
42
43 453 D.M.M., J.R., I.R., G.S., S.D., and M-C.V. served as scientific advisors and reviewed and revised
44
45 454 the full-text manuscript. J.K. wrote the first draft of the manuscript. J.K., V.G., V.M., D.M.M., J.R.,
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47 455 I.R., G.S., S.D., and M-C.V., reviewed, revised and approved the final manuscript.
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4
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6
7 459 Vohl holds a Canada Research Chair in Genomics Applied to Nutrition and Metabolic Health.
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10 460 **Data Sharing Statement:** Data are available upon reasonable request.
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463 **Figure Legend:**

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465 **Figure 1. PRISMA Flow Diagram**

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

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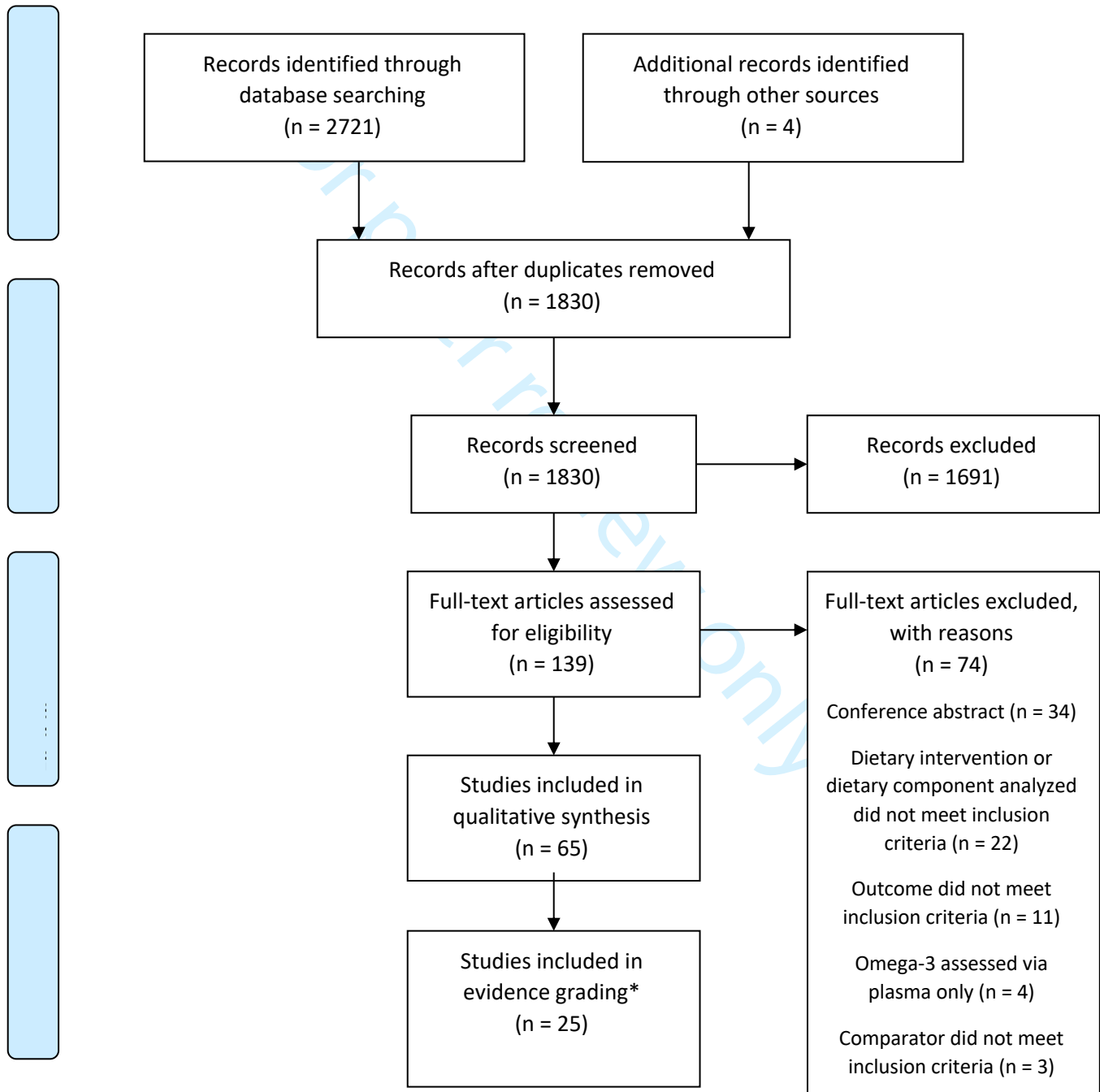
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Figure 1: PRISMA 2009 Flow Diagram



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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 'personalized 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 "personalized 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

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#	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 "personalized 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 drosophila 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)	<i>PPARα</i> , L162V (rs1800206) <i>PPARγ</i> , P12A (rs1801282) <i>PPARδ</i> , -87T→C (rs2016520)	<i>PPARα</i> : 22q13.31 <i>PPARγ</i> : 3p25.2 <i>PPARδ</i> : 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 <i>PPARα</i> L162V (rs1800206) polymorphism, the interaction of <i>PPARα</i> 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)	<i>MC4R</i> , rs17782313 <i>TCF7L2</i> , rs12255372 <i>TCF7L2</i> , rs7903146	<i>MC4R</i> : 18q21.32 <i>TCF7L2</i> : 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 <i>TCF7L2</i> 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 <i>FADS1-FADS2-FADS3</i> gene cluster and variation within 200kb upstream and downstream of the <i>FADS</i> region	<i>FADS1</i> : 11q12.2 <i>FADS2</i> : 11q12.2 <i>FADS3</i> : 11q12.2	High: >1.6 g/day Low: <1.6 g/day (food)	Entire <i>FADS</i> region gene-centric analysis and Variation in individual <i>FADS</i> 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 <i>FADS</i> 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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.

1 2 3 4 5 6 7 8 9	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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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	--
10 11 12 13 14 15 16 17 18	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)	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E4 vs. <i>APOE</i> -E4+	Total-c	Total-c: Cross-sectional (baseline) analysis demonstrated a significant genotype effect for <i>APOE</i> , omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for <i>APOE</i> , change in omega-3 intake (increase or decrease) and total-c.
19 20 21 22 23 24	Fontaine-Bisson and El-Sohemy 2007 (8)	Cross-Sectional	Genetic Score	Men and women aged 20-29 years (n=595)	<i>TNFα</i> , rs361525, rs1800629	<i>TNFα</i> : 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	--
25 26 27 28	Fontaine-Bisson et al. 2009 (9)	Cross-Sectional	Single SNP	Healthy men and women aged 20-29 years (n=593)	<i>NF-κB</i> -94Ins/Del ATTG (rs28362491)	<i>NF-κB</i> : 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 <i>NF-κB</i> genotype and omega-3 intake on HDL-c
29 30 31 32 33 34 35 36 37 38	Hellstrand et al. 2012 (10)	Cross-Sectional	Single SNP	Healthy men and women aged 45-68 years from Sweden (n=4635)	<i>FADS</i> , rs174547	<i>FADS</i> : 11q12.2	Low: \leq 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 <i>FADS</i> 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.
39 40 41 42 43 44 45 46 47	Hosseini-Esfahani et al. 2017 (11)	Nested Case-Control	Single SNP	Healthy men and women aged \geq 18 years from Iran	<i>ZNT8</i> , rs13266634	<i>ZNT8</i> : 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 <i>ZNT8</i> 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 <i>ZNF78</i> 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)	<i>PCSK5</i> , rs1029035	<i>PCSK5</i> : 9q21.13	Based on overall median intake (further detailed elsewhere (12)): Low: <0.4 %kcal (food) High: >0.4 %kcal (food)	CC vs. CA vs. AA	HDL-c	HDL-c: Significant interaction between <i>PCSK5</i> 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)	<i>TNFA</i> , rs1800629	<i>TNFA</i> : 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 <i>TNFA</i> , 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)	<i>TNFA</i> , rs361525	<i>TNFA</i> : 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 <i>TNFA</i> , 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 <i>TNFA</i> 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 <i>TNFA</i> rs361525.
Joffe et al. 2014 (15)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=268)	<i>IL-6</i> , -174 G>C, IVS3 (rs1800795), +281 G>T, IVS4 (rs1554606), +869 A>G (rs2069845)	<i>IL-6</i> : 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: HDL-c: Significant interaction whereby HDL-c increased with increasing omega-3 and/or DHA and/or ALA intake in <i>IL-6</i> rs1800795 C allele carriers and increasing ALA intake in <i>IL-6</i> rs1554606 T allele carriers. HDL-c decreased with increasing EPA and/or DHA intake in <i>IL-6</i> rs2069845 G allele carriers. TG: Significant interaction whereby TG reduced with increasing EPA intake in <i>IL-6</i> rs1800795 C allele carriers Total-c:HDL-c: Significant interaction whereby total-c:HDL-c ratio decreased with increasing EPA intake in <i>IL-6</i> rs1800795 CC genotypes and <i>IL-6</i> rs1554606 TT genotypes, increasing DHA intake in <i>IL-6</i> rs1800795 CC genotypes, and increasing ALA intake in <i>IL-6</i> rs1554606 TT genotypes.
Lai et al. 2006 (16)	Cross-Sectional	Single SNP	Men and women from the Framingham	<i>APOA5</i> , rs662799, rs651821, rs3135506,	<i>APOA5</i> : 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		omega-3: 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)	<i>FADS</i> , rs174546, rs482548, rs174570	<i>FADS</i> : 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)	<i>ANGPTL4</i> E40K (rs116843064)	<i>ANGPTL4</i> : 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)	<i>PLIN4</i> , rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	<i>PLIN4</i> : 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 <i>PLIN4</i> , 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 LISApplus birth cohort studies (n=1697)	<i>FADS1/FADS2</i> , rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	<i>FADS1/2</i> : 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)	<i>PPARα</i> , L162V (rs1800206)	<i>PPARα</i> : 22q13.31	High: >0.69 %kcal Low: <0.69 %kcal (food)	<i>PPARα</i> : 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)	<i>PPARα</i> , L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	<i>PPARα</i> : 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 <i>PPARα</i> (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)

1 2 3 4 5 6 7	Warodomwich et al. 2009 (23)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	<i>TCF7L2</i> rs7903146, rs12255372	<i>TCF7L2</i> : 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	--
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8 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

9 1. Intakes are total omega-3 unless otherwise specified

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

11 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.”

12 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.

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

14 *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	<i>FADS1</i> , rs174561 <i>FADS2</i> , rs174583 <i>ELOVL2</i> , rs953413 <i>ELOVL5</i> , rs2397142 <i>CETP</i> , rs5882 <i>SCD1</i> , rs2234970, <i>PPARA</i> , rs6008259 <i>LIPF</i> , rs814628 and <i>APOE</i> , rs429358, rs7412	<i>FADS1/2</i> : 11q12.2 <i>ELOVL2</i> : 6p24.2 <i>ELOVL5</i> : 6p12.1 <i>CETP</i> : 16q13 <i>SCD1</i> : 10q24.31 <i>PPARA</i> : 22q13.31 <i>LIPF</i> : 10q23.31 <i>APOE</i> : 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except <i>PPARA</i> and <i>LIPF</i> whereby analyses were major allele homozygotes vs. minor allele carriers) and <i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -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	<i>CETP</i> , rs3764261, <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5/ABCG</i> , rs4299376 <i>TIMD4/HAVCR1</i> , rs6882076 <i>GCKR</i> , rs1260326 <i>TRIB1</i> , rs2954029 <i>ANGPTL3/DOCK7</i> , rs2131925 <i>FADS1/2/3</i> , rs174546 <i>GALNT2</i> , rs4846914 <i>ABCA1</i> , rs4149268 <i>APOE/APOC1/APOC2</i> , rs439401	<i>CETP</i> : 16q13 <i>LIPC</i> : 15q21.3 <i>APOB</i> : 2p24.1 <i>ABCG5/ABCG8</i> : 2p.21 <i>TIMD4/HAVCR1</i> : 5q33.3 <i>GCKR</i> : 2p23.3 <i>TRIB1</i> : 8q24.13 <i>ANGPTL3/DOCK7</i> : 7: 1p31.3 <i>FADS</i> : 11q12.2 <i>GALNT2</i> : 1q42.13 <i>ABCA1</i> : 9q31.1 <i>APOE/APOC1/APOC2</i> : 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 <i>FADS1</i> rs174546

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Armstrong et al. 2012 (26)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	<i>ALOX5</i> , dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	<i>ALOX5</i> : 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	<i>PPARA</i> , L162V (rs1800206), <i>PPARγ2</i> , P12A (rs1801282)	<i>PPARA</i> : 22q13.31 <i>PPARγ2</i> : 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 (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> Pro12Pro genotypes only for individuals with BMI>25.0 kg/m ² Total-c : significant increase in total-c among minor allele carriers (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> 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	<i>SREBF1</i> , rs4925115, rs4925118, rs12953299 <i>ACLY</i> , rs8071753, rs8065502, rs2304497 <i>ACACA</i> rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	<i>SREBF1</i> : 17p11.2 <i>ACLY</i> : 17q21.2 <i>ACACA</i> : 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 <i>ACLY</i> rs8071753 and individuals with the GG or CG genotype of <i>ACACA</i> 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 <i>ACLY</i> 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	<i>RXRα</i> (12 SNPs), <i>CPT1A</i> (9 SNPs), <i>ACADVL</i> (1 SNP), <i>ACAA2</i> (6 SNPs), <i>ABCD2</i> (8 SNPs), <i>ACOX1</i> (8 SNPs), <i>ACAA1</i> (3 SNPs) [outlined in Supplementary Table 5]	<i>RXRα</i> : 9q34.2 <i>CPT1A</i> : 11q13.3 <i>ACADVL</i> : 17p13.1 <i>ACAA2</i> : 18q21.1 <i>ABCD2</i> : 12q12 <i>ACOX1</i> : 17q25.1 <i>ACAA1</i> : 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 <i>RXRα</i> rs11185660 genotype dependent on total fat intake, <i>RXRα</i> rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and <i>ACOX1</i> 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	<i>GCK</i> (13 SNPs) [outlined in Supplementary Table 5]	<i>GCK</i> : 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 <i>GCK</i> 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.

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6	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	<i>PPARA</i> , L162V (rs1800206)	<i>PPARA</i> : 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	--
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14	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -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 <i>APOE</i> -E3/4 carriers (compared to high-SFA diet alone)
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23	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E2/E2 + E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	TG: Significant interaction between treatment x sex x genotype whereby <i>APOE</i> -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
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28	Cormier et al. 2012 (35)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	<i>FADS</i> gene cluster (19 SNPs) [outlined in Supplementary Table 5]	<i>FADS</i> : 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	--
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32	Dang et al. 2015 (36)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	<i>APOE</i> -E4+ vs. <i>APOE</i> -E4-	HDL-c LDL-c TG Total-c	--
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37	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	<i>CD36</i> , rs1761667, rs1049673	<i>CD36</i> : 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 <i>CD36</i> rs1761667 and CG genotype of <i>CD36</i> rs1049673. TG: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of <i>CD36</i> rs1761667.
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							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-I 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

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									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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -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	<i>PPAR</i> γ 2, Pro12Ala (rs1801282)	<i>PPAR</i> γ 2: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	<i>PPAR</i> γ 2, 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 \leq 37 %kcal or SFA intake was \leq 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	<i>FVII</i> , rs6046	<i>FVII</i> : 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	<i>CD36</i> , rs1527483, rs1049673, rs1761667, rs1984112	<i>CD36</i> : 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	<i>TNF</i> α , -308 (rs1800629) <i>LT</i> - α , +252 (rs909253) <i>IL</i> -1 β , -511 (rs16944) <i>IL</i> -6, -174 (rs1800795)	<i>TNF</i> α : 6p21.33 <i>LT</i> - α : 6p21.33 <i>IL</i> -1 β : 2q14.1 <i>IL</i> -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 <i>LT</i> - α rs909253 GG genotype and <i>IL</i> -1 β rs16944 TT genotype. In <i>LT</i> - α rs909253 AA genotype and <i>TNF</i> α 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	<i>FABP</i> 2, rs1799883	<i>FABP</i> 2: 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	--

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3 4 5 6 7	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.0 g/d EPA and DHA, Control oil: 6.0 g/d olive oil capsule (supplement)	<i>APOE</i> -E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -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 <i>APOE</i> -E2/E3 relative to other <i>APOE</i> genotype categories Total-c : 6-week: <i>APOE</i> -E3/E4 + E4/E4 genotype group exhibited significantly different changes in total-c (increase), relative to other <i>APOE</i> genotypes, whereby reductions in total-c occurred
8 9 10 11 12 13	Olano-Martin et al. 2010 (49)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemic men (n=38)	4 weeks per diet	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4 (carriers)	apoB apoE HDL-c LDL-c TG TG:HDL-c Total-c	apoB, LDL-c : In <i>APOE</i> -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 <i>APOE</i> -E3/E3 group; significant reduction in TG in <i>APOE</i> -E4 carriers with EPA only. No significant interactions. Total-c : Significant genotype x treatment interaction whereby <i>APOE</i> -E4 carriers exhibit total-c reductions in response to EPA-rich oil.
14 15 16 17 18 19	Quellette et al. 2013 (50)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (n=210)	6 weeks	<i>GPAM</i> (3 SNPs), <i>AGPAT3</i> (13 SNPs), <i>AGPAT4</i> (35 SNPs) [outlined in Supplementary Table 5]	<i>GPAM</i> : 10q25.2 <i>AGPAT3</i> : 21q22.3 <i>AGPAT4</i> : 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 <i>GPAM</i> , rs2792751 genotype x supplementation interaction on LDL-c TG : Significant genotype x supplementation interaction on TG for <i>GPAM</i> , rs2792751 and rs17129561 as well as <i>AGPAT4</i> , rs9458172 and rs3798943
20 21 22 23 24 25 26 27 28	Quellette et al. 2014 (51)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18-50 years (n=208)	6 weeks	<i>MGLL</i> (18 SNPs) [outlined in Supplementary Table 5]	<i>MGLL</i> : 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 <i>MGLL</i> 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 <i>MGLL</i> 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)
29 30 31 32	Paschos et al. 2005 (52)	Single-Arm Clinical Trial	Single SNP*	Men with dyslipidemia, aged 35 to 67 years (n=50)	12 weeks	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	<i>APOE</i> -E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -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
33 34 35 36 37 38 39 40	Pishva et al. 2010 (53)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	<i>FABP2</i> , Ala54Thr (rs1799883)	<i>FABP2</i> : 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.
41	Pishva et al.	Single-Arm	Single SNP	Adults with	8 weeks	<i>PPARα</i> ,	<i>PPARα</i> : 22q13.31	2.0 g/day pure	Leu162	ApoB	--

