Fish oil supplementation modifies the genetic potential for blood lipids

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1

1   **Abstract**

2

3   **Background**

4   Dyslipidemia is a well-known risk factor for cardiovascular disease, which has been the leading

5   cause of mortality worldwide. Although habitual intake of fish oil has been implicated in

6   offering cardioprotective effects through triglyceride reduction, the interactions of fish oil with

7   the genetic predisposition to dysregulated lipids remain elusive.

8

9   **Objectives**

10   We examined whether fish oil supplementation can modify the genetic potential for the

11   circulating levels of four lipids, including total cholesterol, low-density lipoprotein cholesterol

12   (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides.

13

14   **Methods**

15   A total of 441,985 participants with complete genetic and phenotypic data from the UK Biobank

16   were included in our study. Polygenic scores (PGS) were calculated in participants of diverse

17   ancestries. Multivariable linear regression models were used to assess associations with

18   adjustment for relevant risk factors.

19

20   **Results**

21   Fish oil supplementation mitigated genetic susceptibility to elevated levels of total cholesterol,

22   LDL-C, and triglycerides, while amplifying genetic potential for increased HDL-C among

23   424,090 participants of European ancestry ($P_{\text{interaction}} < 0.05$). Consistent significant findings

24   were obtained using PGS calculated based on multiple genome-wide association studies or

25   alternative PGS methods. We also showed that fish oil significantly attenuated genetic

26   predisposition to high triglycerides in African-ancestry participants.

27

28   **Conclusions**

29   Fish oil supplementation attenuated the genetic susceptibility to elevated blood levels of total

30   cholesterol, LDL-C, and triglycerides, while accentuating genetic potential for higher HDL-C.

31   These results suggest that fish oil may have a beneficial impact on modifying genome-wide

32   genetic   effects   on   elevated   lipid   levels   in   the   general   population.

Introduction

34

35 Dyslipidemia is well-known to be a major risk factor for cardiovascular disease (CVD), the

36 leading cause of death globally (1). Elevated levels of total cholesterol, low-density lipoprotein

37 cholesterol (LDL-C), and triglyceride serve as major risk factors for increased risks of ischemic

38 events, as shown in epidemiologic and Mendelian randomization studies (2-7). Conversely, a

39 raised level of high-density lipoprotein cholesterol (HDL-C) may have protective roles against

40 CVD, autoimmune disease, and cancers (8, 9). Numerous studies have found that fish oil

41 supplementation, predominantly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA),

42 exerts cardioprotective effects through the reduction of triglyceride level (10-12). However, the

43 roles of fish oil supplementation in modulating genetic susceptibility to elevated lipid levels

44 remains insufficiently investigated.

45

46 In addition to environmental factors, studies have highlighted the essential role of genetic factors

47 in dyslipidemia (13). Genetic effects have been estimated to explain more than 50% of the

48 phenotypic variance in blood lipid levels (14). The differential effect of a genotype in individuals

49 with different environmental exposures, known as gene-environment interaction, also plays a

50 crucial role in determining outcomes (15, 16). A prior genome-wide interaction study identified

51 four novel loci, whose associations with blood lipids were modified by fish oil supplementation

52 (17). Expanding the previous single-variant analysis to a genome-scale, we hypothesized that the

53 genome-wide genetic effects on blood lipid levels, captured by polygenic scores (PGS), could be

54 modified by habitual fish oil supplementation.

55

56   In the current study, we aimed to explore the associations between fish oil supplementation

57   status and genetic predispositions to high levels of total cholesterol, LDL-C, HDL-C, and

58   triglyceride. Large-scale genome-wide association studies (GWAS) have identified numerous

59   single nucleotide polymorphisms (SNPs) significantly associated with elevated lipid levels (18).

60   Leveraging this information and employing novel PGS approaches, we aggregated individual

61   lipid-associated SNPs into genome-scale PGS for estimating the genetic predispositions to high

62   lipids among participants in UK Biobank (UKB). Then, we examined the interaction effects

63   between fish oil supplementation and these PGS on the observed levels of blood lipids. While

64   our primary analysis focused on participants of European (EUR) ancestry, we also investigated

65   the interactions in African (AFR), Central/South Asian (CSA), and East Asian (EAS)

66   populations.

