# Omega & MDD MR: Supplementary Materials

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## S1: Supplementary Methods

### **Assessing instrument strength and validity**

1. Calculating variance

The variance explained in our exposure by each SNP was calculated by using the GWAS effect size (*beta)* effect allele frequency (EAF), standard error (SE), and sample size (N) for each SNP using the following equation:

2 x beta2x EAF x (1-EAF) / (2 x beta2 x EAF x (1-EAF) + SE2 x 2 x N x EAF x (1-EAF))

The total variance explained in each exposure (R2) was calculated as the sum of individual SNP variances.

1. Instrument Strength (F)

F-statistics for each exposure were calculated using the formula:

F= (Σ r2/nSNP)/ ((1-Σ r2)/(N-nSNP-1))

Where Σ r2 is the sum of the variance explained in the exposure for each SNP, nSNP is the number of SNPs and N is the sample size of the exposure GWAS instrument strength was quantified using the mean F statistic ()1, and the conditional *F* statistic2, 3 for MVMR analyses. We considered the conventional threshold ( <10) as weak instruments for our exposure of interest, and at risk of bias.

### **Additional Methods specific to CHARGE Exposure Data**

*Identifying Instruments*

As the GWAS study of EPA in theCohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) Consortium were on a much smaller sample (n=8,866), only 2 SNPs for EPA remained after clumping, prohibiting the use of sensitivity analyses requiring more SNPs. We therefore took the instruments identified from the UKBB total omega 3 GWAS and extracted the SNP-EPA effect sizes from the EPA GWAS study. For the multivariable analysis of EPA and DHA, conditional F statistics were very low using UKBB SNPs (FEPA =6, and FDHA =4). We confirmed the findings using instruments derived from a previous GWAS of total omega 3 by Kettunen et al.4 5 genome wide significant SNPs were identified from this GWAS, and the SNP-exposure effect sizes were extracted from the CHARGE consortium EPA and DHA GWAS summary statistics. Conditional F statistics were stronger for this analysis, and hence are reported in the main paper, with the details of supplementary MVMR analysis in the supplementary S8 (‘MVMR.xls’).

*Standardizing Effect Estimates*

As CHARGE Consortium GWAS effect estimates are presented as % of total fatty acids- they were converted to standardized units (SD (mmol/L)) to help interpretation. This was achieved using GWIS (Genome-wide Inferred Study),5 a method that approximates GWAS summary statistics from phenotypes for which GWAS summary statistics, phenotypic means, and covariances are available. SD (mmol/L) SNP-effect estimates were derived as a linear function of the allele frequencies, population means of the fatty acid concentrations, and SNP-% fatty acid effect estimates.

### **Validation Methods**

*Effect Direction*

We used two methods to confirm that the association between the SNPs and MDD resulted from an effect on the exposure, and not the reverse. Firstly, we used ‘Steiger filtering’6 to retain only SNPs explaining a greater amount of variance in the exposure than the outcome, as would be expected for a true causal effect in this direction. Secondly, we used ‘reverse MR’ to consider whether genetic liability to MDD affected circulating omega 3, potentially causing a spurious result. For MR in the reverse direction, we identified genome wide significant SNPs (p<5x10-8) from the PGC MDD GWAS(minus UKBB samples). After clumping (r2<0.001) 27 MDD SNPs remained. Outcome data for these 27 SNPs were then extracted from the total omega-3 and DHA UKBB GWASs, and MR undertaken using the TwoSampleMR package as described above.

*Biological Plausibility and Potential Pleiotropy*

To investigate the biological plausibility of the effect, we restricted MR to biologically defined pathways relating to omega-3 fatty acid biosynthesis, using only the strongest single SNP within the *FADS* gene cluster on chromosome 11 (*rs174564*), and the *ELOVL2* gene on chromosome 6 (*rs2295602*). These genes code enzymes that convert shorter chain fatty acids (derived from dietary sources, such as alpha-linoleic acid (ALA)), into longer chain fatty acids (such as EPA and DHA,) thought to be the most relevant biological omega-3 fatty acids for the development of MDD.

Multivariable MR is a method used to account for genetically correlated traits in MR, and establish the direct effect of an exposure, after accounting for the effect of the instruments on genetically correlated exposures.7 We used the TwoSampleMR package mv\_multiple function to estimate the direct effects of omega-3 FA after accounting for correlated traits. MVMR models were limited to a few simultaneous exposures, as an increasing number of exposures reduced the conditional F statistics and therefore the precision of our estimates. To calculate conditional F statistics, we used the PhenoSpD R package(ref) to estimate the correlation between phenotypes using summary statistics,, and input the covariance matrices into the MVMR package.8

We fitted three MVMR models (see table 1). The first model looked at differential effects between omega 3 and omega 6 fatty acids, using SNPs identified from our primary analyses.

In the second model, we included the commonly measured lipids in clinical practice- triglycerides, high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol- to establish a direct effect of omega-3 fatty acids on MDD, adjusting for broader lipid profile. Genome wide significant SNPs for triglycerides, HDL and LDL cholesterol were obtained from a GWAS study of these exposures among UKBB participants.9

In the third model we considered whether there was a difference in effect between EPA and DHA on MDD, using effect sizes for each exposure derived from the CHARGE consortium.10 As MVMR models using SNP-exposure effect sizes of UKBB instruments gave poor conditional F statistics and high heterogeneity (model 3a), we compared these results with MVMR models using alternative instruments. In model 3b, SNPs were selected from a GWAS study of total omega 3, as EPA was unavailable. In both models the SNP-exposure effects were extracted from the relevant CHARGE GWAS. We used a pairwise t-test to calculate the likelihood that the difference between the observed effect sizes for each exposure in the model had occurred by chance.

*Exploring Biological Pathways - FADS and ELOVL Analyses*

To explore biological mechanisms, we identified SNPs for the *FADS* gene cluster and *ELOVL2* gene which encode key desaturase and elongase enzymes involved in omega-3 and omega-6 fatty acid biosynthesis pathways. SNP-exposure data for SNPs within the *FADS* gene cluster locus (chr11:61560452-61659523 ± 500kb) and *ELOVL2* gene locus (chr6:10980992-11044624 ± 500kb) were extracted from the UKBB DHA GWAS. SNP-outcome data was then extracted from the MDD GWAS, followed by LD clumping to identify the single strongest SNP for each genetic locus. As no SNPs on the *ELOVL2* gene were strongly associated with UKBB GWAS Omega-3 or -6 measures, none of the SNPs identified through this approach gave satisfactory F statistics, leading to extreme confidence intervals and highly variable point estimates. We therefore have omitted *ELOVL2* analyses.

*Colocalization*

**Linkage disequilibrium (LD) could lead to biased results in Mendelian randomization if, by chance, the selected genetic instrument influencing fatty acids is** correlated (i.e. in LD) with another genetic variant influencing the risk of MDD independently. We used the ‘*coloc’* R package,11 a method for pairwise genetic colocalization analysis, to estimate the posterior probability for the association with both traits being explained by the same causal variant in the FADS region. To do this, we selected the top SNP in the *FADS* region (*rs174564),* and all SNPs within a 500kbp radius. We used the ‘*gassocplot’* R package to plot the SNPs for total omega 3, EPA and DHA, along with MDD, rMDD and the MDD sample including UKBB.

Colocalization methods apply Bayesian probabilities to the SNP-trait associations of all SNPs within a defined region, to establish the likelihood that two traits are genetically linked. The *coloc* package in R uses prior probabilities that a SNP is associated with a trait (with a default of 1E-4) for each trait, and presents four distinct posterior probabilities of association (PPA):

H0 There is no causal variant for either trait in the region

H1 Causal variant for trait 1 only

H2 Causal variant for trait 2 only

H3 Both traits are associated, but have distinct causal variants

H4 Both traits are associated and share a single common causal variant

The *coloc* package provides a ‘posterior probability of association’ (PPA), with ≥ 70% (PPA for H4) considered as suggestive of a shared single causal variant between omega-3 fatty acids and MDD risk. This method assumes that a single common genetic variant exists for both traits, which may be unrealistic. An extension to this method ‘runsusie’ relaxes the single causal variant assumption,12 however, excessive prior probability in the outcome, (possibly as a result of the binary outcome measure, inherent to large scale psychiatric genomics research,) prohibited its use.

Results for the colocalization analyses are presented in S7: Colocalization, below.

*PheWAS*

As a supplementary, post-hoc analysis, we used the ieugwasr R package to undertake a Phenome Wide Association Study ‘PheWAS’ of the *FADS* SNP driving the apparent causal effect on depression (*rs174564).* A PheWAS is a technique used to scan multiple GWAS studies for association of a given SNP with multiple different phenotypes, to identify other potential phenotypes of interest. For our analyses, the PheWAS served two purposes. The first was to confirm variables included within our MVMR models were relevant, and the second was to consider potential mediating mechanisms and intermediate phenotypes on the biological pathway between omega-3 fatty acids and MDD, to facilitate further mechanistic research.

The *ieugwasr* package in R scans all traits contained within the IEU Open GWAS Database,13 which contains 14,582 harmonized GWAS datasets across a range of phenotypes and disease outcomes. By nature of the data, there are often multiple GWAS studies for traits (for example blood pressure, pulse rate or obesity). We used the default p-value threshold given in the ieugwasr package (p<5e-5). There are multiple highly correlated phenotypes that appear as individual ‘hits’. As the *FADS2* SNP contained many correlated traits relating to lipid metabolism, we have presented this as a separate category.

Results for the PheWAS are attached as the supplementary material S10 (‘PheWAS.xls’), with an annotated plot of some key associations shown in S8 below.

## S2: SNP- exposure associations for Omega fatty acids from UKBB

The following tables contain details of the instruments used for each exposure, along with estimated variance they each explain, and Steiger p values for the MR analysis with MDD. SNP-exposure associations for total omega 3 fatty acids, total omega 6 fatty acids, DHA, LA and omega 3% were selected from the UKBB GWAS (Borges 2020) using the ieugwasr:: R package. Instruments for analyses of EPA (and DHA in MVMR model 3), were identified from the UKBB total Omega 3 GWAS, and SNP-exposure associations were extracted from the relevant CHARGE consortium GWAS study.

Betas for each exposure are given in SD units. SNPs excluded from the analyses are denoted in ~~strikethrough~~.