2014 (54)	Clinical Trial		hypertriglyceridemia (n=46)		Leu162Val (rs1800206) <i>PPARα</i> , Intron 7 SNP		EPA (supplement)	vs. Val162 carriers <i>and</i> 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)	<i>FADS1</i> , rs174537 <i>FADS2</i> , rs174576 (LD=1.0 therefore presented results for rs174537)	<i>FADS1/2</i> : 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	<i>SCD1</i> , rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	<i>SCD1</i> : 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 <i>SCD1</i> 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: <i>IQCJ-SCHIP1</i> (4 SNPs), <i>SLIT2</i> (3 SNPs), <i>PHF17</i> (3 SNPs), <i>MYB</i> (1 SNP), <i>NXP1</i> (1 SNP), <i>NELL1</i> (1 SNP) [outlined in Supplementary Table 5]	<i>IQCJ-SCHIP1</i> : 3q25.32 <i>SLIT2</i> : 4p15.31 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 6q23.3 <i>NXP1</i> : 7p21.3 <i>NELL1</i> : 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	<i>PNPLA3</i> , 1148M (rs738409) <i>TM6SF2</i> , E167K (rs58542926)	<i>PNPLA3</i> : 22q13.31 <i>TM6SF2</i> : 19p13.11	1.8 g/day EPA+ 1.5 g/day DHA (supplement)	Comparison between three genotypes <i>and</i> 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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	<i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -E4	apoB HDL-c LDL-c TG Total-c	--
Tremblay et	Single-Arm	Single SNP	Healthy men	6 weeks	<i>PLA2G2A</i> (5)	<i>PLA2G2A</i> :	Fish oil containing	Major allele	apoB-100	TG: omega-3 supplementation significantly reduced TG in

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3 4 5 6 7 8 9 10 11 12 13	al. 2015 (60)	Clinical Trial		and women aged 18-50 years (n=208)		SNPs), <i>PLA2G2C</i> (6 SNPs), <i>PLA2G2D</i> (8 SNPs), <i>PLA2G2F</i> (6 SNPs), <i>PLA2G4A</i> (22 SNPs), <i>PLA2G6</i> (5 SNPs), <i>PLA2G7</i> (9 SNPs) [outlined in Supplementary Table 5]	1p36.13 <i>PLA2G2C</i> : 1p36.13 <i>PLA2G2D</i> : 1p36.12 <i>PLA2G2F</i> : 1p36.12 <i>PLA2G4A</i> : 1q31.1 <i>PLA2G6</i> : 22q13.1 <i>PLA2G7</i> : 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	<i>PLA2G7</i> rs1805018 as well as <i>PLA2G4A</i> rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, <i>PLA2G6</i> rs132989, <i>PLA2G7</i> rs679667, <i>PLA2G2D</i> rs12045689, <i>PLA2G4A</i> rs 10752979 and rs1160719 together explained 5.9% of post-supplementation TG levels
14 15 16 17 18 19 20 21 22 23 24 25	Vallée Marcotte et al. 2016 (61)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Men and woman aged 18-50 years (n=208)	6 weeks	<i>IQCJ</i> (16 SNPs), <i>NXPPI</i> (34 SNPs), <i>PHF17</i> (8 SNPs), <i>MYB</i> (9 SNPs) [outlined in Supplementary Table 5]	<i>IQCJ</i> : 3q25.32 <i>NXPPI</i> : 7p21.3 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 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: <i>IQCJ</i> (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), <i>NXPPI</i> (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), <i>MYB</i> (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 <i>IQCJ</i> ; rs7805772 in <i>NXPPI</i> . There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in <i>IQCJ</i> , rs7805772 in <i>NXPPI</i> and rs11154794 in <i>MYB</i> . Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for <i>IQCJ</i> rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, <i>NXPPI</i> rs7806226, rs7805772, <i>MYB</i> rs11154794 and rs210936.
26 27 28 29 30 31 32	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 (<i>NXPPI</i> rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and <i>IQCJ-SCHIP1</i> 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.
33 34 35 36 37	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).
38 39 40 41	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.

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			years (n=122)					Non-Responders vs. Adverse Responders <i>and</i> Responders vs. Adverse Responders			
3 4 5 6 7 8 9 10 11	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	<i>eNOS</i> Glu298Asp (rs1799983)	<i>NOS3</i> : 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	--
12 13 14 15 16 17 18 19	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 postmenopausa l and 80 years for women (n=139)	25 weeks	<i>CD36</i> , rs1527483 <i>NOS3</i> , rs1799983 <i>PPARγ2</i> , rs1801282	<i>CD36</i> : 7q21.11 <i>NOS3</i> : 7q36.1 <i>PPARγ2</i> : 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 <i>PPARγ2</i> rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of <i>PPARγ2</i> rs1801282 compared to CC genotype <i>only in the control</i> (corn oil) group TG : omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the <i>CD36</i> 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

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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
<i>APOE</i> : 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)
<i>APOE</i> : 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>CD36</i> : rs1761667	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1761667	TG	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1049673	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1527483	TG	Madden et al. 2008 (45) Zheng et al. 2018 (66)
<i>FADS</i> : 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)	<p><i>FADS2</i>, rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276</p> <p><i>FADS3</i>, rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285</p> <p><i>RAB31L1</i>, rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252</p>
Cormier et al. 2012	<p><i>FADS</i> gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567</p>
Vallée Marcotte et al. Am J Clin Nutr;109:176–185 (2019)	<p><i>IQCJ-SCHIP1</i>, rs7639707, rs62270407</p> <p><i>NXPH1</i>, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523</p> <p><i>PHF17</i>, rs1216346, rs114348423, rs75007521</p> <p><i>MYB</i>, rs72560788, rs72974149, rs210962, rs6933462</p> <p><i>NELL1</i>, rs79624996, rs1850875, rs78786240, rs117114492</p> <p><i>SLIT2</i>, rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249</p>
Tremblay et al. Lipids in Health and Disease (2015) 14:12	<p><i>PLA2G2A</i>, rs876018, rs955587, rs3753827, rs11573156, rs11573142</p> <p><i>PLA2G2C</i>, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718</p> <p><i>PLA2G2D</i>, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671</p> <p><i>PLA2G2F</i>, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904</p>

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

	rs11651351, rs3643, rs7213998, rs17583163 <i>ACAA1</i> , rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	<i>CETP</i> , rs3764261, rs247616, rs7205804 <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5</i> , <i>ABCG8</i> , rs4299376 <i>TIMD4</i> , <i>HAVCR1</i> , rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 <i>ANGPTL3</i> , <i>DOCK7</i> , rs3850634, rs1167998, rs2131925 <i>FADS1</i> , <i>FADS2</i> , <i>FADS3</i> , rs174550, rs174547, rs174546, rs174583 <i>GALNT2</i> , rs4846914, rs1321257 <i>ABCA1</i> , rs4149268 <i>APOE</i> , <i>APOC1</i> , <i>APOC2</i> , rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	<i>IQCJ-SCHIP1</i> , rs7639707, rs62270407 NXP1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 <i>PHF17</i> , rs1216346, rs114348423, rs75007521 <i>MYB</i> , rs72560788, rs72974149, rs210962, rs6933462 <i>NELL1</i> , rs79624996, rs1850875, rs78786240, rs117114492 <i>SLIT2</i> , rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	<i>IQCJ-SCHIP1</i> , <i>MYB</i> , <i>NELL1</i> , <i>NXP1</i> , <i>PHF17</i> , <i>SLIT2</i> , rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	<i>IQCJ</i> , rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	<p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308</p>
<p>Vallée Marcotte et al. Nutrients; 11, 737 (2019)</p>	<p><i>IQCJ-SCHIP1</i>, 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</p> <p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, <i>SLIT2</i>, rs2952724</p> <p><i>NELLI</i>, rs752088</p>

Supplementary Table 6: 31-SNP Nutri-GRS

Gene, rs Number	Alleles ¹	Associated Points
<i>IQCJ-SCHIP1</i> , rs7639707	<u>A</u> /G	+1
<i>IQCJ-SCHIP1</i> , rs62270407	C/ <u>T</u>	-1
<i>NXPH1</i> , rs61569932,	<u>G</u> /T	+1
<i>NXPH1</i> , rs1990554	<u>A</u> /C	+1
<i>NXPH1</i> , rs6463808	<u>A</u> /G	+1
<i>NXPH1</i> , rs6966968	<u>A</u> /G	+1
<i>NXPH1</i> , rs28473103	<u>A</u> /G	-1
<i>NXPH1</i> , rs28673635	<u>A</u> /G	+1
<i>NXPH1</i> , rs12702829	<u>C</u> /T	+1
<i>NXPH1</i> , rs78943417	A/ <u>T</u>	-1
<i>NXPH1</i> , rs293180	G/ <u>T</u>	+1
<i>NXPH1</i> , rs1837523	<u>C</u> /T	-1
<i>PHF17</i> , rs1216346	<u>C</u> /T	+1
<i>PHF17</i> , rs114348423	<u>A</u> /G	+1
<i>PHF17</i> , rs75007521	<u>G</u> /T	-1
<i>MYB</i> , rs72560788	<u>C</u> /T	-1
<i>MYB</i> , rs72974149	<u>A</u> /G	-1
<i>MYB</i> , rs210962	<u>C</u> /T	-1
<i>MYB</i> , rs6933462	<u>C</u> /G	+1
<i>NELL1</i> , rs79624996	<u>A</u> /G	+1
<i>NELL1</i> , rs1850875	<u>C</u> /T	+1
<i>NELL1</i> , rs78786240	<u>C</u> /T	-1
<i>NELL1</i> , rs117114492	<u>G</u> /T	+1
<i>SLIT2</i> , rs184945470	<u>C</u> /T	+1
<i>SLIT2</i> , rs143662727	<u>A</u> /G	-1
<i>SLIT2</i> , rs10009109	<u>C</u> /T	+1
<i>SLIT2</i> , rs10009535	<u>A</u> /G	+1
<i>SLIT2</i> , rs61790364	<u>A</u> /G	+1
<i>SLIT2</i> , rs73241936	<u>C</u> /T	+1
<i>SLIT2</i> , rs16869663	<u>A</u> /G	+1
<i>SLIT2</i> , rs76015249	<u>A</u> /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)
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Page 1 of 2

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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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
For more information, visit: www.prisma-statement.org.

Page 2 of 2

For peer review only

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

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

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

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

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

29 ABSTRACT

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

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

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

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

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

67 STRENGTHS AND LIMITATIONS

68 - Strength: Comprehensive systematic review guided by PRISMA

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3 69 - Strength: Critical appraisal of the evidence guided by GRADE
4 70 - Limitation: Inability to conduct a meta-analysis given the comprehensive
5 71 overview of studies and thus heterogeneity
6 72 - Limitation: Several included studies without replication; most evidence was low
7 73 or very low quality according to GRADE
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74 INTRODUCTION

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76 Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research
77 demonstrates that there is significant inter-individual variability in cardiometabolic risk
78 factor levels, in part based on a combination of genetic and nutrition-related risk factors
79 (2,3). For example, protein intake has consistently been shown to influence measures of
80 body weight and composition dependent on *FTO* genotype (rs9939609 or loci in strong
81 linkage disequilibrium) (4,5). Consumers indicate great interest in personalized nutrition
82 based on genetics (6,7), however, a lack of industry oversight (8,9) has led to highly
83 variable scientific validity of nutrigenetic tests available to consumers. While recognizing
84 that some groups question whether genetic testing for personalized nutrition is ready for
85 ‘prime time’, Gorman and colleagues suggested that there are certain specific nutrigenetic
86 interactions with strong evidence that could be considered for implementation into
87 clinical practice by expert committees who are responsible for creating dietary guidelines
88 (10). With this in mind, systematic reviews that include an evaluation of levels of
89 evidence are urgently needed in order to determine if there are any nutrigenetic
90 associations that may warrant potential implementation into practice.

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

1
2
3 97 terms of their lipid and lipoprotein lowering effects, omega-3s have consistently
4
5 98 demonstrated an impact on triglycerides (TG) (14). High-quality evidence from
6
7 99 population-based studies suggests that long-chain omega-3s (EPA and DHA) reduce
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10 100 plasma TG by about 15% (14). There is also high-quality evidence suggesting that EPA
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12 101 and DHA can raise high-density lipoprotein (HDL) cholesterol (14). Other studies have
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14 102 further demonstrated a relationship between omega-3 and HDL-cholesterol (15), low-
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16 103 density lipoprotein (LDL)-cholesterol (15), total cholesterol (16–18), apolipoproteins
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18 104 (19), and LDL particle size (20). Despite several studies with significant findings for
19
20 105 these outcomes, when reviewing the evidence, studies have demonstrated conflicting
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22 106 results for the impact of omega-3 on many lipid profile outcomes (14). Genetic variation
23
24 107 could explain this heterogeneity. EPA and DHA have been shown to significantly impact
25
26 108 the expression of thousands of genes including those involved in inflammatory and
27
28 109 atherogenic pathways (21,22). Evidence now demonstrates that the health impacts of
29
30 110 omega-3 intake could differ based on genetic variation (23,24). Despite the potential for
31
32 111 omega-3s to have a significant positive impact on health outcomes, population intakes of
33
34 112 omega-3s tend to be low (25). While the World Health Organization's Adequate Intake
35
36 113 level for adults is 200-250 mg EPA+DHA daily (26,27), the mean reported intake of
37
38 114 EPA+DHA in the United States is only approximately 100 mg daily (25). Nutrigenetic
39
40 115 interventions have the potential to motivate improvements in dietary intake beyond
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42 116 population-based interventions (28). Additionally, evidence suggests that genetic
43
44 117 variability affects health responses to omega-3s (23). Thus, critically appraising and
45
46 118 grading the evidence for nutrigenetic interactions related to omega-3s and plasma lipids,
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48 119 lipoproteins and apolipoproteins is an important research priority. The most recent
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3 120 systematic review on nutrigenetic interactions related to omega-3s and intermediate
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5 121 phenotypes of cardiovascular disease was conducted nearly a decade ago, and this study
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7 122 did not evaluate the quality of evidence using an established methodology (29).
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10 123 Therefore, we aimed to provide a comprehensive summary of current evidence related to
11
12 124 inter-individual variability in plasma lipid, lipoprotein and apolipoprotein responses to
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14 125 omega-3 intake (plant and marine sources) based on genetic variations. Overall, the
15
16 126 specific objectives of this study were as follows:

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20 127 **Objective 1.** Systematically search, identify (select), and provide a narrative
21
22 128 synthesis of all studies that assessed nutrigenetic associations/interactions for genetic
23
24 129 variants (comparators; i.e. outcomes in those with a specific genotype for a genetic
25
26 130 variant compared to a different genotype) influencing the plasma lipid, lipoprotein
27
28 131 and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake
29
30 132 (intervention/exposure) in humans – both pediatric and adult populations
31
32 133 (population).

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37 134 **Objective 2.** Assess the overall quality of evidence for specific priority nutrigenetic
38
39 135 associations/interactions based on the following inclusion criteria: nutrigenetic
40
41 136 associations/interactions reported for the same genetic variants (comparators)
42
43 137 influencing the same plasma lipid, lipoprotein and/or apolipoprotein response
44
45 138 (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both
46
47 139 pediatric and adult populations (population) in two independent studies, irrespective
48
49 140 of the findings.
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3 **142 Methods**

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5 144 **Patient and Public Involvement:** No patient involvement.

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7
8 145 *Literature Search*

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10
11 146 The systematic review protocol was registered with PROSPERO (CRD42020185087).

12
13 147 The review process was guided by previously established methods, including a
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15 previously outlined five-step systematic review process (30,31). The search engines
16 148 Embase, Web of Science and Medline OVID were used to conduct the search starting in
17
18 149 May 2020 and screen for articles meeting inclusion criteria, using the comprehensive
19
20 150 search terms outlined in Supplementary Table 1, properly combined by Boolean
21
22 151 operators. The literature was searched up until August 1, 2020 (there was no minimum
23
24 152 start date; any article published prior to this date was included in the search). A PRISMA
25
26 153 diagram (Figure 1) guided the article screening process (32).
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33 155 *Inclusion and Exclusion Criteria*

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36 156 Original studies were included if they were written in English or French. Inclusion
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38 157 criteria were developed using the Population, Intervention, Comparison, Outcomes,
39
40 158 (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (33,34) for
41
42 159 interventional and observational research, respectively. These are detailed in Table 1 for
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44 160 each study objective.
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49 161 **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

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

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

181 prioritized for evidence grading. This is further detailed in Table 1 and the section below
182 entitled “Evidence Grading.”

183 *Article Selection and Data Extraction*

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

199 *Evidence Grading*

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

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3 203 evidence grading, if a specific nutrigenetic association/interaction was reported in at least
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5 204 two independent studies. To clarify, this refers to the same SNP(s)/nutri-GRS [or SNPs
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8 205 in strong linkage disequilibrium (LD)] being assessed and influencing the same
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10 206 lipid/lipoprotein outcome in at least two studies. For these nutrigenetic
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12 207 associations/interactions, we proceeded with evidence grading, while including **all**
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14 208 studies relevant to the particular nutrigenetic association/interaction, irrespective of the
15
16 209 findings. Consistency of results was then one of several factors considered when grading
17
18 210 the body of evidence. The Grading of Recommendations Assessment, Development and
19
20 211 Evaluation (GRADE) approach indicates that a single study rarely (if ever) results in
21
22 212 strong evidence, but two studies (typically RCTs) can indicate strong evidence if they are
23
24 213 graded highly using the GRADE criteria (36). Prior to selecting the nutrigenetic
25
26 214 associations/interactions (genetic variants and lipid/lipoprotein/apolipoprotein outcomes)
27
28 215 for evidence grading, LD was assessed using the SNIPA SNP Annotator Software (37)
29
30 216 for genes located on the same chromosome and arm (determined using the Online
31
32 217 Mendelian Inheritance in Man® [OMIM] database) as outlined in the summary of
33
34 218 results' tables in the column labelled 'Cytogenic Location of Gene(s)' (Tables 1 and 2).
35
36 219 Strong LD was defined as $r^2 > 0.8$ and location < 250 kb away from the index SNP
37
38 220 location. SNPs in strong LD were considered together for the purposes of evidencing
39
40 221 grading.

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43 222 Based on our abovementioned predetermined criteria for specific nutrigenetic topic
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45 223 selection for evidence grading, nutrigenetic associations/interactions that were not
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47 224 included in the evidence grading process likely have weak evidence (at minimum due to
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49 225 lack of replication, for example, *ZNT8* rs13266634 and HDL-c or TG responsiveness to
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3 226 omega-3, which has only been assessed in a single study (38)). According to the GRADE
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5 227 guidelines, when only a single study exists indicating significant findings for an outcome
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7 228 of interest (especially when the study is observational), the overall quality of the evidence
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10 229 is generally rated to be low or very low (39). Therefore, our process for prioritizing
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12 230 nutrigenetic topics for evidence grading aimed to filter out specific nutrigenetic
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14 231 associations/interactions that would likely be deemed low or very low quality (based on,
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16 232 at minimum, lack of replication). Two authors (JK and VG) critically appraised the
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18 233 selected nutrigenetic interactions using the GRADE methodology (39,40). Nutrigenetic
19
20 234 interactions were grouped according to studies assessing the same SNP(s)/nutri-GRS and
21
22 235 lipid/lipoprotein/apolipoprotein outcome, and the quality of the body of evidence (studies
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24 236 with significant and non-significant results) was rated; this process was guided by the
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26 237 GRADE Evidence Profile, which included consideration of risk of bias, inconsistency,
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28 238 indirectness, imprecision, publication bias, plausible confounding, dose-response and
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30 239 other factors (39). For example, different sources of omega-3s (e.g. EPA+DHA vs. ALA;
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32 240 food sources vs. supplementation) were taken into consideration when grading the
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34 241 evidence through the analysis of indirectness within the GRADE approach (39,40). Risk
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36 242 of bias was assessed in each of the included interventional and observational studies
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38 243 using the National Institutes of Health Study Quality Assessment Tools, in line with
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40 244 recently published recommendations for risk of bias assessments (41). To assess
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42 245 measures of precision, coefficients of variation (CV) were calculated based on outcome
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44 246 means (mean change or absolute values – whichever was used for the analyses) and
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46 247 standard deviations. In cases where standard errors of the mean were reported, these were
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48 248 converted to standard deviations to calculate the CV. The nutrigenetic interactions were
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249 each given an evidence grade of high, moderate, low or very low.

