

## Electronic Supplementary Information

# Circulating fatty acids and risk of severe non-alcoholic fatty liver disease: a prospective cohort of 116,223 individuals

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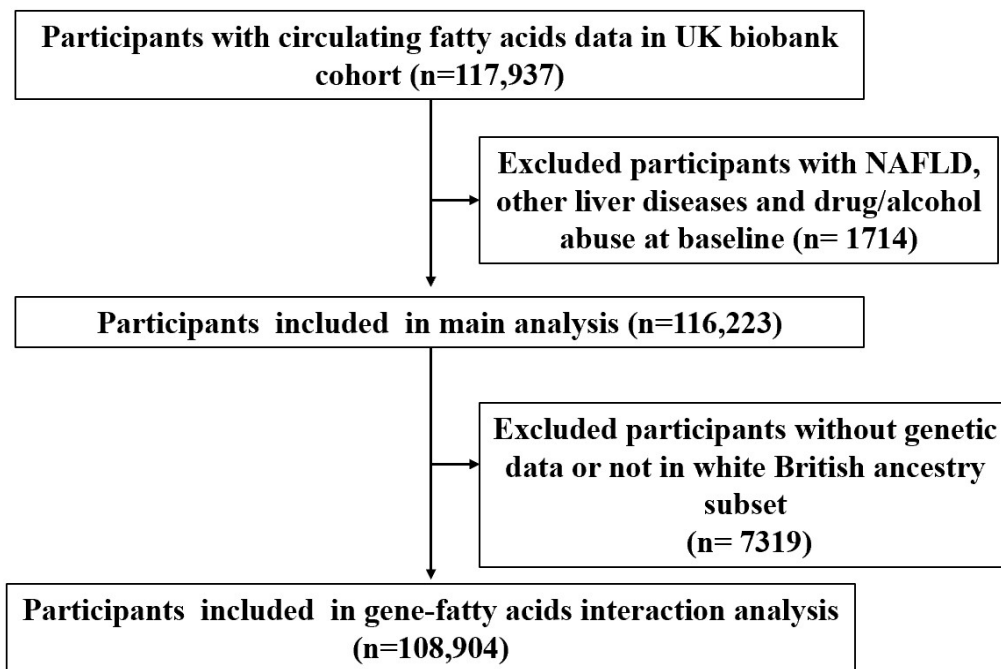
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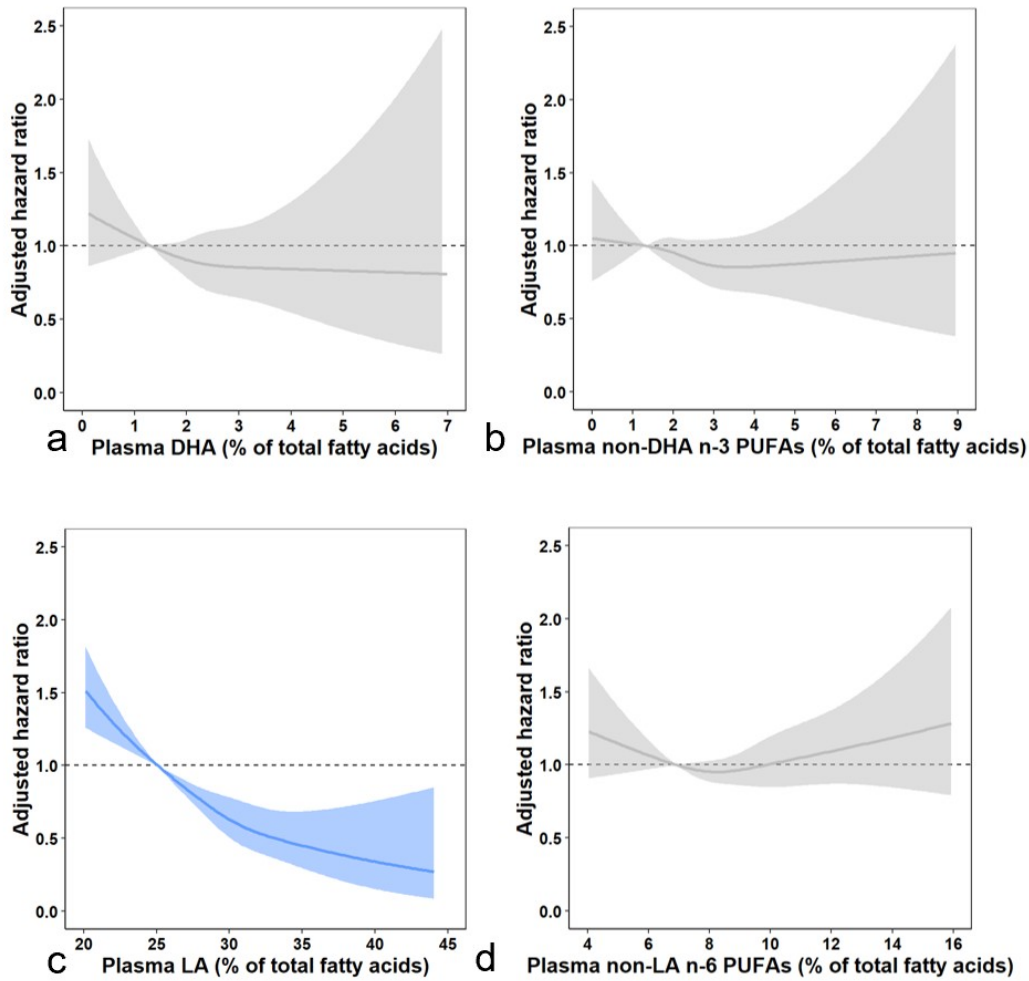
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**Supplemental Figure 1.** Flow chart of study participants for analysis. *NAFLD* non-alcoholic fatty liver disease.



**Supplemental Figure 2.** Dose-response relationships between specific n-3 PUFAs/n-6 PUFAs and NAFLD risk. HRs for NAFLD associated with plasma DHA (a), non-DHA n-3 PUFA (b), LA (c), and non-LA n-6 PUFA (d) were estimated by restricted cubic-spline regression adjusted for age, sex, race, BMI, education, household income, smoking status, alcohol consumption, physical activity, history of hypertension, CVD, high cholesterol and cancer, diabetes, aspirin use, vitamin use, mineral use, and remaining circulating fatty acids. *LA* linoleic acid, *DHA* docosahexaenoic acid, *NAFLD* non-alcoholic fatty liver disease.

