Associations of habitual fish oil supplementation with cardiovascular outcomes and all cause mortality: evidence from a large population based cohort study

Zhi-Hao Li,[1] Wen-Fang Zhong,[1] Simin Liu,[2] Virginia Byers Kraus,[3] Yu-Jie Zhang,[1] Xiang Gao,[4] Yue-Bin Lv,[5] Dong Shen,[1] Xi-Ru Zhang,[1] Pei-Dong Zhang,[1] Qing-Mei Huang,[1] Qing Chen,[1] Xian-Bo Wu,[1] Xiao-Ming Shi,[5] Dong Wang,[6] Chen Mao[1]

[1]Department of Epidemiology, School of Public Health, Southern Medical University, Guangzhou, Guangdong, China

[2]Departments of Epidemiology, Medicine, and Surgery, and Center for Global Cardiometabolic Health, Brown University, Providence, RI, USA

[3]Duke Molecular Physiology Institute and Division of Rheumatology, Department of Medicine, Duke University School of Medicine, Durham, NC, USA

[4]Department of Nutritional Sciences, Pennsylvania State University, University Park, PA, USA

[5]National Institute of Environmental Health, Chinese Centre for Disease Control and Prevention, Beijing, China

[6]School of Health Services Management, Southern Medical University, Guangzhou, Guangdong, China

Correspondence to: C Mao
maochen9@smu.edu.cn

(ORCID 0000-0002-6537-6215)

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ABSTRACT

OBJECTIVES

To evaluate the associations of habitual fish oil supplementation with cardiovascular disease (CVD) and mortality in a large prospective cohort.

DESIGN

Population based, prospective cohort study.

SETTING

UK Biobank.

PARTICIPANTS

A total of 427 678 men and women aged between 40 and 69 who had no CVD or cancer at baseline were enrolled between 2006 and 2010 and followed up to the end of 2018.

MAIN EXPOSURE

All participants answered questions on the habitual use of supplements, including fish oil.

MAIN OUTCOME MEASURES

All cause mortality, CVD mortality, and CVD events.

RESULTS

At baseline, 133 438 (31.2%) of the 427 678 participants reported habitual use of fish oil supplements. The multivariable adjusted hazard ratios for habitual users of fish oil versus non-users were 0.87 (95% confidence interval 0.83 to 0.90) for all cause mortality, 0.84 (0.78 to 0.91) for CVD mortality, and 0.93 (0.90 to 0.96) for incident CVD events. For CVD events, the association seemed to be stronger among those with prevalent hypertension (P for interaction=0.005).

CONCLUSIONS

Habitual use of fish oil seems to be associated with a lower risk of all cause and CVD mortality and to provide a marginal benefit against CVD events among the general population.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Fish oil supplementation is common in the UK and other developed countries

A recent meta-analysis of 13 randomised controlled trials showed a significant marginal protective effect of omega 3 fatty acid supplementation against cardiovascular disease (CVD); however, the performance of fish oil supplements in randomised controlled trials was assessed under ideal and controlled circumstances, making it difficult to generalise the findings to larger, more inclusive populations

Complementary information on the effectiveness of fish oil supplements is needed through evaluation in real life settings of large scale cohort studies

WHAT THIS STUDY ADDS

Habitual fish oil supplementation is associated with a 13% lower risk of all cause mortality, a 16% lower risk of CVD mortality, and a 7% lower risk of CVD events among the general population

These findings indicate that habitual fish oil supplementation could have a marginal benefit for CVD outcomes, but further studies are needed to examine how the dose of fish oil supplements affects its clinically meaningful effectiveness

Introduction

Fish oil is a rich source of long chain omega 3 fatty acids, a group of polyunsaturated fats that primarily include eicosapentaenoic acid and docosahexaenoic acid.[1] Initially, these compounds were recommended for daily omega 3 fatty acid supplementation for the prevention of cardiovascular disease (CVD).[2 3] Consequently, the use of fish oil supplements is widespread in the United Kingdom and other developed countries.[4-6]

