

Supplementary Information

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Supplemental methods

Calculation of F-statistic and R²

Generally, we need an F statistic greater than 10 to effectively avoid bias caused by weak instrumental variables. F statistic, calculated as follows:

$$F = \frac{N - k - 1}{k} \times \frac{R^2}{1 - R^2}$$

N represents the amount of GWAS samples exposed, and R² represents the degree of exposure to IV explanations that are difficult to obtain directly, calculated as follows:

$$R^2 = 2 \times (1 - \text{MAF}) \times \text{MAF} \times \beta^2$$

Here MAF is the minor allele frequency, β is the size of the effect of SNP on exposure. Both MAF and β are directly available, and R² can be equivalent to the effector allele frequency (EAF)¹.

Calculation of MR power

The statistical power can be calculated using the mRnd website <https://shiny.cnsgenomics.com/mRnd/>, which requires four data to calculate MR power: (1) proportion of cases in the (intended) study (case percentage, outcome). (2) Total sample size. (3) True odds ratio of the outcome variable per standard deviation of the exposure variable (MR's OR value). (4) Proportion of variance in exposure variable explained by SNPs.

Supplemental References

1 N. Papadimitriou, N. Dimou, K. K. Tsilidis, B. Banbury, R. M. Martin, S. J. Lewis, N. Kazmi, T. M. Robinson, D. Albanes, K. Aleksandrova, S. I. Berndt, D. Timothy Bishop, H. Brenner, D. D. Buchanan, B. Bueno-de-Mesquita, P. T. Campbell, S. Castellví-Bel, A. T. Chan, J. Chang-Claude, M. Ellingjord-Dale, J. C. Figueiredo, S. J. Gallinger, G. G. Giles, E. Giovannucci, S. B. Gruber, A. Gsur, J. Hampe, H. Hampel, S. Harlid, T. A. Harrison, M. Hoffmeister, J. L. Hopper, L. Hsu, J. María Huerta, J. R. Huyghe, M. A. Jenkins, T. O. Keku, T. Kühn, C. La Vecchia, L. Le Marchand, C. I. Li, L. Li, A. Lindblom, N. M. Lindor, B. Lynch, S. D. Markowitz, G. Masala, A. M. May, R. Milne, E. Monninkhof, L. Moreno, V. Moreno, P. A. Newcomb, K. Offit, V. Perduca, P. D. P. Pharoah, E. A. Platz, J. D. Potter, G. Rennert, E. Riboli, M.-J. Sánchez, S. L. Schmit, R. E. Schoen, G. Severi, S. Sieri, M. L. Slattery, M. Song, C. M. Tangen, S. N. Thibodeau, R. C. Travis, A. Trichopoulou, C. M. Ulrich, F. J. B. van Duijnhoven, B. Van Guelpen, P. Vodicka, E. White, A. Wolk, M. O. Woods, A. H. Wu, U. Peters, M. J. Gunter and N. Murphy, Physical activity and risks of breast and colorectal cancer: a Mendelian randomisation analysis., *Nat. Commun.*, 2020, 11, 597.