### Total Omega 3

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SNP | EA | | eaf | | beta | | | se | | | | pval | | samplesize | | | exposure | | Steiger p |
| 1 | rs6693447 | G | | 0.46 | | 0.02 | | | 0.004 | | | | 4.80E-09 | | 115078 | | | 0.03% | | 3.52E-05 |
| 2 | rs1167998 | A | | 0.64 | | 0.07 | | | 0.004 | | | | 3.60E-66 | | 115078 | | | 0.24% | | 1.57E-35 |
| 3 | rs629301 | T | | 0.78 | | 0.04 | | | 0.005 | | | | 1.30E-14 | | 115078 | | | 0.05% | | 1.68E-08 |
| 4 | rs1260326 | C | | 0.60 | | -0.08 | | | 0.004 | | | | 8.40E-88 | | 115078 | | | 0.34% | | 2.16E-47 |
| 5 | rs11681659 | T | | 0.72 | | -0.03 | | | 0.004 | | | | 2.00E-08 | | 115078 | | | 0.03% | | 5.8E-05 |
| 6 | rs35135293 | T | | 0.52 | | -0.02 | | | 0.004 | | | | 3.90E-08 | | 115078 | | | 0.02% | | 0.000125 |
| 7 | rs13424225 | T | | 0.45 | | 0.02 | | | 0.004 | | | | 2.20E-08 | | 115078 | | | 0.03% | | 0.00074 |
| 8 | rs10184054 | G | | 0.22 | | -0.04 | | | 0.005 | | | | 5.60E-15 | | 115078 | | | 0.05% | | 3.41E-07 |
| 9 | rs11563251 | T | | 0.11 | | 0.03 | | | 0.006 | | | | 3.20E-08 | | 115078 | | | 0.03% | | 0.002718 |
| 10 | rs4860987 | T | | 0.26 | | 0.05 | | | 0.005 | | | | 1.20E-21 | | 115078 | | | 0.08% | | 9.77E-16 |
| 11 | rs11242109 | T | | 0.48 | | 0.02 | | | 0.004 | | | | 2.40E-09 | | 115078 | | | 0.03% | | 5.65E-05 |
| 12 | rs6882345 | A | | 0.63 | | 0.03 | | | 0.004 | | | | 1.90E-13 | | 115078 | | | 0.04% | | 1.69E-06 |
| 13 | rs10455872 | G | | 0.08 | | -0.06 | | | 0.008 | | | | 2.80E-17 | | 115078 | | | 0.06% | | 5.16E-10 |
| 14 | rs117733303 | G | | 0.02 | | -0.12 | | | 0.015 | | | | 1.40E-15 | | 115078 | | | 0.05% | | 8.54E-08 |
| 15 | rs62466318 | T | | 0.20 | | -0.07 | | | 0.005 | | | | 1.20E-45 | | 115078 | | | 0.18% | | 1.9E-24 |
| 16 | rs73109460 | A | | 0.12 | | -0.03 | | | 0.006 | | | | 9.20E-10 | | 115078 | | | 0.03% | | 2.54E-05 |
| 17 | rs4000713 | A | | 0.30 | | -0.03 | | | 0.004 | | | | 1.00E-11 | | 115078 | | | 0.04% | | 2.43E-06 |
| 18 | rs112875651 | A | | 0.39 | | -0.09 | | | 0.004 | | | | 3.50E-98 | | 115078 | | | 0.37% | | 4.06E-56 |
| 19 | rs9987289 | G | | 0.91 | | 0.06 | | | 0.007 | | | | 3.20E-16 | | 115078 | | | 0.06% | | 1.96E-08 |
| 20 | rs7819706 | G | | 0.12 | | -0.04 | | | 0.006 | | | | 1.80E-10 | | 115078 | | | 0.03% | | 3.14E-06 |
| 21 | rs1800978 | G | | 0.12 | | -0.04 | | | 0.006 | | | | 5.20E-09 | | 115078 | | | 0.03% | | 3.62E-05 |
| 22 | rs7924036 | T | | 0.50 | | 0.02 | | | 0.004 | | | | 5.50E-10 | | 115078 | | | 0.03% | | 0.000106 |
| 23 | rs6601924 | C | | 0.85 | | 0.04 | | | 0.006 | | | | 8.50E-10 | | 115078 | | | 0.03% | | 2.7E-05 |
| 24 | rs673335 | C | | 0.16 | | -0.07 | | | 0.006 | | | | 1.10E-34 | | 115078 | | | 0.13% | | 1.14E-17 |
| 25 | rs12226389 | C | | 0.19 | | -0.05 | | | 0.005 | | | | 1.10E-22 | | 115078 | | | 0.08% | | 7.04E-13 |
| 26 | rs3018731 | G | | 0.72 | | -0.04 | | | 0.005 | | | | 2.00E-14 | | 115078 | | | 0.05% | | 7.27E-07 |
| 27 | rs144018203 | C | | 0.01 | | 0.11 | | | 0.020 | | | | 4.20E-08 | | 115078 | | | 0.02% | | 0.0001 |
| 28 | rs143355652 | T | | 0.01 | | -0.15 | | | 0.020 | | | | 9.40E-14 | | 115078 | | | 0.05% | | 4.78E-08 |
| 29 | rs174564 | G | | 0.35 | | -0.34 | | | 0.004 | | | | 1.00E-200 | | 115078 | | | 5.20% | | 0 |
| 30 | rs964184 | C | | 0.87 | | -0.12 | | | 0.006 | | | | 8.90E-87 | | 115078 | | | 0.33% | | 2.42E-47 |
| 31 | rs7970695 | A | | 0.62 | | -0.03 | | | 0.004 | | | | 1.20E-10 | | 115078 | | | 0.03% | | 1.05E-05 |
| 32 | rs261290 | C | | 0.65 | | -0.11 | | | 0.004 | | | | 3.90E-161 | | 115078 | | | 0.62% | | 3.33E-89 |
| 33 | rs139974673 | C | | 0.03 | | 0.12 | | | 0.013 | | | | 2.30E-21 | | 115078 | | | 0.07% | | 1.3E-11 |
| 34 | rs34663616 | A | | 0.14 | | 0.04 | | | 0.006 | | | | 4.40E-10 | | 115078 | | | 0.03% | | 6.86E-06 |
| 35 | rs633695 | G | | 0.29 | | 0.08 | | | 0.004 | | | | 9.10E-80 | | 115078 | | | 0.30% | | 2.96E-44 |
| 36 | rs1672811 | C | | 0.75 | | 0.03 | | | 0.005 | | | | 3.00E-08 | | 115078 | | | 0.02% | | 0.001885 |
| 37 | rs72789541 | A | | 0.30 | | -0.08 | | | 0.004 | | | | 5.60E-75 | | 115078 | | | 0.29% | | 3E-40 |
| 38 | rs9304381 | T | | 0.82 | | 0.05 | | | 0.005 | | | | 5.20E-24 | | 115078 | | | 0.09% | | 1.88E-13 |
| 39 | rs77960347 | G | | 0.01 | | 0.16 | | | 0.018 | | | | 7.20E-22 | | 115078 | | | 0.07% | | 7.25E-11 |
| 40 | rs737338 | T | | 0.04 | | -0.07 | | | 0.011 | | | | 3.50E-11 | | 115078 | | | 0.04% | | 6.09E-05 |
| 41 | rs1132899 | C | | 0.51 | | 0.03 | | | 0.004 | | | | 8.60E-11 | | 115078 | | | 0.04% | | 1.79E-06 |
| 10 | rs6129624 | A | | 0.34 | | -0.03 | | | 0.004 | | | | 5.10E-10 | | 115078 | | | 0.03% | | 1.13E-05 |
| 11 | rs117143374 | C | | 0.14 | | -0.04 | | | 0.006 | | | | 2.20E-10 | | 115078 | | | 0.03% | | 1.5E-05 |
|  |  |  | |  | |  | | |  | | | |  | |  | | |  | |  |
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|  |  |  | |  | |  | | |  | | | |  | |  | | |  | |  |
|  |  |  | |  | |  | | |  | | | | Total Variance Explained | | 9.13% | | |  | |  |
|  |  |  | |  | |  | | |  | | | |  | |  | | |  | |  |
|  |  |  | |  | |  | | |  | | | |  | |  | | |  | |  |
|  |  |  | |  | |  | | |  | | | |  | |  | | |  | |  |
| *1* | *rs2394976* | | *T* | | *0.16* | | *-0.05* | | | | *0.01* | | | *1.20E-15* | | *115078* |  | | Not in Outcome sample | |
| 2 | *rs3129962* | | *A* | | *0.13* | | *-0.04* | | | *0.01* | | | | *1.80E-09* | | *115078* |  | | Not in Outcome sample | |
| 3 | *rs55891451* | | *C* | | *0.20* | | *0.03* | | | | | *0.01* | | *4.60E-12* | | *115078* |  | | Not in Outcome sample | |
| 4 | rs11230829 | | G | | 0.03 | | -0.10 | | | | | 0.01 | | 3.40E-12 | | 115078 |  | | Not in Outcome sample | |
| 5 | rs16940904 | | T | | 0.23 | | -0.04 | | | | | 0.00 | | 3.90E-14 | | 115078 |  | | Not in Outcome sample | |
| 6 | rs182611493 | | G | | 0.01 | | -0.21 | | | | | 0.02 | | 1.10E-27 | | 115078 |  | | Not in Outcome sample | |
| 7 | rs157592 | | C | | 0.19 | | 0.03 | | | | | 0.01 | | 3.60E-09 | | 115078 |  | | Not in Outcome sample | |
| 8 | rs58542926 | | T | | 0.07 | | -0.17 | | | | | 0.008 | | 1.40E-113 | | 115078 |  | | Not in Outcome sample | |
| 9 | rs5112 | | G | | 0.53 | | 0.05 | | | | | 0.004 | | 9.10E-30 | | 115078 |  | | Ambiguous palindrome | |
|  |  |  | |  | |  | |  | | | | |  | |  | | |  | |  |