250 **Results**

251
252 Figure 1 outlines the PRISMA Flow Diagram, which was used to guide the systematic
253 review. Supplementary Tables 2 and 3 provide a summary of the 65 included studies. The
254 results columns of Supplementary Tables 2 and 3 (far right) indicate nutrigenetic findings
255 that were statistically significant. Any results related to the studies' analyzed SNPs and
256 outcomes of interest that were not statistically significant are not indicated in the results
257 column. No studies explicitly reported that they followed STREGA guidelines. LD
258 analysis of SNPs tested in different studies revealed strong LD in several SNPs from the
259 *FADS* gene cluster (see Table 2 footnote). As such, LD was taken into consideration in
260 the selection of nutrigenetic interactions selected for evidence grading.

261 *Observational Studies*

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

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

282 *Interventional Studies*

283 Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-
284 randomized studies included single arm clinical trials and sequential non-randomized
285 cross-over interventions. For interventional studies, n=6,225 participants upon combining
286 all sample sizes of the included studies. Again, these studies assessed relationships
287 between a number of different genetic variants and study outcomes. In more recent years,
288 several studies (n=8) used a nutri-GRS or polygenic approaches (61–68) given the
289 plausibility that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are
290 polygenic in nature. Numerous studies assessed genetic variations in the *FADS* gene
291 cluster (61,62,69–71), *APOE* (61,71–80), *CD36* (67,81,82), *PPAR γ 2* (62,67,83–85) and
292 *PPAR α* (83,86,87). Among these studies, results related to significant gene-diet (omega-
293 3) associations influencing lipid/lipoprotein outcomes were generally inconsistent except
294 for *APOE* (rs429358 and rs7412), omega-3 and TG in males only (71–75,77–80), and for

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3 295 a 31-SNP nutri-GRS, omega-3 and TG (65,66). There was also consistent evidence to
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5 296 indicate a lack of association among *PPAR* γ 2 (rs1801282) genetic variation, EPA+DHA
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7 297 and LDL cholesterol (62,67,84,85,88). Most studies (n=40) used supplemental EPA
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9 298 and/or DHA sources of omega-3s for the dietary intervention (see Supplementary Table
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11 299 3). The dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages
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13 300 ranging from 0.5-3.7 g/day across different studies, and one study with an ALA
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15 301 intervention dosage of 8.1 g/day, as further detailed in Table 3.
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20 302 *Levels of Evidence Using GRADE*

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23 303 A total of 25 articles were included in the evidence grading process, representing 11
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25 304 unique nutrigenetic associations/interactions as outlined in Tables 2 and 3, and
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27 305 Supplementary Table 4. Through the GRADE process, it was determined that there is
28
29 306 strong evidence (GRADE rating: moderate quality) for *APOE* genotypes (rs7412,
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31 307 rs429358), omega-3s and TG lowering in male adults only (71–75,77–80). This evidence
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33 308 suggests that adult males (but not females) with the *APOE*-E3/E4 or E4/E4 genotype
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35 309 (rs429358, rs7412) tend to experience significant reductions in TG in response to 0.7-3.7
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37 310 g/day of EPA and/or DHA, with higher dosages demonstrating greater TG lowering
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39 311 effects (71–75,77–80). Furthermore, it was determined that there is strong evidence
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41 312 (GRADE rating: high quality) for using a 31-SNP nutri-GRS (detailed in Supplementary
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43 313 Tables 5 and 6) to assess the effectiveness of omega-3s for TG lowering in adults with
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45 314 overweight/obesity in various ethnicities (65,66). The evidence suggests that in adults
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47 315 with overweight/obesity, lower genetic risk scores demonstrate greater responsiveness to
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49 316 omega-3 supplementation (65,66).
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3 317 All other evidence that was evaluated was determined to be weak (GRADE rating: low or
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5 318 very low quality), as further detailed in Table 2. Imprecision, indirectness, and
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7 319 inconsistency were common reasons for downgrading the evidence (refer to Table 2
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9 320 footnote). There was evidence for a plausible mechanism of action for most of the
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11 321 nutrigenetic interactions that were graded; evidence of a dose response was less common.
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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 <i>CD36</i> 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 <i>CD36</i> 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 <i>CD36</i> 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 <i>CD36</i> 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 <i>APOE</i> -E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

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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, <i>APOE</i> (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, <i>APOE</i> (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, <i>APOE</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>FADS</i> (rs174547**) does not influence total-c responses to omega-3.

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sectional studies (n=9365) (44,45,47,48,61,69,71)									
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*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*, *NXP1*, *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

<i>CD36, rs1761667 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1761667 and TG</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1049673 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1527483 and TG</i>	
Study	Risk of Bias
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
<i>ApoE, rs429358, rs7412 and TG</i>	
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	⊕
<i>ApoE, rs429358, rs7412 and Total-c</i>	
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	⊕
<i>31-SNP Nutri-GRS and TG</i>	
Study	Risk of Bias
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

<i>PPARG2</i> , 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	⊕
<i>PPARG2</i> , 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	⊕
<i>PPARG2</i> , 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	⊕
<i>FADS</i> , 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

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5 273 Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and
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8 274 high quality evidence) for only a limited amount of evidence in this area: *APOE*
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10 275 (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-
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12 276 SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity.
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14 277 Limited evidence exists for individual genetic-based responsiveness of omega-3s on
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16 278 apolipoprotein and/or LDL particle size, with no studies from the present comprehensive
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18 279 review meeting the criteria for evidence grading. This highlights the need for more
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20 280 replication studies in this area. While more research exists on omega-3 responsiveness for
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22 281 other lipid outcomes such as total-c, HDL-c and LDL-c, the level of evidence for
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24 282 nutrigenetic interactions related to these outcomes remains low. Again, more studies are
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26 283 needed related to these outcomes, including replication studies of previously identified
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28 284 nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the
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30 285 same type and amount of omega-3s as the original study), and recruit samples with
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32 286 similar characteristics to the original study. Once replication is established, research
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34 287 should then seek to expand the population studied to improve generalizability and explore
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36 288 the effectiveness of different interventions (i.e. different formulations and doses of
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38 289 omega-3s). The variability of the interventions and sample sizes in the studies conducted
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40 290 to date often resulted in the quality of evidence being downgraded (see Table 2). It should
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42 291 also be noted that study heterogeneity precluded the ability to conduct a meta-analysis.
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44 292 Thus, the GRADE approach worked well for evaluating the quality of the evidence given
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46 293 that this approach takes into consideration several factors when determining the quality of
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3 294 evidence such as risk of bias, indirectness of evidence, inconsistency or results,
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5 295 imprecision and publication bias (39).
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10 297 It is important to note that our results demonstrating strong evidence for interactions
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12 298 between *APOE* genotypes and lipid responses to omega-3s have notable ethical
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14 299 implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk
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16 300 of developing Alzheimer's disease (90). Moreover, *APOE* genotypes are significantly
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18 301 associated with CVD risk including risk of coronary artery disease and hyperlipidemia
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20 302 (91–93). Interestingly, the pathology of Alzheimer's disease has been linked to
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22 303 cardiovascular mechanisms (90). Future research should explore nutrigenetic interactions,
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24 304 with risk of developing Alzheimer's disease as the study endpoint/outcome of interest.
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26 305 Despite the current lack of knowledge about how diet may play a role in mitigating the
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28 306 genetic-based risk of Alzheimer's disease, several potentially modifiable risk factors
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30 307 account for around 40% of dementia and Alzheimer's disease globally (94), and the link
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32 308 between Alzheimer's disease risk and *APOE* is well-established (95). Therefore, despite
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34 309 the strong scientific validity identified in the present review, there are other factors that
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36 310 must be considered before this test can be recommended for implementation in a practice
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38 311 setting; this includes ethical, legal and social implications (96).
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42 313 In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness
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44 314 to omega-3s in men but not women speaks to the importance of taking biological sex into
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46 315 account in nutrigenetics research. The importance of this has been further highlighted
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48 316 elsewhere, where it has been noted that the results of nutrition and nutrigenetic research
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3 317 may differ in men and women (97). For example, UDP-glucuronidation isoenzyme
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5 318 expression profiles have been demonstrated to be regulated by sex hormones, and thus
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7 319 sex-specific differences in glucuronidation of resveratrol have been observed (98). As
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10 320 more studies are completed, researchers may find that certain nutrigenetic interactions
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12 321 differ depending on biological sex, ethnicity, age or other factors, similar to our findings
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14 322 on *APOE*, omega-3s and TG in which there was robust evidence of a nutrigenetic
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16 323 interaction in males only. Researchers may also find explanations for this, which are
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18 324 currently poorly understood. In general, it is becoming increasingly recognized that
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20 325 health-related responses to different interventions may vary based on biological sex; this
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22 326 is an important consideration of personalized nutrition (97). Nutrigenetic research often
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24 327 groups men and women together, but stratifying based on biological sex could provide
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26 328 further insights for specific nutrigenetic interactions and could also help explain why
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28 329 some replication studies have had conflicting findings (97). Moreover, biomedical
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30 330 research in general historically has been conducted more in men than women; yet such
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32 331 research findings are often generalized to women despite limited research conducted in
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34 332 samples of women, which is problematic for a number of reasons (99). In the present
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36 333 review, the evidence was strong for the *APOE* findings in men only, but not women in
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38 334 part because there were more studies conducted in men. Specifically, there were five
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40 335 studies conducted in men and women (combined) (71,73,74,100,101), and four studies
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42 336 conducted in samples of only men (75,78,79,102), yet no studies conducted in samples of
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44 337 only women. This brings to light important issues of equity and warrants further
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46 338 discussion and consideration.
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3 340 As research continues to develop, it appears likely that lipid and lipoprotein responses are
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5 341 polygenic in nature. Therefore, future research should consider using nutri-GRSs or other
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8 342 polygenic methods of assessing responsiveness to nutrition interventions. This work
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10 343 should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs,
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12 344 such as establishing them from genetic-wide association studies. In addition to the two
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14 345 studies meeting the criteria for evidence grading (65,66), a modified version of the 31-
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16 346 SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs
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18 347 (65). While this did not meet our inclusion criteria for evidence grading given that a
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20 348 different GRS was used, the 23-SNP GRS was significantly associated with TG
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22 349 responsiveness to omega-3 supplementation in this population as well, providing further
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24 350 evidence for the scientific validity of this nutrigenetic interaction (65).
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31 352 While we used the GRADE approach to evaluate the body of evidence, several tools are
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33 353 available for evaluating the quality of scientific evidence, though no generally accepted
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35 354 methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a
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37 355 set of guidelines to assess the scientific validity of genotype-based dietary advice (30).
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39 356 While we originally intended to use these guidelines for assessing the evidence, we came
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41 357 across some limitations that ultimately led us to use the GRADE guidelines. Specifically,
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43 358 Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines
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45 359 should be included in the assessment of scientific validity (30). However, limiting the
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47 360 evidence to only these studies could result in several important studies being missed. In
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49 361 the present review, none of the included studies explicitly indicated that they followed
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51 362 STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA
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3 363 guidelines to assess risk of bias (30). However, the STREGA checklist is only intended
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5 364 for observational genetic association studies - not interventional research (103). In the
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7 365 present review, 42 of the 65 included studies were interventional (65%) (Supplementary
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9 366 Table 3). In addition, the STREGA guidelines are intended to improve the transparency
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11 367 and adequate reporting of genetic association studies, but it is not intended to be used as a
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13 368 study quality assessment tool (103). However, Grimaldi et al. nicely highlighted the
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15 369 importance of understanding the nature of the genetic variation, at a functional level,
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17 370 when assessing scientific validity (30). This is not included in the standard GRADE
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19 371 approach but is an important niche component of nutrigenetic research. As such, an
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21 372 analysis of functional SNPs (biological plausibility) was included as an additional
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23 373 component of the standard GRADE process, as indicated in the methods section above.
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25 374 Overall, we found that the methods used in this systematic review were effective and can
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27 375 be used to synthesize and evaluate nutrigenetic studies assessing other gene-nutrient-
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29 376 health outcome interactions.
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38 378 The additional consideration of functional SNPs to the standard GRADE approach helped
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40 379 to strengthen this review, as biological mechanistic evidence can help ensure that study
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42 380 findings did not occur by chance alone, and this is a component of evidence evaluation
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44 381 frameworks in medical genetics (104,105). Transcriptomic and pathway analyses can
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46 382 help inform the direction of future nutrigenetic studies by generating hypotheses about
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48 383 the impact of specific genetic variations on varying responses to nutrition on health-
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50 384 related outcomes. For example, using transcriptomics and pathway analyses to identify
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52 385 changes in lipid metabolism following omega-3 supplementation, Rudkowska and
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3 386 colleagues identified six genes expressed in opposite directions between responders and
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5 387 non-responders to omega-3 supplementation for TG lowering: *FADS2*, *PLA2G4A*,
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7 388 *ALOX15*, *PEMT*, *MGLL* and *GPAM* (106). Tremblay et al. then built on this knowledge
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10 389 and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689,
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12 390 *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3
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14 391 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a
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16 392 significant impact on the TG lowering effect of omega-3 supplementation (107). Others
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18 393 have built on this mechanistic knowledge as well (108). Future research should now seek
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20 394 to replicate this work given that we found that there have been no replication studies
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22 395 completed and thus, this research (107,108) did not meet the criteria for evidence
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24 396 grading.

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30 398 In the current body of literature, there are some limitations that should be highlighted.
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32 399 Given the variability in allele frequencies for each SNP, it should be noted that study
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34 400 limitations can arise with small sample sizes whereby some genotype groups may not be
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36 401 adequately powered to detect significant differences. For example, Dawczynski et al.
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38 402 (2013) detected significant changes in TG among the GA genotype group of *CD36*
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40 403 rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA:
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42 404 n=8, GG: n=7) exhibited a significant difference, despite similar directions and
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44 405 magnitudes of effect among the GA and GG genotypes (82). It is thus possible that this
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46 406 study was not adequately powered. Some researchers aim to mitigate this issue of small
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48 407 numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for
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50 408 the minor allele) (69). However, such an approach precludes the possibility to detect an
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3 409 allele-dosage effect. From a physiological perspective, an allele dosage effect would be
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5 410 expected whereby a significant change among a heterozygote group would likely be
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7 411 accompanied by a significant change in one of the homozygote groups but with an even
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9 412 greater magnitude of the effect. This consideration highlights the importance of having an
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11 413 adequately powered sample size, while factoring in the prevalence of each genotype.
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17 415 While single SNP research provides important information about individual gene-nutrient
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19 416 interactions, the results of this review indicate that individual responses to omega-3s for
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21 417 altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus,
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23 418 we encourage researchers to further explore the use of nutri-GRSs to improve the
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25 419 accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et
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27 420 al., which obtained a high quality evidence grade in the present review (65,66). This is
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29 421 further exemplified in the analyses recently conducted by Chen et al. (42), which has yet
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31 422 to be replicated and thus was not selected for evidence grading.
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37 424 The present analysis of scientific validity provides an important first step towards the
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39 425 eventual development of clinical practice guidelines for genetic-based responses to
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41 426 dietary intake. With questionable and variable scientific validity of existing consumer
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43 427 nutrigenetic tests, the development of clinical practice guidelines is an important next
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45 428 step as these can be used by HCPs and industry alike to help promote evidence-based
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47 429 practice in personalized nutrition. Ideally, industry should use future clinical practice
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49 430 guidelines to inform the nutrigenetic associations and related dietary recommendations
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51 431 included in their reports. Decision aids can also be useful to guide clinical practice for
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3 432 HCPs (109), and future research should seek to develop a decision aid related to omega-
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5 433 3s and lipid/lipoprotein outcomes based on genetic variation.
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10 435 It should be noted that there are some limitations to the present systematic review. First,
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12 436 the literature was searched up until August 2020; as such, any articles published after this
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14 437 date were not included. Furthermore, certain nutrigenetic associations/interactions were
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16 438 prioritized for evidence grading therefore evidence grades remain unknown for numerous
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18 439 associations/interactions included in the narrative synthesis. However, evidence from a
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20 440 single study typically results in an evidence grade of low or very low using the GRADE
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22 441 approach (39), therefore it is unlikely that any/many nutrigenetic associations/interactions
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24 442 with strong scientific validity (which could be considered for use in clinical practice)
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26 443 were missed. Future research groups may choose to instead select a specific SNP or nutri-
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28 444 GRS as the focus of future systematic reviews. The specific SNP or nutri-GRS chosen
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30 445 may be selected based on the results of a preliminary scoping review. This would allow
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32 446 for all articles included in the systematic review to undergo evidence grading. The
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34 447 approach taken in the present review was more comprehensive, but has its limitations as
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36 448 stated above.
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45 450 Overall, we have provided a comprehensive overview the body of evidence related to
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47 451 nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing
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49 452 an overview of levels of evidence in this field. To our knowledge, this is the first
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51 453 systematic review with GRADE evidence evaluation in the broader field of nutrigenetics.
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53 454 The results of this work should be used in clinical practice guideline development, to
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3 455 ultimately guide evidence-based practice in personalized nutrition and move this
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5 456 emerging field forward.
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8 457
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13 462

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15 464 for the search strategy, in collaboration with J.K., M-C.V., S.D. and V.G. J.K. and V.G. were
16 465 responsible for article screening and selection, summarizing, evidence grading, and developing a
17 466 draft of the systematic review. The first systematic review draft underwent revisions from S.D. and
18 467 M-C.V., who provided overall supervision for the project. Following this, J.K., V.G., V.M.,
19 468 D.M.M., J.R., I.R., G.S., S.D., and M-C.V. served as scientific advisors and reviewed and revised
20 469 the full-text manuscript. J.K. wrote the first draft of the manuscript. J.K., V.G., V.M., D.M.M., J.R.,
21 470 I.R., G.S., S.D., and M-C.V., reviewed, revised and approved the final manuscript.
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41 475 **Data Sharing Statement:** Data are available upon reasonable request.
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478 **Figure Legend:**

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480 **Figure 1. PRISMA Flow Diagram**