Although there have been marked advances in recent years in our understanding of the role of omega 3 fatty acids in the prevention of CVD events, clear gaps in knowledge remain,[7-10] and studies have generated conflicting findings. Data from laboratory studies,[11-13] epidemiological investigations,[14 15] and randomised controlled trials[7 11] indicate that omega 3 fatty acids do have a role in the prevention of CVD. In contrast, several trials and recent meta-analyses have shown that supplementation with omega 3 fatty acids has no benefit in the prevention of CVD.[16-18]

More recently, the large VITAL (Vitamin D and Omega-3 Trial) randomised controlled trial,[16] which included 25 871 participants with a median of five years of follow-up, found that supplementation with omega 3 fatty acids was associated with a significant reduction in the risk of myocardial infarction, but no association with the risk of all CVD events was found (hazard ratio 0.92, 95% confidence interval 0.80 to 1.06). The protective effect of omega 3 fatty acids against CVD events could be negligible, or it could simply be weak.[7] Thus inadequate sample sizes might have limited not only the power of prior randomised controlled trials to detect the clinical effects of omega 3 fatty acids, but also the ability to explore potential modifying factors that could affect the associations between fish oil supplementation and clinical outcomes. In addition, the performance of fish oil supplements in randomised controlled trials is assessed under ideal and controlled circumstances. Although randomised controlled trials generate the best evidence for the effects of interventions, their findings are difficult to generalise to larger, more

inclusive populations because of their well known limitations.[19] Therefore, complementary information on the effectiveness of fish oil supplements is needed through evaluation in real life settings of large scale cohort studies.

In view of the uncertainty,[7] a large scale cohort study could provide the necessary complementary information on the associations between fish oil supplements and clinical outcomes. We used population based cohort data from nearly half a million adults in the UK Biobank study to investigate the associations of habitual use of fish oils with the risk of certain outcomes (the incidence of, and mortality from, CVD as well as all cause mortality) and to explore modifying factors that might affect these associations.

Methods

Study setting and participants

The UK Biobank study design and population have been reported in detail previously.[20 21] Briefly, between 2006 and 2010, the study recruited 502 536 participants, aged 40-69, from the general population at 22 assessment centres across England, Scotland, and Wales. Participants completed a touch screen questionnaire and a face to face interview, and provided biological samples; a series of physical measurements were also taken. Participants with incomplete data on the use of fish oil (n=6160), those with CVD (n=32 493) or cancer (n=34 906) at baseline, and those who subsequently withdrew from the study (n=1299) were excluded from the analysis. In total, our analysis included 427 678 participants (supplementary fig 1S).

Ascertainment of exposure

At baseline, the habitual use of fish oil supplements was recorded using an electronic questionnaire. Participants were asked, "Do you regularly take any of the following?" and could select their answer from a list of supplements, including fish oil supplements. We scored habitual use of fish oil supplements as "1=yes" or "0=no."

Ascertainment of outcomes

The primary outcomes of the study were the incidence of, and mortality from, CVD, and mortality from all causes. The secondary outcomes were the incidence of, and mortality from, myocardial infarction and stroke. The date and cause of death were identified by linking to death registries of the National Health Service (NHS) Information Centre for participants from England and Wales and the NHS Central Register Scotland for participants from Scotland.[20] Additionally, the date and cause of hospital admissions were identified by linking to the Scottish Morbidity Records for participants from Scotland and health episode statistics for participants from England and Wales.[20] Detailed information on the linkage procedures can be found at http://content.digital.nhs.uk/services. At the time of analysis, mortality data were available up to 14 February 2018 for England and Wales and 1 January 2017 for Scotland. Therefore, for the analyses of mortality, we censored follow-up at this date or the date of death, whichever occurred first. Hospital admission data were available for participants until 14 March 2017. Therefore, for incident CVD events, we used this date as the end of follow-up unless death or admission occurred first. We defined incident CVD events as a hospital admission or death with the following ICD-10 (International Classification of Diseases, 10th revision) codes on the hospital or death records: CVD codes I20-I25 and I60-I64, myocardial infarction codes I21, I22, I23, I24.1, or I25.2, stroke codes I60-I64, and CVD death codes I00-I99.