### DHA UKBB

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SNP | EA | EAF | BETA | SE | P | N | % VARIANCE | STEIGER P |
| 1 | rs629301 | T | 0.78 | 0.04 | 0.005 | 1.40E-19 | 115078 | 0.07% | 8.92E-11 |
| 2 | rs11122450 | G | 0.61 | 0.02 | 0.004 | 3.40E-08 | 115078 | 0.03% | 0.000799 |
| 3 | rs638714 | T | 0.35 | -0.04 | 0.004 | 5.40E-20 | 115078 | 0.07% | 1.65E-10 |
| 4 | rs13424225 | T | 0.45 | 0.02 | 0.004 | 1.10E-08 | 115078 | 0.03% | 0.000634 |
| 5 | rs1260326 | C | 0.60 | -0.05 | 0.004 | 8.70E-30 | 115078 | 0.11% | 9.02E-16 |
| 6 | rs34722314 | A | 0.14 | -0.05 | 0.006 | 6.80E-18 | 115078 | 0.06% | 1.85E-09 |
| 7 | rs11681659 | T | 0.72 | -0.03 | 0.004 | 5.30E-12 | 115078 |  | 2.03E-06 |
| 8 | rs4860987 | T | 0.26 | 0.04 | 0.005 | 3.90E-16 | 115078 | 0.06% | 8.95E-11 |
| 9 | rs273912 | T | 0.71 | 0.03 | 0.004 | 6.60E-10 | 115078 | 0.03% | 2.84E-05 |
| 10 | rs6931604 | T | 0.60 | 0.02 | 0.004 | 2.70E-08 | 115078 | 0.03% | 0.001318 |
| 11 | rs73109460 | A | 0.12 | -0.04 | 0.006 | 7.30E-11 | 115078 | 0.03% | 8.92E-06 |
| 12 | rs9987289 | G | 0.91 | 0.06 | 0.007 | 1.30E-17 | 115078 | 0.06% | 7.35E-09 |
| 13 | rs112875651 | A | 0.39 | -0.05 | 0.004 | 1.60E-32 | 115078 | 0.12% | 9.07E-19 |
| 14 | rs325 | C | 0.10 | 0.04 | 0.007 | 3.80E-09 | 115078 | 0.03% | 3.11E-05 |
| 15 | rs1800978 | G | 0.12 | -0.03 | 0.006 | 4.80E-08 | 115078 | 0.03% | 0.000238 |
| 16 | rs7924036 | T | 0.50 | 0.04 | 0.004 | 4.80E-21 | 115078 | 0.07% | 7.48E-10 |
| 17 | rs2807967 | C | 0.72 | 0.03 | 0.004 | 1.20E-08 | 115078 | 0.03% | 0.000136 |
| 18 | rs12226389 | C | 0.19 | -0.04 | 0.005 | 3.80E-18 | 115078 | 0.06% | 5.86E-10 |
| 19 | rs145786300 | A | 0.01 | -0.13 | 0.019 | 4.00E-12 | 115078 | 0.04% | 3.63E-06 |
| 20 | rs149820547 | G | 0.04 | -0.05 | 0.010 | 4.80E-08 | 115078 | 0.03% | 0.000452 |
| 21 | rs143355652 | T | 0.01 | -0.15 | 0.020 | 6.60E-14 | 115078 | 0.05% | 8.49E-08 |
| 22 | rs2232143 | C | 0.02 | 0.08 | 0.014 | 6.60E-09 | 115078 | 0.03% | 5.15E-06 |
| 23 | rs174564 | G | 0.35 | -0.29 | 0.004 | 1.00E-200 | 115078 | 4.02% | 0 |
| 24 | rs673335 | C | 0.16 | -0.06 | 0.005 | 8.10E-25 | 115078 | 0.09% | 2.75E-12 |
| 25 | rs145659493 | A | 0.02 | 0.09 | 0.016 | 1.70E-09 | 115078 | 0.03% | 5.45E-05 |
| 26 | rs525028 | A | 0.71 | -0.03 | 0.004 | 2.70E-12 | 115078 | 0.04% | 9.32E-06 |
| 27 | rs139974673 | C | 0.03 | 0.07 | 0.013 | 8.80E-09 | 115078 | 0.03% | 6.3E-05 |
| 28 | rs261291 | C | 0.36 | 0.12 | 0.004 | 5.40E-172 | 115078 | 0.66% | 2.46E-90 |
| 29 | rs1560390 | C | 0.22 | -0.05 | 0.005 | 2.50E-26 | 115078 | 0.09% | 4.25E-14 |
| 30 | rs12914626 | T | 0.70 | -0.06 | 0.004 | 7.50E-45 | 115078 | 0.17% | 1.61E-24 |
| 31 | rs72789541 | A | 0.30 | -0.08 | 0.004 | 5.60E-71 | 115078 | 0.27% | 4.21E-37 |
| 32 | rs3764261 | A | 0.32 | 0.04 | 0.004 | 1.90E-21 | 115078 | 0.07% | 0.000198 |
| 33 | rs4986970 | T | 0.03 | -0.07 | 0.011 | 1.30E-10 | 115078 | 0.03% | 1.19E-05 |
| 34 | rs72836561 | T | 0.03 | -0.06 | 0.011 | 3.60E-08 | 115078 | 0.03% | 0.000108 |
| 35 | rs9304381 | T | 0.82 | 0.05 | 0.005 | 5.80E-23 | 115078 | 0.08% | 2.49E-12 |
| 36 | rs77960347 | G | 0.01 | 0.14 | 0.017 | 2.50E-17 | 115078 | 0.06% | 1.4E-08 |
| 37 | rs73045691 | A | 0.30 | 0.03 | 0.005 | 3.60E-10 | 115078 | 0.04% | 8.59E-07 |
| 38 | rs2278426 | T | 0.04 | -0.06 | 0.011 | 3.70E-08 | 115078 | 0.03% | 0.001319 |
| 39 | rs58542926 | T | 0.07 | -0.12 | 0.008 | 1.40E-57 | 115078 | 0.21% | 2.73E-28 |
| 40 | rs7412 | T | 0.08 | -0.08 | 0.007 | 5.40E-26 | 115078 | 0.09% | 3.32E-13 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Total Variance Explained | | 7.04% |  |
|  |  |  |  |  |  |  |  |  |  |
| 1 | rs2394976 | T | 0.16 | -0.03 | 0.0054 | 5.60E-11 | 115078 |  | Not in Outcome |
| 2 | rs35177659 | T | 0.52 | 0.02 | 0.0042 | 2.70E-08 | 115078 |  | Not in Outcome |
| 3 | rs55891451 | C | 0.20 | 0.03 | 0.005 | 5.60E-11 | 115078 |  | Not in Outcome |
| 4 | rs11230829 | G | 0.03 | -0.09 | 0.0146 | 9.60E-11 | 115078 |  | Not in Outcome |
| 5 | rs78689694 | C | 0.13 | 0.04 | 0.0059 | 4.40E-10 | 115078 |  | Not in Outcome |
| 6 | rs16940904 | T | 0.23 | -0.04 | 0.0048 | 2.10E-17 | 115078 |  | Not in Outcome |
| 7 | rs182611493 | G | 0.01 | -0.16 | 0.0192 | 1.60E-16 | 115078 |  | Not in Outcome |

### Omega 3 (%)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SNP | EA | EAF | BETA | SE | P | N | % VARIANCE | STEIGER P |
|  |  |  |  |  |  |  |  |  |  |
| 1 | rs638714 | T | 0.35 | -0.03 | 0.004 | 4.9E-15 | 115078 | 0.05% | 3.31908E-08 |
| 2 | rs6693447 | G | 0.46 | 0.03 | 0.004 | 8.3E-12 | 115078 | 0.04% | 1.91472E-06 |
| 3 | rs2011946 | A | 0.73 | -0.03 | 0.005 | 2.6E-09 | 115078 | 0.03% | 4.79373E-05 |
| 4 | rs1260326 | C | 0.60 | -0.04 | 0.004 | 2.3E-19 | 115078 | 0.07% | 1.55163E-10 |
| 5 | rs4860987 | T | 0.26 | 0.04 | 0.005 | 8.1E-17 | 115078 | 0.06% | 6.78285E-07 |
| 6 | rs272888 | C | 0.71 | 0.03 | 0.004 | 1.8E-11 | 115078 | 0.04% | 2.96549E-06 |
| 7 | rs7444298 | G | 0.24 | 0.03 | 0.005 | 2.4E-08 | 115078 | 0.03% | 0.000451764 |
| 8 | rs662138 | G | 0.19 | -0.03 | 0.005 | 6.6E-11 | 115078 | 0.04% | 8.42159E-06 |
| 9 | rs4000713 | A | 0.30 | -0.03 | 0.004 | 1.6E-10 | 115078 | 0.03% | 8.07789E-06 |
| 10 | rs73109460 | A | 0.12 | -0.03 | 0.006 | 7.8E-09 | 115078 | 0.02% | 0.000116707 |
| 11 | rs2236514 | G | 0.66 | -0.02 | 0.004 | 3.1E-08 | 115078 | 0.02% | 0.000284196 |
| 12 | rs7924036 | T | 0.50 | 0.04 | 0.004 | 4.0E-23 | 115078 | 0.08% | 2.34484E-11 |
| 13 | rs56233220 | C | 0.20 | 0.04 | 0.005 | 4.4E-13 | 115078 | 0.04% | 2.25181E-34 |
| 14 | rs11236512 | A | 0.06 | -0.07 | 0.009 | 5.3E-15 | 115078 | 0.05% | 1.03174E-20 |
| 15 | rs2232143 | C | 0.02 | 0.11 | 0.014 | 1.3E-13 | 115078 | 0.05% | 6.55812E-09 |
| 16 | rs191623731 | G | 0.02 | 0.12 | 0.016 | 9.8E-14 | 115078 | 0.05% | 2.56548E-07 |
| 17 | rs964184 | C | 0.87 | -0.04 | 0.006 | 1.2E-10 | 115078 | 0.04% | 5.49707E-06 |
| 18 | rs143355652 | T | 0.01 | -0.18 | 0.020 | 1.2E-18 | 115078 | 0.07% | 1.47775E-10 |
| 19 | rs174564 | G | 0.35 | -0.39 | 0.004 | 1.0E-200 | 115078 | 6.93% | 0 |
| 20 | rs12226389 | C | 0.19 | -0.06 | 0.005 | 2.2E-32 | 115078 | 0.12% | 1.77867E-18 |
| 21 | rs149402055 | T | 0.02 | -0.17 | 0.015 | 9.2E-30 | 115078 | 0.11% | 3.78988E-18 |
| 22 | rs145786300 | A | 0.01 | -0.19 | 0.019 | 1.3E-22 | 115078 | 0.08% | 7.41607E-12 |
| 23 | rs9563335 | G | 0.86 | -0.04 | 0.008 | 5.5E-09 | 115078 | 0.03% | 2.53136E-07 |
| 24 | rs261291 | C | 0.36 | 0.08 | 0.004 | 1.8E-83 | 115078 | 0.31% | 1.19163E-44 |
| 25 | rs11632618 | A | 0.07 | 0.08 | 0.008 | 1.1E-22 | 115078 | 0.08% | 2.91717E-12 |
| 26 | rs1560390 | C | 0.22 | -0.03 | 0.005 | 6.9E-12 | 115078 | 0.04% | 1.32929E-06 |
| 27 | rs139974673 | C | 0.03 | 0.08 | 0.013 | 1.3E-11 | 115078 | 0.04% | 1.90682E-06 |
| 28 | rs72789541 | A | 0.30 | -0.10 | 0.004 | 3.5E-106 | 115078 | 0.41% | 1.80914E-57 |
| 29 | rs8074191 | C | 0.76 | -0.03 | 0.005 | 2.3E-08 | 115078 | 0.03% | 0.00011768 |
| 30 | rs9947684 | G | 0.65 | 0.03 | 0.004 | 2.8E-12 | 115078 | 0.04% | 1.12342E-06 |
| 31 | rs58542926 | T | 0.07 | -0.13 | 0.008 | 1.2E-67 | 115078 | 0.25% | 3.04205E-08 |
| 32 | rs72654473 | A | 0.11 | 0.04 | 0.007 | 6.1E-09 | 115078 | 0.03% | 0.000211995 |
| 33 | rs190921611 | A | 0.31 | 0.03 | 0.005 | 2.0E-11 | 115078 | 0.04% | 1.04825E-07 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Total Variance Explained | | | 9.34% |
|  |  |  |  |  |  |  |  |  |  |
| 8 | rs2394976 | T | 0.16 | -0.03 | 0.006 | 5E-09 | 115078 |  | Not in outcome |
| 23 | rs11230829 | G | 0.03 | -0.12 | 0.015 | 2E-15 | 115078 |  | Not in outcome |
| 34 | rs16940904 | T | 0.23 | -0.04 | 0.005 | 2E-19 | 115078 |  | Not in outcome |
| 39 | rs182611493 | G | 0.01 | -0.17 | 0.020 | 9E-19 | 115078 |  | Not in outcome |
| 11 | rs112875651 | A | 0.39 | -0.05 | 0.004 | 5.70E-35 | 115078 |  | Not in outcome |
| 10 | rs62466318 | T | 0.20 | -0.04 | 0.005 | 3.10E-16 | 115078 |  | Not in outcome |
| 28 | rs35390787 | C | 0.56 | -0.03 | 0.004 | 5.60E-11 | 115078 |  | Not in outcome |