Supplemental Results

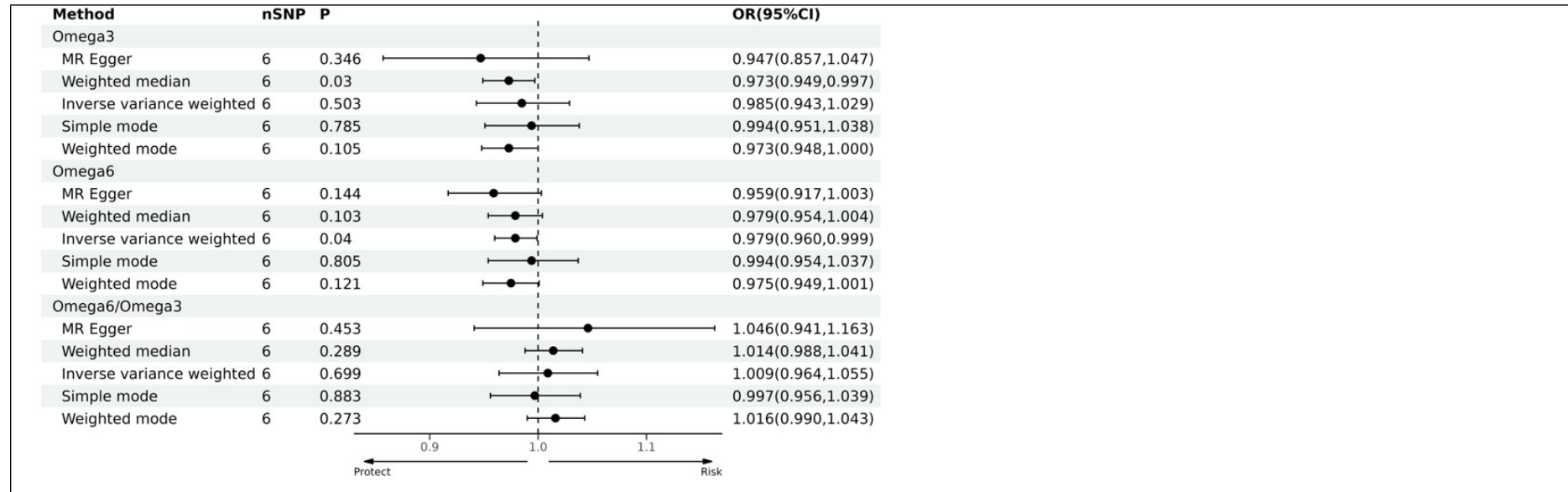


Fig. S1. Causal relationship between exposure to bipolar disorder and outcomes in three fatty acid types. nSNP: number of SNPs.

nSNP: number of SNPs; OR: odds ratio; CI: confidence interval.

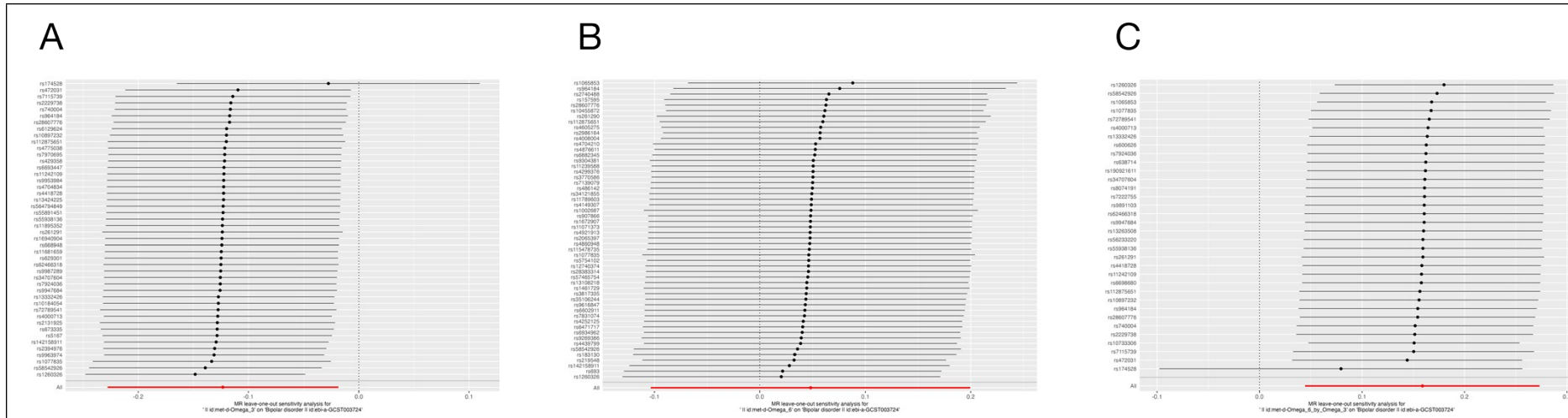


Fig. S2. Leave one out test of the causal relationship between three fatty acid types and the risk of bipolar disorder.

(A) Omega-3-Bipolar disorder. (B) Omega-6-Bipolar disorder. (C) Omega-6/ Omega-3-Bipolar disorder.

Table S1. Univariate Mendelian Randomization Harmonized Dataset and Strength Assessment of the Effects of Omega-3 Fatty Acids on Bipolar Disorder.