Ascertainment of covariates

We used the baseline questionnaire to assess several possible confounding variables: sociodemographic factors (age, sex, assessment centre, ethnicity, and household income), socioeconomic status (Townsend Deprivation Index), lifestyle habits (smoking status, alcohol consumption, body mass index (BMI), physical activity, dietary intake (vegetables, fruit, and oily fish)), comorbidities (hypertension, diabetes, and longstanding illness), drug use (antihypertensive drugs, insulin, statins, and aspirin), vitamin supplementation (vitamin A, vitamin B, vitamin C, vitamin D, vitamin E, multivitamin, or folic acid), and mineral and other dietary supplementation (calcium, iron, zinc, or selenium). The Townsend Deprivation Index, used as an indicator of socioeconomic status, is derived from the residential postcode and is provided directly from the UK Biobank.[22 23] Information on medical history (diabetes and longstanding illness) was collected by self-report at baseline. BMI was calculated as the weight in kilograms (kg) divided by the square of the height in metres (m^2). According to healthy physical activity recommendations,[24] we categorised participants into two groups based on the total time spent in moderate physical activity in minutes each week: less than 150 minutes or 150 minutes or more per week. Prevalent hypertension was defined as a self-reported history of hypertension, the use of antihypertensive drugs, a systolic blood pressure of 140 mm Hg or higher, or a diastolic blood pressure of 90 mm Hg or higher. Details of these assessments can be found on the UK Biobank website (www.ukbiobank.ac.uk).

Statistical analyses

Baseline characteristics are presented as the number (percentage) for categorical variables and the mean (standard deviation) for continuous variables. We used *t* tests or χ^2 tests to examine participant characteristics according to whether participants were users or non-users of fish oil supplements at baseline. To minimise the potential for inferential bias and to maximise the statistical power possible if participants with missing covariate data were excluded from the analyses, we used multiple imputation with chained equations to assign any missing covariate values.[25] Detailed information on the number of missing covariates is shown in supplementary table 1S. The associations

between habitual fish oil supplementation and outcomes (deaths from all causes, CVD, myocardial infarction, or stroke; incidence of CVD, myocardial infarction, or stroke) were explored using Cox proportional hazard models. The proportional hazard assumption was evaluated by tests based on Schoenfeld residuals[26]; no violation of this assumption was seen in our analyses. Two sets of models were used. The basic model (model 1) was adjusted for baseline age (years) and sex (male or female). The multivariable model (model 2) was adjusted for additional variables, including the Townsend Deprivation Index, ethnicity (white, black, Asian (Indian, Pakistani, Bangladeshi, or any other Asian background except Chinese), Chinese, mixed, or other ethnic group), assessment centre (22 categories), household income (<£18 000 (€21 489; $23 253), £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, or >£100 000), BMI, fruit consumption (<2.0, 2.0-3.9, or ≥4.0 servings/day), vegetable consumption (<2.0, 2.0-3.9, or ≥4.0 servings/day), oily fish consumption (<2 or ≥2 times/week), smoking status (never, former, or current), alcohol consumption (never, 1-2, 3-4, or ≥5 times/week), physical activity (<150 or ≥150 min/week), diabetes (yes or no), hypertension (yes or no), longstanding illness (yes or no), antihypertensive drug use (yes or no), statin use (yes or no), insulin treatment (yes or no), aspirin use (yes or no), vitamin supplementation (yes or no), and mineral and other dietary supplementation (yes or no).