### Total Omega 6

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SNP | EA | EAF | BETA | SE | P | N | % VARIANCE | STEIGER P |
| 1 | rs1002687 | A | 0.64 | 0.09 | 0.004 | 1.0E-107 | 115078 | 0.40% | 3.7E-57 |
| 2 | rs534417 | G | 0.88 | 0.04 | 0.006 | 9.3E-11 | 115078 | 0.04% | 1.7E-05 |
| 3 | rs12740374 | T | 0.22 | -0.06 | 0.005 | 1.5E-32 | 115078 | 0.12% | 1.5E-17 |
| 4 | rs1260326 | C | 0.60 | -0.06 | 0.004 | 3.9E-55 | 115078 | 0.21% | 3.0E-29 |
| 5 | rs870526 | T | 0.52 | -0.03 | 0.004 | 7.7E-16 | 115078 | 0.05% | 1.5E-08 |
| 6 | rs4299376 | T | 0.68 | -0.04 | 0.004 | 1.1E-16 | 115078 | 0.06% | 1.8E-09 |
| 7 | rs6547409 | T | 0.05 | -0.08 | 0.009 | 2.4E-20 | 115078 | 0.07% | 7.6E-11 |
| 8 | rs672889 | G | 0.86 | 0.08 | 0.006 | 1.3E-41 | 115078 | 0.15% | 1.4E-22 |
| 9 | rs3770586 | T | 0.48 | -0.02 | 0.004 | 7.1E-09 | 115078 | 0.03% | 5.3E-05 |
| 10 | rs13108218 | G | 0.62 | -0.04 | 0.004 | 3.6E-18 | 115078 | 0.06% | 6.9E-09 |
| 11 | rs4704210 | C | 0.37 | 0.05 | 0.004 | 6.1E-30 | 115078 | 0.11% | 6.4E-16 |
| 12 | rs6882345 | A | 0.63 | 0.04 | 0.004 | 1.2E-27 | 115078 | 0.10% | 2.1E-14 |
| 13 | rs6934962 | T | 0.40 | 0.02 | 0.004 | 2.2E-08 | 115078 | 0.03% | 1.4E-04 |
| 14 | rs3734854 | A | 0.06 | 0.05 | 0.008 | 5.9E-11 | 115078 | 0.03% | 3.9E-04 |
| 15 | rs7750288 | G | 0.29 | 0.02 | 0.004 | 1.3E-08 | 115078 | 0.03% | 1.1E-04 |
| 16 | rs9295128 | T | 0.02 | -0.20 | 0.016 | 3.4E-36 | 115078 | 0.13% | 1.7E-18 |
| 17 | rs114863007 | A | 0.09 | -0.05 | 0.007 | 7.3E-12 | 115078 | 0.04% | 1.3E-05 |
| 18 | rs28383314 | C | 0.62 | 0.04 | 0.004 | 1.7E-18 | 115078 | 0.08% | 3.4E-09 |
| 19 | rs6938647 | C | 0.78 | -0.05 | 0.005 | 1.9E-23 | 115078 | 0.08% | 3.5E-13 |
| 20 | rs55747707 | A | 0.20 | -0.05 | 0.005 | 1.7E-22 | 115078 | 0.08% | 6.1E-12 |
| 21 | rs6471717 | A | 0.66 | -0.03 | 0.004 | 4.0E-12 | 115078 | 0.04% | 4.9E-06 |
| 22 | rs112875651 | A | 0.39 | -0.06 | 0.004 | 2.2E-53 | 115078 | 0.20% | 1.5E-30 |
| 23 | rs2737245 | T | 0.28 | -0.03 | 0.005 | 1.4E-09 | 115078 | 0.03% | 9.3E-06 |
| 24 | rs1461729 | G | 0.90 | 0.08 | 0.007 | 2.8E-36 | 115078 | 0.13% | 1.2E-19 |
| 25 | rs4008004 | A | 0.22 | 0.03 | 0.005 | 8.4E-12 | 115078 | 0.04% | 6.1E-07 |
| 26 | rs11789603 | T | 0.11 | 0.05 | 0.006 | 9.7E-14 | 115078 | 0.05% | 5.3E-07 |
| 27 | rs2740488 | C | 0.27 | -0.05 | 0.005 | 5.4E-28 | 115078 | 0.10% | 3.0E-15 |
| 28 | rs75406471 | A | 0.15 | -0.03 | 0.006 | 2.7E-08 | 115078 | 0.03% | 2.1E-04 |
| 29 | rs141469619 | G | 0.01 | 0.11 | 0.021 | 1.4E-08 | 115078 | 0.02% | 6.9E-05 |
| 30 | rs964184 | C | 0.87 | -0.14 | 0.006 | 1.1E-125 | 115078 | 0.47% | 9.4E-67 |
| 31 | rs72997616 | A | 0.09 | -0.05 | 0.007 | 1.6E-13 | 115078 | 0.05% | 3.1E-08 |
| 32 | rs3817335 | A | 0.35 | -0.03 | 0.004 | 9.8E-12 | 115078 | 0.04% | 4.3E-06 |
| 33 | rs7139079 | A | 0.59 | -0.03 | 0.004 | 3.3E-13 | 115078 | 0.05% | 3.2E-07 |
| 34 | rs6602911 | T | 0.36 | 0.03 | 0.004 | 1.3E-09 | 115078 | 0.03% | 1.9E-05 |
| 35 | rs633695 | G | 0.29 | 0.07 | 0.004 | 1.3E-59 | 115078 | 0.23% | 3.0E-33 |
| 36 | rs261290 | C | 0.65 | -0.10 | 0.004 | 1.0E-116 | 115078 | 0.45% | 7.6E-64 |
| 37 | rs183130 | T | 0.32 | 0.06 | 0.004 | 1.4E-48 | 115078 | 0.18% | 3.3E-25 |
| 38 | rs740516 | G | 0.15 | -0.03 | 0.006 | 1.4E-08 | 115078 | 0.03% | 1.2E-04 |
| 39 | rs4439799 | T | 0.50 | 0.02 | 0.004 | 1.3E-08 | 115078 | 0.03% | 1.6E-04 |
| 40 | rs77960347 | G | 0.01 | 0.28 | 0.018 | 2.8E-56 | 115078 | 0.21% | 8.5E-30 |
| 41 | rs9304381 | T | 0.82 | 0.07 | 0.005 | 7.2E-42 | 115078 | 0.16% | 7.8E-23 |
| 42 | rs56322906 | A | 0.04 | -0.10 | 0.011 | 1.2E-19 | 115078 | 0.07% | 3.6E-09 |
| 43 | rs142158911 | A | 0.12 | -0.09 | 0.006 | 5.2E-52 | 115078 | 0.19% | 3.3E-27 |
| 44 | rs58542926 | T | 0.07 | -0.13 | 0.008 | 2.5E-65 | 115078 | 0.24% | 8.9E-33 |
| 45 | rs1081105 | C | 0.03 | 0.12 | 0.012 | 1.8E-22 | 115078 | 0.08% | 7.5E-13 |
| 46 | rs79429216 | A | 0.01 | 0.15 | 0.018 | 1.3E-17 | 115078 | 0.06% | 1.4E-09 |
| 47 | rs1883711 | C | 0.03 | 0.09 | 0.012 | 3.2E-16 | 115078 | 0.05% | 1.1E-07 |
| 48 | rs1800961 | T | 0.03 | -0.07 | 0.012 | 3.3E-10 | 115078 | 0.03% | 9.1E-06 |
| 49 | rs5754102 | A | 0.18 | -0.03 | 0.005 | 9.9E-10 | 115078 | 0.03% | 1.2E-05 |
| 50 | rs9616847 | T | 0.39 | 0.02 | 0.004 | 1.4E-08 | 115078 | 0.03% | 3.9E-04 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Total Variance Explained | | 4.85% |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| 1 | rs200730299 | C | 0.19 | -0.04 | 0.01 | 7.1E-12 | 115078 |  | Not in outcome |
| 2 | rs2986164 | A | 0.54 | -0.03 | 0 | 3.4E-09 | 115078 |  | Not in outcome |
| 3 | rs4860948 | A | 0.24 | 0.03 | 0 | 1.9E-09 | 115078 |  | Not in outcome |
| 4 | rs35603463 | C | 0.57 | 0.03 | 0 | 4.6E-10 | 115078 |  | Not in outcome |
| 5 | rs7831074 | G | 0.76 | 0.03 | 0.01 | 4.6E-08 | 115078 |  | Not in outcome |
| 6 | rs115478735 | T | 0.18 | 0.04 | 0.01 | 2.2E-17 | 115078 |  | Not in outcome |
| 7 | rs1065853 | T | 0.08 | -0.2 | 0.01 | 4E-160 | 115078 |  | Not in outcome |
| 8 | rs2378390 | A | 0.14 | -0.03 | 0.01 | 3.2E-09 | 115078 |  | Not in outcome |
| 9 | rs4766578 | A | 0.5 | 0.03 | 0 | 1.5E-12 | 115078 |  | Not in outcome |
| 10 | rs7707394 | A | 0.36 | 0.03 | 0 | 1.2E-12 | 115078 |  | Not in outcome |