**Supplemental Table 1.** Single-nucleotide polymorphisms associated with circulating individual FAs

Type of FA	FA	SD	SNP	Chr	Nearby gene	EA	NEA	% Variance explained	Summary statistics for SNP-FA association		
									Beta <sup>a</sup>	SE	P
n-3 PUFA	ALA	0.05	rs174547	11	FADS1	C	T	1	0.02	0.001	3.50E-64
	EPA	0.3	rs3798713	6	ELOVL2	C	G	0.4	0.04	0.005	1.90E-12
			rs174538	11	FADS1/C11orf10	G	A	1.7	0.08	0.005	5.40E-58
			rs780094	2	GCKR	T	C	0.5	0.02	0.003	9.00E-09
	DPA	0.17	rs3734398	6	ELOVL2	C	T	2.7	0.04	0.003	9.70E-43
n-6 PUFA	DHA	0.89	rs174547	11	FADS1	T	C	8.4	0.08	0.003	3.80E-154
			rs2236212	6	ELOVL2	G	C	0.7	0.11	0.014	1.30E-15
	LA	2.69	rs10740118	10	JMJD1C	G	C	0.2-0.7	0.25	0.050	8.10E-09
			rs174547	11	FADS1	C	T	7.6-18.1	1.47	0.050	5.00E-274
			rs16966952	16	NTAN1	G	A	0.5-2.5	0.35	0.040	1.20E-15
AA	1.96	rs174547	11	FADS1	T	C	3.7-37.6	1.69	0.020	3.30E-971	
		rs16966952	16	NTAN1	G	A	0.1-0.6	0.20	0.030	2.40E-10	
		rs780093	2	GCKR	T	C	0.2-0.9	0.02	0.003	9.80E-10	
n-7 MUFA	POA	0.18	rs6722456	2	RN7SKP93	G	A	0.01-0.6	0.05	0.009	4.10E-08
			rs603424	10	SCD/PKD2L1	G	A	0.3-1.6	0.03	0.004	5.70E-15
			rs11190604	10	HIF1AN	G	A	0.02-0.7	0.02	0.004	5.70E-09
n-9 MUFA	OA	1.17	rs102275	11	FADS1/2	C	T	0.15-1.0	0.02	0.003	6.60E-13
			rs102275	11	FADS1/2	C	T	0.3-2.1	0.23	0.020	2.20E-32
SFA	PA	1.64	rs2391388	1	ALG14	C	A	0.2-1.0	0.18	0.030	2.70E-11
			rs6675668	1	ALG14	G	T	0.4-1.4	0.17	0.020	2.20E-18
	SA	1.19	rs11119805	1	LPGAT1	T	A	0.01-0.7	0.17	0.030	2.80E-09
			rs102275	11	FADS1/2	T	C	0.3-1.2	0.18	0.020	1.30E-20

*Abbreviations:* *AA* arachidonic acid, *ALA*  $\alpha$ -linolenic acid, *Chr* chromosome, *DHA* docosahexaenoic acid, *DPA* docosapentaenoic acid, *EA* effect allele, *EAF* effect allele frequency, *EPA* eicosapentaenoic acid, *FA* fatty acid, *LA* linoleic acid, *MUFA* monounsaturated fatty acid, *OA* oleic acid, *PA* palmitic acid, *POA* palmitoleic acid, *PUFA* polyunsaturated fatty acid, *SA* stearic acid, *SD* standard deviation, *SFA* saturated fatty acid, *SNP* single-nucleotide polymorphisms.

<sup>a</sup> The beta coefficients represent the change in the percentage of total fatty acids for each additional effect allele (Yuan S, Larsson SC. Plasma phospholipid fatty acids and risk of atrial fibrillation: A mendelian randomization study. *Nutrients*. 2019;11(7):1651. doi: 10.3390/nu11071651).

**Supplemental Table 2.** Codes used in the UK Biobank to identify NAFLD, other liver diseases and alcohol/drug use disorder

<input type="checkbox"/>	<b>ICD-10</b>
NAFLD	K760, K758
Other liver disease	B16, B17, B18, B19, E83.1, E83.0B, E88.0A, E88.0B, I82.0, K70, K73.9, K73.2, K74.3, K74.4, K74.5, K75.4, K76.5, K83.0A, K83.0F
Alcohol/drug use disorder	E24.4, F10, F11-F14, F16, F18, F19, G31.2, G62.1, G72.1, I42.6, K29.2, K85.2, K86.0, T51.0, T51.9, X65, Y57.3, Z50.2, Z71.4, Z72.1

*Abbreviations: NAFLD non-alcoholic fatty liver disease.*

**Supplemental Table 3.** Spearman correlations between plasma fatty acids (% of total fatty acids)

	SFAs	MUFAs	PUFAs	n-6 PUFAs	LA	non-LA n-6 PUFAs	n-3 PUFAs	DHA	non-DHA n-3 PUFAs
SFAs	1.00	0.26	-0.69	-0.65	-0.64	-0.09	-0.13	-0.27	-0.01
MUFAs		1.00	-0.86	-0.74	-0.47	-0.56	-0.29	-0.65	-0.03
PUFAs			1.00	0.88	0.67	0.45	0.28	0.61	0.03
n-6 PUFAs				1.00	0.83	0.37	-0.14	0.26	-0.38
LA					1.00	-0.14	-0.25	0.06	-0.41
non-LA n-6 PUFAs						1.00	0.19	0.43	0.01
n-3 PUFAs							1.00	0.83	0.93
DHA								1.00	0.60
non-DHA n-3 PUFAs									1.00

DHA=docosahexaenoic acid, LA=linoleic acid, MUFA=monounsaturated fatty acid, PUFA=polyunsaturated fatty acid, SFA=saturated fatty acid.  $P<0.001$  for all correlations.

**Supplemental Table 4.** Association between plasma PUFAs and the risk of NAFLD

□	Quartiles of plasma FAs (% of total FAs)				<i>P</i> trend
	Q1	Q2	Q3	Q4	
DHA					
Range (% of plasma FAs)	<1.6	1.6-1.9	1.9-2.4	>2.4	
Median	1.3	1.8	2.1	2.7	
Cases/person-years	533/354,314	380/356,591	270/357,813	211/358,547	
Model 1	1.00 (ref.)	0.70 (0.61-0.79)	0.48 (0.42-0.56)	0.37 (0.32-0.44)	<0.001
Model 2	1.00 (ref.)	0.82 (0.72-0.94)	0.65 (0.56-0.76)	0.58 (0.49-0.69)	<0.001
Model 3	1.00 (ref.)	0.98 (0.84-1.14)	0.87 (0.72-1.05)	0.92 (0.71-1.19)	0.278
Non-DHA n-3 PUFAs					
Range (% of plasma FAs)	<1.7	1.7-2.3	2.3-3.0	>3.0	
Median	1.3	2.0	2.6	3.5	
Cases/person-years	316/357,133	366/356,823	370/356,745	342/356,564	
Model 1	1.00 (ref.)	1.14 (0.98-1.33)	1.14 (0.98-1.33)	1.05 (0.90-1.23)	0.604
Model 2	1.00 (ref.)	1.03 (0.88-1.20)	1.00 (0.86-1.16)	0.97 (0.82-1.13)	0.592
Model 3	1.00 (ref.)	0.96 (0.82-1.12)	0.91 (0.76-1.08)	0.91 (0.73-1.14)	0.339
LA					
Range (% of plasma FAs)	<26.9	26.9-29.2	29.2-31.4	>31.4	
Median	25.1	28.2	30.3	32.8	
Cases/person-years	655/350,562	353/355,255	228/359,130	158/362,318	
Model 1	1.00 (ref.)	0.52 (0.46-0.60)	0.33 (0.28-0.38)	0.22 (0.19-0.27)	<0.001
Model 2	1.00 (ref.)	0.72 (0.63-0.82)	0.55 (0.47-0.65)	0.44 (0.37-0.54)	<0.001
Model 3	1.00 (ref.)	0.87 (0.74-1.02)	0.77 (0.61-0.96)	0.73 (0.54-0.99)	0.021
Non-LA n-6 PUFAs					