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

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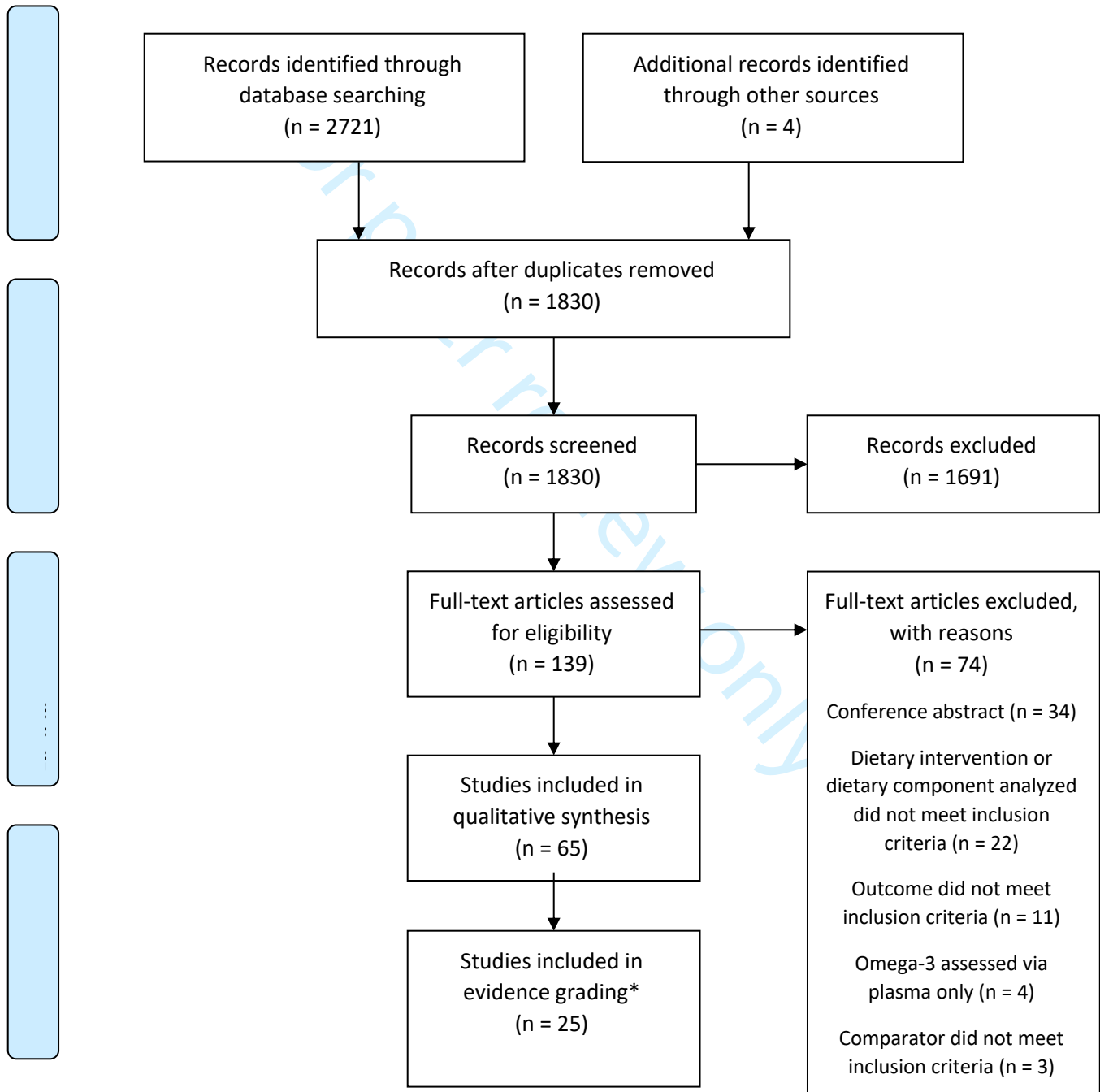
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For peer review only



Figure 1: PRISMA 2009 Flow Diagram



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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 'personalized 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 "personalized 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

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#	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 "personalized 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 drosophila 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)	<i>PPARα</i> , L162V (rs1800206) <i>PPARγ</i> , P12A (rs1801282) <i>PPARδ</i> , -87T→C (rs2016520)	<i>PPARα</i> : 22q13.31 <i>PPARγ</i> : 3p25.2 <i>PPARδ</i> : 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 <i>PPARα</i> L162V (rs1800206) polymorphism, the interaction of <i>PPARα</i> 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)	<i>MC4R</i> , rs17782313 <i>TCF7L2</i> , rs12255372 <i>TCF7L2</i> , rs7903146	<i>MC4R</i> : 18q21.32 <i>TCF7L2</i> : 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 <i>TCF7L2</i> 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 <i>FADS1-FADS2-FADS3</i> gene cluster and variation within 200kb upstream and downstream of the <i>FADS</i> region	<i>FADS1</i> : 11q12.2 <i>FADS2</i> : 11q12.2 <i>FADS3</i> : 11q12.2	High: >1.6 g/day Low: <1.6 g/day (food)	Entire <i>FADS</i> region gene-centric analysis and Variation in individual <i>FADS</i> 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 <i>FADS</i> 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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.

1 2 3 4 5 6 7 8 9	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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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	--
10 11 12 13 14 15 16 17 18	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)	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E4 vs. <i>APOE</i> -E4+	Total-c	Total-c: Cross-sectional (baseline) analysis demonstrated a significant genotype effect for <i>APOE</i> , omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for <i>APOE</i> , change in omega-3 intake (increase or decrease) and total-c.
19 20 21 22 23 24	Fontaine-Bisson and El-Sohemy 2007 (8)	Cross-Sectional	Genetic Score	Men and women aged 20-29 years (n=595)	<i>TNFα</i> , rs361525, rs1800629	<i>TNFα</i> : 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	--
25 26 27 28	Fontaine-Bisson et al. 2009 (9)	Cross-Sectional	Single SNP	Healthy men and women aged 20-29 years (n=593)	<i>NF-κB</i> -94Ins/Del ATTG (rs28362491)	<i>NF-κB</i> : 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 <i>NF-κB</i> genotype and omega-3 intake on HDL-c
29 30 31 32 33 34 35 36 37 38	Hellstrand et al. 2012 (10)	Cross-Sectional	Single SNP	Healthy men and women aged 45-68 years from Sweden (n=4635)	<i>FADS</i> , rs174547	<i>FADS</i> : 11q12.2	Low: \leq 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 <i>FADS</i> 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.
39 40 41 42 43 44 45 46 47	Hosseini-Esfahani et al. 2017 (11)	Nested Case-Control	Single SNP	Healthy men and women aged \geq 18 years from Iran	<i>ZNF8</i> , rs13266634	<i>ZNF8</i> : 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 <i>ZNF8</i> 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 <i>ZNF78</i> 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)	<i>PCSK5</i> , rs1029035	<i>PCSK5</i> : 9q21.13	Based on overall median intake (further detailed elsewhere (12)): Low: <0.4 %kcal (food) High: >0.4 %kcal (food)	CC vs. CA vs. AA	HDL-c	HDL-c: Significant interaction between <i>PCSK5</i> 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)	<i>TNFA</i> , rs1800629	<i>TNFA</i> : 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 <i>TNFA</i> , 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)	<i>TNFA</i> , rs361525	<i>TNFA</i> : 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 <i>TNFA</i> , 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 <i>TNFA</i> 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 <i>TNFA</i> rs361525.
Joffe et al. 2014 (15)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=268)	<i>IL-6</i> , -174 G>C, IVS3 (rs1800795), +281 G>T, IVS4 (rs1554606), +869 A>G (rs2069845)	<i>IL-6</i> : 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: HDL-c: Significant interaction whereby HDL-c increased with increasing omega-3 and/or DHA and/or ALA intake in <i>IL-6</i> rs1800795 C allele carriers and increasing ALA intake in <i>IL-6</i> rs1554606 T allele carriers. HDL-c decreased with increasing EPA and/or DHA intake in <i>IL-6</i> rs2069845 G allele carriers. TG: Significant interaction whereby TG reduced with increasing EPA intake in <i>IL-6</i> rs1800795 C allele carriers Total-c:HDL-c: Significant interaction whereby total-c:HDL-c ratio decreased with increasing EPA intake in <i>IL-6</i> rs1800795 CC genotypes and <i>IL-6</i> rs1554606 TT genotypes, increasing DHA intake in <i>IL-6</i> rs1800795 CC genotypes, and increasing ALA intake in <i>IL-6</i> rs1554606 TT genotypes.
Lai et al. 2006 (16)	Cross-Sectional	Single SNP	Men and women from the Framingham	<i>APOA5</i> , rs662799, rs651821, rs3135506,	<i>APOA5</i> : 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		omega-3: 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)	<i>FADS</i> , rs174546, rs482548, rs174570	<i>FADS</i> : 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)	<i>ANGPTL4</i> E40K (rs116843064)	<i>ANGPTL4</i> : 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)	<i>PLIN4</i> , rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	<i>PLIN4</i> : 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 <i>PLIN4</i> , 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 LISApplus birth cohort studies (n=1697)	<i>FADS1/FADS2</i> , rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	<i>FADS1/2</i> : 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)	<i>PPARα</i> , L162V (rs1800206)	<i>PPARα</i> : 22q13.31	High: >0.69 %kcal Low: <0.69 %kcal (food)	<i>PPARα</i> : 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)	<i>PPARα</i> , L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	<i>PPARα</i> : 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 <i>PPARα</i> (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)

Warodomwich et al. 2009 (23)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	<i>TCF7L2</i> rs7903146, rs12255372	<i>TCF7L2</i> : 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	--
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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	<i>FADS1</i> , rs174561 <i>FADS2</i> , rs174583 <i>ELOVL2</i> , rs953413 <i>ELOVL5</i> , rs2397142 <i>CETP</i> , rs5882 <i>SCD1</i> , rs2234970, <i>PPARA</i> , rs6008259 <i>LIPF</i> , rs814628 and <i>APOE</i> , rs429358, rs7412	<i>FADS1/2</i> : 11q12.2 <i>ELOVL2</i> : 6p24.2 <i>ELOVL5</i> : 6p12.1 <i>CETP</i> : 16q13 <i>SCD1</i> : 10q24.31 <i>PPARA</i> : 22q13.31 <i>LIPF</i> : 10q23.31 <i>APOE</i> : 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except <i>PPARA</i> and <i>LIPF</i> whereby analyses were major allele homozygotes vs. minor allele carriers) and <i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -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	<i>CETP</i> , rs3764261, <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5/ABCG</i> , rs4299376 <i>TIMD4/HAVCR1</i> , rs6882076 <i>GCKR</i> , rs1260326 <i>TRIB1</i> , rs2954029 <i>ANGPTL3/DOCK7</i> , rs2131925 <i>FADS1/2/3</i> , rs174546 <i>GALNT2</i> , rs4846914 <i>ABCA1</i> , rs4149268 <i>APOE/APOC1/APOC2</i> , rs439401	<i>CETP</i> : 16q13 <i>LIPC</i> : 15q21.3 <i>APOB</i> : 2p24.1 <i>ABCG5/ABCG8</i> : 2p.21 <i>TIMD4/HAVCR1</i> : 5q33.3 <i>GCKR</i> : 2p23.3 <i>TRIB1</i> : 8q24.13 <i>ANGPTL3/DOCK7</i> : 7: 1p31.3 <i>FADS</i> : 11q12.2 <i>GALNT2</i> : 1q42.13 <i>ABCA1</i> : 9q31.1 <i>APOE/APOC1/APOC2</i> : 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 <i>FADS1</i> rs174546

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Armstrong et al. 2012 (26)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	<i>ALOX5</i> , dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	<i>ALOX5</i> : 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	<i>PPARA</i> , L162V (rs1800206), <i>PPARγ2</i> , P12A (rs1801282)	<i>PPARA</i> : 22q13.31 <i>PPARγ2</i> : 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 (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> Pro12Pro genotypes only for individuals with BMI>25.0 kg/m ² Total-c : significant increase in total-c among minor allele carriers (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> 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	<i>SREBF1</i> , rs4925115, rs4925118, rs12953299 <i>ACLY</i> , rs8071753, rs8065502, rs2304497 <i>ACACA</i> rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	<i>SREBF1</i> : 17p11.2 <i>ACLY</i> : 17q21.2 <i>ACACA</i> : 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 <i>ACLY</i> rs8071753 and individuals with the GG or CG genotype of <i>ACACA</i> 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 <i>ACLY</i> 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	<i>RXRα</i> (12 SNPs), <i>CPT1A</i> (9 SNPs), <i>ACADVL</i> (1 SNP), <i>ACAA2</i> (6 SNPs), <i>ABCD2</i> (8 SNPs), <i>ACOX1</i> (8 SNPs), <i>ACAA1</i> (3 SNPs) [outlined in Supplementary Table 5]	<i>RXRα</i> : 9q34.2 <i>CPT1A</i> : 11q13.3 <i>ACADVL</i> : 17p13.1 <i>ACAA2</i> : 18q21.1 <i>ABCD2</i> : 12q12 <i>ACOX1</i> : 17q25.1 <i>ACAA1</i> : 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 <i>RXRα</i> rs11185660 genotype dependent on total fat intake, <i>RXRα</i> rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and <i>ACOX1</i> 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	<i>GCK</i> (13 SNPs) [outlined in Supplementary Table 5]	<i>GCK</i> : 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 <i>GCK</i> 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.

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6	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	<i>PPARα</i> , L162V (rs1800206)	<i>PPARα</i> : 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	--
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14	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -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 <i>APOE</i> -E3/4 carriers (compared to high-SFA diet alone)
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23	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E2/E2 + E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	TG: Significant interaction between treatment x sex x genotype whereby <i>APOE</i> -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
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28	Cormier et al. 2012 (35)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	<i>FADS</i> gene cluster (19 SNPs) [outlined in Supplementary Table 5]	<i>FADS</i> : 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	--
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32	Dang et al. 2015 (36)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	<i>APOE</i> -E4+ vs. <i>APOE</i> -E4-	HDL-c LDL-c TG Total-c	--
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37	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	<i>CD36</i> , rs1761667, rs1049673	<i>CD36</i> : 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 <i>CD36</i> rs1761667 and CG genotype of <i>CD36</i> rs1049673. TG: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of <i>CD36</i> rs1761667.
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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-I 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

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5	Jackson et al. 2017 (42)	Non-Randomized Intervention	Single SNP*	Healthy men aged 35-70 years (n=23)	480-min postprandial	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4	apoB-48 apoB-100	--
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7	Lindi et al. 2003 (43)	Randomized Intervention	Single SNP	Healthy men and women aged 30-65 years (n=150)	3 months	<i>PPAR</i> γ 2, Pro12Ala (rs1801282)	<i>PPAR</i> γ 2: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	<i>PPAR</i> γ 2, 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 \leq 37 %kcal or SFA intake was \leq 10 %kcal
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13	Lindman et al. (44)	Randomized, Controlled Intervention	Single SNP	Men at high risk of cardiovascular disease aged 65-75 years (n=204)	6 months	<i>FVII</i> , rs6046	<i>FVII</i> : 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	--
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22	Madden et al. 2008 (45)	Non-Randomized Intervention	Single SNP	Healthy men aged 43-84 years (n=111)	12 weeks	<i>CD36</i> , rs1527483, rs1049673, rs1761667, rs1984112	<i>CD36</i> : 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 HDL-c:LDL-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)
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30	Markovic et al. 2004 (46)	Single-Arm Clinical Trial	Single SNP	Healthy men (n=159)	12 weeks	<i>TNF</i> α , -308 (rs1800629) <i>LT</i> - α , +252 (rs909253) <i>IL</i> -1 β , -511 (rs16944) <i>IL</i> -6, -174 (rs1800795)	<i>TNF</i> α : 6p21.33 <i>LT</i> - α : 6p21.33 <i>IL</i> -1 β : 2q14.1 <i>IL</i> -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 <i>LT</i> - α rs909253 GG genotype and <i>IL</i> -1 β rs16944 TT genotype. In <i>LT</i> - α rs909253 AA genotype and <i>TNF</i> α rs1800629 AA genotype, signification association between BMI (divided in tertiles) and TG changes.
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37	McColley et al. 2011 (47)	Crossover Intervention	Single SNP	Healthy post-menopausal women (n=16)	8 weeks per diet	<i>FABP</i> 2, rs1799883	<i>FABP</i> 2: 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	--
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8 9 10 11 12 13	Olano-Martin et al. 2010 (49)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemic men (n=38)	4 weeks per diet	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4 (carriers)	apoB apoE HDL-c LDL-c LDL-c TG TG:HDL-c Total-c	apoB, LDL-c : In <i>APOE</i> -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 <i>APOE</i> -E3/E3 group; significant reduction in TG in <i>APOE</i> -E4 carriers with EPA only. No significant interactions. Total-c : Significant genotype x treatment interaction whereby <i>APOE</i> -E4 carriers exhibit total-c reductions in response to EPA-rich oil.
14 15 16 17 18 19	Quellette et al. 2013 (50)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (n=210)	6 weeks	<i>GPAM</i> (3 SNPs), <i>AGPAT3</i> (13 SNPs), <i>AGPAT4</i> (35 SNPs) [outlined in Supplementary Table 5]	<i>GPAM</i> : 10q25.2 <i>AGPAT3</i> : 21q22.3 <i>AGPAT4</i> : 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 <i>GPAM</i> , rs2792751 genotype x supplementation interaction on LDL-c TG : Significant genotype x supplementation interaction on TG for <i>GPAM</i> , rs2792751 and rs17129561 as well as <i>AGPAT4</i> , rs9458172 and rs3798943
20 21 22 23 24 25 26 27 28	Quellette et al. 2014 (51)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18-50 years (n=208)	6 weeks	<i>MGLL</i> (18 SNPs) [outlined in Supplementary Table 5]	<i>MGLL</i> : 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 <i>MGLL</i> 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 <i>MGLL</i> 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)
29 30 31 32	Paschos et al. 2005 (52)	Single-Arm Clinical Trial	Single SNP*	Men with dyslipidemia, aged 35 to 67 years (n=50)	12 weeks	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	<i>APOE</i> -E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -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
33 34 35 36 37 38 39 40	Pishva et al. 2010 (53)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	<i>FABP2</i> , Ala54Thr (rs1799883)	<i>FABP2</i> : 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.
41 42	Pishva et al.	Single-Arm	Single SNP	Adults with	8 weeks	<i>PPARα</i> ,	<i>PPARα</i> : 22q13.31	2.0 g/day pure	Leu162	ApoB	--

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2014 (54)	Clinical Trial		hypertriglyceridemia (n=46)		Leu162Val (rs1800206) <i>PPARα</i> , Intron 7 SNP		EPA (supplement)	vs. Val162 carriers <i>and</i> 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)	<i>FADS1</i> , rs174537 <i>FADS2</i> , rs174576 (LD=1.0 therefore presented results for rs174537)	<i>FADS1/2</i> : 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	<i>SCD1</i> , rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	<i>SCD1</i> : 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 <i>SCD1</i> 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: <i>IQCJ-SCHIP1</i> (4 SNPs), <i>SLIT2</i> (3 SNPs), <i>PHF17</i> (3 SNPs), <i>MYB</i> (1 SNP), <i>NXP1</i> (1 SNP), <i>NELL1</i> (1 SNP) [outlined in Supplementary Table 5]	<i>IQCJ-SCHIP1</i> : 3q25.32 <i>SLIT2</i> : 4p15.31 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 6q23.3 <i>NXP1</i> : 7p21.3 <i>NELL1</i> : 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	<i>PNPLA3</i> , 1148M (rs738409) <i>TM6SF2</i> , E167K (rs58542926)	<i>PNPLA3</i> : 22q13.31 <i>TM6SF2</i> : 19p13.11	1.8 g/day EPA+ 1.5 g/day DHA (supplement)	Comparison between three genotypes <i>and</i> 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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	<i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -E4	apoB HDL-c LDL-c TG Total-c	--
Tremblay et	Single-Arm	Single SNP	Healthy men	6 weeks	<i>PLA2G2A</i> (5)	<i>PLA2G2A</i> :	Fish oil containing	Major allele	apoB-100	TG: omega-3 supplementation significantly reduced TG in

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3 4 5 6 7 8 9 10 11 12 13	al. 2015 (60)	Clinical Trial		and women aged 18-50 years (n=208)		SNPs), <i>PLA2G2C</i> (6 SNPs), <i>PLA2G2D</i> (8 SNPs), <i>PLA2G2F</i> (6 SNPs), <i>PLA2G4A</i> (22 SNPs), <i>PLA2G6</i> (5 SNPs), <i>PLA2G7</i> (9 SNPs) [outlined in Supplementary Table 5]	1p36.13 <i>PLA2G2C</i> : 1p36.13 <i>PLA2G2D</i> : 1p36.12 <i>PLA2G2F</i> : 1p36.12 <i>PLA2G4A</i> : 1q31.1 <i>PLA2G6</i> : 22q13.1 <i>PLA2G7</i> : 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	<i>PLA2G7</i> rs1805018 as well as <i>PLA2G4A</i> rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, <i>PLA2G6</i> rs132989, <i>PLA2G7</i> rs679667, <i>PLA2G2D</i> rs12045689, <i>PLA2G4A</i> rs 10752979 and rs1160719 together explained 5.9% of post-supplementation TG levels
14 15 16 17 18 19 20 21 22 23 24 25	Vallée Marcotte et al. 2016 (61)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Men and woman aged 18-50 years (n=208)	6 weeks	<i>IQCJ</i> (16 SNPs), <i>NXPPI</i> (34 SNPs), <i>PHF17</i> (8 SNPs), <i>MYB</i> (9 SNPs) [outlined in Supplementary Table 5]	<i>IQCJ</i> : 3q25.32 <i>NXPPI</i> : 7p21.3 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 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: <i>IQCJ</i> (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), <i>NXPPI</i> (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), <i>MYB</i> (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 <i>IQCJ</i> ; rs7805772 in <i>NXPPI</i> . There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in <i>IQCJ</i> , rs7805772 in <i>NXPPI</i> and rs11154794 in <i>MYB</i> . Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for <i>IQCJ</i> rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, <i>NXPPI</i> rs7806226, rs7805772, <i>MYB</i> rs11154794 and rs210936.
26 27 28 29 30 31 32	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 (<i>NXPPI</i> rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and <i>IQCJ-SCHIP1</i> 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.
33 34 35 36 37	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).
38 39 40 41	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.