### Linoleic Acid (LA)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SNP | EA | EAF | BETA | SE | P | N | % VARIANCE | STEIGER P |
| 1 | rs34232196 | T | 0.25 | -0.03 | 0.005 | 8.3E-11 | 115078 | 0.04% | 8.02E-06 |
| 2 | rs534417 | G | 0.88 | 0.04 | 0.006 | 2.5E-09 | 115078 | 0.03% | 8.66E-05 |
| 3 | rs1002687 | A | 0.64 | 0.09 | 0.004 | 1.8E-97 | 115078 | 0.36% | 3.58E-52 |
| 4 | rs602633 | G | 0.78 | 0.05 | 0.005 | 7.5E-28 | 115078 | 0.10% | 2.09E-14 |
| 5 | rs35633876 | T | 0.48 | -0.03 | 0.004 | 2.4E-17 | 115078 | 0.06% | 4.54E-10 |
| 6 | rs4665972 | C | 0.60 | -0.05 | 0.004 | 1.3E-35 | 115078 | 0.13% | 4.9E-19 |
| 7 | rs693 | A | 0.52 | 0.06 | 0.004 | 3.4E-54 | 115078 | 0.20% | 3.99E-29 |
| 8 | rs4299376 | T | 0.68 | -0.04 | 0.004 | 2.5E-19 | 115078 | 0.07% | 4.29E-11 |
| 9 | rs13108218 | G | 0.62 | -0.03 | 0.004 | 5.9E-16 | 115078 | 0.05% | 8.85E-08 |
| 10 | rs4704210 | C | 0.37 | 0.05 | 0.004 | 2.0E-35 | 115078 | 0.13% | 7.24E-19 |
| 11 | rs6882345 | A | 0.63 | 0.04 | 0.004 | 2.0E-26 | 115078 | 0.10% | 5.92E-14 |
| 12 | rs3011437 | G | 0.29 | 0.04 | 0.004 | 1.3E-16 | 115078 | 0.06% | 8.39E-09 |
| 13 | rs186696265 | T | 0.01 | -0.23 | 0.017 | 2.2E-41 | 115078 | 0.15% | 2.28E-23 |
| 14 | rs36018387 | T | 0.11 | -0.04 | 0.007 | 6.4E-12 | 115078 | 0.04% | 4.63E-06 |
| 15 | rs7750288 | G | 0.29 | 0.03 | 0.004 | 1.1E-09 | 115078 | 0.03% | 3.28E-05 |
| 16 | rs55747707 | A | 0.20 | -0.04 | 0.005 | 1.5E-18 | 115078 | 0.07% | 5.45E-10 |
| 17 | rs1461729 | G | 0.90 | 0.07 | 0.007 | 5.4E-26 | 115078 | 0.09% | 3.01E-14 |
| 18 | rs112875651 | A | 0.39 | -0.05 | 0.004 | 5.0E-35 | 115078 | 0.13% | 3.32E-20 |
| 19 | rs7816447 | C | 0.10 | -0.05 | 0.007 | 8.2E-13 | 115078 | 0.05% | 2.08E-07 |
| 20 | rs6471717 | A | 0.66 | -0.03 | 0.004 | 1.4E-13 | 115078 | 0.04% | 1.02E-06 |
| 21 | rs11789603 | T | 0.11 | 0.05 | 0.007 | 1.7E-12 | 115078 | 0.04% | 2.26E-06 |
| 22 | rs4008004 | A | 0.22 | 0.03 | 0.005 | 1.9E-10 | 115078 | 0.03% | 2.99E-06 |
| 23 | rs2740488 | C | 0.27 | -0.05 | 0.005 | 1.0E-25 | 115078 | 0.10% | 3.25E-14 |
| 24 | rs10838724 | T | 0.37 | -0.03 | 0.004 | 1.6E-10 | 115078 | 0.03% | 0.000004 |
| 25 | rs174564 | G | 0.35 | 0.08 | 0.004 | 5.1E-88 | 115078 | 0.34% | 2.29E-40 |
| 26 | rs964184 | C | 0.87 | -0.15 | 0.006 | 2.0E-136 | 115078 | 0.51% | 2.79E-73 |
| 27 | rs141469619 | G | 0.01 | 0.12 | 0.021 | 3.8E-10 | 115078 | 0.03% | 7.71E-06 |
| 28 | rs7139079 | A | 0.59 | -0.03 | 0.004 | 4.8E-10 | 115078 | 0.03% | 9.67E-06 |
| 29 | rs6602911 | T | 0.36 | 0.02 | 0.004 | 1.4E-08 | 115078 | 0.03% | 8.43E-05 |
| 30 | rs261290 | C | 0.65 | -0.09 | 0.004 | 7.9E-99 | 115078 | 0.38% | 1.47E-54 |
| 31 | rs633695 | G | 0.29 | 0.07 | 0.004 | 2.0E-54 | 115078 | 0.21% | 8.44E-31 |
| 32 | rs247617 | A | 0.32 | 0.05 | 0.004 | 6.5E-33 | 115078 | 0.12% | 1.78E-17 |
| 33 | rs9302635 | C | 0.18 | -0.03 | 0.005 | 3.4E-08 | 115078 | 0.03% | 0.000728 |
| 34 | rs740516 | G | 0.15 | -0.03 | 0.006 | 1.9E-09 | 115078 | 0.03% | 3.68E-05 |
| 35 | rs77960347 | G | 0.01 | 0.25 | 0.018 | 1.1E-45 | 115078 | 0.17% | 2.06E-24 |
| 36 | rs9304381 | T | 0.82 | 0.06 | 0.005 | 1.0E-33 | 115078 | 0.12% | 1.62E-18 |
| 37 | rs79429216 | A | 0.01 | 0.15 | 0.018 | 1.6E-16 | 115078 | 0.06% | 3.8E-09 |
| 38 | rs142158911 | A | 0.12 | -0.09 | 0.006 | 1.2E-48 | 115078 | 0.18% | 1.2E-25 |
| 39 | rs56322906 | A | 0.04 | -0.09 | 0.011 | 2.9E-15 | 115078 | 0.06% | 3.85E-07 |
| 40 | rs58542926 | T | 0.07 | -0.11 | 0.008 | 7.5E-48 | 115078 | 0.18% | 3.36E-24 |
| 41 | rs1081105 | C | 0.03 | 0.12 | 0.012 | 8.2E-23 | 115078 | 0.08% | 3.2E-13 |
| 42 | rs1883711 | C | 0.03 | 0.09 | 0.012 | 3.7E-15 | 115078 | 0.05% | 2.52E-07 |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  | Total Variance Explained | | | 4.75% |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| 1 | rs2986164 | A | 0.54 | -0.03 | 0.004 | 5.0E-10 | 115078 |  | Not in outcome |
| 2 | rs7707394 | A | 0.36 | 0.03 | 0.004 | 3.9E-14 | 115078 |  | Not in outcome |
| 3 | rs13217434 | C | 0.26 | 0.04 | 0.005 | 4.3E-20 | 115078 |  | Not in outcome |
| 4 | rs115478735 | T | 0.18 | 0.04 | 0.005 | 1.2E-17 | 115078 |  | Not in outcome |
| 5 | rs12948283 | C | 0.30 | 0.03 | 0.005 | 6.4E-09 | 115078 |  | Not in outcome |
| 6 | rs1065853 | T | 0.08 | -0.19 | 0.007 | 1.9E-143 | 115078 |  | Not in outcome |
| 7 | rs2378390 | A | 0.14 | -0.03 | 0.006 | 7.0E-09 | 115078 |  | Not in outcome |
| 8 | rs35599691 | A | 0.58 | 0.04 | 0.005 | 6.6E-12 | 115078 |  | Not in outcome |
| 9 | rs4947302 | T | 0.06 | 0.05 | 0.008 | 4.8E-10 | 115078 |  | Not in outcome |
| 10 | rs2389599 | C | 0.52 | 0.02 | 0.004 | 6.8E-09 | 115078 | 0.03% | Ambiguous palindrome |
| 11 | rs4766578 | A | 0.50 | 0.03 | 0.004 | 1.9E-10 | 115078 | 0.03% | Ambiguous palindrome |
| 12 | rs9848779 | G | 0.53 | -0.02 | 0.004 | 3.4E-08 | 115078 | 0.02% | Ambiguous palindrome |