Range (% of plasma FAs)	<7.7	7.7-8.9	8.9-10.2	>10.2	
Median	6.9	8.3	9.5	11.3	
Cases/person-years	392/358,169	350/358,179	315/356,826	337/354,092	
Model 1	1.00 (ref.)	0.90 (0.78-1.04)	0.82 (0.70-0.95)	0.88 (0.76-1.02)	0.043
Model 2	1.00 (ref.)	0.92 (0.80-1.07)	0.82 (0.70-0.95)	0.75 (0.64-0.87)	<0.001
Model 3	1.00 (ref.)	1.01 (0.87-1.18)	1.00 (0.84-1.19)	1.08 (0.87-1.33)	0.613

*Abbreviations: FAs fatty acids, DHA docosahexaenoic acid, LA linoleic acid, NAFLD non-alcoholic fatty liver disease.*

Model 1: adjusted for age, sex

Model 2: model 1+race (White, non-White, or other ethnic group), assessment centers (22 categories), BMI (in kg/m<sup>2</sup>; < 25, 25 to 30, ≥30, or missing), education (college or university degree, vocational qualifications, optional national exams at ages 17–18 years, national exams at age 16 years, others, or missing), household income (<£18,000, £18,000-£30,999, £31,000-£51,999, £52,000-£100,000, >£100,000, or missing), smoking status (never, former, current, or missing), alcohol consumption (never, special occasions only, 1–3 times/month, 1 or 2 times/week, 3 or 4 times/week, or daily/almost daily), physical activity (in MET-h/week; quartiles), history of hypertension (yes, no), CVD (yes, no), high cholesterol (yes, no) and cancer (yes, no), diabetes (yes, no), aspirin use (yes, no), vitamin use (yes, no), mineral use (yes, no),

Model 3: model 2+ remain circulating fatty acids (quartiles)

**Supplemental Table 5.** Mediating effects of biomarkers on the association of plasma FAs with risk of NAFLD

Mediators	N	Total effect	Direct effect	Proportion mediated	P value
SFAs and NAFLD					
CRP	110,769	1.22(1.15-1.32)	1.24(1.16-1.33)	NA	NA
TG	110,881	1.23(1.15-1.31)	1.21(1.12-1.30)	7.5% (1.3%-32.8%)	0.117
TC	110,968	1.23(1.15-1.32)	1.25(1.17-1.34)	NA	NA
HDL	101,692	1.23(1.14-1.32)	1.23(1.15-1.32)	NA	NA
Blood glucose	101,615	1.23(1.15-1.32)	1.23(1.14-1.32)	1.1% (0.3%-4.3%)	0.075
LDL	110,803	1.23(1.15-1.32)	1.24(1.16-1.33)	NA	NA
HbA1c	110,835	1.22(1.14-1.31)	1.22(1.14-1.30)	NA	NA
MUFAs and NAFLD					
CRP	110,769	1.21 (1.10-1.34)	1.19 (1.07-1.31)	10.1% (5.1%-18.9%)	<0.001
TG	110,881	1.21 (1.10-1.34)	1.21 (1.08-1.37)	NA	NA
TC	110,968	1.21 (1.10-1.33)	1.21 (1.10-1.34)	NA	NA
HDL	101,692	1.16(1.05-1.29)	1.11(1.00-1.23)	32.6% (11.1%-65.2%)	0.001
Blood glucose	101,615	1.17(1.05-1.29)	1.16(1.05-1.29)	4.3% (1.0%-16.4%)	0.059
LDL	110,803	1.21 (1.10-1.34)	1.21 (1.09-1.33)	1.6% (0.6%-4.0%)	0.013
HbA1c	110,835	1.22(1.10-1.35)	1.22(1.10-1.34)	1.4% (0.1%-13.0%)	0.192
N3 PUFAs and NAFLD					
CRP	110,769	0.91(0.83-1.00)	0.93(0.85-1.02)	24.7% (8.3%-54.1%)	<0.001
TG	110,881	0.91(0.83-1.00)	0.90(0.83-0.99)	NA	NA
TC	110,968	0.91(0.83-1.00)	0.92(0.84-1.01)	11.4% (3.5%-31.5%)	0.002
HDL	101,692	0.91(0.83-1.00)	0.92(0.84-1.01)	9.6% (2.9%-27.6%)	0.001
Blood glucose	101,615	0.91(0.83-1.00)	0.91(0.83-1.00)	NA	NA
LDL	110,803	0.91(0.83-1.00)	0.92(0.84-1.00)	8.0% (2.5%-23.0%)	0.002

HbA1c	110,835	0.90(0.83-0.99)	0.91(0.83-0.99)	1.5% (0.2%-10.9%)	0.145
N6 PUFAs and NAFLD					
CRP	110,769	0.78(0.70-0.86)	0.78(0.70-0.87)	NA	NA
TG	110,881	0.78(0.70-0.87)	0.78(0.68-0.89)	NA	NA
TC	110,968	0.78(0.70-0.87)	0.77(0.70-0.86)	NA	NA
HDL	101,692	0.80(0.72-0.89)	0.82(0.73-0.92)	12.2% (5.1%-26.6%)	0.002
Blood glucose	101,615	0.80(0.71-0.89)	0.80(0.72-0.89)	3.0% (0.7%-11.2%)	0.063
LDL	110,803	0.78(0.70-0.87)	0.78(0.70-0.86)	NA	NA
HbA1c	110,835	0.77(0.70-0.86)	0.77(0.70-0.86)	1.0% (0.1%-10.9%)	0.207
LA and NAFLD					
CRP	110,769	0.74(0.67-0.83)	0.76(0.68-0.85)	8.0% (4.7%-13.3%)	<0.001
TG	110,881	0.75(0.67-0.83)	0.77(0.69-0.87)	12.3% (3.0%-38.9%)	0.062
TC	110,968	0.74(0.67-0.83)	0.76(0.68-0.85)	6.1% (1.5%-21.4%)	0.065
HDL	101,692	0.76(0.68-0.85)	0.78(0.69-0.88)	10.8% (4.0%-25.8%)	0.010
Blood glucose	101,615	0.75(0.67-0.84)	0.76(0.67-0.85)	1.6% (0.4%-5.7%)	0.058
LDL	110,803	0.75(0.67-0.83)	0.76(0.68-0.85)	6.2% (1.4%-23.8%)	0.084
HbA1c	110,835	0.74(0.66-0.82)	0.74(0.66-0.82)	NA	NA