SNP	EA exposure	Other allele exposure	EA outcome	Other allele outcome	Chromosome	Exposure			Outcome			F
						β	SE	<i>p</i>	β	SE	<i>p</i>	
rs10184054	G	C	G	C	2	-0.036	0.005	5.60E-15	-0.026	0.026	0.243	18.397
rs1077835	G	A	G	A	15	0.126	0.005	1.80E-149	0.008	0.028	0.773	216.899
rs10897232	T	C	T	C	11	0.048	0.005	2.50E-27	-0.023	0.025	0.347	43.361
rs11242109	T	G	T	G	5	0.024	0.004	2.40E-09	-0.011	0.022	0.550	16.755
rs112875651	A	G	A	G	8	-0.087	0.004	3.50E-98	0.018	0.023	0.339	196.224
rs11681659	T	C	T	C	2	-0.025	0.004	2.00E-08	-0.010	0.024	0.708	12.215
rs11895352	T	C	T	C	2	-0.021	0.004	1.50E-08	-0.002	0.022	0.980	13.103
rs1260326	C	T	C	T	2	-0.082	0.004	8.40E-88	-0.050	0.023	0.041	179.233
rs13332426	C	G	C	G	16	0.040	0.004	3.80E-21	0.022	0.026	0.360	40.020
rs13424225	T	G	T	G	2	0.022	0.004	2.20E-08	-0.009	0.023	0.636	13.912
rs142158911	A	G	A	G	19	-0.046	0.006	7.20E-13	-0.069	0.037	0.064	10.144

rs16940904	T	C	T	C	17	-0.036	0.005	3.90E-14	-0.002	0.026	0.868	17.826
rs174528	C	T	C	T	11	-0.310	0.004	1.00E-200	0.073	0.023	0.002	2533.620
rs2131925	T	G	T	G	1	0.071	0.004	1.20E-66	0.006	0.023	0.767	123.662
rs2229738	T	C	T	C	11	-0.124	0.008	4.50E-55	0.078	0.052	0.124	27.363
rs2394976	T	G	T	G	6	-0.046	0.006	1.20E-15	-0.066	0.034	0.058	18.229
rs261291	C	T	C	T	15	0.113	0.004	1.70E-161	-0.013	0.024	0.663	314.247
rs28607776	G	A	G	A	15	-0.075	0.006	9.00E-38	0.046	0.034	0.285	33.441
rs34707604	C	T	C	T	4	0.046	0.005	1.90E-21	0.017	0.034	0.637	32.497
rs4000713	A	G	A	G	7	-0.029	0.004	1.00E-11	-0.036	0.025	0.147	16.657
rs429358	C	T	C	T	19	0.036	0.006	1.60E-11	-0.024	0.034	0.500	10.114
rs4418728	T	G	T	G	10	-0.024	0.004	5.60E-10	0.009	0.023	0.644	17.047
rs4704834	G	A	G	A	5	0.029	0.004	1.70E-13	-0.009	0.023	0.707	20.513
rs472031	A	G	A	G	11	0.103	0.007	4.20E-48	-0.093	0.039	0.023	34.589
rs4775038	T	C	T	C	15	-0.056	0.007	5.60E-17	0.024	0.037	0.586	12.602
rs5112	G	C	G	C	19	0.048	0.004	9.10E-30	-0.024	0.028	0.442	56.777
rs5167	G	T	G	T	19	0.035	0.004	6.00E-16	0.030	0.024	0.216	29.852
rs55891451	C	A	C	A	10	0.034	0.005	4.60E-12	-0.006	0.028	0.813	13.974

rs55938136	G	A	G	A	17	-0.033	0.005	1.80E-12	-0.003	0.045	0.963	15.264
rs564794849	G	T	G	T	6	0.032	0.005	6.00E-10	-0.007	0.030	0.843	15.879
rs58542926	T	C	T	C	19	-0.172	0.008	1.40E-113	-0.045	0.043	0.241	64.745
rs6129624	A	G	A	G	20	-0.026	0.004	5.10E-10	0.033	0.024	0.156	14.780
rs62466318	T	C	T	C	7	-0.072	0.005	1.20E-45	0.001	0.028	0.962	63.233
rs629301	T	G	T	G	1	0.038	0.005	1.30E-14	0.007	0.027	0.955	20.348
rs668948	A	G	A	G	2	0.046	0.005	1.10E-19	0.001	0.029	0.997	21.295
rs6693447	G	T	G	T	1	0.023	0.004	4.80E-09	-0.012	0.023	0.574	15.089
rs673335	C	T	C	T	11	-0.067	0.006	1.10E-34	-0.018	0.029	0.624	37.623
rs7115739	G	T	G	T	11	0.221	0.013	1.50E-71	-0.088	0.062	0.128	15.591
rs72789541	A	T	A	T	16	-0.081	0.004	5.60E-75	-0.002	0.024	0.883	132.171
rs740004	T	C	T	C	11	-0.062	0.005	8.90E-37	0.040	0.027	0.137	49.439
rs7924036	T	G	T	G	10	0.023	0.004	5.50E-10	0.016	0.022	0.366	15.818
rs7970695	A	G	A	G	12	-0.025	0.004	1.20E-10	0.017	0.023	0.455	16.415
rs964184	C	G	C	G	11	-0.117	0.006	8.90E-87	0.036	0.032	0.258	84.441
rs9947684	G	A	G	A	18	0.042	0.004	7.40E-25	0.008	0.024	0.690	42.598
rs9953984	C	T	C	T	18	0.026	0.004	7.20E-10	-0.010	0.024	0.631	15.592