### DHA Lemaitre (MVMR models)

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SNP | EA | BETA | EAF | SE | P | N | % VARIANCE | STEIGER DIR | STEIGER P |
| 1 | rs10184054 | G | -0.047 | 0.26 | 0.017 | 0.007 | 8866 | 0.08% | TRUE | 1.36E-02 |
| 2 | rs10455872 | G | 0.003 | 0.06 | 0.031 | 0.920 | 8866 | 0.00% | TRUE | 9.43E-01 |
| 3 | rs11242109 | T | 0.016 | 0.43 | 0.015 | 0.282 | 8866 | 0.01% | TRUE | 3.68E-01 |
| 4 | rs112875651 | A | -0.061 | 0.40 | 0.015 | 7.10E-05 | 8866 | 0.18% | TRUE | 1.14E-04 |
| 5 | rs1132899 | C | -0.002 | 0.51 | 0.015 | 0.880 | 8866 | 0.00% | TRUE | 9.49E-01 |
| 6 | rs11563251 | T | 0.024 | 0.12 | 0.023 | 0.289 | 8866 | 0.01% | TRUE | 5.08E-01 |
| 7 | rs1167998 | A | 0.081 | 0.68 | 0.016 | 4.81E-07 | 8866 | 0.28% | TRUE | 1.38E-06 |
| 8 | rs11681659 | T | -0.026 | 0.54 | 0.015 | 0.083 | 8866 | 0.03% | TRUE | 1.03E-01 |
| 9 | rs117143374 | C | -0.019 | 0.13 | 0.022 | 0.386 | 8866 | 0.01% | TRUE | 4.97E-01 |
| 10 | rs117733303 | G | -0.063 | 0.01 | 0.079 | 0.421 | 8866 | 0.01% | TRUE | 5.28E-01 |
| 11 | rs12226389 | C | -0.027 | 0.19 | 0.019 | 0.160 | 8866 | 0.02% | TRUE | 1.83E-01 |
| 12 | rs1260326 | C | -0.068 | 0.58 | 0.015 | 7.84E-06 | 8866 | 0.22% | TRUE | 2.57E-05 |
| 13 | rs13424225 | T | -0.019 | 0.47 | 0.015 | 0.203 | 8866 | 0.02% | TRUE | 3.20E-01 |
| 14 | rs1672811 | C | 0.044 | 0.74 | 0.017 | 0.011 | 8866 | 0.07% | TRUE | 3.19E-02 |
| 15 | rs174564 | G | -0.072 | 0.37 | 0.016 | 0.000 | 8866 | 0.24% | TRUE | 7.50E-05 |
| 16 | rs1800978 | G | 0.003 | 0.12 | 0.023 | 0.911 | 8866 | 0.00% | FALSE | 9.67E-01 |
| 17 | rs261290 | C | -0.058 | 0.68 | 0.016 | 3.00E-04 | 8866 | 0.15% | TRUE | 5.23E-04 |
| 18 | rs3018731 | G | -0.039 | 0.79 | 0.018 | 0.036 | 8866 | 0.05% | TRUE | 8.63E-02 |
| 19 | rs34663616 | A | 0.024 | 0.13 | 0.023 | 0.284 | 8866 | 0.01% | TRUE | 3.05E-01 |
| 20 | rs35135293 | T | -0.032 | 0.49 | 0.015 | 0.032 | 8866 | 0.05% | TRUE | 3.74E-02 |
| 21 | rs4000713 | A | -0.007 | 0.32 | 0.016 | 0.677 | 8866 | 0.00% | TRUE | 7.26E-01 |
| 23 | rs58542926 | T | -0.099 | 0.07 | 0.029 | 0.001 | 8866 | 0.13% | TRUE | 1.80E-03 |
| 24 | rs6129624 | A | -0.050 | 0.31 | 0.016 | 0.002 | 8866 | 0.11% | TRUE | 2.99E-03 |
| 25 | rs62466318 | T | -0.031 | 0.20 | 0.019 | 0.098 | 8866 | 0.03% | TRUE | 1.58E-01 |
| 26 | rs629301 | T | 0.044 | 0.79 | 0.018 | 0.016 | 8866 | 0.07% | TRUE | 2.39E-02 |
| 27 | rs633695 | G | 0.039 | 0.28 | 0.017 | 0.018 | 8866 | 0.06% | TRUE | 2.59E-02 |
| 28 | rs6601924 | C | -0.002 | 0.87 | 0.022 | 0.945 | 8866 | 0.00% | FALSE | 9.16E-01 |
| 29 | rs6693447 | G | 0.003 | 0.47 | 0.015 | 0.839 | 8866 | 0.00% | TRUE | 8.71E-01 |
| 30 | rs673335 | C | -0.052 | 0.18 | 0.019 | 0.008 | 8866 | 0.08% | TRUE | 1.67E-02 |
| 31 | rs6882345 | A | 0.036 | 0.67 | 0.016 | 0.024 | 8866 | 0.06% | TRUE | 3.86E-02 |
| 32 | rs72789541 | A | -0.023 | 0.31 | 0.016 | 0.151 | 8866 | 0.02% | TRUE | 2.14E-01 |
| 33 | rs73109460 | A | 0.000 | 0.09 | 0.026 | 0.992 | 8866 | 0.00% | FALSE | 9.94E-01 |
| 34 | rs737338 | T | -0.027 | 0.04 | 0.038 | 0.471 | 8866 | 0.01% | TRUE | 7.12E-01 |
| 35 | rs77960347 | G | 0.077 | 0.01 | 0.074 | 0.298 | 8866 | 0.01% | TRUE | 3.70E-01 |
| 36 | rs7819706 | G | -0.057 | 0.16 | 0.020 | 0.005 | 8866 | 0.09% | TRUE | 7.36E-03 |
| 37 | rs7924036 | T | 0.000 | 0.49 | 0.015 | 0.979 | 8866 | 0.00% | FALSE | 8.96E-01 |
| 38 | rs7970695 | A | -0.018 | 0.59 | 0.015 | 0.243 | 8866 | 0.02% | TRUE | 2.76E-01 |
| 39 | rs9304381 | T | 0.035 | 0.82 | 0.019 | 0.068 | 8866 | 0.04% | TRUE | 8.73E-02 |
| 40 | rs964184 | C | -0.136 | 0.85 | 0.021 | 8.19E-11 | 8866 | 0.47% | TRUE | 4.09E-10 |
| 41 | rs9987289 | G | 0.042 | 0.93 | 0.029 | 0.141 | 8866 | 0.02% | TRUE | 1.98E-01 |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  | Total Variance | | 2.7% |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| 22 | rs5112 | G | 0.018 | 0.56 | TRUE | RClMh5 | 0.0064 | 0.08819 | Ambiguous palindrome | |

### EPA Lemaitre

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | SNP | EA | BETA | EAF | SE | P | N | % VARIANCE | STEIGER DIR | STEIGER P |
| 1 | rs10184054 | G | 0.01 | 0.26 | 0.02 | 0.55 | 8866 | 0.00% | TRUE | 0.68 |
| 2 | rs10455872 | G | 0.03 | 0.06 | 0.03 | 0.35 | 8866 | 0.01% | TRUE | 0.37 |
| 3 | rs11242109 | T | 0.03 | 0.43 | 0.02 | 0.02 | 8866 | 0.06% | TRUE | 0.04 |
| 4 | rs112875651 | A | -0.04 | 0.40 | 0.02 | 0.02 | 8866 | 0.06% | TRUE | 0.02 |
| 5 | rs1132899 | C | 0.01 | 0.51 | 0.02 | 0.70 | 8866 | 0.00% | TRUE | 0.77 |
| 6 | rs11563251 | T | -0.02 | 0.12 | 0.02 | 0.45 | 8866 | 0.01% | TRUE | 0.72 |
| 7 | rs1167998 | A | -0.01 | 0.68 | 0.02 | 0.72 | 8866 | 0.00% | TRUE | 0.78 |
| 8 | rs11681659 | T | -0.01 | 0.54 | 0.02 | 0.36 | 8866 | 0.01% | TRUE | 0.41 |
| 9 | rs117143374 | C | 0.01 | 0.13 | 0.02 | 0.80 | 8866 | 0.00% | TRUE | 0.94 |
| 10 | rs117733303 | G | -0.04 | 0.01 | 0.08 | 0.61 | 8866 | 0.00% | TRUE | 0.73 |
| 11 | rs12226389 | C | -0.05 | 0.19 | 0.02 | 0.01 | 8866 | 0.07% | TRUE | 0.01 |
| 12 | rs1260326 | C | -0.05 | 0.58 | 0.02 | 0.00 | 8866 | 0.15% | TRUE | 0.00 |
| 13 | rs13424225 | T | 0.01 | 0.47 | 0.02 | 0.43 | 8866 | 0.01% | TRUE | 0.60 |
| 14 | rs1672811 | C | 0.02 | 0.74 | 0.02 | 0.33 | 8866 | 0.01% | TRUE | 0.54 |
| 15 | rs174564 | G | -0.25 | 0.37 | 0.02 | 1.00E-200 | 8866 | 2.91% | TRUE | 0.00 |
| 16 | rs1800978 | G | 0.02 | 0.12 | 0.02 | 0.46 | 8866 | 0.01% | TRUE | 0.57 |
| 17 | rs261290 | C | -0.04 | 0.68 | 0.02 | 0.01 | 8866 | 0.07% | TRUE | 0.02 |
| 18 | rs3018731 | G | -0.02 | 0.79 | 0.02 | 0.24 | 8866 | 0.02% | TRUE | 0.41 |
| 19 | rs34663616 | A | -0.03 | 0.13 | 0.02 | 0.21 | 8866 | 0.02% | TRUE | 0.23 |
| 20 | rs35135293 | T | -0.02 | 0.49 | 0.02 | 0.16 | 8866 | 0.02% | TRUE | 0.18 |
| 21 | rs4000713 | A | 0.01 | 0.32 | 0.02 | 0.42 | 8866 | 0.01% | TRUE | 0.47 |
| 23 | rs58542926 | T | -0.04 | 0.07 | 0.03 | 0.16 | 8866 | 0.02% | TRUE | 0.23 |
| 24 | rs6129624 | A | -0.02 | 0.31 | 0.02 | 0.32 | 8866 | 0.01% | TRUE | 0.35 |
| 25 | rs62466318 | T | 0.02 | 0.20 | 0.02 | 0.24 | 8866 | 0.02% | TRUE | 0.35 |
| 26 | rs629301 | T | 0.00 | 0.79 | 0.02 | 0.91 | 8866 | 0.00% | TRUE | 0.98 |
| 27 | rs633695 | G | 0.00 | 0.28 | 0.02 | 0.82 | 8866 | 0.00% | TRUE | 0.88 |
| 28 | rs6601924 | C | -0.01 | 0.87 | 0.02 | 0.74 | 8866 | 0.00% | TRUE | 0.88 |
| 29 | rs6693447 | G | 0.03 | 0.47 | 0.02 | 0.08 | 8866 | 0.04% | TRUE | 0.09 |
| 30 | rs673335 | C | -0.05 | 0.18 | 0.02 | 0.02 | 8866 | 0.06% | TRUE | 0.04 |
| 31 | rs6882345 | A | -0.02 | 0.67 | 0.02 | 0.23 | 8866 | 0.02% | TRUE | 0.30 |
| 32 | rs72789541 | A | -0.04 | 0.31 | 0.02 | 0.03 | 8866 | 0.05% | TRUE | 0.05 |
| 33 | rs73109460 | A | -0.02 | 0.09 | 0.03 | 0.38 | 8866 | 0.01% | TRUE | 0.40 |
| 34 | rs737338 | T | 0.01 | 0.04 | 0.04 | 0.78 | 8866 | 9E-06 | FALSE | 0.95 |
| 35 | rs77960347 | G | 0.03 | 0.01 | 0.07 | 0.69 | 8866 | 0.00% | TRUE | 0.79 |
| 36 | rs7819706 | G | 0.02 | 0.16 | 0.02 | 0.23 | 8866 | 0.02% | TRUE | 0.25 |
| 37 | rs7924036 | T | -0.01 | 0.49 | 0.02 | 0.71 | 8866 | 0.00% | TRUE | 0.84 |
| 38 | rs7970695 | A | 0.02 | 0.59 | 0.02 | 0.28 | 8866 | 0.01% | TRUE | 0.31 |
| 39 | rs9304381 | T | -0.02 | 0.82 | 0.02 | 0.25 | 8866 | 0.02% | TRUE | 0.29 |
| 40 | rs964184 | C | 0.04 | 0.85 | 0.02 | 0.06 | 8866 | 0.04% | TRUE | 0.07 |
| 41 | rs9987289 | G | 0.02 | 0.93 | 0.03 | 0.52 | 8866 | 0.00% | TRUE | 0.63 |
|  |  |  |  |  |  | Total Variance | | 3.77% |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| 22 | rs5112 | G | -0.01 | 0.56 | 0.547 | FALSE | Ambiguous Palindrome | | |  |