We performed a stratified analysis to estimate potential modification effects according to sex (male or female), age (<60 or ≥60 years), obesity (yes (BMI ≥30) or no (BMI <30)), oily fish consumption (<2 or ≥2 times/week), physical activity (<150 or ≥150 min/week), current smoking (yes or no), diabetes (yes or no), hypertension (yes or no), statin use (yes or no), and aspirin use (yes or no). We assessed potential modifying effects by modelling the cross product term of the stratifying variable with fish oil supplement use. Furthermore, to test the robustness of the results, we performed several sensitivity analyses. Firstly, because participants who take fish oil could be more likely to use other supplements than those who do not take fish oil, we conducted a sensitivity analysis by excluding participants who took any other supplements. Secondly, to minimise the influence of reverse causation, we conducted a sensitivity analysis by excluding participants who developed CVD events or died during the first two years of follow-up. Moreover, we restricted the analyses to participants with no missing covariate data.

We performed all analyses using R software version 3.6.0 (R Development Core Team, Vienna, Austria). We considered a P value less than 0.05 (two sided) to be statistically significant.

Patient and public involvement

No patients were involved in setting the research question or the outcome measures, or in developing plans for design or implementation of the study. No patients were asked to advise on interpretation or writing up of results.

Results

Baseline characteristics

Table 1 shows the baseline characteristics of the study participants stratified by fish oil supplementation status (users versus non-users). Of the 427 678 participants, 235 438 (55.1%) were female, with a mean age of 55.9 years. Overall, 133 438 (31.2%) of the 427 678 participants reported habitual fish oil supplementation at baseline. Compared with non-users, fish oil users were older and were more likely to be female, not current smokers, and physically active. In addition, they ate oily fish more frequently and had a higher prevalence of hypertension and longstanding illness, but a lower prevalence of diabetes. Fish oil users were also more likely than non-users to take antihypertensive drugs, aspirin, vitamin supplements, and mineral and other dietary supplements.

Fish oil use and outcomes

The median times to follow-up were 9.0 years (interquartile range 8.3-9.7) for mortality outcomes and 8.1 years (7.4-8.8) for CVD events. During the follow-up period, the following deaths and events were recorded: 12 928 all cause deaths (including 3282 deaths from CVD, 1423 from myocardial infarction, 664 from stroke), and 18 297 incident CVD events, 7754 myocardial infarctions, and 4009 strokes. Table 2 shows the associations of habitual use of fish oil with the outcomes. In the analyses, adjusted for age and sex, we found significant inverse associations of fish oil use with the risk of all cause mortality, and the incidence of, and mortality from, CVD events, myocardial infarction and stroke (all P<0.05). In the multivariable adjusted models (model 2), the adjusted hazard ratios associated with fish oil use were 0.87 (95% confidence interval 0.83 to 0.90) for all cause mortality; 0.84 (0.78 to 0.91) for CVD mortality; 0.80 (0.70 to 0.91) for myocardial infarction mortality; 0.93 (0.90 to 0.96) for CVD; 0.92 (0.88 to 0.96) for myocardial infarction; and 0.90 (0.84 to 0.97) for stroke. However, no significant association between fish oil use and death from stroke was found (hazard ratio 0.87; 95% confidence interval 0.73 to 1.04; P=0.14).

Subgroup and sensitivity analyses

We conducted stratified analyses according to potential risk factors (fig 1 and fig 2). For all cause mortality. The associations between use of fish oil and the risk of all cause mortality were stronger among men (P for interaction=0.010) and current smokers (P for interaction=0.009; fig 1). For CVD events, the associations were stronger among participants with prevalent hypertension (P for interaction=0.005; fig 2). No other significant interactions were found (all P for interaction ≥0.05;fig 1 and fig 2). Sensitivity analyses showed no substantial change when we excluded participants who developed health events during the first two years of follow-up (supplementary table 2S),

Table 1 | Baseline characteristics of the study participants stratified by fish oil use. Values are numbers (percentages) unless stated otherwise