rs9963974	A	T	A	T	18	0.031	0.004	3.90E-12	0.053	0.023	0.025	20.709
rs9987289	G	A	G	A	8	0.057	0.007	3.20E-16	0.015	0.040	0.569	10.177

SE: Standard Error.

Table S2. Univariate Mendelian Randomization Harmonized Dataset and Strength Assessment of the Effects of Omega-6 Fatty Acids on Bipolar Disorder.

SNP	Other allele exposure	EA outcome	Other allele outcome	Chromosome	Exposure			Outcome			F
					β	SE	p	β	SE	p	
rs1002687	G	A	G	1	0.091	0.004	1.00E-107	0.004	0.023	0.854	205.079
rs10455872	A	G	A	6	-0.080	0.007	2.50E-27	0.078	0.047	0.069	15.803
rs1065853	G	T	G	19	-0.199	0.007	3.60E-160	0.072	0.045	0.137	101.357
rs1077835	A	G	A	15	0.101	0.005	6.30E-96	0.008	0.028	0.773	141.789
rs11071373	A	G	A	15	-0.032	0.005	3.20E-10	-0.003	0.029	0.778	11.898
rs11239588	A	G	A	10	0.029	0.005	1.70E-10	-0.011	0.026	0.636	14.723
rs11287565 1	G	A	G	8	-0.064	0.004	2.20E-53	0.018	0.023	0.339	105.779
rs11547873 5	A	T	A	9	0.042	0.005	2.20E-17	0.007	0.028	0.612	18.850
rs11789603	C	T	C	9	0.048	0.006	9.70E-14	-0.003	0.036	0.863	10.116
rs1260326	T	C	T	2	-0.064	0.004	3.90E-55	-0.050	0.023	0.041	111.508

rs12740374	G	T	G	1	-0.057	0.005	1.50E-32	-0.008	0.027	0.912	45.959
rs13108218	A	G	A	4	-0.035	0.004	3.60E-18	-0.015	0.024	0.523	32.179
rs14215891 1	G	A	G	19	-0.094	0.006	5.20E-52	-0.069	0.037	0.064	44.130
rs1461729	A	G	A	8	0.084	0.007	2.80E-36	0.018	0.038	0.531	26.964
rs157595	A	G	A	19	0.069	0.004	8.90E-61	-0.028	0.026	0.284	121.243
rs1672907	G	A	G	12	-0.026	0.004	5.80E-11	-0.002	0.022	0.920	19.079
rs183130	C	T	C	16	0.062	0.004	1.40E-48	0.034	0.024	0.156	85.537
rs2065397	G	A	G	6	-0.030	0.004	1.70E-13	-0.004	0.023	0.787	23.165
rs2179372	C	G	C	20	0.024	0.004	7.10E-10	-0.005	0.022	0.876	16.861
rs219548	A	C	A	2	-0.029	0.004	3.40E-11	-0.071	0.024	0.003	17.830
rs2241212	T	A	T	12	0.024	0.004	8.60E-10	-0.008	0.022	0.687	16.181
rs261290	T	C	T	15	-0.097	0.004	1.00E-116	0.011	0.024	0.762	223.988
rs2740488	A	C	A	9	-0.050	0.005	5.40E-28	0.046	0.025	0.091	44.799
rs28383314	T	C	T	6	0.039	0.004	1.70E-18	0.008	0.023	0.695	39.289
rs28607776	A	G	A	15	-0.074	0.006	3.80E-35	0.046	0.034	0.285	32.641
rs2986164	G	A	G	1	-0.025	0.004	3.40E-09	0.049	0.025	0.044	15.333