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			years (n=122)					Non-Responders vs. Adverse Responders and Responders vs. Adverse Responders			
3 4 5 6 7 8 9 10 11	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	<i>eNOS</i> Glu298Asp (rs1799983)	<i>NOS3</i> : 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	--
12 13 14 15 16 17 18 19	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	<i>CD36</i> , rs1527483 <i>NOS3</i> , rs1799983 <i>PPARγ2</i> , rs1801282	<i>CD36</i> : 7q21.11 <i>NOS3</i> : 7q36.1 <i>PPARγ2</i> : 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 <i>PPARγ2</i> rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of <i>PPARγ2</i> rs1801282 compared to CC genotype <i>only in the control</i> (corn oil) group TG : omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the <i>CD36</i> 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

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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
<i>APOE</i> : 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)
<i>APOE</i> : 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>CD36</i> : rs1761667	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1761667	TG	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1049673	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1527483	TG	Madden et al. 2008 (45) Zheng et al. 2018 (66)
<i>FADS</i> : 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. <i>Int J Obes</i> ;43:808-820 (2019)	<p><i>FADS2</i>, rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276</p> <p><i>FADS3</i>, rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285</p> <p><i>RAB31L1</i>, rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252</p>
Cormier et al. 2012	<p><i>FADS</i> gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567</p>
Vallée Marcotte et al. <i>Am J Clin Nutr</i> ;109:176–185 (2019)	<p><i>IQCJ-SCHIP1</i>, rs7639707, rs62270407</p> <p><i>NXPH1</i>, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523</p> <p><i>PHF17</i>, rs1216346, rs114348423, rs75007521</p> <p><i>MYB</i>, rs72560788, rs72974149, rs210962, rs6933462</p> <p><i>NELL1</i>, rs79624996, rs1850875, rs78786240, rs117114492</p> <p><i>SLIT2</i>, rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249</p>
Tremblay et al. <i>Lipids in Health and Disease</i> (2015) 14:12	<p><i>PLA2G2A</i>, rs876018, rs955587, rs3753827, rs11573156, rs11573142</p> <p><i>PLA2G2C</i>, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718</p> <p><i>PLA2G2D</i>, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671</p> <p><i>PLA2G2F</i>, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904</p>

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

	rs11651351, rs3643, rs7213998, rs17583163 <i>ACAA1</i> , rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	<i>CETP</i> , rs3764261, rs247616, rs7205804 <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5</i> , <i>ABCG8</i> , rs4299376 <i>TIMD4</i> , <i>HAVCR1</i> , rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 <i>ANGPTL3</i> , <i>DOCK7</i> , rs3850634, rs1167998, rs2131925 <i>FADS1</i> , <i>FADS2</i> , <i>FADS3</i> , rs174550, rs174547, rs174546, rs174583 <i>GALNT2</i> , rs4846914, rs1321257 <i>ABCA1</i> , rs4149268 <i>APOE</i> , <i>APOC1</i> , <i>APOC2</i> , rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	<i>IQCJ-SCHIP1</i> , rs7639707, rs62270407 NXP1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 <i>PHF17</i> , rs1216346, rs114348423, rs75007521 <i>MYB</i> , rs72560788, rs72974149, rs210962, rs6933462 <i>NELL1</i> , rs79624996, rs1850875, rs78786240, rs117114492 <i>SLIT2</i> , rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	<i>IQCJ-SCHIP1</i> , <i>MYB</i> , <i>NELL1</i> , <i>NXP1</i> , <i>PHF17</i> , <i>SLIT2</i> , rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	<i>IQCJ</i> , rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	<p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308</p>
<p>Vallée Marcotte et al. Nutrients; 11, 737 (2019)</p>	<p><i>IQCJ-SCHIP1</i>, 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</p> <p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, <i>SLIT2</i>, rs2952724</p> <p><i>NELLI</i>, rs752088</p>

Supplementary Table 6: 31-SNP Nutri-GRS

Gene, rs Number	Alleles¹	Associated Points
<i>IQCJ-SCHIP1</i> , rs7639707	<u>A</u> /G	+1
<i>IQCJ-SCHIP1</i> , rs62270407	C/ <u>T</u>	-1
<i>NXPH1</i> , rs61569932,	<u>G</u> /T	+1
<i>NXPH1</i> , rs1990554	<u>A</u> /C	+1
<i>NXPH1</i> , rs6463808	<u>A</u> /G	+1
<i>NXPH1</i> , rs6966968	<u>A</u> /G	+1
<i>NXPH1</i> , rs28473103	<u>A</u> /G	-1
<i>NXPH1</i> , rs28673635	<u>A</u> /G	+1
<i>NXPH1</i> , rs12702829	<u>C</u> /T	+1
<i>NXPH1</i> , rs78943417	A/ <u>T</u>	-1
<i>NXPH1</i> , rs293180	G/ <u>T</u>	+1
<i>NXPH1</i> , rs1837523	<u>C</u> /T	-1
<i>PHF17</i> , rs1216346	<u>C</u> /T	+1
<i>PHF17</i> , rs114348423	<u>A</u> /G	+1
<i>PHF17</i> , rs75007521	<u>G</u> /T	-1
<i>MYB</i> , rs72560788	<u>C</u> /T	-1
<i>MYB</i> , rs72974149	<u>A</u> /G	-1
<i>MYB</i> , rs210962	<u>C</u> /T	-1
<i>MYB</i> , rs6933462	<u>C</u> /G	+1
<i>NELL1</i> , rs79624996	<u>A</u> /G	+1
<i>NELL1</i> , rs1850875	<u>C</u> /T	+1
<i>NELL1</i> , rs78786240	<u>C</u> /T	-1
<i>NELL1</i> , rs117114492	<u>G</u> /T	+1
<i>SLIT2</i> , rs184945470	<u>C</u> /T	+1
<i>SLIT2</i> , rs143662727	<u>A</u> /G	-1
<i>SLIT2</i> , rs10009109	<u>C</u> /T	+1
<i>SLIT2</i> , rs10009535	<u>A</u> /G	+1
<i>SLIT2</i> , rs61790364	<u>A</u> /G	+1
<i>SLIT2</i> , rs73241936	<u>C</u> /T	+1
<i>SLIT2</i> , rs16869663	<u>A</u> /G	+1
<i>SLIT2</i> , rs76015249	<u>A</u> /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)
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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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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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For peer review only

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

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

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

21 **Running Head:** Nutrigenetics, omega-3 and lipids/lipoproteins
22 Data described in the manuscript will be made available upon request pending approval
23 from the corresponding author.

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

29 ABSTRACT

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

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

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

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

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

68 STRENGTHS AND LIMITATIONS

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3 69 - Strength: Comprehensive systematic review guided by PRISMA
4 70 - Strength: Critical appraisal of the evidence guided by GRADE with a
5 71 modification to further consider biological plausibility in addition to the standard
6 72 components of the GRADE approach
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8 73 - Limitation: Inability to conduct a meta-analysis given the comprehensive
9 74 overview of studies and thus heterogeneity
10 75 - Limitation: Several included studies without replication; most evidence was low
11 76 or very low quality according to GRADE
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77 INTRODUCTION

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79 Cardiometabolic disease is a health concern worldwide (1). Nutrigenetic research
80 demonstrates that there is significant inter-individual variability in cardiometabolic risk
81 factor levels, in part based on a combination of genetic and nutrition-related risk factors
82 (2,3). For example, protein intake has consistently been shown to influence measures of
83 body weight and composition dependent on *FTO* genotype (rs9939609 or loci in strong
84 linkage disequilibrium) (4,5). Consumers indicate great interest in personalized nutrition
85 based on genetics (6,7), however, a lack of industry oversight (8,9) has led to highly
86 variable scientific validity of nutrigenetic tests available to consumers. While recognizing
87 that some groups question whether genetic testing for personalized nutrition is ready for
88 ‘prime time’, Gorman and colleagues suggested that there are certain specific nutrigenetic
89 interactions with strong evidence that could be considered for implementation into
90 clinical practice by expert committees who are responsible for creating dietary guidelines
91 (10). With this in mind, systematic reviews that include an evaluation of levels of
92 evidence are urgently needed in order to determine if there are any nutrigenetic
93 associations that may warrant potential implementation into practice.

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

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3 100 terms of their lipid and lipoprotein lowering effects, omega-3s have consistently
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5 101 demonstrated an impact on triglycerides (TG) (14). High-quality evidence from
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7 102 population-based studies suggests that long-chain omega-3s (EPA and DHA) reduce
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9 103 plasma TG by about 15% (14). There is also high-quality evidence suggesting that EPA
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11 104 and DHA can raise high-density lipoprotein (HDL) cholesterol (14). Other studies have
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13 105 further demonstrated a relationship between omega-3 and HDL-cholesterol (15), low-
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15 106 density lipoprotein (LDL)-cholesterol (15), total cholesterol (16–18), apolipoproteins
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17 107 (19), and LDL particle size (20). Despite several studies with significant findings for
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19 108 these outcomes, when reviewing the evidence, studies have demonstrated conflicting
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21 109 results for the impact of omega-3 on many lipid profile outcomes (14). Genetic variation
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23 110 could explain this heterogeneity. EPA and DHA have been shown to significantly impact
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25 111 the expression of thousands of genes including those involved in inflammatory and
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27 112 atherogenic pathways (21,22). Evidence now demonstrates that the health impacts of
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29 113 omega-3 intake could differ based on genetic variation (23,24). Despite the potential for
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31 114 omega-3s to have a significant positive impact on health outcomes, population intakes of
32
33 115 omega-3s tend to be low (25). While the World Health Organization's Adequate Intake
34
35 116 level for adults is 200-250 mg EPA+DHA daily (26,27), the mean reported intake of
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37 117 EPA+DHA in the United States is only approximately 100 mg daily (25). Nutrigenetic
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39 118 interventions have the potential to motivate improvements in dietary intake beyond
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41 119 population-based interventions (28). Additionally, evidence suggests that genetic
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43 120 variability affects health responses to omega-3s (23). Thus, critically appraising and
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45 121 grading the evidence for nutrigenetic interactions related to omega-3s and plasma lipids,
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47 122 lipoproteins and apolipoproteins is an important research priority. The most recent
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3 123 systematic review on nutrigenetic interactions related to omega-3s and intermediate
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5 124 phenotypes of cardiovascular disease was conducted nearly a decade ago, and this study
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8 125 did not evaluate the quality of evidence using an established methodology (29).
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10 126 Therefore, we aimed to provide a comprehensive summary of current evidence related to
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12 127 inter-individual variability in plasma lipid, lipoprotein and apolipoprotein responses to
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14 128 omega-3 intake (plant and marine sources) based on genetic variations. Overall, the
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17 129 specific objectives of this study were as follows:

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20 130 **Objective 1.** Systematically search, identify (select), and provide a narrative
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22 131 synthesis of all studies that assessed nutrigenetic associations/interactions for genetic
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24 132 variants (comparators; i.e. outcomes in those with a specific genotype for a genetic
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26 133 variant compared to a different genotype) influencing the plasma lipid, lipoprotein
27
28 134 and/or apolipoprotein response (outcomes) to omega-3 fatty acid intake
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30 135 (intervention/exposure) in humans – both pediatric and adult populations
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32 136 (population).
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37 137 **Objective 2.** Assess the overall quality of evidence for specific priority nutrigenetic
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39 138 associations/interactions based on the following inclusion criteria: nutrigenetic
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41 139 associations/interactions reported for the same genetic variants (comparators)
42
43 140 influencing the same plasma lipid, lipoprotein and/or apolipoprotein response
44
45 141 (outcomes) to omega-3 fatty acid intake (intervention/exposure) in humans – both
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47 142 pediatric and adult populations (population) in two independent studies, irrespective
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49 143 of the findings.
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3 **145 Methods**

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5 147 **Patient and Public Involvement:** No patient involvement.

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8 148 *Literature Search*

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11 149 The systematic review protocol was registered with PROSPERO (CRD42020185087).
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13 150 The review process was guided by previously established methods, including a
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15 151 previously outlined five-step systematic review process (30,31). The search engines
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17 152 Embase, Web of Science and Medline OVID were used to conduct the search starting in
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19 153 May 2020 and screen for articles meeting inclusion criteria, using the comprehensive
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21 154 search terms outlined in Supplementary Table 1, properly combined by Boolean
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23 155 operators. The literature was searched up until August 1, 2020 (there was no minimum
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25 156 start date; any article published prior to this date was included in the search). A PRISMA
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27 157 diagram (Figure 1) guided the article screening process (32).
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33 158 *Inclusion and Exclusion Criteria*

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36 159 Original studies were included if they were written in English or French. Inclusion
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38 160 criteria were developed using the Population, Intervention, Comparison, Outcomes,
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40 161 (PICO) and Population, Exposure, Comparison, Outcomes (PECO) methods (33,34) for
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42 162 interventional and observational research, respectively. These are detailed in Table 1 for
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44 163 each study objective.
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49 164 **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

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

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

184 prioritized for evidence grading. This is further detailed in Table 1 and the section below
185 entitled “Evidence Grading.”

186 *Article Selection and Data Extraction*

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

202 *Evidence Grading*

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

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3 206 evidence grading, if a specific nutrigenetic association/interaction was reported in at least
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5 207 two independent studies. To clarify, this refers to the same SNP(s)/nutri-GRS [or SNPs
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7 208 in strong linkage disequilibrium (LD)] being assessed and influencing the same
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9 209 lipid/lipoprotein outcome in at least two studies. For these nutrigenetic
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11 210 associations/interactions, we proceeded with evidence grading, while including **all**
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13 211 studies relevant to the particular nutrigenetic association/interaction, irrespective of the
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15 212 findings. Consistency of results was then one of several factors considered when grading
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17 213 the body of evidence. The Grading of Recommendations Assessment, Development and
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19 214 Evaluation (GRADE) approach indicates that a single study rarely (if ever) results in
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21 215 strong evidence, but two studies (typically RCTs) can indicate strong evidence if they are
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23 216 graded highly using the GRADE criteria (36). Prior to selecting the nutrigenetic
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25 217 associations/interactions (genetic variants and lipid/lipoprotein/apolipoprotein outcomes)
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27 218 for evidence grading, LD was assessed using the SNIPA SNP Annotator Software (37)
28
29 219 for genes located on the same chromosome and arm (determined using the Online
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31 220 Mendelian Inheritance in Man® [OMIM] database) as outlined in the summary of
32
33 221 results' tables in the column labelled 'Cytogenic Location of Gene(s)' (Tables 1 and 2).
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35 222 Strong LD was defined as $r^2 > 0.8$ and location < 250 kb away from the index SNP
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37 223 location. SNPs in strong LD were considered together for the purposes of evidencing
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39 224 grading.

