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Supplementary material

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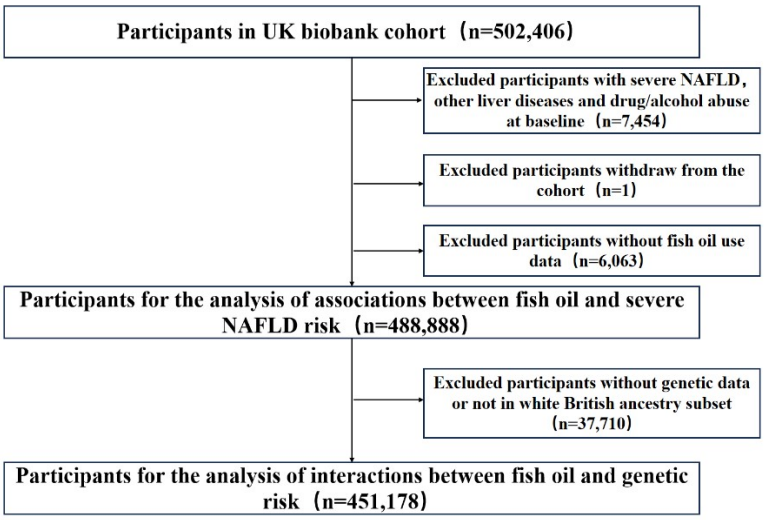
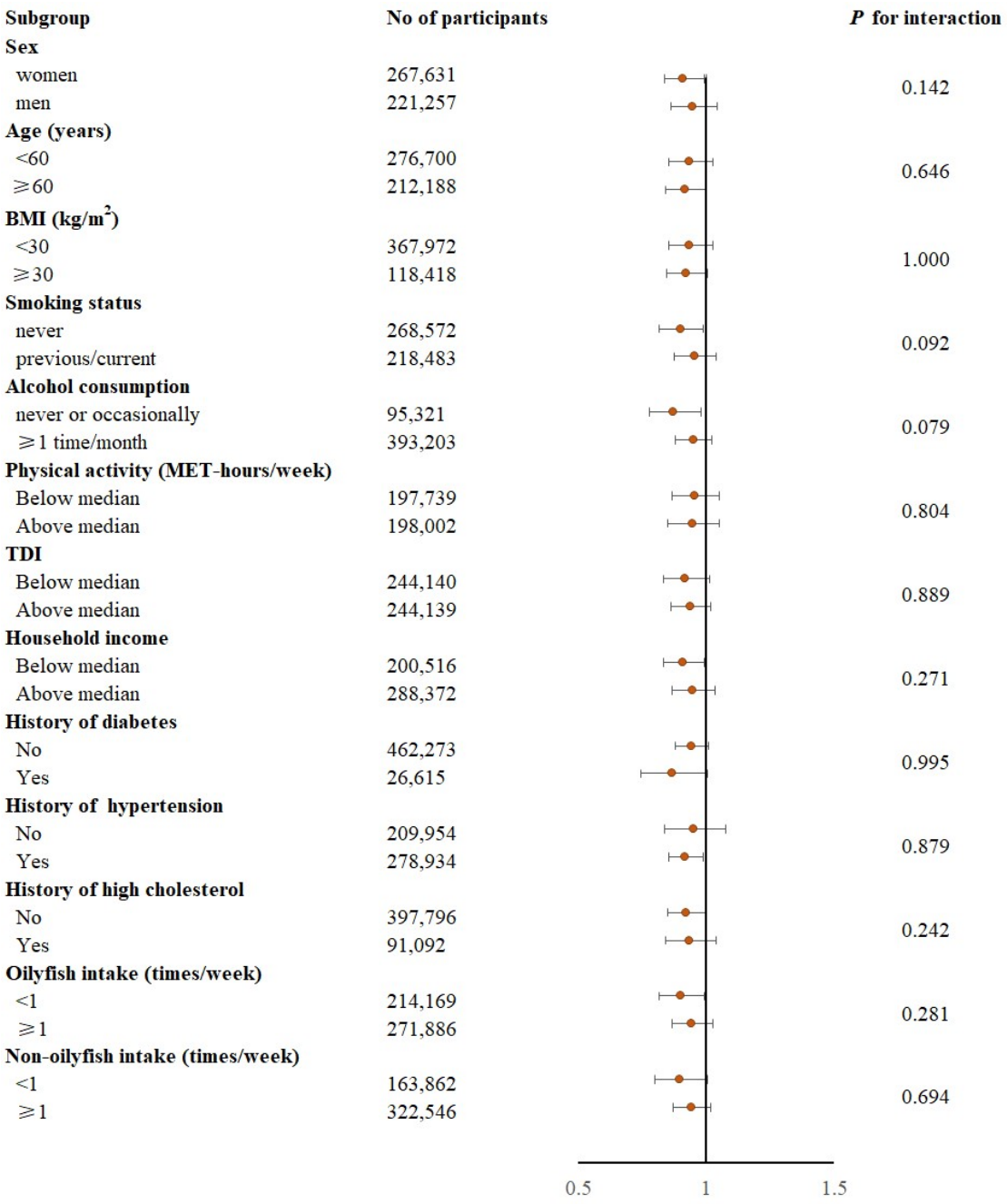


Supplementary Figure 1 The flow chart of the analysis.