Methods

Study population

This study was conducted using data from UKB (application number 48818), which is a prospective population-based study of over 0.5 million participants aged 37–73 years at recruitment from 2006 to 2010 across the United Kingdom (19). The UKB study received ethical approval from the National Health Service North West Centre for Research Ethics Committee, and all participants provided electronically signed consent before joining the study. Participants provided information on sociodemographic, lifestyle, and medical records via questionnaires at baseline. Blood samples for genotyping and biomarker measurements were also collected at recruitment. Of 502,369 individuals who attended baseline assessment, we excluded 6,705 individuals from the analysis due to missing fish oil supplementation data, mismatched information between phenotypic and genetic sex, sex chromosome aneuploidy, outliers for heterogeneity and missing genotype rate, and having a high degree of genetic kinship (ten or more third-degree relatives identified). Our analysis primarily focused on EUR ancestry participants, as they comprised the largest ancestral group in this resource. We also conducted analyses with participants of AFR, CSA, and EAS ancestries. Figure 1 presents a flowchart outlining the inclusion and exclusion of participants throughout our study.

Assessment of fish oil supplementation status

The fish oil supplementation status of study participants was determined during their initial assessment center visit using a touchscreen questionnaire. Specifically, participants were asked

89   about their regular consumption of certain supplements, with those reporting fish oil intake

90   (including cod liver oil) classified as supplementing with fish oil.

91

92   **Assessment of blood lipids**

93   Four baseline serum lipid parameters, including total cholesterol, LDL-C, HDL-C, and

94   triglycerides, were ascertained using standard hematological methodologies. These lipids were

95   directly quantified via a robust analytical platform, the Beckman Coulter AU5800 chemistry

96   analyzer, to ensure precision and reproducibility.

97

98   **Polygenic score calculation**

99   We computed PGS for participants of EUR, AFR, CSA, and EAS ancestries in the UKB, which

100   measures the aggregated effects of genetic variants on total cholesterol, LDL-C, HDL-C, and

101   triglycerides. In our primary discovery analysis, we used summary statistics from the largest and

102   most recent GWAS to date, called the Graham SE *et al.* no UKB study, which excluded UKB

103   and included up to 930,672 EUR, 92,555 AFR, and 34,135 CSA ancestry participants (20). In the

104   replication analysis, we employed two additional GWAS summary statistics to calculate PGS.

105   The first is the GWAS meta-analysis using UKB and other cohorts, which was released by

106   Graham SE *et al.*, containing up to 1,320,016 EUR, 99,432 AFR, 40,963 CSA, and 146,492 EAS

107   ancestry participants. The second is a GWAS that included up to 187,365 EUR individuals, as

108   previously reported by Willer CJ *et al.* (21).

109

110   The PGS of UKB participants was calculated with the weighted method: weighted PGS = $\beta_1 \times$

111    $SNP_1 + \beta_2 \times SNP_2 + \ldots + \beta_n \times SNP_n$, where SNP_n is the number of effect alleles of the nth SNP,

112   and the β-coefficient is the effect size of the corresponding allele, which was extracted from

113   GWAS summary statistics. Quality control for genotypic data was based on the following criteria:

114   (1) imputation quality score > 0.3, (2) minor allele frequency > 0.1%, (3) genotype missingness

115   per individual < 5%, 4) genotype call rate < 5%, and (5) Hardy-Weinberg test P-value $> 1 \times 10^{-8}$.

116   Independent significant SNPs were identified at a GWAS threshold of P-value $< 5 \times 10^{-8}$ with

117   linkage disequilibrium (LD) clumping ($r^2 = 0.1$, 250 kb). We also utilized the PGS β-coefficient

118   previously generated by Weissbrod O *et al.* employing the methods of PolyPred, PolyPred+, and

119   LD-pruning + P-value thresholding (P+T) (clump $r^2 = 0.5$, 250 kb) (22). To facilitate the

120   comparison of effects across four blood lipids, PGS was standardized to a mean of 0 and a

121   standard deviation (SD) of 1, enabling interpretation per one SD change.