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41 225 Based on our abovementioned predetermined criteria for specific nutrigenetic topic
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43 226 selection for evidence grading, nutrigenetic associations/interactions that were not
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45 227 included in the evidence grading process likely have weak evidence (at minimum due to
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47 228 lack of replication, for example, *ZNT8* rs13266634 and HDL-c or TG responsiveness to
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3 229 omega-3, which has only been assessed in a single study (38)). According to the GRADE
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5 230 guidelines, when only a single study exists indicating significant findings for an outcome
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7 231 of interest (especially when the study is observational), the overall quality of the evidence
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9 232 is generally rated to be low or very low (39). Therefore, our process for prioritizing
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11 233 nutrigenetic topics for evidence grading aimed to filter out specific nutrigenetic
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13 234 associations/interactions that would likely be deemed low or very low quality (based on,
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15 235 at minimum, lack of replication). Two authors (JK and VG) critically appraised the
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17 236 selected nutrigenetic interactions using the GRADE methodology, with one modification
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19 237 (39,40). The modified GRADE approach consisted of the additional consideration of
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21 238 biological plausibility whereby evidence was considered for upgrading if there was
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23 239 evidence of biological plausibility for the nutrigenetic interaction. Nutrigenetic
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25 240 interactions were grouped according to studies assessing the same SNP(s)/nutri-GRS and
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27 241 lipid/lipoprotein/apolipoprotein outcome, and the quality of the body of evidence (studies
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29 242 with significant and non-significant results) was rated; this process was guided by the
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31 243 GRADE Evidence Profile, which included consideration of risk of bias, inconsistency,
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33 244 indirectness, imprecision, publication bias, plausible confounding, dose-response and
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35 245 other factors (39). For example, different sources of omega-3s (e.g. EPA+DHA vs. ALA;
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37 246 food sources vs. supplementation) were taken into consideration when grading the
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39 247 evidence through the analysis of indirectness within the modified GRADE approach
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41 248 (39,40). Risk of bias was assessed in each of the included interventional and
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43 249 observational studies using the National Institutes of Health Study Quality Assessment
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45 250 Tools, in line with recently published recommendations for risk of bias assessments (41).
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47 251 To assess measures of precision, coefficients of variation (CV) were calculated based on
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3 252 outcome means (mean change or absolute values – whichever was used for the analyses)
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5 253 and standard deviations. In cases where standard errors of the mean were reported, these
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8 254 were converted to standard deviations to calculate the CV. The nutrigenetic interactions
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10 255 were each given an evidence grade of high, moderate, low or very low.
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13 256 **Results**

14 257
15 258 Figure 1 outlines the PRISMA Flow Diagram, which was used to guide the systematic
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18 259 review. Supplementary Tables 2 and 3 provide a summary of the 65 included studies. The
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20 260 results columns of Supplementary Tables 2 and 3 (far right) indicate nutrigenetic findings
21
22 261 that were statistically significant. There were many results from the included studies that
23
24 262 were not statistically significant. It is important to highlight that any results related to the
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26 263 studies' analyzed SNPs and outcomes of interest that were not statistically significant are
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28 264 not indicated in the results column. No studies explicitly reported that they followed
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30 265 STREGA guidelines. LD analysis of SNPs tested in different studies revealed strong LD
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32 266 in several SNPs from the *FADS* gene cluster (see Table 2 footnote). As such, LD was
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34 267 taken into consideration in the selection of nutrigenetic interactions selected for evidence
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36 268 grading.
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42 269 *Observational Studies*

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45 270 Of the 65 included studies, 23 were observational with the majority of these being cross-
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47 271 sectional, as outlined in Supplementary Table 2. A total of 62,221 participants were
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49 272 included in the observational studies. These studies assessed correlations among a
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51 273 number of different genetic variations and outcomes, with several studies assessing
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53 274 genetic variations in the *FADS* gene cluster (42–48), *TNF α* (49–51) and *PPAR α* (52–54).
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3 275 Most studies (n=13) assessed total omega-3s (38,42,47–49,51,54–60). The intake and
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5 276 type of omega-3s, lipid/lipoprotein/apolipoprotein outcomes and associations revealed
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7
8 277 from these studies were variable as further detailed in Supplementary Table 2. In the
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10 278 observational studies assessing genetic variation in the *FADS* gene cluster, some studies
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12 279 indicated significant gene-diet findings related to HDL-cholesterol, LDL-cholesterol, TG,
13
14 280 total-cholesterol while other studies demonstrated no significant gene-diet interactions for
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16 281 these outcomes thus indicating notable inconsistency among the results, while
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18
19 282 considering that SNPs differed by studies (42–48). In the observational studies focused
20
21 283 on genetic variation in the *TNF α* gene, there was some evidence of a gene-diet
22
23 284 relationship for omega-3 and LDL-cholesterol, total-cholesterol and total-
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25 285 cholesterol:HDL-cholesterol ratio, but again, results differed between studies (49–51).
26
27 286 For gene-diet relationships and *PPAR α* genetic variation, individual studies indicated
28
29 287 significant findings related to total-cholesterol, LDL-cholesterol, TG, apoC-III and LDL
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31 288 peak particle diameter (52–54). Comprehensive details of the observational studies are
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33 289 outlined in Supplementary Table 2.
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38 290 *Interventional Studies*

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42 291 Of the 65 included studies, 42 were interventional including 16 randomized trials. Non-
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44 292 randomized studies included single arm clinical trials and sequential non-randomized
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46 293 cross-over interventions. For interventional studies, n=6,225 participants upon combining
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48 294 all sample sizes of the included studies. Again, these studies assessed relationships
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50 295 between a number of different genetic variants and study outcomes. In more recent years,
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52 296 several studies (n=8) used a nutri-GRS or polygenic approaches (61–68) given the
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54 297 plausibility that many gene-lipid/lipoprotein/apolipoprotein and omega-3 interactions are
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3 298 polygenic in nature. Numerous studies assessed genetic variations in the *FADS* gene
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5 299 cluster (61,62,69–71), *APOE* (61,71–80), *CD36* (67,81,82), *PPAR γ 2* (62,67,83–85) and
6
7 300 *PPAR α* (83,86,87). Among these studies, results related to significant gene-diet (omega-
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9 301 3) associations influencing lipid/lipoprotein outcomes were generally inconsistent except
10
11 302 for *APOE* (rs429358 and rs7412), omega-3 and TG in males only (71–75,77–80), and for
12
13 303 a 31-SNP nutri-GRS, omega-3 and TG (65,66). There was also consistent evidence to
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15 304 indicate a lack of association among *PPAR γ 2* (rs1801282) genetic variation, EPA+DHA
16
17 305 and LDL cholesterol (62,67,84,85,88). Most studies (n=40) used supplemental EPA
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19 306 and/or DHA sources of omega-3s for the dietary intervention (see Supplementary Table
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21 307 3). The dosage/intake and type of omega-3s were variable with EPA and/or DHA dosages
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23 308 ranging from 0.5-3.7 g/day across different studies, and one study with an ALA
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25 309 intervention dosage of 8.1 g/day, as further detailed in Table 3.
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31 *Levels of Evidence Using GRADE*

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35 311 A total of 25 articles were included in the evidence grading process, representing 11
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37 312 unique nutrigenetic associations/interactions as outlined in Tables 2 and 3, and
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39 313 Supplementary Table 4. Through the modified GRADE process, it was determined that
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41 314 there is strong evidence (GRADE rating: moderate quality) for *APOE* genotypes (rs7412,
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43 315 rs429358), omega-3s and TG lowering in male adults only (71–75,77–80). This evidence
44
45 316 suggests that adult males (but not females) with the *APOE*-E3/E4 or E4/E4 genotype
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47 317 (rs429358, rs7412) tend to experience significant reductions in TG in response to 0.7-3.7
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49 318 g/day of EPA and/or DHA, with higher dosages demonstrating greater TG lowering
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51 319 effects (71–75,77–80). Furthermore, it was determined that there is strong evidence
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53 320 (GRADE rating: high quality) for using a 31-SNP nutri-GRS (detailed in Supplementary
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3 321 Tables 5 and 6) to assess the effectiveness of omega-3s for TG lowering in adults with
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5 322 overweight/obesity in various ethnicities (65,66). The evidence suggests that in adults
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7 323 with overweight/obesity, lower genetic risk scores demonstrate greater responsiveness to
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9 324 omega-3 supplementation (65,66).

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13 325 All other evidence that was evaluated was determined to be weak (GRADE rating: low or
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15 326 very low quality), as further detailed in Table 2. Imprecision, indirectness, and
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17 327 inconsistency were common reasons for downgrading the evidence (refer to Table 2
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19 328 footnote). There was evidence for a plausible mechanism of action for most of the
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21 329 nutrigenetic interactions that were graded; evidence of a dose response was less common.
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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 <i>CD36</i> 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 <i>CD36</i> 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 <i>CD36</i> 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 <i>CD36</i> 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 <i>APOE</i> -E3/E4 or E4/E4 genotype (rs429358, rs7412) experience significant reductions in TG in

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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, <i>APOE</i> (rs429358, rs7412) and total-c. There is no evidence of a nutrigenetic interaction between ALA, <i>APOE</i> (rs429358, rs7412) and total-c. In male subgroups, weak evidence suggests that there is no nutrigenetic interaction between ALA or EPA and/or DHA, <i>APOE</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>PPARG2</i> (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 <i>FADS</i> (rs174547**) does not influence total-c responses to omega-3.

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sectional studies (n=9365) (44,45,47,48,61,69,71)									
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*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*, *NXP1*, *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

<i>CD36, rs1761667 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1761667 and TG</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1049673 and HDL-c</i>	
Study	Risk of Bias
Dawczynski et al. 2013	⊖
Madden et al. 2008	⊖
<i>CD36, rs1527483 and TG</i>	
Study	Risk of Bias
Zheng et al. 2018	⊕
Madden et al. 2008	⊖
<i>ApoE, rs429358, rs7412 and TG</i>	
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	⊕
<i>ApoE, rs429358, rs7412 and Total-c</i>	
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	⊕
<i>31-SNP Nutri-GRS and TG</i>	
Study	Risk of Bias
Vallée Marcotte et al. 2019	⊕
Vallée Marcotte et al. 2020	⊕

<i>PPARG2, rs1801282 and LDL-c</i>	
Study	Risk of Bias
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
<i>PPARG2, rs1801282 and Total-c</i>	
Study	Risk of Bias
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
<i>PPARG2, rs1801282 and TG</i>	
Study	Risk of Bias
Binia et al. 2017	⊖
Harslof et al. 2014	⊕
Itariu et al. 2012	⊕
Lindi et al. 2003	⊖
Zheng et al. 2018	⊕
<i>FADS, rs174547 and Total-c</i>	
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

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5 273 Overall, this systematic review found strong evidence (i.e. GRADE ratings: moderate and
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8 274 high quality evidence) for only a limited amount of evidence in this area: *APOE*
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10 275 (rs429358 and rs7412) genotypes and TG responsiveness to omega-3s in men, and a 31-
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12 276 SNP nutri-GRS and TG responsiveness to omega-3s in adults with overweight/obesity.
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14 277 Limited evidence exists for individual genetic-based responsiveness of omega-3s on
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16 278 apolipoprotein and/or LDL particle size, with no studies from the present comprehensive
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18 279 review meeting the criteria for evidence grading. This highlights the need for more
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20 280 replication studies in this area. While more research exists on omega-3 responsiveness for
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22 281 other lipid outcomes such as total-c, HDL-c and LDL-c, the level of evidence for
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24 282 nutrigenetic interactions related to these outcomes remains low. Again, more studies are
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26 283 needed related to these outcomes, including replication studies of previously identified
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28 284 nutrigenetic interactions. These studies should first replicate the interventions (i.e. use the
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30 285 same type and amount of omega-3s as the original study), and recruit samples with
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32 286 similar characteristics to the original study. Once replication is established, research
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34 287 should then seek to expand the population studied to improve generalizability and explore
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36 288 the effectiveness of different interventions (i.e. different formulations and doses of
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38 289 omega-3s). The variability of the interventions and sample sizes in the studies conducted
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40 290 to date often resulted in the quality of evidence being downgraded (see Table 2). It should
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42 291 also be noted that study heterogeneity precluded the ability to conduct a meta-analysis.
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44 292 Thus, the GRADE approach worked well for evaluating the quality of the evidence given
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46 293 that this approach takes into consideration several factors when determining the quality of
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3 294 evidence such as risk of bias, indirectness of evidence, inconsistency or results,
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5 295 imprecision and publication bias (39).

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10 297 It is important to note that our results demonstrating strong evidence for interactions
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12 298 between *APOE* genotypes and lipid responses to omega-3s have notable ethical
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14 299 implications. Compared to non-carriers, carriers of *APOE*-E4 have a 15 times greater risk
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16 300 of developing Alzheimer's disease (90). Moreover, *APOE* genotypes are significantly
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18 301 associated with CVD risk including risk of coronary artery disease and hyperlipidemia
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20 302 (91–93). Interestingly, the pathology of Alzheimer's disease has been linked to
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22 303 cardiovascular mechanisms (90). Future research should explore nutrigenetic interactions,
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24 304 with risk of developing Alzheimer's disease as the study endpoint/outcome of interest.
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26 305 Despite the current lack of knowledge about how diet may play a role in mitigating the
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28 306 genetic-based risk of Alzheimer's disease, several potentially modifiable risk factors
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30 307 account for around 40% of dementia and Alzheimer's disease globally (94), and the link
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32 308 between Alzheimer's disease risk and *APOE* is well-established (95). Therefore, despite
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34 309 the strong scientific validity identified in the present review, there are other factors that
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36 310 must be considered before this test can be recommended for implementation in a practice
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38 311 setting; this includes ethical, legal and social implications (96).
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48 313 In addition, our finding of strong evidence for *APOE* genotypes and TG responsiveness
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50 314 to omega-3s in men but not women speaks to the importance of taking biological sex into
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52 315 account in nutrigenetics research. The importance of this has been further highlighted
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54 316 elsewhere, where it has been noted that the results of nutrition and nutrigenetic research
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3 317 may differ in men and women (97). For example, UDP-glucuronidation isoenzyme
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5 318 expression profiles have been demonstrated to be regulated by sex hormones, and thus
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7 319 sex-specific differences in glucuronidation of resveratrol have been observed (98). As
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10 320 more studies are completed, researchers may find that certain nutrigenetic interactions
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12 321 differ depending on biological sex, ethnicity, age or other factors, similar to our findings
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14 322 on *APOE*, omega-3s and TG in which there was robust evidence of a nutrigenetic
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16 323 interaction in males only. Researchers may also find explanations for this, which are
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18 324 currently poorly understood. In general, it is becoming increasingly recognized that
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20 325 health-related responses to different interventions may vary based on biological sex; this
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22 326 is an important consideration of personalized nutrition (97). Nutrigenetic research often
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24 327 groups men and women together, but stratifying based on biological sex could provide
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26 328 further insights for specific nutrigenetic interactions and could also help explain why
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28 329 some replication studies have had conflicting findings (97). Moreover, biomedical
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30 330 research in general historically has been conducted more in men than women; yet such
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32 331 research findings are often generalized to women despite limited research conducted in
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34 332 samples of women, which is problematic for a number of reasons (99). In the present
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36 333 review, the evidence was strong for the *APOE* findings in men only, but not women in
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38 334 part because there were more studies conducted in men. Specifically, there were five
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40 335 studies conducted in men and women (combined) (71,73,74,100,101), and four studies
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42 336 conducted in samples of only men (75,78,79,102), yet no studies conducted in samples of
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44 337 only women. This brings to light important issues of equity and warrants further
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46 338 discussion and consideration.
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3 340 As research continues to develop, it appears likely that lipid and lipoprotein responses are
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5 341 polygenic in nature. Therefore, future research should consider using nutri-GRSs or other
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7 342 polygenic methods of assessing responsiveness to nutrition interventions. This work
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10 343 should use unbiased approaches or non-hypothesis driven approach to derive nutri-GRSs,
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12 344 such as establishing them from genetic-wide association studies. In addition to the two
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14 345 studies meeting the criteria for evidence grading (65,66), a modified version of the 31-
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16 346 SNP GRS was tested in men and women in the FINGEN study, using 23 of the 31 SNPs
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18 347 (65). While this did not meet our inclusion criteria for evidence grading given that a
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20 348 different GRS was used, the 23-SNP GRS was significantly associated with TG
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22 349 responsiveness to omega-3 supplementation in this population as well, providing further
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24 350 evidence for the scientific validity of this nutrigenetic interaction (65).
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31 352 While we used a modified version of the GRADE approach (with the additional
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33 353 consideration of biological plausibility) to evaluate the body of evidence, several tools are
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35 354 available for evaluating the quality of scientific evidence, though no generally accepted
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37 355 methods exist for nutrigenetic research specifically. In 2017, Grimaldi et al. proposed a
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39 356 set of guidelines to assess the scientific validity of genotype-based dietary advice (30).
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42 357 While we originally intended to use these guidelines for assessing the evidence, we came
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44 358 across some limitations that ultimately led us to use the GRADE guidelines. Specifically,
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46 359 Grimaldi et al. (2017) suggested that only studies that include STREGA guidelines
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48 360 should be included in the assessment of scientific validity (30). However, limiting the
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50 361 evidence to only these studies could result in several important studies being missed. In
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53 362 the present review, none of the included studies explicitly indicated that they followed
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3 363 STREGA guidelines. In addition, it was recommended by Grimaldi et al. to use STREGA
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5 364 guidelines to assess risk of bias (30). However, the STREGA checklist is only intended
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7 365 for observational genetic association studies - not interventional research (103). In the
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9 366 present review, 42 of the 65 included studies were interventional (65%) (Supplementary
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11 367 Table 3). In addition, the STREGA guidelines are intended to improve the transparency
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13 368 and adequate reporting of genetic association studies, but it is not intended to be used as a
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15 369 study quality assessment tool (103). However, Grimaldi et al. nicely highlighted the
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17 370 importance of understanding the nature of the genetic variation, at a functional level,
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19 371 when assessing scientific validity (30). This is not included in the standard GRADE
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21 372 approach but is an important niche component of nutrigenetic research. As such, an
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23 373 analysis of functional SNPs (biological plausibility) was included as an additional
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25 374 component of the standard GRADE process, as indicated in the methods section above.
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27 375 Overall, we found that the methods used in this systematic review were effective and can
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29 376 be used to synthesize and evaluate nutrigenetic studies assessing other gene-nutrient-
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31 377 health outcome interactions.
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40 379 The additional consideration of functional SNPs to the standard GRADE approach helped
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42 380 to strengthen this review, as biological mechanistic evidence can help ensure that study
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44 381 findings did not occur by chance alone, and this is a component of evidence evaluation
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46 382 frameworks in medical genetics (104,105). Transcriptomic and pathway analyses can
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48 383 help inform the direction of future nutrigenetic studies by generating hypotheses about
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50 384 the impact of specific genetic variations on varying responses to nutrition on health-
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52 385 related outcomes. For example, using transcriptomics and pathway analyses to identify
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3 386 changes in lipid metabolism following omega-3 supplementation, Rudkowska and
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5 387 colleagues identified six genes expressed in opposite directions between responders and
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7 388 non-responders to omega-3 supplementation for TG lowering: *FADS2*, *PLA2G4A*,
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10 389 *ALOX15*, *PEMT*, *MGLL* and *GPAM* (106). Tremblay et al. then built on this knowledge
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12 390 and discovered that *PLA2G6* rs132989, *PLA2G7* rs679667, *PLA2G2D* rs12045689,
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14 391 *PLA2G4A* rs10752979 and rs1160719 together explained 5.9% of post- omega-3
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16 392 supplementation TG levels, with several individual *PLA2G4A* SNPs also having a
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18 393 significant impact on the TG lowering effect of omega-3 supplementation (107). Others
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20 394 have built on this mechanistic knowledge as well (108). Future research should now seek
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22 395 to replicate this work given that we found that there have been no replication studies
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24 396 completed and thus, this research (107,108) did not meet the criteria for evidence
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26 397 grading.