*Abbreviations: FAs* fatty acids, *CRP* C-reactive protein, *HbA1c* Hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *TG* triglyceride, *TC* total cholesterol, *MUFA* monounsaturated fatty acid, *PUFA* polyunsaturated fatty acid, *SFA* saturated fatty acid.

NA: proportion mediated was not calculated when the point estimate of the direct effect was in a direction opposite to that of the indirect effect.

**Supplemental Table 6.** Interactions of plasma FAs with number of FA-associated alleles for NAFLD risk

□	□	Number of alleles			□ FA			□ Number of alleles×FA		
		□ β	□ SE	□ P	□ β	□ SE	□ P	□ β	□ SE	□ P
SFA-associated alleles	SFA	0.044	0.035	0.211	0.487	0.141	0.001	-0.060	0.028	0.032
MUFA-associated alleles	MUFA	0.002	0.019	0.906	0.140	0.111	0.208	0.007	0.015	0.654
EPA-associated alleles	n-3 PUFA	0.036	0.031	0.244	-0.090	0.085	0.290	-0.007	0.033	0.843
	DHA	0.036	0.033	0.277	-0.112	0.089	0.211	0.015	0.032	0.646
	non-DHA PUFA	0.032	0.030	0.292	-0.046	0.087	0.598	-0.021	0.032	0.517
DPA-associated alleles	n-3 PUFA	0.041	0.024	0.097	-0.114	0.090	0.205	0.002	0.027	0.935
	DHA	0.040	0.026	0.128	-0.113	0.094	0.232	0.011	0.026	0.661
	non-DHA PUFA	0.038	0.024	0.117	-0.079	0.091	0.384	-0.006	0.026	0.828
DHA-associated allele (rs2236212)	n-3 PUFA	-0.044	0.041	0.278	-0.092	0.067	0.174	-0.004	0.046	0.928
	DHA	-0.041	0.043	0.345	-0.080	0.075	0.285	0.0005	0.044	0.991
	non-DHA PUFA	-0.042	0.040	0.287	-0.075	0.070	0.284	-0.006	0.044	0.886
LA-associated alleles	n-6 PUFA	-0.045	0.027	0.104	-0.099	0.092	0.285	-0.037	0.022	0.086
	LA	-0.040	0.028	0.145	-0.134	0.095	0.160	-0.040	0.023	0.078
	non-LA n-6 PUFA	-0.019	0.024	0.440	0.049	0.089	0.581	-0.010	0.024	0.686
AA-associated alleles	n-6 PUFA	0.005	0.035	0.895	-0.242	0.088	0.006	0.007	0.027	0.806
	LA	-0.013	0.036	0.713	-0.253	0.093	0.006	-0.006	0.028	0.825
	non-LA n-6 PUFA	-0.004	0.032	0.893	-0.060	0.091	0.510	0.030	0.029	0.300

Abbreviations: FAs fatty acids, MUFA monounsaturated fatty acid, PUFA polyunsaturated fatty acid, SFA saturated fatty acid, NAFLD non-

alcoholic fatty liver disease, *DHA* docosahexaenoic acid, *LA* linoleic acid, *SNP* single nucleotide polymorphism.

$\beta$ -Coefficients were adjusted for age, sex, race, BMI, education, household income, smoking status, alcohol consumption, physical activity, history of hypertension, CVD, high cholesterol and cancer, diabetes, aspirin use, vitamin use, mineral use, remain circulating fatty acids.

**Supplemental Table 7.** Interactions between plasma FAs and individual FA-associated SNPs for NAFLD risk

□	□	SNP			FAs			SNP*FAs		
		β	SE	<i>p</i>	β	SE	<i>p</i>	β	SE	<i>p</i>
rs2391388	SFAs	0.035	0.042	0.412	0.216	0.048	<0.001	-0.026	0.035	0.463
rs6675668	SFAs	-0.015	0.042	0.724	0.181	0.050	<0.001	0.011	0.035	0.750
rs11119805	SFAs	0.053	0.065	0.412	0.336	0.096	0.001	-0.082	0.052	0.110
rs102275	SFAs	0.025	0.045	0.578	0.248	0.057	<0.001	-0.045	0.036	0.217
rs780093	MUFAs	0.014	0.047	0.769	0.182	0.059	0.002	0.004	0.038	0.914
rs6722456	MUFAs	0.375	0.187	0.045	0.513	0.272	0.059	-0.166	0.137	0.225
rs603424	MUFAs	-0.016	0.059	0.787	0.135	0.095	0.156	0.031	0.049	0.530
rs11190604	MUFAs	0.071	0.055	0.191	0.202	0.052	<0.001	-0.036	0.044	0.410
rs102275	MUFAs	-0.040	0.050	0.424	0.163	0.058	0.005	0.032	0.038	0.406
rs174547	n-3 PUFAs	-0.039	0.046	0.394	-0.117	0.056	0.036	0.014	0.047	0.763
	DHA	-0.038	0.050	0.440	-0.063	0.065	0.333	-0.023	0.046	0.622
	non-DHA n-3 PUFAs	-0.030	0.045	0.510	-0.121	0.061	0.046	0.041	0.046	0.374
rs3798713	n-3 PUFAs	0.035	0.041	0.390	-0.091	0.059	0.121	-0.006	0.046	0.892
	DHA	0.029	0.043	0.497	-0.071	0.067	0.291	-0.011	0.044	0.807
	non-DHA n-3 PUFAs	0.035	0.040	0.382	-0.082	0.062	0.190	-0.001	0.044	0.982
rs174538	n-3 PUFAs	0.037	0.047	0.435	-0.096	0.080	0.229	-0.007	0.048	0.889
	DHA	0.045	0.051	0.374	-0.138	0.083	0.098	0.043	0.047	0.356
	non-DHA n-3 PUFAs	0.024	0.046	0.598	-0.030	0.082	0.710	-0.044	0.047	0.351
rs780094	n-3 PUFAs	0.029	0.041	0.483	-0.112	0.057	0.050	0.018	0.046	0.692
	DHA	0.034	0.044	0.444	-0.095	0.067	0.152	0.017	0.045	0.708
	non-DHA n-3 PUFAs	0.028	0.041	0.496	-0.095	0.061	0.122	0.015	0.044	0.734
rs3734398	n-3 PUFAs	0.051	0.041	0.205	-0.098	0.059	0.095	0.002	0.046	0.959