122

123   **Covariates**

124   A series of sociodemographic, behavioral, and genetic covariates were included in our study.

125   Age, sex, and body mass index (BMI) were obtained from baseline assessments at recruitment.

126   The 22 baseline assessment center locations were situated throughout England, Scotland, and

127   Wales. Socioeconomic status, as calculated by the Townsend deprivation index, was assigned to

128   each participant corresponding to their home postcode at recruitment. Smoking and alcohol

129   drinking status were defined as never, former, and current. Physical activity levels were

130   categorized as low, moderate, and high following the International Physical Activity

131   Questionnaire protocol. Statin use was ascertained through self-report during verbal interviews.

132   Genetic data were generated through genotyping by either the UK Biobank Axiom Array or the

133   UK BiLEVE Array. Participants were divided into ancestry groups based on the multi-ancestry

134   analysis from the Pan-ancestry genetic analysis of the UK Biobank (Pan-UKBB). The top 20

135   ancestry principal components derived from the Pan-UKBB were employed as covariates.

136

137   **Statistical analysis**

138   Multivariable linear regression models were conducted to assess the modifying impacts of fish

139   oil supplementation on the genetic potential for blood lipids. Two groups of covariates were used

140   to apply these models. In the first model, we adjusted for sex, age, age^2, assessment centers,

141   genotyping array, and the top 20 genetic principal components. The second model added

142   additional covariates, including BMI, Townsend deprivation index, smoking status, alcohol

143   status, physical activity, and statin use. We investigated the association between lipid PGS and

144   lipid levels, stratifying by fish oil intake status among 424,090 participants of EUR ancestry to

145   scrutinize the influence of fish oil supplementation on genetic predisposition for lipid levels. We

146   further examined interactions between fish oil supplementation and PGS for four lipids on lipid

147   levels by adding an interaction term between fish oil intake and lipid PGS and by incorporating

148   both fish oil supplementation status and PGS as covariates in both models. Moreover, we

149   conducted these interaction analyses using 6,577 AFR, 8,648 CSA, and 2,670 EAS ancestry

150   participants. Serum levels of total cholesterol, LDL-C, HDL-C, and triglycerides were

151   standardized, and their comparable effect sizes were expressed per one SD increase in the

152   corresponding blood lipid. All analyses were conducted using R (version 4.2.1).

153   **Results**

154

155   **Study cohorts**

156   A total of 441,985 participants from the UKB with complete genetic and phenotypic data were

157   included in this study, consisting mostly of individuals of EUR ancestry and a small proportion

158   of other ancestries. We present the baseline characteristics of participants of EUR ancestry

159   according to their fish oil intake status at baseline in Table 1. After quality control, 134,720

160   (31.8%) of study participants reported habitual use of fish oil supplements, while the remaining

161   289,370 participants were grouped as non-consumers of fish oil. The majority of fish oil users

162   were women (56%), with a mean age of 59 years. Those in the fish oil intake group were more

163   likely to be older, female, current alcohol drinkers, statin users, engaging in high physical

164   activity, and having higher levels of total cholesterol, LDL-C, and HDL-C, but less likely to be

165   current smokers or have an elevated BMI or triglyceride level. Among other ancestry groups,

166   2,289 (34.8%) AFR, 1,942 (22.5%) CSA, and 845 (31.6%) EAS participants took fish oil

167   supplementation and displayed similar characteristics to the EUR participants (Supplementary

168   Table 1).

169

170   **Effect modification by fish oil supplementation on genetic predisposition to elevated lipids**

171   In general, fish oil supplementation provided protection against genetic susceptibility to elevated

172   levels of total cholesterol, LDL-C, and triglycerides, while it amplified genetic potential for

173   higher HDL-C level. For the primary analysis using PGS (excluded UKB, Graham SE *et al.*),

174   there was strong evidence that fish oil supplementation modified the effect of the genetic

175   potential for four lipids in either the partially or fully adjusted model ($P_{\text{interaction}} < 0.05$) (Figure 2

176   and Table 2). When we generated PGS using two other GWAS summary statistics of Graham SE

177   *et al.* (included UKB) and Willer CJ *et al.*, consistently significant results were observed for the

178   four lipids (Supplementary Figure 1 and Supplementary Table 2). We also calculated PGS based

179   on the β-coefficient previously generated by Weissbrod O *et al.* employing PolyPred, which is

180   another PGS method employing functionally informed fine-mapping methods to obtain the

181   posterior association coefficients. Utilizing PGS calculated via the PolyPred and P+T methods,

182   we also discovered that fish oil supplementation significantly modified the genetic potential for

183   elevated blood lipids (Supplementary Figure 2 and Supplementary Table 2).