rs34121855	T	G	T	7	-0.050	0.005	1.40E-22	0.002	0.028	0.973	30.345
rs35106244	C	T	C	19	0.024	0.004	7.30E-09	0.027	0.025	0.362	16.050
rs3770586	C	T	C	2	-0.023	0.004	7.10E-09	0.010	0.023	0.754	15.384
rs3817335	T	A	T	11	-0.028	0.004	9.80E-12	-0.019	0.023	0.391	18.936
rs4008004	C	A	C	9	0.033	0.005	8.40E-12	-0.041	0.027	0.149	15.123
rs4149307	C	T	C	9	0.039	0.006	6.00E-13	-0.002	0.031	0.964	12.510
rs4252125	G	A	G	6	0.025	0.004	2.40E-09	0.038	0.024	0.107	12.259
rs4299376	G	T	G	2	-0.035	0.004	1.10E-16	0.007	0.025	0.827	28.171
rs4439799	C	T	C	17	0.022	0.004	1.30E-08	0.048	0.022	0.020	14.721
rs4605275	T	C	T	19	0.034	0.004	4.20E-15	-0.037	0.025	0.124	24.378
rs4704210	G	C	G	5	0.047	0.004	6.10E-30	-0.009	0.023	0.600	56.447
rs4766578	T	A	T	12	0.028	0.004	1.50E-12	-0.020	0.022	0.432	22.644
rs4860948	T	A	T	4	0.028	0.005	1.90E-09	0.009	0.033	0.835	12.440
rs486142	G	A	G	1	0.030	0.004	2.90E-15	-0.004	0.022	0.858	27.171
rs4876611	A	G	A	8	0.028	0.004	7.30E-10	-0.021	0.025	0.389	14.786
rs4921913	C	T	C	8	-0.028	0.005	1.10E-08	-0.004	0.026	0.946	10.833
rs57465754	C	G	C	19	0.044	0.005	1.30E-18	0.012	0.027	0.615	23.810

rs5754102	C	A	C	22	-0.032	0.005	9.90E-10	-0.012	0.029	0.450	10.297
rs58542926	C	T	C	19	-0.128	0.008	2.50E-65	-0.045	0.043	0.241	36.621
rs6471717	G	A	G	8	-0.029	0.004	4.00E-12	-0.032	0.023	0.175	19.722
rs6602911	C	T	C	13	0.026	0.004	1.30E-09	0.030	0.025	0.298	16.598
rs6882345	G	A	G	5	0.045	0.004	1.20E-27	-0.008	0.023	0.748	51.380
rs693	G	A	G	2	0.060	0.004	3.80E-52	0.049	0.022	0.028	105.015
rs6934962	C	T	C	6	0.023	0.004	2.20E-08	0.041	0.023	0.059	14.179
rs7139079	G	A	G	12	-0.030	0.004	3.30E-13	0.006	0.023	0.785	24.168
rs7831074	C	G	C	8	0.028	0.005	4.60E-08	0.039	0.028	0.136	10.661
rs907866	G	A	G	2	-0.038	0.004	2.60E-21	-0.002	0.022	0.945	40.612
rs9269386	G	A	G	6	0.039	0.005	2.10E-14	0.043	0.028	0.137	28.997
rs9304381	C	T	C	18	0.070	0.005	7.20E-42	-0.004	0.030	0.966	51.266
rs9616847	A	T	A	22	0.024	0.004	1.40E-08	0.026	0.023	0.198	14.940
rs964184	G	C	G	11	-0.139	0.006	1.10E-125	0.036	0.032	0.258	120.621

SE: Standard Error.

Table S3. Univariate Mendelian Randomization Harmonized Dataset and Strength Assessment of the Effects of Omega-6/Omega-3 Fatty Acids on Bipolar Disorder.