Characteristics	Overall (n=427 678)	Fish oil non-users (n=294 240)	Fish oil users (n=133 438)	P value
Mean (SD) age (years)	55.9 (8.1)	54.9 (8.2)	58.2 (7.5)	<0.001
Female	235 438 (55.1)	158 662 (53.9)	76 776 (57.5)	<0.001
Mean (SD) Townsend Deprivation Index	−1.35 (3.06)	−1.26 (3.11)	−1.56 (2.95)	<0.001
Ethnicity				
White	392 958 (91.9)	269 605 (91.6)	123 353 (92.4)	<0.001
Asian	19 481 (4.6)	14 046 (4.8)	5435 (4.1)	
Black	7177 (1.7)	4859 (1.7)	2318 (1.7)	
Chinese	1440 (0.3)	957 (0.3)	483 (0.4)	
Mixed	2621 (0.6)	1829 (0.6)	792 (0.6)	
Others	4001 (0.9)	2944 (1.0)	1057 (0.8)	
Household income (£)				
<18 000*	92 686 (21.7)	61 180 (20.8)	31 506 (23.6)	<0.001
18 000-30 999	108 753 (25.4)	70 982 (24.1)	37 771 (28.3)	
31 000-51 999	113 525 (26.5)	79 134 (26.9)	34 391 (25.8)	
52 000-100 000	89 068 (20.8)	65 022 (22.1)	24 046 (18.0)	
>100 000	23 646 (5.5)	17 922 (6.1)	5724 (4.3)	
Mean (SD) body mass index	27.31 (4.75)	27.42 (4.84)	27.07 (4.52)	<0.001
Fruit consumption (servings/day)				
<2.0	152 429 (35.6)	114 609 (39.0)	37 820 (28.3)	<0.001
2.0-3.9	206 788 (48.4)	137 060 (46.6)	69 728 (52.3)	
≥4.0	68 461 (16.0)	42 571 (14.5)	25 890 (19.4)	
Vegetable consumption (servings/day)				
<2.0	148 868 (34.8)	108 102 (36.7)	40 766 (30.6)	<0.001
2.0-3.9	220 068 (51.5)	147 636 (50.2)	72 432 (54.3)	
≥4.0	58 742 (13.7)	38 502 (13.1)	20 240 (15.2)	
Oily fish consumption (times/week)				
<2	191 926 (44.9)	143 119 (48.6)	48 807 (36.6)	<0.001
≥2	235 752 (55.1)	151 121 (51.4)	84 631 (63.4)	
Smoking status				
Never	240 251 (56.2)	166 672 (56.6)	73 579 (55.1)	<0.001
Former	142 810 (33.4)	93 819 (31.9)	48 991 (36.7)	
Current	44 617 (10.4)	33 749 (11.5)	10 868 (8.1)	
Alcohol consumption (times/week)				
Never	128 881 (30.1)	90 588 (30.8)	38 293 (28.7)	<0.001
1-2	111 320 (26.0)	76 441 (26.0)	34 879 (26.1)	
3-4	100 322 (23.5)	67 953 (23.1)	32 369 (24.3)	
≥5	87 155 (20.4)	59 258 (20.1)	27 897 (20.9)	
Physical activity (min/week)				
<150	195 246 (45.7)	139 769 (47.5)	55 477 (41.6)	<0.001
≥150	232 432 (54.3)	154 471 (52.5)	77 961 (58.4)	
Diabetes	18 894 (4.4)	13 480 (4.6)	5414 (4.1)	<0.001
Hypertension	230 974 (54.0)	154 366 (52.5)	76 608 (57.4)	<0.001
Longstanding illness	122 579 (28.7)	83 483 (28.4)	39 096 (29.3)	<0.001
Antihypertensive drug use	43 069 (10.1)	28 511 (9.7)	14 558 (10.9)	<0.001
Statin use	40 990 (9.6)	26 651 (9.1)	14 339 (10.7)	<0.001
Insulin treatment	687 (0.2)	532 (0.2)	155 (0.1)	<0.001
Aspirin use	42 550 (9.9)	25 920 (8.8)	16 630 (12.5)	<0.001
Vitamin supplementation	135 308 (31.6)	59 868 (20.3)	75 440 (56.5)	<0.001
Mineral and other dietary supplementation	119 822 (28.0)	52 325 (17.8)	67 497 (50.6)	<0.001

*£18 000=€21 489; $23 253.

used any other supplements (supplementary table 3S), or those for whom covariate data were missing (supplementary table 4S).