184

185   In the stratified analysis, fish oil supplementation significantly attenuated the genetic association

186   with total cholesterol: each 1 SD increase in PGS was associated with a 0.304 SD increase (95%

187   CI = 0.299 – 0.309) in total cholesterol among fish oil supplement users, compared to a 0.313 SD

188   increase (95% CI = 0.310 – 0.317) among non-users (Figure 2 and Table 2). Similarly, for LDL-

189   C, a 1 SD increment in PGS resulted in an increase of 0.323 SD (95% CI = 0.318 – 0.328) in

190   LDL-C level among fish oil users, in comparison to 0.332 SD increase (95% CI = 0.328 – 0.335)

191   for people without fish oil intake. Genetic susceptibility to high triglycerides was 0.254 (95% CI

192   = 0.248 – 0.259) in the fish oil group and 0.267 (95% CI = 0.263 – 0.270) in the group not taking

193   fish oil. Lastly, the impact of PGS was more pronounced in the fish oil group (0.234, 95% CI =

194   0.229 – 0.240) for HDL-C compared to participants without fish oil intake (0.227, 95% CI =

195   0.224 – 0.231). In summary, fish oil supplementation attenuates the genetic potential for elevated

196   levels of total cholesterol, LDL-C, and triglycerides, while amplifying the genetic predisposition

197   to a high level of HDL-C.

198

Interaction effects in other ancestry groups

In participants of AFR ancestry from UKB, we found that fish oil supplementation was consistently associated with a diminished risk of genetic susceptibility to high triglycerides (Supplementary Table 3). When stratified by fish oil supplementation status, each SD increase in PGS correlated to a 0.099 SD (95% CI = 0.070 – 0.128) rise in triglyceride level among fish oil users, compared to a 0.150 SD (95% CI = 0.125 – 0.174) increase among those not taking fish oil. However, this modification effect of fish oil supplementation was not observed in participants of CSA and EAS ancestries (Supplementary Tables 4 and 5). Moreover, analyses involving participants from other ancestry groups did not indicate significant interaction effects on total cholesterol, LDL-C, and HDL-C. In these diverse populations, the influence of PGS on lipid levels remained statistically significant even after adjusting for fish oil supplementation and multiple covariates (Supplementary Table 6).

Discussion

211

212

213   In this extensive prospective study involving 424,090 participants of EUR ancestry, our results

214   indicated that fish oil supplementation could modify the genetic susceptibility to elevated levels

215   of four lipids. Our findings suggested that fish oil supplementation attenuated genetic

216   predispositions to high levels of total cholesterol, LDL-C, and triglycerides, while accentuating

217   the genetic potential for increased HDL-C level. Analyzing 6,577 AFR, 8,648 CSA, and 2,670

218   EAS ancestry participants, no consistent significant interactions were found. However, for

219   participants of AFR ancestry, our results indicated that fish oil supplementation mitigates the

220   genetic risk on increased triglycerides. Collectively, our findings supported the hypothesis that

221   genome-wide genetic effects on blood lipid levels, captured by PGS, could be modified by

222   habitual fish oil supplementation.

223

224   Although substantial studies have highlighted the effects of fish oil supplements in improving the

225   lipid profile in hyperlipidemic patients, their influence on genetic susceptibility to dyslipidemia

226   remains unclear (2, 11, 23-26). A recent dose-response meta□analysis of 90 randomized

227   controlled trials with 72,598 participants demonstrated that DHA□+□EPA supplementation (>2

228   g/d) reduced triglyceride level (27). Skulas-Ray AC *et al.* concluded that pharmacological doses

229   of omega-3 fatty acids (>3 g/d total EPA+DHA) effectively decrease triglycerides and can be

230   safely combined with other lipid-lowering agents, particularly statins (28). The Japan EPA Lipid

231   Intervention Study, involving 14,981 hypercholesterolemia Japanese patients, found that 1.8 g/d

232   EPA in combination with a statin led to lower triglycerides compared with statin therapy alone

233   (29). In the current study of non-EUR ancestry groups, we also observed fish oil attenuates

234   genetic susceptibility to elevated triglycerides among participants of AFR ancestry, but no

235   significant interaction was detected among participants of CSA and EAS ancestries, which may

236   be due to insufficient sample sizes. Large-scale studies covering more representative samples

237   from diverse ancestries are needed to further validate our findings. Regarding genetic factors,

238   some studies have investigated the interactions between fish oil and lipid-related genetic variants

239   (17, 30-33). Our findings, leveraging cumulative effects of many genetic variants across the

240   genome to assess individual genetic predisposition to dyslipidemia, affirmed the protective role

241   of fish oil against genetic susceptibility to dyslipidemia.