Supplementary Figure 2 Subgroup analyses for the association between fish oil supplementation and the risk of severe NAFLD stratified by potential risk factors. HR, hazard ratio; CI, confidence interval; BMI, body mass index; MET, metabolic equivalent of task; TDI, Townsend deprivation index. Forest plots show the multivariable HRs of severe NAFLD associated with fish oil use in subgroups. HRs were adjusted for age, sex, race, assessment centers, education, TDI, household income, smoking status, alcohol consumption, physical activity, aspirin use, vitamin supplementation use, mineral supplementation use, BMI, history of hypertension, history of cardiovascular disease, history of high cholesterol, history of diabetes, history of cancer, and healthy diet score.

Supplemental Table 1 Spearman correlations between fish oil supplement use assessed at baseline and in follow-up surveys.

□	Baseline	First repeat assessment (2012-2013)	Second repeat assessment (2014 and later)
No. of participants	488,888	19,637	54,322
Baseline	1.00	0.61	0.46
First repeat assessment (2012-2013)		1.00	0.61
Second repeat assessment (2014 and later)			1.00

The Spearman method was used to calculate correlation coefficients among baseline fish oil supplement use and two repeated assessments （2012 to 2013 and 2014 and later）fish oil supplement use.

Supplementary Table 2 Single-nucleotide polymorphisms associated with circulating individual n-3 PUFA.

FA	SNP	Nearby Gene	Chr	EA	NEA	% Variance Explained	Association with FA Levels		
							Beta *	SE	*P*
ALA	rs174547	FADS1	11	C	T	1	0.02	0.001	3.5×10^{-64}
EPA	rs3798713	ELOVL2	6	C	G	0.4	0.04	0.005	1.9×10^{-12}
	rs174538	FADS1/C11orf10	11	G	A	0.7	0.08	0.005	5.4×10^{-58}
DPA	rs780094	GCKR	2	T	C	0.5	0.02	0.003	9.0×10^{-9}
	rs3734398	ELOVL2	6	C	T	2.7	0.04	0.003	9.7×10^{-43}
	rs174547	FADS1	11	T	C	8.4	0.08	0.003	3.8×10^{-154}
DHA	rs2236212	ELOVL2	6	G	C	0.7	0.11	0.014	1.3×10^{-15}

FA, fatty acid; SNP, single–nucleotide polymorphisms; Chr, chromosome; EA, effect allele; NEA, none-effect allele; SE, standard error; ALA, α-linolenic acid; EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid. * The beta coefficients represent the change in percentage of total plasma fatty acid levels for each additional effect allele.

Supplementary Table 3 Mediating effects of biomarkers on the association of fish oil supplementation with risk of severe NAFLD in the UK Biobank study.

Mediators	n	Total	Direct	Proportion mediated	*P* value
CRP*	459,847	0.92 (0.86-0.98)	0.93 (0.87-0.99)	8.8% (3.6%-20.0%）	<0.001
TG	460,475	0.92 (0.87-0.99)	0.92 (0.86-0.98)	/	/
TC	460,835	0.93 (0.87-0.99)	0.93 (0.87-0.99)	/	/
HDL-C	421,844	0.93 (0.87-1.00)	0.94 (0.87-1.00)	7.5% (2.7%-19.6%)	<0.001
Blood glucose	421,536	0.93 (0.87-0.99)	0.93 (0.87-0.99)	/	/
LDL-C	459,975	0.93 (0.87-0.99)	0.92 (0.87-0.99)	/	/
HbA1c	457,831	0.94 (0.88-1.00)	0.94 (0.88-1.00)	2.2% (0.6%-8.3%)	0.015
Cystatin C	460,805	0.93 (0.87-0.99)	0.93 (0.88-1.00)	10.0% (3.8%-23.7%)	<0.001
Creatinine	460,604	0.93 (0.87-0.99)	0.92 (0.87-0.99)	/	/
ApoA	419,557	0.93 (0.87-0.99)	0.93 (0.87-0.99)	3.0% (1.0%-8.5%)	<0.001
ApoB	458,521	0.92 (0.86-0.98)	0.92 (0.86-0.98)	/	/

CRP, C-reactive protein; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; HbA1c, glycosylated hemoglobin; ApoA, apolipoprotein A; ApoB, apolipoprotein B

*CRP was log transformed due to right distribution.