Discussion

In our study involving nearly half a million individuals from the UK, habitual fish oil supplementation was associated with a significantly lower all cause mortality and incidence of, and mortality from, CVD and myocardial infarction. These associations were independent of risk factors, including sex, age, Townsend Deprivation Index, ethnicity, household income, BMI, fruit consumption, vegetable consumption, oily fish consumption, smoking status, alcohol consumption, physical activity, major comorbidities, drug use, and other confounding factors. Furthermore, the protective association of fish oil use against CVD events was somewhat stronger in those with prevalent hypertension. In our study, 133 438 (31.2%) of the 427 678 participants reported habitual use of fish oil supplements. Similarly, the Norfolk-based European Prospective Investigation into Cancer and Nutrition reported that 33% of the participants took fish oil

Table 2 | Associations of use of fish oil supplements with the risk of cardiovascular outcomes and all cause mortality. Values are numbers (percentages) unless stated otherwise

Outcomes	Fish oil non-users (n=294 240)	Fish oil users (n=133 438)	Model 1*		Model 2†	
			HR (95% CI)	P value	HR (95% CI)	P value
All cause mortality	8781 (3.0)	4147 (3.1)	0.83 (0.80 to 0.86)	<0.001	0.87 (0.83 to 0.90)	<0.001
Cardiovascular mortality	2274 (0.8)	1008 (0.8)	0.77 (0.72 to 0.83)	<0.001	0.84 (0.78 to 0.91)	<0.001
Myocardial infarction mortality	1017 (0.3)	406 (0.3)	0.73 (0.65 to 0.81)	<0.001	0.80 (0.70 to 0.91)	<0.001
Stroke mortality	441 (0.2)	223 (0.2)	0.83 (0.71 to 0.98)	0.03	0.87 (0.73 to 1.04)	0.14
Cardiovascular events	12 388 (4.2)	5909 (4.4)	0.88 (0.85 to 0.91)	<0.001	0.93 (0.90 to 0.96)	<0.001
Myocardial infarction	5306 (1.8)	2448 (1.8)	0.86 (0.82 to 0.90)	<0.001	0.92 (0.88 to 0.96)	<0.001
Stroke	2680 (0.9)	1329 (1.0)	0.88 (0.82 to 0.94)	<0.001	0.90 (0.84 to 0.97)	0.01

HR=hazard ratio.
*Model 1: adjusted for age and sex.
†Model 2: included model 1 variables and additionally the Townsend Deprivation Index, assessment centre (22 categories), ethnicity (white, black, Asian, Chinese, mixed, or other ethnic group), household income (<£18 000 (€21 489; $23 253), £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, or >£100 000), body mass index, fruit consumption (<2.0, 2.0-3.9, or ≥4.0 servings/day), vegetable consumption (<2.0, 2.0-3.9, or ≥4.0 servings/day), oily fish consumption (<2 or ≥2 times/week), smoking status (never, former, or current), alcohol consumption (never, 1-2, 3-4, or ≥5 times/week), physical activity (<150 or ≥150 min/week), diabetes (yes or no), hypertension (yes or no), longstanding illness (yes or no), antihypertensive drug use (yes or no), statin use (yes or no), insulin treatment use (yes or no), aspirin use (yes or no), vitamin supplementation (yes or no), and mineral and other dietary supplementation (yes or no).