242

243   The precise mechanisms underlying the observed interactions between fish oil supplementation

244   and genetic predisposition to elevated lipid levels are not yet fully elucidated. These modifying

245   effects could potentially be attributed to the multifaceted benefits derived from fish oil

246   supplements. The putative mechanisms through which fish oil supplementation influences

247   human lipoprotein metabolism include inhibition of very low-density lipoprotein (VLDL)

248   triglyceride synthesis, decreased apoprotein B synthesis, enhancement of VLDL turnover via an

249   increased fractional catabolic rate of VLDL, depression of LDL synthesis, and reduction of

250   postprandial lipemia (34). Additionally, fish oil intake has been found to exert beneficial effects

251   on several factors implicated in cardiovascular health, including inflammatory, oxidative,

252   thrombotic, vascular, and arrhythmogenic parameters (11, 35-40). However, it is plausible that

253   other mechanisms may also be involved in this modifying effect. Future functional studies are

254   warranted to discern the underlying biological mechanisms.

255

256   To the best of our knowledge, this is the first study to evaluate the modifying effects of fish oil

257   supplementation on genetic susceptibility to elevated lipid levels. The major strength of our

258   study lies in the large number of participants of EUR ancestry, providing sufficient statistical

259   power to detect significant interactions. Another strength of our study is the inclusion of other

260   ancestry groups, where we confirmed that fish oil attenuated genetic susceptibility to high

261   triglycerides in the AFR population. We used various GWAS summary statistics and PGS

262   methodologies to calculate PGS and applied a fully adjusted model with a wealth of data on

263   covariates, including socioeconomic characteristics, lifestyle factors, and statin use. Notably, the

264   PGS for the primary analysis incorporated multiple SNPs from the largest and most recent

265   GWAS across different cohorts, excluding any sample overlap with the UKB, thereby

266   circumventing the potential issue of spurious candidate gene interactions (41). Population

267   structure can lead to inflated estimates of PGS prediction (41). To address this, we adjusted all

268   models for the top 20 genetic principal components to minimize potential bias. This

269   comprehensive study design ensured the robustness and consistency of our findings.

270

271   Several potential limitations should also be considered. First, the self-reported fish oil intake is

272   vulnerable to both measurement error and recall bias. Second, since fish oil supplementation

273   status was assessed only at baseline, we were unable to evaluate the effects of longitudinal

274   changes or extended duration of use. Third, our data lacked details on specific doses of fish oil

275   supplementation, and future research is needed to discern the independent roles of DHA and

276   EPA at specific doses. Fourth, UKB recruited people aged between 37 and 73 years at baseline,

277   and our findings may not be generalizable to other age groups, such as children and adolescents

278   (42). Fifth, though our study included multiple ancestries, caution is advised when extrapolating

279   our findings to non-EUR populations, and future investigations with larger sample sizes are

280   necessary. Lastly, given the observational design of our study, we cannot completely rule out

281   reverse causation or residual confounding.

282

283   In conclusion, our findings reveal that fish oil supplementation attenuates genetic susceptibility

284   to elevated blood levels of total cholesterol, LDL-C, and triglycerides, while accentuating

285   genetic potential for higher HDL-C. Moreover, we detected fish oil modulates genetic

286   predisposition to high triglycerides among participants of AFR ancestry. These findings suggest

287   that fish oil could serve a beneficial role in modulating genetic susceptibility to elevated lipid

288   levels in the general population. Further studies with larger sample sizes from diverse ancestry

289   and accurate dose information of fish oil supplements are warranted to corroborate and expand

290   our findings.

Acknowledgments

Disclosure

The authors declare that there is no conflict of interest.

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Data availability

Access to the UK Biobank resource is available via the application (http://www.ukbiobank.ac.uk). PGS coefficients generated by Graham SE *et al.* are available for public download at http://csg.sph.umich.edu/willer/public/glgc-

313   lipids2021/results/ancestry_specific/. PGS coefficients generated by Willer CJ *et al.* are available

314   for   public   download   at

315   http://ftp.ebi.ac.uk/pub/databases/gwas/summary_statistics/GCST002001-

316   GCST003000/GCST002221/harmonised/. PGS coefficients generated by Weissbrod O *et al.* are

317   available for public download at https://alkesgroup.broadinstitute.org/polypred_results.