### *FADS* and *ELOVL* analyses

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Pathway | SNP | Chr | EA | exposure | EAF | beta | se | pval | N | % variance |
|  |  |  |  |  |  |  |  |  |  |  |
| *FADS2* | rs174564 | 11 | G | UKBB\_Omega3 | 0.35 | -0.34 | 0.00 | 1.00E-200 | 115078 | 5.20% |
|  |  |  |  | UKBB\_DHA | 0.35 | -0.29 | 0.00 | 1E-200 | 115078 | 4.02% |
|  |  |  |  | UKBB\_Omega\_pct | 0.35 | -0.39 | 0.00 | 1.00E-200 | 115078 | 6.93% |
|  |  |  |  | UKBB\_Total\_Omega6 | 0.35 | -0.02 | 0.00 | 2.40E-05 | 115078 | 0.01% |
|  |  |  |  | UKBB\_LA | 0.35 | 0.08 | 0.00 | 5.1E-88 | 115078 | 0.34% |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  | Lemaitre\_DHA | 0.37 | -0.07 | 0.02 | 3.66E-06 | 115078 | 0.02% |
|  |  |  |  | Lemaitre\_EPA | 0.37 | -0.25 | 0.02 | 1E-200 | 115078 | 0.23% |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |  |
| *ELOVL2* | rs4711171 | 6 | T | UKBB\_Total\_Omega3 | 0.43 | 0.00 | 0.00 | 0.92 | 115078 | 0.00001% |
|  |  |  |  | UKBB\_Omega\_pct | 0.43 | 0.00 | 0.00 | 0.93 | 115078 | 0.0000001% |
|  |  |  |  | UKBB\_DHA | 0.43 | -0.01 | 0.00 | 0.002 | 115078 | 0.01% |
|  |  |  |  | UKBB\_Total\_Omega6 | 0.43 | 0.00 | 0.00 | 0.56 | 115078 | 0.001% |
|  |  |  |  | UKBB\_LA | 0.43 | -0.01 | 0.00 | 0.016 | 115078 | 0.01% |
|  |  |  |  |  |  |  |  |  |  |  |
|  |  |  |  | Lemaitre\_DHA | 0.44 | -0.09 | 0.02 | 1.78E-09 | 8866 | 0.41% |
|  |  |  |  | Lemaitre\_EPA | 0.44 | 0.10 | 0.02 | 8.22E-11 | 8866 | 0.47% |

## S3. Data Sources

1. Further details on cohorts used for Analyses

|  |  |
| --- | --- |
| **Cohorts included within the CHARGE consortium** |  |
| Atherosclerosis Risk in Communities (ARIC) Study | 3,268 |
| Cardiovascular Health Study (CHS) | 2,326 |
| Coronary Artery Risk Development in Young Adults (CARDIA) | 1,507 |
| Invecchiare in Chianti (InCHIANTI) Study | 1,075 |
| Multi-Ethnic Study of Atherosclerosis (MESA) | 690 |
|  |  |

Numbers in columns do no add up to final sample size due to the presence of sample overlap and shared controls.

|  |  |  |  |
| --- | --- | --- | --- |
| Cohorts included within the PGC MDD Samples | Cases | Controls | Total |
| UK Biobank (UKBB- removed for primary Analyses) |  |  |  |
| *23andMe* | 70,813 | 217,316 | 288,129 |
| *GERA* | 7,162 | 38,307 | 45,469 |
| *DeCODE* | 1,980 | 9,536 | 11,516 |
| *Generation Scotland (GenScot)* | 951 | 6,114 | 7,065 |
| *iPsych* | 18,629 | 17,841 | 36,470 |
| Mdd29 (With UKBB Removed) | 16,674 | 25,452 | 42,126 |
| *Genetic Association Information Network (GAIN)-MDD* | 1,696 | 1,765 | 3,461 |
| *Genetics of Recurrent Early-Onset Depression (GENRED)* | 1,030 | 1,253 | 2,283 |
| *Glaxo-Smith-Kline (GSK)* | 887 | 864 | 1,751 |
| *MDD 2000-qimr\_610* | 433 | 751 | 1,184 |
| *MDD 2000-qimr\_317* | 1,017 | 960 | 1,977 |
| *Max Planck Instutute of Psychiatry, Munich* | 376 | 537 | 913 |
| *RADIANT + Bonn/Manheim* | 935 | 1,290 | 2,225 |
| *RADIANT* | 1,625 | 1,588 | 3,213 |
| *Sequenced Treatment Alternatives to Relieve Depression (STAR\*D)* | 1,241 | 511\* | 1,752 |
| *GenPod/NEWMEDS* | 477 | 5,462 | 5,939 |
| *Harvard i2b2* | 460 | 442 | 902 |
| *PsyCoLaus* | 1,303 | 1,491 | 2,794 |
| *Study of Health in Pomerania (SHIP-LEGEND)* | 313 | 1,493 | 1,806 |
| *TwinGene* | 1,861 | 7,701 | 9,562 |
| *Genetics of Recurrent Early Onset Depression (GenRED) Phase 2/Depression Genes and Networks* | 1,302 | 944 | 2,246 |
|  | 14,956 | 27,052 | 42,008 |

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Exposure** |  | **GWAS**  **mean (SD)** | **nSNPs** | **Variance explained (%)** |  | **Cochran’s Q (p)** | **Rucker’s Q (p)** | **Egger Intercept (p)** |
| **UKBB Omega 3** |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| **Total Omega 3** |  | 0.53 mmol/l (0.22) | 43 | 9.84 | 241 | 65 (0.01) | 64 (0.01) | 0.001 (0.71) |
|  |  |  | *FADS* | 5.20 | 6315 | NA | NA | NA |
|  |  |  |  |  |  |  |  |  |
| **Omega 3 %** |  | 4.42% (1.56) | 33 | 9.81 | 316 | 33 (0.39) | 33 (0.37) | 0.001 (0.47) |
|  |  |  | FADS | 6.93 | 8572 | NA | NA | NA |
|  |  |  |  |  |  |  |  |  |
| **DHA** |  | 0.23 mmol/l (0.08) | 40 | 7.47 | 189 | 55 (0.05) | 54 (0.04) | 0.002 (0.53) |
|  |  |  | FADS | 4.20 | 4826 | NA | NA | NA |
|  |  |  |  |  |  |  |  |  |
| **EPA** |  | 0.67% (0.41) | 39 | 0.65 | 9 | 63 (0.01) | 60 (0.01) | 0.001 (0.16) |
|  |  |  | *FADS* | 2.91 | 266 | NA | NA | NA |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| **Total Omega 6** |  | 4.45 mmol/l (0.68) | 50 | 6.31 | 120 | 62 (0.11) | 61 (0.10) | 0.001 (0.44) |
|  |  |  | FADS | 0.01 | 15 | NA | NA | NA |
|  |  |  |  |  |  |  |  |  |
| **LA** |  | 3.41mmol/l (0.69) | 42 | 4.75 | 124 | 61 (0.02) | 60 (0.02) | -0.002 (0.46) |
|  |  |  | FADS | 0.34 | 394 | NA | NA | NA |
|  |  |  |  |  |  |  |  |  |
| **Reverse MR** |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| **MDD** |  | NA | 25 | 0.87 | 37 | 25 (0.39) | 23 (0.48) | 0.005 (0.12) |
|  |  |  |  |  |  |  |  |  |

## S4: Cochran’s Q Statistics and MR Egger Intercepts for MDD analyses.

Instrument strength for single SNP analyses was variable. The *FADS* SNP (rs174564) explained a large proportion of the variance in all exposures, with mean F statistics between15- 6,315 (see supplement S3).

In contrast, no *ELOVL2* SNPs were strongly associated with omega 3 measures in UK Biobank, and poor F statistics across all exposures led to extreme confidence intervals among analyses, which are therefore unreported.

S5: Comparison between MR analyses using complete MDD outcome sample (n=807,553), and MDD sample removing UKBB sample overlap (n=480,359)