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33 399 In the current body of literature, there are some limitations that should be highlighted.
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35 400 Given the variability in allele frequencies for each SNP, it should be noted that study
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37 401 limitations can arise with small sample sizes whereby some genotype groups may not be
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39 402 adequately powered to detect significant differences. For example, Dawczynski et al.
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41 403 (2013) detected significant changes in TG among the GA genotype group of *CD36*
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43 404 rs1761667 (n=18) in response to omega-3s but neither of the homozygote groups (AA:
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45 405 n=8, GG: n=7) exhibited a significant difference, despite similar directions and
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47 406 magnitudes of effect among the GA and GG genotypes (82). It is thus possible that this
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49 407 study was not adequately powered. Some researchers aim to mitigate this issue of small
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51 408 numbers by grouping minor allele carriers together (i.e. heterozygotes + homozygotes for
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3 409 the minor allele) (69). However, such an approach precludes the possibility to detect an
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5 410 allele-dosage effect. From a physiological perspective, an allele dosage effect would be
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7 411 expected whereby a significant change among a heterozygote group would likely be
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9 412 accompanied by a significant change in one of the homozygote groups but with an even
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11 413 greater magnitude of the effect. This consideration highlights the importance of having an
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13 414 adequately powered sample size, while factoring in the prevalence of each genotype.
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19 416 While single SNP research provides important information about individual gene-nutrient
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21 417 interactions, the results of this review indicate that individual responses to omega-3s for
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23 418 altering lipids, lipoproteins and apolipoproteins appear to be polygenic in nature. Thus,
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25 419 we encourage researchers to further explore the use of nutri-GRSs to improve the
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27 420 accuracy of genetic-based predictions. See, for example, the work of Vallée Marcotte et
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29 421 al., which obtained a high quality evidence grade in the present review (65,66). This is
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31 422 further exemplified in the analyses recently conducted by Chen et al. (42), which has yet
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33 423 to be replicated and thus was not selected for evidence grading.
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39 425 The present analysis of scientific validity provides an important first step towards the
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41 426 eventual development of clinical practice guidelines for genetic-based responses to
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43 427 dietary intake. With questionable and variable scientific validity of existing consumer
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45 428 nutrigenetic tests, the development of clinical practice guidelines is an important next
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47 429 step as these can be used by HCPs and industry alike to help promote evidence-based
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49 430 practice in personalized nutrition. Ideally, industry should use future clinical practice
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51 431 guidelines to inform the nutrigenetic associations and related dietary recommendations
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3 432 included in their reports. Decision aids can also be useful to guide clinical practice for
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5 433 HCPs (109), and future research should seek to develop a decision aid related to omega-
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7 434 3s and lipid/lipoprotein outcomes based on genetic variation.
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12 436 It should be noted that there are some limitations to the present systematic review. First,
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14 437 the literature was searched up until August 2020; as such, any articles published after this
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16 438 date were not included. Furthermore, certain nutrigenetic associations/interactions were
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18 439 prioritized for evidence grading therefore evidence grades remain unknown for numerous
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20 440 associations/interactions included in the narrative synthesis. However, evidence from a
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22 441 single study typically results in an evidence grade of low or very low using the GRADE
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24 442 approach (39), therefore it is unlikely that any/many nutrigenetic associations/interactions
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26 443 with strong scientific validity (which could be considered for use in clinical practice)
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28 444 were missed. Future research groups may choose to instead select a specific SNP or nutri-
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30 445 GRS as the focus of future systematic reviews. The specific SNP or nutri-GRS chosen
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32 446 may be selected based on the results of a preliminary scoping review. This would allow
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34 447 for all articles included in the systematic review to undergo evidence grading. The
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36 448 approach taken in the present review was more comprehensive, but has its limitations as
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38 449 stated above.
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47 451 Overall, we have provided a comprehensive overview the body of evidence related to
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49 452 nutrigenetics, omega-3s and plasma lipids/lipoproteins/apolipoproteins, while providing
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51 453 an overview of levels of evidence in this field. To our knowledge, this is the first
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53 454 systematic review with GRADE evidence evaluation in the broader field of nutrigenetics.
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3 455 The results of this work should be used in clinical practice guideline development, to
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5 456 ultimately guide evidence-based practice in personalized nutrition and move this
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7 457 emerging field forward.
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10 458
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14 462 Nutrition Applied to Genetics and Metabolic Health.
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16 463
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18
19 465 for the search strategy, in collaboration with J.K., M-C.V., S.D. and V.G. J.K. and V.G. were
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21 466 responsible for article screening and selection, summarizing, evidence grading, and developing a
22
23 467 draft of the systematic review. The first systematic review draft underwent revisions from S.D. and
24
25 468 M-C.V., who provided overall supervision for the project. Following this, J.K., V.G., V.M.,
26
27 469 D.M.M., J.R., I.R., G.S., S.D., and M-C.V. served as scientific advisors and reviewed and revised
28
29 470 the full-text manuscript. J.K. wrote the first draft of the manuscript. J.K., V.G., V.M., D.M.M., J.R.,
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31 471 I.R., G.S., S.D., and M-C.V., reviewed, revised and approved the final manuscript.
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36

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41 475 Vohl holds a Canada Research Chair in Genomics Applied to Nutrition and Metabolic Health.
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44 476 **Data Sharing Statement:** Data are available upon reasonable request.
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479 **Figure Legend:**

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481 **Figure 1. PRISMA Flow Diagram**

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

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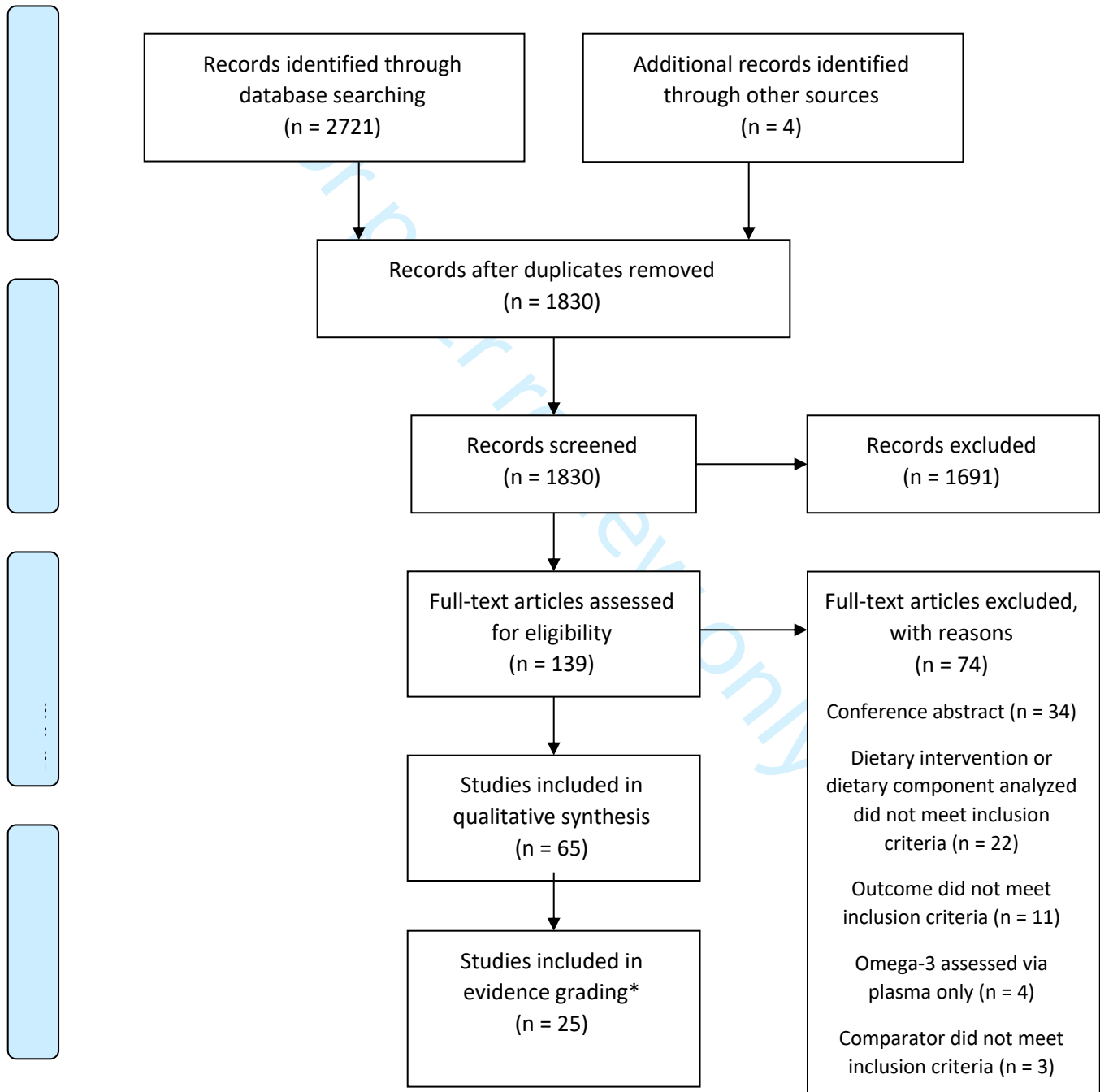
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Figure 1: PRISMA 2009 Flow Diagram



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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 'personalized 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 "personalized 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

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#	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 "personalized 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 drosophila 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)	<i>PPARα</i> , L162V (rs1800206) <i>PPARγ</i> , P12A (rs1801282) <i>PPARδ</i> , -87T→C (rs2016520)	<i>PPARα</i> : 22q13.31 <i>PPARγ</i> : 3p25.2 <i>PPARδ</i> : 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 <i>PPARα</i> L162V (rs1800206) polymorphism, the interaction of <i>PPARα</i> 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)	<i>MC4R</i> , rs17782313 <i>TCF7L2</i> , rs12255372 <i>TCF7L2</i> , rs7903146	<i>MC4R</i> : 18q21.32 <i>TCF7L2</i> : 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 <i>TCF7L2</i> 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 <i>FADS1-FADS2-FADS3</i> gene cluster and variation within 200kb upstream and downstream of the <i>FADS</i> region	<i>FADS1</i> : 11q12.2 <i>FADS2</i> : 11q12.2 <i>FADS3</i> : 11q12.2	High: >1.6 g/day Low: <1.6 g/day (food)	Entire <i>FADS</i> region gene-centric analysis and Variation in individual <i>FADS</i> 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 <i>FADS</i> 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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)	<i>FADS1</i> , rs174547	<i>FADS1</i> : 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)	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E4 vs. <i>APOE</i> -E4+	Total-c	Total-c: Cross-sectional (baseline) analysis demonstrated a significant genotype effect for <i>APOE</i> , omega-3 intake, and total-c. Longitudinal analysis (baseline to month 6) demonstrated a significant genotype effect for <i>APOE</i> , 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)	<i>TNFα</i> , rs361525, rs1800629	<i>TNFα</i> : 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)	<i>NF-κB</i> -94Ins/Del ATTG (rs28362491)	<i>NF-κB</i> : 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 <i>NF-κB</i> 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)	<i>FADS</i> , rs174547	<i>FADS</i> : 11q12.2	Low: \leq 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 <i>FADS</i> 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 \geq 18 years from Iran	<i>ZNF8</i> , rs13266634	<i>ZNF8</i> : 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 <i>ZNF8</i> 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 <i>ZNF78</i> 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)	<i>PCSK5</i> , rs1029035	<i>PCSK5</i> : 9q21.13	Based on overall median intake (further detailed elsewhere (12)): Low: <0.4 %kcal (food) High: >0.4 %kcal (food)	CC vs. CA vs. AA	HDL-c	HDL-c: Significant interaction between <i>PCSK5</i> 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)	<i>TNFA</i> , rs1800629	<i>TNFA</i> : 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 <i>TNFA</i> , 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)	<i>TNFA</i> , rs361525	<i>TNFA</i> : 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 <i>TNFA</i> , 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 <i>TNFA</i> 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 <i>TNFA</i> rs361525.
Joffe et al. 2014 (15)	Cross-Sectional	Single SNP	Black and white women from South Africa, normal weight or with obesity (n=268)	<i>IL-6</i> , -174 G>C, IVS3 (rs1800795), +281 G>T, IVS4 (rs1554606), +869 A>G (rs2069845)	<i>IL-6</i> : 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: HDL-c: Significant interaction whereby HDL-c increased with increasing omega-3 and/or DHA and/or ALA intake in <i>IL-6</i> rs1800795 C allele carriers and increasing ALA intake in <i>IL-6</i> rs1554606 T allele carriers. HDL-c decreased with increasing EPA and/or DHA intake in <i>IL-6</i> rs2069845 G allele carriers. TG: Significant interaction whereby TG reduced with increasing EPA intake in <i>IL-6</i> rs1800795 C allele carriers Total-c:HDL-c: Significant interaction whereby total-c:HDL-c ratio decreased with increasing EPA intake in <i>IL-6</i> rs1800795 CC genotypes and <i>IL-6</i> rs1554606 TT genotypes, increasing DHA intake in <i>IL-6</i> rs1800795 CC genotypes, and increasing ALA intake in <i>IL-6</i> rs1554606 TT genotypes.
Lai et al. 2006 (16)	Cross-Sectional	Single SNP	Men and women from the Framingham	<i>APOA5</i> , rs662799, rs651821, rs3135506,	<i>APOA5</i> : 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		omega-3: 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)	<i>FADS</i> , rs174546, rs482548, rs174570	<i>FADS</i> : 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)	<i>ANGPTL4</i> E40K (rs116843064)	<i>ANGPTL4</i> : 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)	<i>PLIN4</i> , rs8887, rs11673616, rs892158, rs7250947, rs8102428, rs1609717, rs884164	<i>PLIN4</i> : 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 <i>PLIN4</i> , 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 LISApplus birth cohort studies (n=1697)	<i>FADS1/FADS2</i> , rs174545, rs174546, rs174556, rs174561, rs174575, rs3834458	<i>FADS1/2</i> : 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)	<i>PPARα</i> , L162V (rs1800206)	<i>PPARα</i> : 22q13.31	High: >0.69 %kcal Low: <0.69 %kcal (food)	<i>PPARα</i> : 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)	<i>PPARα</i> , L162V (rs1800206), 3'UTR G>A (rs6008259), 3'UTR C>T (rs3892755)	<i>PPARα</i> : 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 <i>PPARα</i> (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)

Warodomwich et al. 2009 (23)	Cross-sectional with fasting and postprandial measures	Single SNP	Men and women of GOLDN study (n=1083)	<i>TCF7L2</i> rs7903146, rs12255372	<i>TCF7L2</i> : 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	--
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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	<i>FADS1</i> , rs174561 <i>FADS2</i> , rs174583 <i>ELOVL2</i> , rs953413 <i>ELOVL5</i> , rs2397142 <i>CETP</i> , rs5882 <i>SCD1</i> , rs2234970, <i>PPARA</i> , rs6008259 <i>LIPF</i> , rs814628 and <i>APOE</i> , rs429358, rs7412	<i>FADS1/2</i> : 11q12.2 <i>ELOVL2</i> : 6p24.2 <i>ELOVL5</i> : 6p12.1 <i>CETP</i> : 16q13 <i>SCD1</i> : 10q24.31 <i>PPARA</i> : 22q13.31 <i>LIPF</i> : 10q23.31 <i>APOE</i> : 19q13.32	Intake range: 1.0 – 2.5 g/day DHA (supplement)	Comparison between three genotypes for each single SNP (except <i>PPARA</i> and <i>LIPF</i> whereby analyses were major allele homozygotes vs. minor allele carriers) and <i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -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	<i>CETP</i> , rs3764261, <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5/ABCG</i> , rs4299376 <i>TIMD4/HAVCR1</i> , rs6882076 <i>GCKR</i> , rs1260326 <i>TRIB1</i> , rs2954029 <i>ANGPTL3/DOCK7</i> , rs2131925 <i>FADS1/2/3</i> , rs174546 <i>GALNT2</i> , rs4846914 <i>ABCA1</i> , rs4149268 <i>APOE/APOC1/APOC2</i> , rs439401	<i>CETP</i> : 16q13 <i>LIPC</i> : 15q21.3 <i>APOB</i> : 2p24.1 <i>ABCG5/ABCG8</i> : 2p.21 <i>TIMD4/HAVCR1</i> : 5q33.3 <i>GCKR</i> : 2p23.3 <i>TRIB1</i> : 8q24.13 <i>ANGPTL3/DOCK7</i> : 7: 1p31.3 <i>FADS</i> : 11q12.2 <i>GALNT2</i> : 1q42.13 <i>ABCA1</i> : 9q31.1 <i>APOE/APOC1/APOC2</i> : 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 <i>FADS1</i> rs174546

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Armstrong et al. 2012 (26)	Double-Blind, Placebo-Controlled Randomized Intervention	Single SNP (deletion polymorphism)	Healthy adults of African ancestry (n=98)	6 weeks	<i>ALOX5</i> , dd (33, 34 or 44), d5 (35, 45) and 55 (control) genotypes	<i>ALOX5</i> : 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	<i>PPARA</i> , L162V (rs1800206), <i>PPARγ2</i> , P12A (rs1801282)	<i>PPARA</i> : 22q13.31 <i>PPARγ2</i> : 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 (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> Pro12Pro genotypes only for individuals with BMI>25.0 kg/m ² Total-c : significant increase in total-c among minor allele carriers (<i>PPARγ2</i> Pro12Ala and Ala12Ala) only vs. <i>PPARγ2</i> 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	<i>SREBF1</i> , rs4925115, rs4925118, rs12953299 <i>ACLY</i> , rs8071753, rs8065502, rs2304497 <i>ACACA</i> rs2017571, rs29221368, rs9906044, rs2229416, rs1714987, rs1266175, rs3815059, rs829165	<i>SREBF1</i> : 17p11.2 <i>ACLY</i> : 17q21.2 <i>ACACA</i> : 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 <i>ACLY</i> rs8071753 and individuals with the GG or CG genotype of <i>ACACA</i> 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 <i>ACLY</i> 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	<i>RXRα</i> (12 SNPs), <i>CPT1A</i> (9 SNPs), <i>ACADVL</i> (1 SNP), <i>ACAA2</i> (6 SNPs), <i>ABCD2</i> (8 SNPs), <i>ACOX1</i> (8 SNPs), <i>ACAA1</i> (3 SNPs) [outlined in Supplementary Table 5]	<i>RXRα</i> : 9q34.2 <i>CPT1A</i> : 11q13.3 <i>ACADVL</i> : 17p13.1 <i>ACAA2</i> : 18q21.1 <i>ABCD2</i> : 12q12 <i>ACOX1</i> : 17q25.1 <i>ACAA1</i> : 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 <i>RXRα</i> rs11185660 genotype dependent on total fat intake, <i>RXRα</i> rs10881576, rs12339187 and rs11185660 genotypes dependent on saturated fat intake, and <i>ACOX1</i> 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	<i>GCK</i> (13 SNPs) [outlined in Supplementary Table 5]	<i>GCK</i> : 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 <i>GCK</i> 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.