	DHA	0.047	0.043	0.278	-0.075	0.067	0.264	-0.005	0.044	0.908
	non-DHA n-3 PUFAs	0.050	0.040	0.208	-0.089	0.062	0.155	0.007	0.044	0.874
rs174547	n-3 PUFAs	0.039	0.046	0.394	-0.089	0.076	0.242	-0.014	0.047	0.763
	DHA	0.038	0.050	0.440	-0.109	0.080	0.174	0.023	0.046	0.622
	non-DHA n-3 PUFAs	0.030	0.045	0.510	-0.040	0.078	0.611	-0.041	0.046	0.374
	n-3 PUFAs	-0.044	0.041	0.278	-0.092	0.067	0.174	-0.004	0.046	0.928
rs2236212	DHA	-0.041	0.043	0.345	-0.080	0.075	0.285	0.0005	0.044	0.991
	non-DHA n-3 PUFAs	-0.042	0.040	0.287	-0.075	0.070	0.284	-0.006	0.044	0.886
	n-6 PUFAs	0.001	0.046	0.978	-0.202	0.070	0.004	-0.019	0.036	0.599
rs10740118	LA	-0.012	0.046	0.796	-0.216	0.073	0.003	-0.044	0.038	0.254
	non-LA n-6 PUFAs	0.018	0.040	0.648	-0.023	0.065	0.725	0.037	0.040	0.357
	PUFAs	-0.065	0.050	0.193	-0.218	0.066	0.001	-0.048	0.037	0.199
rs174547	n-6 PUFAs	-0.077	0.050	0.123	-0.184	0.062	0.003	-0.051	0.037	0.167
	LA	-0.046	0.050	0.362	-0.245	0.064	<0.001	-0.030	0.039	0.438
	non-LA n-6 PUFAs	-0.044	0.046	0.341	0.061	0.053	0.253	-0.066	0.041	0.109
	n-6 PUFAs	-0.067	0.049	0.169	-0.167	0.077	0.029	-0.041	0.039	0.283
rs16966952	LA	-0.071	0.049	0.149	-0.206	0.080	0.010	-0.046	0.041	0.259
	non-LA n-6 PUFAs	-0.044	0.043	0.304	0.027	0.073	0.715	-0.004	0.042	0.928

*Abbreviations: FA* fatty acid, *MUFA* monounsaturated fatty acid, *PUFA* polyunsaturated fatty acid, *SFA* saturated fatty acid, *NAFLD* non-alcoholic fatty liver disease, *DHA* docosahexaenoic acid, *LA* linoleic acid, *SNP* single nucleotide polymorphism.

$\beta$ -Coefficients were adjusted for age, sex, race, BMI, education, household income, smoking status, alcohol consumption, physical activity, history of hypertension, CVD, high cholesterol and cancer, diabetes, aspirin use, vitamin use, mineral use, remain circulating fatty acids.

**Supplemental Table 8.** The subgroup analysis of plasma FAs and NAFLD risk

□	<b>Sex</b>				□
	<b>Women (cases/N: 739/63309)</b>		<b>Men (cases/N: 655/52914)</b>		
□	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	
Plasma SFAs	1.92(1.37-2.71)	<0.001	1.82(1.28-2.60)	<0.001	0.284
Plasma MUFAs	1.88(1.19-2.97)	0.007	1.57(0.94-2.63)	0.087	0.084
Plasma PUFAs	0.89(0.58-1.38)	0.609	0.67(0.43-1.06)	0.086	0.029
Plasma n-3 PUFAs	0.73(0.56-0.96)	0.025	0.85(0.64-1.13)	0.266	0.284
Plasma DHA	0.90(0.63-1.28)	0.554	0.94(0.64-1.38)	0.736	0.110
Plasma other n-3 PUFAs	0.84(0.61-1.15)	0.282	0.97(0.71-1.34)	0.870	0.752
Plasma n-6 PUFAs	0.63(0.39-1.00)	0.050	0.70(0.42-1.16)	0.166	0.120
Plasma LA	0.60(0.39-0.91)	0.017	0.93(0.60-1.45)	0.759	0.033
Plasma other n-6 PUFAs	1.09(0.80-1.47)	0.292	1.04(0.77-1.42)	0.796	0.907
□	<b>Baseline age (years)</b>				□
□	<b>&lt;60 (cases/N: 783/65920)</b>		<b>≥60 (cases/N: 611/50303)</b>		
□	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	
Plasma SFAs	1.63(1.19-2.24)	0.002	2.20(1.50-3.24)	<0.001	0.116
Plasma MUFAs	1.34(0.86-2.11)	0.198	2.37(1.40-4.00)	0.001	0.086
Plasma PUFAs	0.58(0.38-0.89)	0.012	0.98(0.62-1.56)	0.945	0.964
Plasma n-3 PUFAs	0.90(0.69-1.18)	0.435	0.69(0.52-0.92)	0.011	0.029
Plasma DHA	0.93(0.64-1.34)	0.679	0.88(0.60-1.29)	0.507	0.100
Plasma other n-3 PUFAs	0.97(0.72-1.31)	0.853	0.84(0.59-1.17)	0.300	0.021
Plasma n-6 PUFAs	0.61(0.39-0.97)	0.036	0.81(0.48-1.35)	0.410	0.649
Plasma LA	0.66(0.44-1.00)	0.048	0.88(0.55-1.40)	0.591	0.302
Plasma other n-6 PUFAs	0.96(0.72-1.29)	0.799	1.25(0.91-1.73)	0.172	0.565
□	<b>Baseline BMI</b>				□