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **MDD with UKBB removed (n=480,359)** |  |  | **MDD inc. UKBB (n=807,553)** |  |  |
|  | **nSNP** | **Method** |  | **OR (95%CI)** | **p** |  | **OR (95%CI)** | **p** |  |
|  |  |  |  |  |  |  |  |  |  |
| **OMEGA 3** |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| **Total Omega 3** | 43 | IVW |  | 0.96 (0.93-0.98) | 0.003 | 42 | 0.96 (0.95 -0.98) | 0.0005 |  |
|  |  | Egger |  | 0.95(0.92-0.99) | 0.02 |  | 0.96 (0.93 -0.99) | 0.007 |  |
|  |  | Weighted Median |  | 0.93 (0.92- 0.96) | 0.00001 |  | 0.95 (0.93 -0.97) | 0.0000009 |  |
|  |  | Weighted Mode |  | 0.94 (0.91 -0.97) | 0.0001 |  | 0.95 (0.93 -0.97) | 0.00004 |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| **Omega 3 %** | 33 | IVW |  | 0.96 (0.93-0.98) | 0.0002 | 28 | 0.96 (0.94 -0.98) | 0.00004 |  |
|  |  | Egger |  | 0.95 (0.92-0.98) | 0.002 |  | 0.95 (0.93 -0.97) | 0.0003 |  |
|  |  | Weighted Median |  | 0.94 (0.92-0.97) | 0.00001 |  | 0.95 (0.94 -0.97) | 0.0000005 |  |
|  |  | Weighted Mode |  | 0.94 (0.92-0.97) | 0.0002 |  | 0.96 (0.94 -0.97) | 0.00006 |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| **DHA** | 40 | IVW |  | 0.95 (0.92-0.98) | 0.001 | 37 | 0.96 (0.94 -0.98) | 0.00019 |  |
|  |  | Egger |  | 0.94 (0.89-0.98) | 0.01 |  | 0.94 (0.91 -0.97) | 0.00048 |  |
|  |  | Weighted Median |  | 0.93(0.89-0.96) | 0.00003 |  | 0.94 (0.92 -0.96) | 0.00000069 |  |
|  |  | Weighted Mode |  | 0.92(0.89-0.96) | 0.0001 |  | 0.94 (0.92 -0.97) | 0.000050 |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| **EPA** | 40 | IVW |  | 0.92 (0.88 - 0.96) | 0.0002 | 39 | 0.94 (0.91 - 0.97) | 0.0003 |  |
|  |  | Egger |  | 0.91 (0.87 - 0.96) | 0.002 |  | 0.93 (0.89 - 0.96) | 0.0004 |  |
|  |  | Weighted Median |  | 0.91 (0.88 - 0.95) | 0.00001 |  | 0.93 (0.9 - 0.96) | 0.000008 |  |
|  |  | Weighted Mode |  | 0.92 (0.87 - 0.96) | 0.001 |  | 0.94 (0.91 - 0.97) | 0.0002 |  |
|  |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| **OMEGA 6** |  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |  |
| **Omega 6** | 50 | IVW |  | 1.01 (0.97-1.05) | 0.60 | 49 | 1.02 (0.99 -1.04) | 0.24 |  |
|  |  | Egger |  | 1.01 (0.92-1.06) | 0.68 |  | 0.97 (0.92 -1.02) | 0.23 |  |
|  |  | Weighted Median |  | 0.99 (0.94-1.03) | 0.61 |  | 1.00 (0.97 -1.03) | 0.92 |  |
|  |  | Weighted Mode |  | 0.98 (0.93-1.04) | 0.48 |  | 1.00 (0.96 -1.04) | 0.95 |  |
|  |  |  |  |  |  |  |  |  |  |

## S6 Comparison of multivariable MR models using different instruments.

As MVMR models using SNP-exposure effect sizes of UKBB instruments gave poor conditional F statistics and high heterogeneity (model 3a), we compared these results with MVMR models using alternative instruments. In model 3b, SNPs were selected from a GWAS study of total omega 3, as EPA was unavailable. In both models the SNP-exposure effects were extracted from the relevant CHARGE GWAS. Conditional F statistics were calculated assuming phenotypic covariance of 0.46, which was calculated using the PhenoSpD R package.

We used a pairwise t-test to calculate the likelihood that the difference between the observed effect sizes for each exposure in the model had occurred by chance. A t-test for differences between EPA and DHA effects sizes in model 3b suggested differential effects (p=0.02), but this was not found in Model 3a (p=0.14).

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | **Instruments** | **nSNP** | **OR (95% CI)** | **p** | **p value for difference** | **Conditional F** | **Q (p)** |
|  |  |  |  |  |  |  |  |  |
| **MODEL 3a.** | **EPA** | UK Biobank | 40 | 0.93(0.88-0.97) | 0.002 | 0.14 | 10 | 52 (0.05) |
|  | **DHA** |  |  | 0.98 (0.92-1.04) | 0.46 |  | 7 |  |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |
| **MODEL 3a** | **EPA** | Kettunen et al4 | 4 | 0.92(0.91-0.94) | 1.42E-20 | 0.02 | 35 | 2 (0.16) |
|  | **DHA** |  |  | 0.96 (0.93-0.99) | 0.02 |  | 14 |  |
|  |  |  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |  |  |

## S7: Individual MR sensitivity plots for causal effects of specific fatty acid exposures on MDD

For each exposure, the following plots are shown:

i) Scatter plot showing how MR estimates compare between MR methods.

ii) Funnel plot depicting instrumental variable presicion. The log(odds ratios) of each IV is plotted on the x-axis (βIV) against instrument strength on the y axis (1/ SEIV). Asymmetry may suggest directional pleiotropy.

iii) Forest plot showing individual SNP ratio estimates (SNP-outcome estimate / SNP-exposure estimate), and

iv) Leave one out plot showing inverse variance weighted (IVW) estimates after omitting each SNP

### Total Omega 3

Chart, scatter chart

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Description automatically generated with low confidence

### Omega 3(%)

Chart

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Description automatically generated

### DHA

Chart

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Description automatically generatedChart

Description automatically generatedA screenshot of a computer

Description automatically generated with low confidence

### Omega 6

Chart, scatter chart

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Description automatically generated

### LA

Chart, scatter chart

Description automatically generated Chart, scatter chart

Description automatically generated

Chart

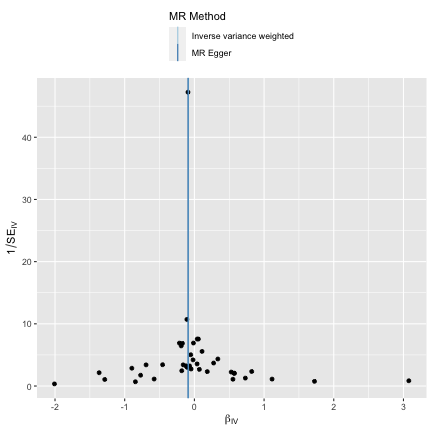
Description automatically generatedA picture containing text, appliance, air conditioner

Description automatically generated

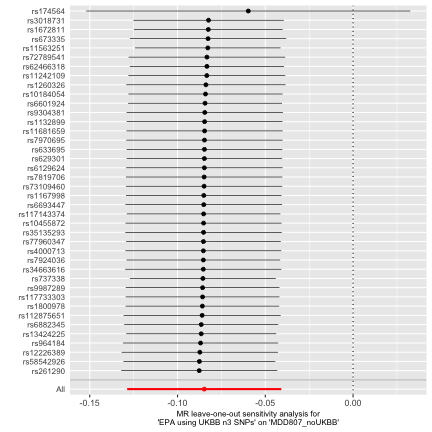
### EPA

As EPA is not measured in UK Biobank, these analyses use instruments identified from UK Biobank GWAS of Total Omega 3, with SNP-effect sizes taken from the Cohorts for Heart and Aging Consortium (CHARGE)14

Chart

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Table

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## S8 Colocalization

Results for the colocalization analysis are shown below, using a 500,000 base pair region around *FADS2* (Ensemble reference ENSG00000134824). The posterior probability of association is given in columns H0 to H4.

Analyses using the primary outcome sample (MDD without UKBB, n=480,359), suggested a high likelihood for a shared causal variant between MDD and total omega 3 (88.9%), DHA (88.9%) and EPA (97.1%). This variant localised to the *FADS2* gene (‘*rs174564’*), strengthening evidence for the association. However, colocalization analyses using the complete MDD (including UKBB participants, n=807,553), and rMDD (n=80,933) samples were less consistent with the hypothesis of a shared causal variant (see table S8a). For rMDD, the high probability of H1 (ie a causal variant for omega 3 only) suggests that this discrepancy is due to low power, in keeping with the smaller sample size. Reasons for the discrepancies between MDD samples with and without UKBB are less clear, with ‘H3’ (i.e. the traits are related but have distinct causal variants) the most likely in the larger sample. As the colocalization plots of these traits appear very similar (figure 2,) we used the gassocplot R package for a more detailed view of the region (Figure S8c). These plots highlight a further variant (*rs198457*) in the region, located on the *DAGLA* gene. Excluding the variant in sensitivity analyses yielded similar results to colocalization using the primary outcome. As the SNP is moderate LD with the *FADS2* variant (r2 0.1), it remains possible that our findings are driven by Linkage Disequilibrium. However, it could represent an additional independent locus in the region, which would violate coloc’s underlying assumption of a single common causal variant.

Table S8a. Probability for a single shared causal variant between traits as given by the ‘coloc’ R package.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Exposure | Outcome Sample | N | SNPs | H0 (%) | H1 (%) | H2 (%) | H3 (%) | H4 (%) |
| Omega 3 | No UKBB | 480,359 | 2,051 | 0.0% | 2.5% | 0.0% | 8.6% | 88.9% |
|  | UKBB included | 807,553 | 2,051 | 0.0% | 0.1% | 0.0% | 72.5% | 27.4% |
|  | rMDD | 80,933 | 2,051 | 0.0% | 91.9% | 0.0% | 4.8% | 3.4% |
|  | UKBB included (minus DAGLA) | 807,553 | 2,050 | 0.0% | 2.5% | 0.0% | 8.6% | 88.9% |
|  |  |  |  |  |  |  |  |  |
| DHA | No UKBB | 480,359 | 2,051 | 0.0% | 2.5% | 0.0% | 8.6% | 88.9% |
|  | UKBB included | 807,553 | 2,051 | 0.0% | 0.1% | 0.0% | 72.5% | 27.4% |
|  | rMDD | 80,933 | 2,051 | 0.0% | 91.9% | 0.0% | 4.8% | 3.4% |
|  | UKBB included (minus DAGLA SNP) | 807,553 | 2,050 | 0.0% | 0.2% | 0.0% | 5.6% | 94.3% |
|  |  |  |  |  |  |  |  |  |
| EPA | No UKBB | 480,359 | 2,051 | 0.0% | 0.7% | 0.0% | 2.2% | 97.1% |
|  | UKBB included | 807,553 | 2,051 | 0.0% | 0.1% | 0.0% | 83.6% | 16.3% |
|  | rMDD | 80,933 | 2,051 | 0.0% | 92.8% | 0.0% | 4.8% | 2.4% |
|  | UKBB included (minus DAGLA SNP) | 807,553 | 2,050 | 0.0% | 0.7% | 0.0% | 2.2% | 97.1% |
|  |  |  |  |  |  |  |  |  |

Figure S8b. Gassocplots to compare MDD (with and without UKBB) and Omega 3. MDD807 is the complete sample including UKBB (n=807,553), MDD is the sample with UKBB removed (n=480,539). Chart

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## S9 Phewas results

Complete output from the PheWAS is provided in an excel spreadsheet (“phewas.xlsx”). A plot of the top results by category is shown below. Several psychiatrically relevant phenotypes associated with *rs174564* included bipolar disorder (p=8.35E-7, n=51,710), intelligence (p=6.2E-6, n=269,867), cognitive performance (p=5.27E-6, n=257,841), irritability (p=1.8E-7, n=51,710), sleep duration (p=6.3E-9, n=460,099), and daytime naps (p=1.11E-10, n= 337,074).

A picture containing timeline

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