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Figure and Table captions

Main Tables

Table 1. Baseline characteristics of participants of European ancestry in the UK Biobank[a]

	Fish oil intake (*n*=134720)	No fish oil intake (*n*=289370)	*P*-value
Age, years (SD)	59 (7.3)	56 (8.1)	<0.001
Sex, female (%)	75726 (56)	153758 (53)	<0.001
Body mass index, kg/m^2 (SD)	27 (4.5)	28 (4.9)	<0.001
Total cholesterol, mmol/L (SD)	5.78 (1.16)	5.68 (1.14)	<0.001
LDL cholesterol, mmol/L (SD)	3.61 (0.88)	3.55 (0.87)	<0.001
HDL cholesterol, mmol/L (SD)	1.48 (0.39)	1.44 (0.38)	<0.001
Triglycerides, mmol/L (SD)	1.75 (1.00)	1.76 (1.04)	0.036

	Fish oil intake (*n*=134720)	No fish oil intake (*n*=289370)	*P*-value
Smoking status (%)			<0.001
Never	71756 (53)	157498 (54)	
Previous	51940 (39)	97930 (34)	
Current	10527 (8)	32968 (11)	
Alcohol status (%)			<0.001
Never	4075 (3)	9220 (3)	
Previous	4302 (3)	10411 (4)	
Current	126232 (94)	269500 (93)	
Physical activity (%)			<0.001
Low	16930 (13)	47061 (16)	
Moderate	43674 (32)	96758 (33)	
High	48761 (36)	90921 (31)	
Statin use, yes (%)	24121 (18)	45463 (16)	<0.001

^a Values are numbers (%) for categorical variables, and mean (SD) for continuous variables. P-values were obtained from the Chi-squared test (categorical variables) or the 2-sample t-test (continuous variables). LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Table 2. Association of lipid polygenic scores with observed lipid levels stratified by the fish oil intake status in UKB participants of European ancestry using GWAS summary statistics from Graham SE *et al.* (excluded UKB)[a]

Lipids		Fish oil intake			No fish oil intake		$P_{interaction}$[b]
	n	β (95% CI)	*P*-value	n	β (95% CI)	*P*-value	
Total cholesterol, SD							
Partially adjusted association[c]	128634	0.244 (0.239, 0.249)	$<2.0\times10^{-16}$	276134	0.265 (0.261, 0.268)	$<2.0\times10^{-16}$	9.98×10^{-12}
Fully adjusted association[d]	103738	0.304 (0.299, 0.309)	$<2.0\times10^{-16}$	222391	0.313 (0.310, 0.317)	$<2.0\times10^{-16}$	3.53×10^{-4}
LDL cholesterol, SD							
Partially adjusted association[c]	128393	0.262 (0.257, 0.267)	$<2.0\times10^{-16}$	275625	0.280 (0.277, 0.284)	$<2.0\times10^{-16}$	6.27×10^{-9}
Fully adjusted association[d]	103538	0.323 (0.318, 0.328)	$<2.0\times10^{-16}$	221994	0.332 (0.328, 0.335)	$<2.0\times10^{-16}$	0.001
HDL cholesterol, SD							
Partially adjusted association[c]	117709	0.235 (0.230, 0.240)	$<2.0\times10^{-16}$	252786	0.230 (0.227, 0.234)	$<2.0\times10^{-16}$	0.139
Fully adjusted association[d]	94880	0.234 (0.229, 0.240)	$<2.0\times10^{-16}$	203514	0.227 (0.224, 0.231)	$<2.0\times10^{-16}$	0.025
Triglycerides, SD							
Partially adjusted association[c]	128544	0.252 (0.247, 0.257)	$<2.0\times10^{-16}$	275897	0.265 (0.262, 0.269)	$<2.0\times10^{-16}$	2.45×10^{-5}
Fully adjusted association[d]	103674	0.254 (0.248, 0.259)	$<2.0\times10^{-16}$	222215	0.267 (0.263, 0.270)	$<2.0\times10^{-16}$	5.42×10^{-5}

[a] UKB, UK Biobank; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

^b *P*-value was obtained from the interaction term between lipid PGS and fish oil supplementation. Models were adjusted for lipids PGS, fish oil supplementation, sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

^c Models were adjusted for sex, age, age^2, assessment centers, genotyping array, and the top 20 genetic principal components.