Supplementary Table 4 Interactions between fish oil and both the number of n-3 PUFA-associated alleles and individual n-3 PUFA-associated SNPs for NAFLD.

	Number of alleles/SNP			fish oil			Number of alleles/SNP×fish oil		
	β	SE	*P*	β	SE	*P*	β	SE	*P*
N-3 PUFA -associated alleles[a]	0.022	0.014	0.107	-0.031	0.185	0.866	-0.006	0.026	0.831
EPA-associated alleles[b]	-0.023	0.017	0.172	-0.083	0.078	0.288	0.006	0.032	0.854
DPA-associated alleles[c]	0.021	0.014	0.126	-0.082	0.083	0.323	0.004	0.026	0.873
DHA-associated allele[d]	0.004	0.024	0.860	-0.038	0.061	0.527	-0.028	0.044	0.529
rs174547_C	0.046	0.024	0.057	-0.062	0.047	0.186	-0.012	0.046	0.790
rs3798713_C	-0.002	0.024	0.928	-0.087	0.051	0.087	0.019	0.044	0.667
rs174538_G	-0.047	0.025	0.057	-0.058	0.071	0.416	-0.009	0.046	0.844
rs780094_T	0.112	0.024	<0.001	-0.047	0.049	0.343	-0.028	0.044	0.521
rs3734398_C	-0.004	0.024	0.850	-0.094	0.051	0.062	0.028	0.044	0.525

[a] n-3 PUFA-associated allele: rs174547_C+rs3798713_C+rs174538_G+rs780094_T+rs3734398_C+rs174547_T+rs2236212_G.
[b] EPA-associated alleles: rs3798713_C+rs174538_G.
[c] DPA-associated alleles: rs780094_T+rs3734398_C+rs174547_T.
[d] DHA-associated allele: rs2236212_G

Supplementary Table 5 Sensitivity analyses for the HRs (95% CIs) of severe NAFLD according to fish oil supplement use.

	Fish oil non-users	Fish oil users	*P* values
Further adjusting for oily fish and non-oily fish intake			
Number of participants	334,991	153,897	
Number of case (%)	4,030 (1.2)	1,641 (1.1)	
Multivariable-adjusted HR (95% CI)	1[Reference]	0.93 (0.87-0.99)	0.022
Further adjusting for lipid-lowering medicine			
Number of participants	334,991	153,897	
Number of case (%)	4,030 (1.2)	1,641 (1.1)	
Multivariable-adjusted HR (95% CI)	1[Reference]	0.93 (0.87-0.99)	0.020
Further adjusting for anti-hypertension medicine			
Number of participants	334,991	153,897	
Number of case (%)	4,030 (1.2)	1,641 (1.1)	
Multivariable-adjusted HR (95% CI)	1[Reference]	0.93 (0.87-0.99)	0.021
Excluding case within first 2 years			
Number of participants	334,791	153,814	
Number of case (%)	3,330 (1.1)	1,558 (1.0)	
Multivariable-adjusted HR (95% CI)	1[Reference]	0.92 (0.87-0.99)	0.017
Excluding participants with extreme BMI (<18.5 or >40, kg/m^2)			
Number of participants	326,194	150,880	
Number of case (%)	3,671 (1.1)	1,532 (1.0)	
Multivariable-adjusted HR (95% CI)	1[Reference]	0.93 (0.87-0.99)	0.031
Further adjusting for other major food groups			
Number of participants	334,991	153,897	
Number of case (%)	4,030 (1.2)	1,641 (1.1)	

Multivariable-adjusted HR (95% CI)	1[Reference]	0.93 (0.88-0.99)	0.030

HR, hazard ratio; CI, confidence interval.
HR were estimated from Cox proportional hazards models adjusted for age, sex, race (White, non-White, or other ethnic group), assessment centers (22 categories), education (college or university degree, vocational qualifications, optional national exams at ages 17–18 years, national exams at age 16 years, others, or missing), Townsend deprivation index (quartiles), 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), aspirin use (yes, no), vitamin use (yes, no), mineral use (yes, no), BMI (in kg/m^2; <18.5, 18.5 to 25, 25 to 30, 30 to 35, ≥35, or missing), history of hypertension (yes, no), history of cardiovascular disease (yes, no), history of high cholesterol (yes, no), history of diabetes (yes, no) and history of cancer (yes, no), healthy diet score (quintiles).