	<b>&lt;30 (cases/N: 643/87588)</b>		<b>≥30 (cases/N: 744/28223)</b>		<i>P</i> for interaction
□	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	
Plasma SFAs	1.87(1.31-2.68)	<0.001	1.87(1.33-2.63)	<0.001	0.067
Plasma MUFAs	1.75(1.10-2.78)	0.019	1.62(0.96-2.72)	0.070	0.004
Plasma PUFAs	0.82(0.52-1.29)	0.380	0.78(0.50-1.22)	0.279	0.001
Plasma n-3 PUFAs	0.83(0.62-1.11)	0.211	0.77(0.59-1.01)	0.056	0.228
Plasma DHA	0.97(0.66-1.42)	0.873	0.88(0.61-1.27)	0.480	0.795
Plasma other n-3 PUFAs	1.06(0.76-1.48)	0.737	0.82(0.61-1.11)	0.203	0.080
Plasma n-6 PUFAs	0.64(0.39-1.04)	0.071	0.73(0.45-1.19)	0.208	0.001
Plasma LA	0.91(0.59-1.41)	0.675	0.62(0.40-0.97)	0.034	0.013
Plasma other n-6 PUFAs	1.10(0.80-1.51)	0.578	1.05(0.78-1.41)	0.751	0.456
□	<b>Smoking status</b>				□
	<b>Never (cases/N: 649/63521)</b>		<b>Previous/current (cases/N: 736/52108)</b>		<i>P</i> for interaction
□	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	
Plasma SFAs	1.75(1.23-2.49)	0.002	1.97(1.40-2.77)	<0.001	0.892
Plasma MUFAs	1.55(0.95-2.51)	0.079	1.92(1.19-3.12)	0.008	0.915
Plasma PUFAs	0.82(0.51-1.32)	0.410	0.73(0.47-1.11)	0.139	0.678
Plasma n-3 PUFAs	0.84(0.63-1.11)	0.220	0.78(0.59-1.02)	0.069	0.659
Plasma DHA	1.12(0.77-1.64)	0.557	0.80(0.55-1.15)	0.218	0.368
Plasma other n-3 PUFAs	0.77(0.56-1.08)	0.126	1.03(0.76-1.40)	0.845	0.914
Plasma n-6 PUFAs	0.91 (0.77-1.07)	0.245	0.74(0.45-1.22)	0.236	0.794
Plasma LA	0.73(0.47-1.13)	0.158	0.70(0.45-1.09)	0.113	0.787
Plasma other n-6 PUFAs	0.91(0.66-1.25)	0.562	1.21(0.91-1.62)	0.198	0.680
□	<b>Alcohol consumption</b>				□
	<b>Never/special occasions only (cases/N: 410/22405)</b>		<b>≥1 time/month (cases/N: 979/93591)</b>		<i>P</i> for interaction

<input type="checkbox"/>	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	
Plasma SFAs	2.44 (1.57-3.80)	<0.001	1.60 (1.19-2.15)	0.002	0.794
Plasma MUFAs	2.09 (1.10-3.97)	0.024	1.52 (1.01-2.28)	0.043	0.179
Plasma PUFAs	0.83 (0.47-1.47)	0.513	0.68 (0.47-0.99)	0.042	0.119
Plasma n-3 PUFAs	0.90 (0.63-1.29)	0.558	0.75 (0.59-0.94)	0.014	0.590
Plasma DHA	1.00 (0.62-1.61)	0.991	0.88 (0.64-1.21)	0.434	0.396
Plasma other n-3 PUFAs	1.08 (0.71-1.66)	0.709	0.84 (0.65-1.10)	0.205	0.614
Plasma n-6 PUFAs	0.66 (0.36-1.22)	0.186	0.66 (0.44-1.01)	0.054	0.462
Plasma LA	0.94 (0.54-1.62)	0.813	0.63 (0.43-0.92)	0.016	0.339
Plasma other n-6 PUFAs	1.08 (0.73-1.61)	0.688	1.07 (0.83-1.38)	0.615	0.841
<input type="checkbox"/>	<b>Physical activity (MET-h/week)</b>				<input type="checkbox"/>
	<b>Below median (cases/N: 614/46898)</b>		<b>Above median (cases/N: 452/47044)</b>		<i>P</i> for interaction
<input type="checkbox"/>	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	
Plasma SFAs	2.03 (1.41-2.94)	<0.001	1.60 (1.04-2.45)	0.032	0.948
Plasma MUFAs	1.78 (1.05-3.00)	0.037	1.60 (0.89-2.87)	0.116	0.682
Plasma PUFAs	0.76 (0.47-1.22)	0.254	0.94 (0.54-1.63)	0.830	0.560
Plasma n-3 PUFAs	0.74 (0.55-0.98)	0.039	0.82 (0.59-1.15)	0.254	0.752
Plasma DHA	0.98 (0.67-1.44)	0.907	0.81 (0.51-1.30)	0.386	0.581
Plasma other n-3 PUFAs	0.82 (0.59-1.15)	0.248	0.94 (0.65-1.37)	0.754	0.944
Plasma n-6 PUFAs	0.69 (0.41-1.16)	0.163	0.60 (0.33-1.09)	0.095	0.821
Plasma LA	0.78 (0.49-1.23)	0.289	0.58 (0.34-1.00)	0.048	0.706
Plasma other n-6 PUFAs	1.17 (0.85-1.61)	0.350	0.75 (0.51-1.10)	0.135	0.200
<input type="checkbox"/>	<b>History of diabetes</b>				<input type="checkbox"/>
	<b>No (cases/N: 1150/109828)</b>		<b>Yes (cases/N: 244/6395)</b>		<i>P</i> for interaction
<input type="checkbox"/>	HR (95% CI)	<i>p</i> value	HR (95% CI)	<i>p</i> value	
Plasma SFAs	1.71 (1.31-2.25)	<0.001	2.64 (1.49-4.70)	<0.001	0.654