^d Models were adjusted for sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

Figure and Table captions

Main Figures

Figure 1. Flowchart of the study population selection.

UKB, UK Biobank; Pan-UKBB, Pan-ancestry genetic analysis of the UK Biobank; EUR, European; AFR, African; CSA, Central/South Asian; EAS, East Asian; GWAS, genome-wide association study; PGS, polygenic scores.

Figure 2. Interaction between fish oil and genetic predisposition to elevated blood lipids using GWAS summary statistics from Graham SE *et al.* (excluded UKB).

Effect estimates and 95% confidence intervals are scaled to per 1 SD increase in PGS measured in SD units. UKB, UK Biobank; GWAS, genome-wide association study; PGS, polygenic scores; Pint, *P*-value for interaction.

Supplementary Figures

Supplementary Figure 1. Interaction between fish oil and genetic predisposition to elevated blood lipids using GWAS summary statistics from Graham SE *et al.* (included UKB) and Willer CJ *et al.*.

Effect estimates and 95% confidence intervals are scaled to per 1 SD increase in PGS measured in SD units. UKB, UK Biobank; GWAS, genome-wide association study; PGS, polygenic scores; Pint, *P*-value for interaction.

Supplementary Figure 2. Interaction between fish oil and genetic predisposition to elevated blood lipids using the PGS β-coefficient generated by Weissbrod O *et al.*, including PolyPred and P+T.

Effect estimates and 95% confidence intervals are scaled to per 1 SD increase in PGS measured in SD units. PGS, polygenic scores; Pint, *P*-value for interaction.

Supplementary Tables

Supplementary Table 1. Baseline characteristics of participants of African, Central/South Asian, and East Asian ancestries in the UK Biobank [a]

[a] Values are numbers (%) for categorical variables, and mean (SD) for continuous variables. LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Supplementary Table 2. Association of lipid polygenic scores with observed lipid levels stratified by the fish oil intake status in participants of European ancestry[a]

[a] UKB, UK Biobank; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[b] *P*-value was obtained from the interaction term between lipid PGS and fish oil supplementation. Models were adjusted for lipids PGS, fish oil supplementation, sex, age, age[2], assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

[c] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, and the top 20 genetic principal components.

[d] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

Supplementary Table 3. Association of lipid polygenic scores with observed lipid levels stratified by the fish oil intake status in participants of African ancestry[a]

[a] UKB, UK Biobank; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[b] *P*-value was obtained from the interaction term between lipid PGS and fish oil supplementation. Models were adjusted for lipids PGS, fish oil supplementation, sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

[c] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, and the top 20 genetic principal components.

[d] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

Supplementary Table 4. Association of lipid polygenic scores with observed lipid levels stratified by the fish oil intake status in participants of Central/South Asian ancestry[a]

[a] UKB, UK Biobank; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[b] P-value was obtained from the interaction term between lipid PGS and fish oil supplementation. Models were adjusted for lipids PGS, fish oil supplementation, sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

[c] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, and the top 20 genetic principal components.

[d] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

Supplementary Table 5. Association of lipid polygenic scores with observed lipid levels stratified by the fish oil intake status in participants of East Asian ancestry[a]

[a] UKB, UK Biobank; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein.

[b] P-value was obtained from the interaction term between lipid PGS and fish oil supplementation. Models were adjusted for lipids PGS, fish oil supplementation, sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

[c] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, and the top 20 genetic principal components.

[d] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.

Supplementary Table 6. Effects of fish oil supplementation and PGS on observed lipid levels in UKB participants of diverse ancestries[a]

[a] UKB, UK Biobank; SD, standard deviation; LDL, low-density lipoprotein; HDL, high-density lipoprotein; EUR, European; AFR, African; CSA, Central/South Asian; EAS, East Asian.

[b] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, and the top 20 genetic principal components.