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6	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	<i>PPARα</i> , L162V (rs1800206)	<i>PPARα</i> : 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	--
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14	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -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 <i>APOE</i> -E3/4 carriers (compared to high-SFA diet alone)
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23	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E2/E2 + E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -E3/E4 + E4/E4	HDL-c LDL-c TG Total-c	TG: Significant interaction between treatment x sex x genotype whereby <i>APOE</i> -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
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28	Cormier et al. 2012 (35)	Single Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 years (n=208)	6 weeks	<i>FADS</i> gene cluster (19 SNPs) [outlined in Supplementary Table 5]	<i>FADS</i> : 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	--
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32	Dang et al. 2015 (36)	Single Arm Clinical Trial	Single SNP*	Healthy men and women aged 20-35 years (n=80)	4 weeks	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 900 mg EPA and 680 mg DHA (supplement)	<i>APOE</i> -E4+ vs. <i>APOE</i> -E4-	HDL-c LDL-c TG Total-c	--
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37	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	<i>CD36</i> , rs1761667, rs1049673	<i>CD36</i> : 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 <i>CD36</i> rs1761667 and CG genotype of <i>CD36</i> rs1049673. TG: In response to omega-3 supplementation (0.8-3.0 g/day), TG decreased in GA genotype of <i>CD36</i> rs1761667.
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							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	<i>NOS3</i> , rs11771443, rs1800783, rs1800779, rs1799983, rs3918227, rs743507	<i>NOS3</i> : 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-I apoB apoB-48 apoC-II apoC-III apoE HDL-c LDL-c TG Total-c	TG: For <i>NOS3</i> 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	<i>PPARγ2</i> , Pro12Ala (rs1801282), <i>FADS1</i> , rs1535, <i>FADS2</i> , rs174575, <i>FADS3</i> , rs174448, <i>COX2</i> , rs5275, rs689466	<i>PPARγ2</i> : 3p25.2 <i>FADS</i> : 11q12.2 <i>COX2</i> : 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)	<i>PPARγ2</i> genotype analyses were by major allele homozygotes vs. heterozygotes and <i>FADS</i> genotype analyses were by the number of DHA-increasing alleles and <i>COX2</i> genotype analyses were by major allele homozygotes vs. heterozygotes vs. minor allele homozygotes	HDL-c LDL-c TG Total-c	TG: <i>PPARγ2</i> heterozygotes exhibited reduced TG in response to omega-3 when compared to <i>PPARγ2</i> 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	<i>PPARγ2</i> , Pro12Ala (rs1801282)	<i>PPARγ2</i> : 3p25.2	Fish oil containing 3.4 g/day EPA + DHA (supplement)	<i>PPARγ2</i> , 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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4	apoB apoC-III apoE HDL-c LDL-c TG	TG: <i>APOE</i> -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 <i>APOE</i> -E3/4 consuming a high saturated fat + DHA intervention exhibited significantly lower

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									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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.45 g/day DHA (supplement)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -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	<i>PPAR</i> γ 2, Pro12Ala (rs1801282)	<i>PPAR</i> γ 2: 3p25.2	Fish oil containing 2.4 g/d EPA + DHA (supplement)	<i>PPAR</i> γ 2, 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 \leq 37 %kcal or SFA intake was \leq 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	<i>FVII</i> , rs6046	<i>FVII</i> : 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	<i>CD36</i> , rs1527483, rs1049673, rs1761667, rs1984112	<i>CD36</i> : 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	<i>TNF</i> α , -308 (rs1800629) <i>LT</i> - α , +252 (rs909253) <i>IL</i> -1 β , -511 (rs16944) <i>IL</i> -6, -174 (rs1800795)	<i>TNF</i> α : 6p21.33 <i>LT</i> - α : 6p21.33 <i>IL</i> -1 β : 2q14.1 <i>IL</i> -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 <i>LT</i> - α rs909253 GG genotype and <i>IL</i> -1 β rs16944 TT genotype. In <i>LT</i> - α rs909253 AA genotype and <i>TNF</i> α 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	<i>FABP</i> 2, rs1799883	<i>FABP</i> 2: 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	--

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3 4 5 6 7	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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 3.0 g/d EPA and DHA, Control oil: 6.0 g/d olive oil capsule (supplement)	<i>APOE</i> -E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -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 <i>APOE</i> -E2/E3 relative to other <i>APOE</i> genotype categories Total-c : 6-week: <i>APOE</i> -E3/E4 + E4/E4 genotype group exhibited significantly different changes in total-c (increase), relative to other <i>APOE</i> genotypes, whereby reductions in total-c occurred
8 9 10 11 12 13	Olano-Martin et al. 2010 (49)	Randomized, Cross-Over Intervention	Single SNP*	Healthy normolipidemic men (n=38)	4 weeks per diet	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 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)	<i>APOE</i> -E3/3 vs. <i>APOE</i> -E3/4 (carriers)	apoB apoE HDL-c LDL-c TG TG:HDL-c Total-c	apoB, LDL-c : In <i>APOE</i> -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 <i>APOE</i> -E3/E3 group; significant reduction in TG in <i>APOE</i> -E4 carriers with EPA only. No significant interactions. Total-c : Significant genotype x treatment interaction whereby <i>APOE</i> -E4 carriers exhibit total-c reductions in response to EPA-rich oil.
14 15 16 17 18 19	Quellette et al. 2013 (50)	Single-Arm Clinical Trial	Single SNP	Healthy men and women aged 18-50 (n=210)	6 weeks	<i>GPAM</i> (3 SNPs), <i>AGPAT3</i> (13 SNPs), <i>AGPAT4</i> (35 SNPs) [outlined in Supplementary Table 5]	<i>GPAM</i> : 10q25.2 <i>AGPAT3</i> : 21q22.3 <i>AGPAT4</i> : 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 <i>GPAM</i> , rs2792751 genotype x supplementation interaction on LDL-c TG : Significant genotype x supplementation interaction on TG for <i>GPAM</i> , rs2792751 and rs17129561 as well as <i>AGPAT4</i> , rs9458172 and rs3798943
20 21 22 23 24 25 26 27 28	Quellette et al. 2014 (51)	Single-Arm Clinical Trial	Single SNP	Healthy men and women 18-50 years (n=208)	6 weeks	<i>MGLL</i> (18 SNPs) [outlined in Supplementary Table 5]	<i>MGLL</i> : 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 <i>MGLL</i> 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 <i>MGLL</i> 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)
29 30 31 32	Paschos et al. 2005 (52)	Single-Arm Clinical Trial	Single SNP*	Men with dyslipidemia, aged 35 to 67 years (n=50)	12 weeks	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	8.1 g/day ALA (via 15 ml of Flaxseed oil supplementation)	<i>APOE</i> -E2/E3 vs. <i>APOE</i> -E3/E3 vs. <i>APOE</i> -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
33 34 35 36 37 38 39 40	Pishva et al. 2010 (53)	Single-Arm Clinical Trial	Single SNP	Adults with hypertriglyceridemia (n=46)	8 weeks	<i>FABP2</i> , Ala54Thr (rs1799883)	<i>FABP2</i> : 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.
41	Pishva et al.	Single-Arm	Single SNP	Adults with	8 weeks	<i>PPARα</i> ,	<i>PPARα</i> : 22q13.31	2.0 g/day pure	Leu162	ApoB	--

2014 (54)	Clinical Trial		hypertriglyceridemia (n=46)		Leu162Val (rs1800206) <i>PPARα</i> , Intron 7 SNP		EPA (supplement)	vs. Val162 carriers <i>and</i> 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)	<i>FADS1</i> , rs174537 <i>FADS2</i> , rs174576 (LD=1.0 therefore presented results for rs174537)	<i>FADS1/2</i> : 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	<i>SCD1</i> , rs1502593, rs522951, rs11190480, rs3071, rs3829160, rs2234970, rs10883463, rs508384	<i>SCD1</i> : 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 <i>SCD1</i> 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: <i>IQCJ-SCHIP1</i> (4 SNPs), <i>SLIT2</i> (3 SNPs), <i>PHF17</i> (3 SNPs), <i>MYB</i> (1 SNP), <i>NXP1</i> (1 SNP), <i>NELLI1</i> (1 SNP) [outlined in Supplementary Table 5]	<i>IQCJ-SCHIP1</i> : 3q25.32 <i>SLIT2</i> : 4p15.31 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 6q23.3 <i>NXP1</i> : 7p21.3 <i>NELLI1</i> : 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	<i>PNPLA3</i> , 1148M (rs738409) <i>TM6SF2</i> , E167K (rs58542926)	<i>PNPLA3</i> : 22q13.31 <i>TM6SF2</i> : 19p13.11	1.8 g/day EPA+ 1.5 g/day DHA (supplement)	Comparison between three genotypes <i>and</i> 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	<i>APOE</i> , rs429358, rs7412	<i>APOE</i> : 19q13.32	Fish oil containing 1.9-2.2 g/d EPA and 1.1 g/d DHA (supplement)	<i>APOE</i> -E2 vs. <i>APOE</i> -E3 vs. <i>APOE</i> -E4	apoB HDL-c LDL-c TG Total-c	--
Tremblay et	Single-Arm	Single SNP	Healthy men	6 weeks	<i>PLA2G2A</i> (5)	<i>PLA2G2A</i> :	Fish oil containing	Major allele	apoB-100	TG: omega-3 supplementation significantly reduced TG in

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3 4 5 6 7 8 9 10 11 12 13	al. 2015 (60)	Clinical Trial		and women aged 18-50 years (n=208)		SNPs), <i>PLA2G2C</i> (6 SNPs), <i>PLA2G2D</i> (8 SNPs), <i>PLA2G2F</i> (6 SNPs), <i>PLA2G4A</i> (22 SNPs), <i>PLA2G6</i> (5 SNPs), <i>PLA2G7</i> (9 SNPs) [outlined in Supplementary Table 5]	1p36.13 <i>PLA2G2C</i> : 1p36.13 <i>PLA2G2D</i> : 1p36.12 <i>PLA2G2F</i> : 1p36.12 <i>PLA2G4A</i> : 1q31.1 <i>PLA2G6</i> : 22q13.1 <i>PLA2G7</i> : 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	<i>PLA2G7</i> rs1805018 as well as <i>PLA2G4A</i> rs10752979, rs10737277, rs7540602 and rs3820185; in the linear regression model, <i>PLA2G6</i> rs132989, <i>PLA2G7</i> rs679667, <i>PLA2G2D</i> rs12045689, <i>PLA2G4A</i> rs 10752979 and rs1160719 together explained 5.9% of post-supplementation TG levels
14 15 16 17 18 19 20 21 22 23 24 25	Vallée Marcotte et al. 2016 (61)	Single-Arm Clinical Trial	Nutrigenomic GWAS	Men and woman aged 18-50 years (n=208)	6 weeks	<i>IQCJ</i> (16 SNPs), <i>NXPPI</i> (34 SNPs), <i>PHF17</i> (8 SNPs), <i>MYB</i> (9 SNPs) [outlined in Supplementary Table 5]	<i>IQCJ</i> : 3q25.32 <i>NXPPI</i> : 7p21.3 <i>PHF17</i> : 4q28.2 <i>MYB</i> : 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: <i>IQCJ</i> (10 SNPs: rs2044704, rs1962071, rs6800211, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355), <i>NXPPI</i> (4 SNPs: rs7806226, rs7805772, rs2349780, rs6974252), <i>MYB</i> (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 <i>IQCJ</i> ; rs7805772 in <i>NXPPI</i> . There were four dominant SNPs driving the association with the TG response: rs61332355 and rs9827242 in <i>IQCJ</i> , rs7805772 in <i>NXPPI</i> and rs11154794 in <i>MYB</i> . Significant differences in genotype frequencies between positive and negative responders to omega-3 for TG changes for <i>IQCJ</i> rs2044704, rs1962071, rs17782879, rs1868414, rs2595260, rs9827242, rs1449009, rs2621309, rs61332355, <i>NXPPI</i> rs7806226, rs7805772, <i>MYB</i> rs11154794 and rs210936.
26 27 28 29 30 31 32	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 (<i>NXPPI</i> rs10265408, rs10486228, rs10486228, rs17150341, rs6974252 and <i>IQCJ-SCHIP1</i> 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.
33 34 35 36 37	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).
38 39 40 41	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.

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			years (n=122)					Non-Responders vs. Adverse Responders <i>and</i> Responders vs. Adverse Responders			
3 4 5 6 7 8 9 10 11	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	<i>eNOS</i> Glu298Asp (rs1799983)	<i>NOS3</i> : 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	--
12 13 14 15 16 17 18 19	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 postmenopausa l and 80 years for women (n=139)	25 weeks	<i>CD36</i> , rs1527483 <i>NOS3</i> , rs1799983 <i>PPARγ2</i> , rs1801282	<i>CD36</i> : 7q21.11 <i>NOS3</i> : 7q36.1 <i>PPARγ2</i> : 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 <i>PPARγ2</i> rs1801282 genotype, intervention group and LDL-c change; but increased LDL-c in G allele carriers of <i>PPARγ2</i> rs1801282 compared to CC genotype <i>only in the control</i> (corn oil) group TG : omega-3 fish oil (but not flaxseed oil) supplementation reduced TG for individuals with the <i>CD36</i> 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

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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
<i>APOE</i> : 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)
<i>APOE</i> : 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>PPAR</i> γ 2: 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)
<i>CD36</i> : rs1761667	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1761667	TG	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1049673	HDL-c	Dawczynski et al. 2013 (37) Madden et al. 2008 (45)
<i>CD36</i> : rs1527483	TG	Madden et al. 2008 (45) Zheng et al. 2018 (66)
<i>FADS</i> : 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. <i>Int J Obes</i> ;43:808-820 (2019)	<p><i>FADS2</i>, rs174599, rs174601, rs556656, rs11501631, rs74771917, rs3168072, rs182008711, rs73487492, rs174602, rs12577276</p> <p><i>FADS3</i>, rs191972868, rs115905177, rs174635, rs174634, rs174454, rs12292968, rs174570, rs7930349, rs116672159, rs116139751, rs7942717, rs7115739, rs174450, rs74626285</p> <p><i>RAB31L1</i>, rs741887, rs2521561, rs2727258, rs2524288, rs117518711, rs74957100, rs77071864, rs78243280, rs741888, rs2524287, rs12420625, rs77229376, rs187943834, rs78156005, rs190738753, rs11230827, rs76133863, rs116985542, rs73491252</p>
Cormier et al. 2012	<p><i>FADS</i> gene cluster rs174456, rs174627, rs482548, rs2072114, rs12807005, rs174448, rs2845573, rs7394871, rs7942717, rs74823126, rs174602, rs498793, rs7935946, rs174546, rs174570, rs174579, rs174611, rs174616, rs968567</p>
Vallée Marcotte et al. <i>Am J Clin Nutr</i> ;109:176–185 (2019)	<p><i>IQCJ-SCHIP1</i>, rs7639707, rs62270407</p> <p><i>NXPH1</i>, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523</p> <p><i>PHF17</i>, rs1216346, rs114348423, rs75007521</p> <p><i>MYB</i>, rs72560788, rs72974149, rs210962, rs6933462</p> <p><i>NELL1</i>, rs79624996, rs1850875, rs78786240, rs117114492</p> <p><i>SLIT2</i>, rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249</p>
Tremblay et al. <i>Lipids in Health and Disease</i> (2015) 14:12	<p><i>PLA2G2A</i>, rs876018, rs955587, rs3753827, rs11573156, rs11573142</p> <p><i>PLA2G2C</i>, rs6426616, rs12139100, rs10916716, rs2301475, rs10916712, rs10916718</p> <p><i>PLA2G2D</i>, rs578459, rs16823482, rs3736979, rs584367, rs12045689, rs679667, rs17354769, rs1091671</p> <p><i>PLA2G2F</i>, rs12065685, rs6657574, rs11582551, rs818571, rs631134, rs11583904</p>

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

	rs11651351, rs3643, rs7213998, rs17583163 <i>ACAA1</i> , rs2239621, rs156265, rs5875
AlSaleh et al. Genes Nutr 9:412 (2014)	<i>CETP</i> , rs3764261, rs247616, rs7205804 <i>LIPC</i> , rs1532085 <i>APOB</i> , rs1367117 <i>ABCG5</i> , <i>ABCG8</i> , rs4299376 <i>TIMD4</i> , <i>HAVCR1</i> , rs6882076, rs1501908, rs1553318 GCKR, rs1260326, rs780094 TRIB1, rs2954022, rs10808546, rs2954029 <i>ANGPTL3</i> , <i>DOCK7</i> , rs3850634, rs1167998, rs2131925 <i>FADS1</i> , <i>FADS2</i> , <i>FADS3</i> , rs174550, rs174547, rs174546, rs174583 <i>GALNT2</i> , rs4846914, rs1321257 <i>ABCA1</i> , rs4149268 <i>APOE</i> , <i>APOC1</i> , <i>APOC2</i> , rs439401
Vallée Marcotte et al. Genes & Nutrition 15:10 (2020)	<i>IQCJ-SCHIP1</i> , rs7639707, rs62270407 NXP1, rs61569932, rs1990554, rs6463808, rs6966968, rs28473103, rs28673635, rs12702829, rs78943417, rs293180, rs1837523 <i>PHF17</i> , rs1216346, rs114348423, rs75007521 <i>MYB</i> , rs72560788, rs72974149, rs210962, rs6933462 <i>NELL1</i> , rs79624996, rs1850875, rs78786240, rs117114492 <i>SLIT2</i> , rs184945470, rs143662727, rs10009109, rs10009535, rs61790364, rs73241936, rs16869663, rs76015249
Rudkowska et al. Journal of Lipid Research 55 (2014)	<i>IQCJ-SCHIP1</i> , <i>MYB</i> , <i>NELL1</i> , <i>NXP1</i> , <i>PHF17</i> , <i>SLIT2</i> , rs2621308, rs1449009, rs61332355, rs2621309, rs2952724, rs2629715, rs1216352, rs1216365, rs931681, rs6920829, rs6463808, rs752088
Vallée Marcotte et al. J Nutrigenet Nutrigenomics;9 :1-11 (2016)	<i>IQCJ</i> , rs12497650, rs4501157, rs13091349, rs2044704, rs1062071, rs7634829, rs2621294, rs6800211, rs17782879, rs1868414, rs2595260, rs6763890, rs9827242, rs1449009, rs2621309, rs61332355

	<p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs210962, rs17639758, rs1013891, rs2179308</p>
<p>Vallée Marcotte et al. Nutrients; 11, 737 (2019)</p>	<p><i>IQCJ-SCHIP1</i>, 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</p> <p><i>NXPFI</i>, 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</p> <p><i>PHF17</i>, rs2217023, rs4975270, rs11722830, rs12505447, rs6534704, rs13148510, rs13143771, rs13142964, rs1216352, rs1216365</p> <p><i>MYB</i>, rs9321493, rs11154794, rs210798, rs210936, rs7757388, rs17639758, rs1013891, rs2179308, rs6920829, <i>SLIT2</i>, rs2952724</p> <p><i>NELLI</i>, rs752088</p>

Supplementary Table 6: 31-SNP Nutri-GRS

Gene, rs Number	Alleles¹	Associated Points
<i>IQCJ-SCHIP1</i> , rs7639707	<u>A</u> /G	+1
<i>IQCJ-SCHIP1</i> , rs62270407	C/ <u>T</u>	-1
NXPH1, rs61569932,	<u>G</u> /T	+1
NXPH1, rs1990554	<u>A</u> /C	+1
NXPH1, rs6463808	<u>A</u> /G	+1
NXPH1, rs6966968	<u>A</u> /G	+1
NXPH1, rs28473103	<u>A</u> /G	-1
NXPH1, rs28673635	<u>A</u> /G	+1
NXPH1, rs12702829	<u>C</u> /T	+1
NXPH1, rs78943417	A/ <u>T</u>	-1
NXPH1, rs293180	G/ <u>T</u>	+1
NXPH1, rs1837523	<u>C</u> /T	-1
<i>PHF17</i> , rs1216346	<u>C</u> /T	+1
<i>PHF17</i> , rs114348423	<u>A</u> /G	+1
<i>PHF17</i> , rs75007521	<u>G</u> /T	-1
<i>MYB</i> , rs72560788	<u>C</u> /T	-1
<i>MYB</i> , rs72974149	<u>A</u> /G	-1
<i>MYB</i> , rs210962	<u>C</u> /T	-1
<i>MYB</i> , rs6933462	<u>C</u> /G	+1
<i>NELL1</i> , rs79624996	<u>A</u> /G	+1
<i>NELL1</i> , rs1850875	<u>C</u> /T	+1
<i>NELL1</i> , rs78786240	<u>C</u> /T	-1
<i>NELL1</i> , rs117114492	<u>G</u> /T	+1
<i>SLIT2</i> , rs184945470	<u>C</u> /T	+1
<i>SLIT2</i> , rs143662727	<u>A</u> /G	-1
<i>SLIT2</i> , rs10009109	<u>C</u> /T	+1
<i>SLIT2</i> , rs10009535	<u>A</u> /G	+1
<i>SLIT2</i> , rs61790364	<u>A</u> /G	+1
<i>SLIT2</i> , rs73241936	<u>C</u> /T	+1
<i>SLIT2</i> , rs16869663	<u>A</u> /G	+1
<i>SLIT2</i> , rs76015249	<u>A</u> /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)
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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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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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