Plasma MUFAs	1.97 (1.35-2.86)	0.002	0.67 (0.29-1.54)	0.342	<0.001
Plasma PUFAs	0.78 (0.55-1.09)	0.145	0.64 (0.29-1.39)	0.259	0.005
Plasma n-3 PUFAs	0.87 (0.70-1.08)	0.204	0.50 (0.31-0.81)	0.004	0.259
Plasma DHA	0.90 (0.67-1.21)	0.475	0.96 (0.53-1.74)	0.881	0.634
Plasma other n-3 PUFAs	0.97 (0.76-1.24)	0.798	0.70 (0.41-1.21)	0.202	0.189
Plasma n-6 PUFAs	0.71 (0.49-1.03)	0.072	0.49 (0.21-1.13)	0.095	0.020
Plasma LA	0.74 (0.53-1.04)	0.080	0.85 (0.37-1.93)	0.692	0.011
Plasma other n-6 PUFAs	1.17 (0.92-1.50)	0.194	0.84 (0.51-1.38)	0.489	0.731
<input type="checkbox"/>	<b>History of hypertension</b>				<input type="checkbox"/>
	<b>No (cases/N: 365/49887)</b>		<b>Yes (cases/N: 1029/66336)</b>		<i>P</i> for interaction
<input type="checkbox"/>	HR (95% CI)	p value	HR (95% CI)	p value	<input type="checkbox"/>
Plasma SFAs	1.95 (1.23-3.09)	0.0044	1.86 (1.39-2.49)	<0.001	0.323
Plasma MUFAs	1.50 (0.80-2.81)	0.2032	1.91 (1.27-2.88)	0.002	0.545
Plasma PUFAs	0.74 (0.39-1.40)	0.3586	0.74 (0.52-1.07)	0.111	0.214
Plasma n-3 PUFAs	0.74 (0.50-1.10)	0.1362	0.82 (0.66-1.03)	0.088	0.763
Plasma DHA	1.00 (0.59-1.68)	0.9862	0.91 (0.67-1.23)	0.535	0.934
Plasma other n-3 PUFAs	0.90 (0.58-1.39)	0.6228	0.90 (0.70-1.17)	0.430	0.615
Plasma n-6 PUFAs	0.37 (0.19-0.70)	0.0025	0.90 (0.60-1.36)	0.626	0.065
Plasma LA	0.52 (0.29-0.94)	0.0303	0.88 (0.61-1.26)	0.479	0.015
Plasma other n-6 PUFAs	1.28 (0.84-1.96)	0.2454	1.02 (0.79-1.31)	0.897	0.116
<input type="checkbox"/>	<b>Household income</b>				<input type="checkbox"/>
	<b>Below median (cases/N: 705/47827)</b>		<b>Above median (cases/N: 689/68396)</b>		<i>P</i> for interaction
<input type="checkbox"/>	HR (95% CI)	p value	HR (95% CI)	p value	<input type="checkbox"/>
Plasma SFAs	1.66 (1.18-2.33)	0.003	2.06 (1.45-2.93)	<0.001	0.372
Plasma MUFAs	2.17 (1.30-3.60)	0.003	1.51 (0.95-2.42)	0.082	0.220
Plasma PUFAs	0.53 (0.34-0.84)	0.006	0.96 (0.62-1.49)	0.849	0.640

Plasma n-3 PUFAs	0.62 (0.47-0.81)	<0.001	1.04 (0.79-1.38)	0.774	0.044
Plasma DHA	0.91 (0.63-1.31)	0.603	0.93 (0.64-1.35)	0.687	0.203
Plasma other n-3 PUFAs	0.81 (0.59-1.11)	0.193	1.01 (0.74-1.39)	0.945	0.095
Plasma n-6 PUFAs	0.49 (0.30-0.79)	0.003	0.96 (0.59-1.56)	0.854	0.452
Plasma LA	0.69 (0.45-1.06)	0.093	0.77 (0.50-1.19)	0.232	0.983
Plasma other n-6 PUFAs	1.19 (0.88-1.60)	0.256	0.95 (0.70-1.29)	0.732	0.673

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*Abbreviations:* *FAs* fatty acids, *MUFA* monounsaturated fatty acid, *PUFA* polyunsaturated fatty acid, *SFA* saturated fatty acid, *NAFLD* non-alcoholic fatty liver disease, *DHA* docosahexaenoic acid, *LA* linoleic acid, *BMI* body mass index, *MET* metabolic equivalent of task.

**Supplemental Table 9.** The sensitivity analysis of plasma FAs and NAFLD risk

□	Quartiles of plasma fatty acids (% of total fatty acids)				□
	Q1	Q2	Q3	Q4	
<b>Further adjusted for lipid-lowering medications</b>					
Plasma SFA	1.00	1.36 (1.11-1.66)	1.48 (1.19-1.85)	1.85 (1.45-2.36)	<0.001
Plasma MUFA	1.00	1.43 (1.11-1.84)	1.63 (1.22-2.19)	1.73 (1.23-2.44)	0.007
Plasma PUFA	1.00	1.00 (0.83-1.19)	0.84 (0.66-1.06)	0.72 (0.53-0.99)	0.018
Plasma n-3 PUFA	1.00	0.92 (0.79-1.06)	0.87 (0.75-1.02)	0.79 (0.65-0.96)	0.017
Plasma DHA	1.00	0.98 (0.84-1.14)	0.87 (0.71-1.05)	0.92 (0.71-1.19)	0.279
Plasma non-DHA n-3 PUFA	1.00	0.95 (0.81-1.12)	0.89 (0.75-1.07)	0.90 (0.72-1.12)	0.275
Plasma n-6 PUFA	1.00	0.87 (0.73-1.04)	0.75 (0.58-0.97)	0.68 (0.48-0.95)	0.017
Plasma LA	1.00	0.88 (0.75-1.03)	0.77 (0.62-0.97)	0.73 (0.54-1.00)	0.024
Plasma non-LA n-6 PUFA	1.00	1.00 (0.86-1.17)	0.99 (0.83-1.17)	1.05 (0.85-1.31)	0.767
<b>Further adjusted for healthy diet score</b>					
Plasma SFA	1.00	1.36 (1.11-1.66)	1.48 (1.18-1.84)	1.83 (1.44-2.34)	<0.001
Plasma MUFA	1.00	1.43 (1.11-1.83)	1.63 (1.22-2.18)	1.73 (1.23-2.43)	0.007
Plasma PUFA	1.00	1.00 (0.83-1.19)	0.84 (0.66-1.07)	0.73 (0.53-1.00)	0.021
Plasma n-3 PUFA	1.00	0.93 (0.80-1.07)	0.89 (0.76-1.04)	0.81 (0.66-0.98)	0.032
Plasma DHA	1.00	0.98 (0.84-1.14)	0.87 (0.72-1.06)	0.92 (0.71-1.20)	0.307
Plasma non-DHA n-3 PUFA	1.00	0.96 (0.81-1.12)	0.90 (0.75-1.08)	0.91 (0.73-1.14)	0.330
Plasma n-6 PUFA	1.00	0.87 (0.73-1.04)	0.75 (0.58-0.97)	0.68 (0.48-0.96)	0.018
Plasma LA	1.00	0.87 (0.74-1.02)	0.77 (0.61-0.96)	0.73 (0.54-0.99)	0.022
Plasma non-LA n-6 PUFA	1.00	1.01 (0.87-1.17)	1.00 (0.84-1.18)	1.07 (0.86-1.33)	0.649
<b>Excluding the initial 2 years of follow-up</b>					
Plasma SFA	1.00	1.31 (1.06-1.63)	1.43 (1.13-1.81)	1.67 (1.29-2.18)	<0.001
Plasma MUFA	1.00	1.43 (1.10-1.87)	1.45 (1.06-1.98)	1.62 (1.12-2.34)	0.034