[c] Models were adjusted for sex, age, age^2, assessment centers, genotyping array, the top 20 genetic principal components, body mass index, Townsend deprivation index, smoking status, alcohol status, physical activity, and statin use.
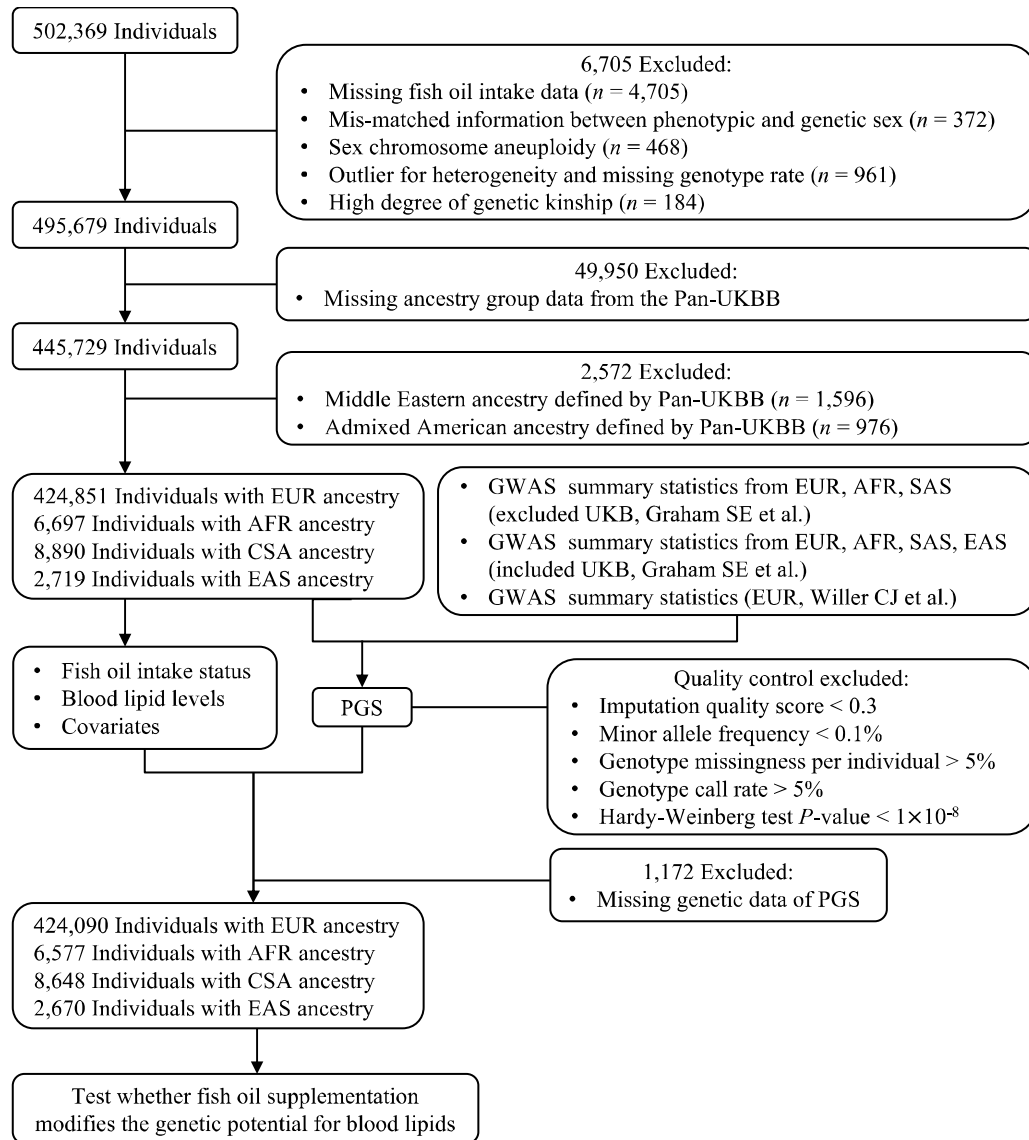
Figure 1

Figure 2

Lipids	Beta [95% CI]	P−value	Pint
Total cholesterol (SD)			**3.53e−04**
Fish oil intake	0.30 [0.30−0.31]	<2.0e−16	
No fish oil intake	0.31 [0.31−0.32]	<2.0e−16	
LDL cholesterol (SD)			**0.001**
Fish oil intake	0.32 [0.32−0.33]	<2.0e−16	
No fish oil intake	0.33 [0.33−0.33]	<2.0e−16	
HDL cholesterol (SD)			**0.025**
Fish oil intake	0.23 [0.23−0.24]	<2.0e−16	
No fish oil intake	0.23 [0.22−0.23]	<2.0e−16	
Triglycerides (SD)			**5.42e−05**
Fish oil intake	0.25 [0.25−0.26]	<2.0e−16	
No fish oil intake	0.27 [0.26−0.27]	<2.0e−16	

0.22   0.26   0.3   0.34