SNP	EA exposure	Other allele exposure	EA outcome	Other allele outcome	Chromosome	Exposure			Outcome			F
						β	SE	p	β	SE	p	
rs1065853	T	G	T	G	19	-0.079	0.008	1.20E-26	0.072	0.045	0.137	15.629
rs10733306	T	C	T	C	9	0.023	0.004	3.20E-08	0.071	0.022	0.001	14.166
rs1077835	G	A	G	A	15	-0.100	0.005	1.60E-94	0.008	0.028	0.773	134.235
rs10897232	T	C	T	C	11	-0.054	0.005	2.90E-33	-0.023	0.025	0.347	55.055
rs11242109	T	G	T	G	5	-0.024	0.004	1.40E-09	-0.011	0.022	0.550	16.449
rs11287565 1	A	G	A	G	8	0.072	0.004	6.50E-65	0.018	0.023	0.339	131.024

rs1260326	C	T	C	T	2	0.065	0.004	4.20E-55	-0.050	0.023	0.041	112.575
rs13263508	T	G	T	G	8	0.022	0.004	2.80E-08	-0.007	0.023	0.746	14.217
rs13332426	C	G	C	G	16	-0.041	0.004	4.50E-22	0.022	0.026	0.360	42.634
rs174528	C	T	C	T	11	0.341	0.004	1.00E-200	0.073	0.023	0.002	3057.49 9
rs19092161 1	A	G	A	G	19	-0.031	0.005	6.80E-11	0.019	0.026	0.458	17.815
rs2229738	T	C	T	C	11	0.134	0.008	8.10E-62	0.078	0.052	0.124	31.596
rs261291	C	T	C	T	15	-0.089	0.004	9.90E-99	-0.013	0.024	0.663	191.390
rs28607776	G	A	G	A	15	0.054	0.006	2.30E-20	0.046	0.034	0.285	16.871
rs34707604	C	T	C	T	4	-0.042	0.005	9.20E-18	0.017	0.034	0.637	27.230

rs4000713	A	G	A	G	7	0.031	0.004	6.10E-13	-0.036	0.025	0.147	18.906
rs4418728	T	G	T	G	10	0.024	0.004	1.70E-09	0.009	0.023	0.644	16.867
rs472031	A	G	A	G	11	-0.113	0.007	1.20E-56	-0.093	0.039	0.023	40.770
rs55938136	G	A	G	A	17	0.039	0.005	7.80E-17	-0.003	0.045	0.963	21.388
rs56233220	C	G	C	G	10	-0.036	0.005	1.10E-12	-0.002	0.028	0.926	14.824
rs58542926	T	C	T	C	19	0.143	0.008	3.40E-79	-0.045	0.043	0.241	44.576
rs600626	G	A	G	A	11	0.060	0.006	6.60E-28	-0.011	0.030	0.801	29.280
rs62466318	T	C	T	C	7	0.061	0.005	4.40E-33	0.001	0.028	0.962	44.122
rs638714	T	G	T	G	1	0.044	0.004	3.70E-25	-0.009	0.024	0.680	44.883

rs6698680	G	A	G	A	1	-0.026	0.004	2.10E-11	-0.013	0.023	0.568	18.922
rs7115739	G	T	G	T	11	-0.239	0.013	1.90E-81	-0.088	0.062	0.128	18.079
rs7222755	G	A	G	A	17	0.024	0.005	4.10E-08	-0.016	0.025	0.532	11.190
rs72789541	A	T	A	T	16	0.088	0.004	1.40E-86	-0.002	0.024	0.883	154.496
rs740004	T	C	T	C	11	0.067	0.005	3.00E-42	0.040	0.027	0.137	58.090
rs7924036	T	G	T	G	10	-0.029	0.004	4.70E-14	0.016	0.022	0.366	24.882
rs8074191	C	T	C	T	17	0.028	0.005	4.80E-09	-0.014	0.026	0.701	11.975
rs964184	C	G	C	G	11	0.074	0.006	5.30E-35	0.036	0.032	0.258	33.172
rs9891103	T	C	T	C	17	0.041	0.005	2.20E-18	-0.005	0.026	0.784	23.840

rs9947684	G	A	G	A	18	-0.028	0.004	5.70E-12	0.008	0.024	0.690	18.911
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SE: Standard Error.

Table S4. Calculate power statistics to reflect true cause and effect ($p < 5e-8$).

Exposure	Sample size	OR(95%CI, IVW)	R² of instrument(%)	Power
Omega-3 FA	114,999	0.884(0.796,0.982)	0.057	0.98
Omega-6 FA	114,999	1.049(0.902,1.221)	0.084	0.50
Omega-6:Omega-3	114,999	1.172(1.046,1.314)	0.054	1.00

IVW: Inverse variance weighting. OR = odds ratio; CI = confidence interval.