Plasma PUFA	1.00	0.98 (0.82-1.18)	0.83 (0.65-1.06)	0.73 (0.53-1.00)	0.023
Plasma n-3 PUFA	1.00	0.92 (0.78-1.08)	0.89 (0.75-1.06)	0.80 (0.65-0.99)	0.045
Plasma DHA	1.00	0.94 (0.79-1.10)	0.90 (0.73-1.11)	0.93 (0.70-1.23)	0.436
Plasma non-DHA n-3 PUFA	1.00	0.97 (0.82-1.15)	0.88 (0.72-1.06)	0.85 (0.67-1.09)	0.127
Plasma n-6 PUFA	1.00	0.89 (0.73-1.08)	0.77 (0.58-1.01)	0.70 (0.49-1.02)	0.046
Plasma LA	1.00	0.83 (0.70-0.99)	0.74 (0.58-0.94)	0.67 (0.48-0.93)	0.010
Plasma non-LA n-6 PUFA	1.00	1.01 (0.85-1.18)	0.96 (0.80-1.16)	1.03 (0.82-1.31)	0.946
<b>Further adjusted for hormone</b>					
Plasma SFA	1.00	1.36 (1.11-1.66)	1.48 (1.18-1.84)	1.82 (1.42-2.32)	<0.001
Plasma MUFA	1.00	1.44 (1.12-1.84)	1.65 (1.23-2.21)	1.76 (1.25-2.47)	0.006
Plasma PUFA	1.00	1.00 (0.83-1.19)	0.84 (0.66-1.07)	0.73 (0.53-0.99)	0.020
Plasma n-3 PUFA	1.00	0.92 (0.79-1.06)	0.87 (0.74-1.02)	0.78 (0.64-0.95)	0.013
Plasma DHA	1.00	0.97 (0.84-1.13)	0.86 (0.71-1.04)	0.91 (0.70-1.18)	0.235
Plasma non-DHA n-3 PUFA	1.00	0.96 (0.81-1.12)	0.90 (0.75-1.07)	0.90 (0.72-1.12)	0.266
Plasma n-6 PUFA	1.00	0.87 (0.73-1.04)	0.75 (0.58-0.97)	0.68 (0.48-0.96)	0.018
Plasma LA	1.00	0.87 (0.74-1.03)	0.77 (0.61-0.96)	0.73 (0.54-0.99)	0.022
Plasma non-LA n-6 PUFA	1.00	1.00 (0.86-1.17)	0.99 (0.83-1.17)	1.05 (0.85-1.31)	0.767
<b>Further adjusted for TDI</b>					
Plasma SFA	1.00	1.36 (1.11-1.66)	1.48 (1.19-1.85)	1.85 (1.45-2.36)	<0.001
Plasma MUFA	1.00	1.43 (1.11-1.83)	1.63 (1.22-2.19)	1.73 (1.23-2.43)	0.007
Plasma PUFA	1.00	1.00 (0.83-1.19)	0.84 (0.66-1.06)	0.72 (0.53-0.99)	0.018
Plasma n-3 PUFA	1.00	0.93 (0.80-1.07)	0.89 (0.76-1.04)	0.80 (0.66-0.98)	0.029
Plasma DHA	1.00	0.98 (0.84-1.14)	0.87 (0.72-1.06)	0.92 (0.71-1.20)	0.299
Plasma non-DHA n-3 PUFA	1.00	0.95 (0.81-1.12)	0.90 (0.75-1.08)	0.91 (0.73-1.14)	0.320
Plasma n-6 PUFA	1.00	0.87 (0.73-1.04)	0.75 (0.58-0.97)	0.68 (0.48-0.96)	0.018
Plasma LA	1.00	0.87 (0.74-1.02)	0.77 (0.61-0.96)	0.73 (0.54-0.99)	0.022

Plasma non-LA n-6 PUFA	1.00	1.01 (0.87-1.18)	1.00 (0.84-1.19)	1.07 (0.86-1.33)	0.636
<b>Excluding the adjustment for aspirin, vitamin and mineral use</b>					
Plasma SFA	1.00	1.36 (1.11-1.66)	1.48 (1.18-1.84)	1.85 (1.45-2.36)	<0.001
Plasma MUFA	1.00	1.43 (1.11-1.83)	1.63 (1.22-2.18)	1.73 (1.23-2.44)	0.007
Plasma PUFA	1.00	0.88 (0.73-1.07)	0.79 (0.59-1.06)	0.77 (0.52-1.16)	0.024
Plasma n-3 PUFA	1.00	0.93 (0.80-1.07)	0.89 (0.76-1.04)	0.81 (0.67-0.99)	0.037
Plasma DHA	1.00	0.98 (0.84-1.14)	0.87 (0.72-1.06)	0.93 (0.71-1.20)	0.320
Plasma non-DHA n-3 PUFA	1.00	0.96 (0.82-1.12)	0.91 (0.76-1.08)	0.92 (0.73-1.14)	0.355
Plasma n-6 PUFA	1.00	0.87 (0.73-1.04)	0.75 (0.58-0.97)	0.68 (0.48-0.96)	0.018
Plasma LA	1.00	0.87 (0.74-1.02)	0.77 (0.61-0.96)	0.73 (0.54-0.99)	0.022
Plasma non-LA n-6 PUFA	1.00	1.01 (0.87-1.18)	1.00 (0.84-1.19)	1.07 (0.87-1.33)	0.624
<b>Further adjusted for total energy intake</b>					
Plasma SFA	1.00	1.36 (1.11-1.66)	1.48 (1.19-1.85)	1.84 (1.44-2.36)	<0.001
Plasma MUFA	1.00	1.43 (1.11-1.83)	1.63 (1.22-2.19)	1.73 (1.23-2.44)	0.007
Plasma PUFA	1.00	0.88 (0.73-1.07)	0.79 (0.59-1.06)	0.77 (0.51-1.16)	0.019
Plasma n-3 PUFA	1.00	0.92 (0.80-1.07)	0.88 (0.75-1.03)	0.80 (0.66-0.97)	0.023
Plasma DHA	1.00	0.98 (0.84-1.14)	0.87 (0.72-1.05)	0.92 (0.71-1.19)	0.283
Plasma non-DHA n-3 PUFA	1.00	0.95 (0.81-1.12)	0.90 (0.75-1.07)	0.90 (0.72-1.13)	0.297
Plasma n-6 PUFA	1.00	0.87 (0.73-1.04)	0.75 (0.58-0.97)	0.68 (0.48-0.96)	0.018
Plasma LA	1.00	0.87 (0.74-1.02)	0.77 (0.61-0.96)	0.73 (0.54-0.99)	0.022
Plasma non-LA n-6 PUFA	1.00	1.01 (0.87-1.18)	1.00 (0.84-1.19)	1.08 (0.87-1.33)	0.613

Abbreviations: *FAs* fatty acids, MUFA monounsaturated fatty acid, PUFA polyunsaturated fatty acid, SFA saturated fatty acid, NAFLD non-alcoholic fatty liver disease, DHA docosahexaenoic acid, LA linoleic acid, BMI body mass index, TDI Townsend deprivation index.