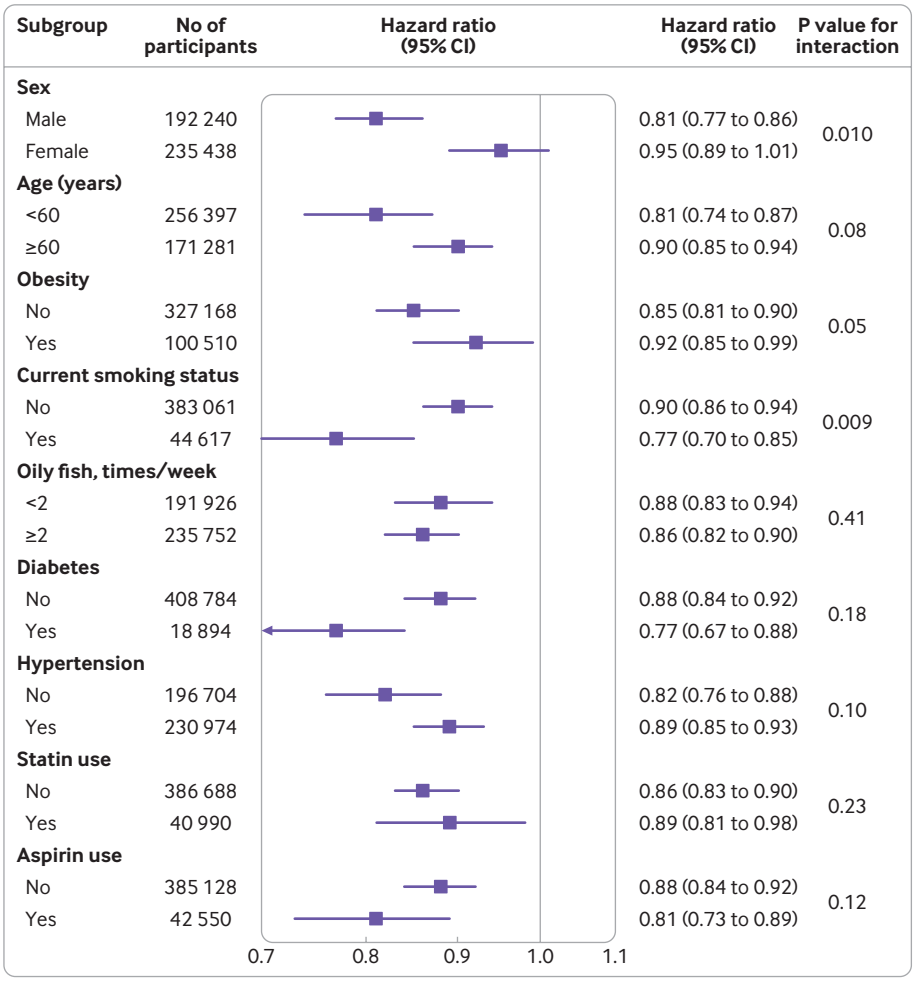

Fig 1 | Association of fish oil supplement use and the risk of all cause mortality stratified by potential risk factors. Results were adjusted for age, sex, Townsend Deprivation Index, assessment centre (22 categories), ethnicity (white, black, Asian, Chinese, mixed, or other ethnic group), household income (‹£18 000 (€21 489; $23 253), £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, or ›£100 000), body mass index, fruit consumption (‹2.0, 2.0-3.9, or ≥4.0 servings/day), vegetable consumption (‹2.0, 2.0-3.9, or ≥4.0 servings/day), oily fish consumption (‹2 or ≥2 times/week), smoking status (never, former, or current), alcohol consumption (never, 1-2, 3-4, or ≥5 times/week), physical activity (‹150 or ≥150 min/week), diabetes (yes or no), hypertension (yes or no), longstanding illness (yes or no), antihypertensive drug use (yes or no), statin use (yes or no), insulin treatment use (yes or no), aspirin use (yes or no), vitamin supplementation (yes or no), and mineral and other dietary supplementation (yes or no)

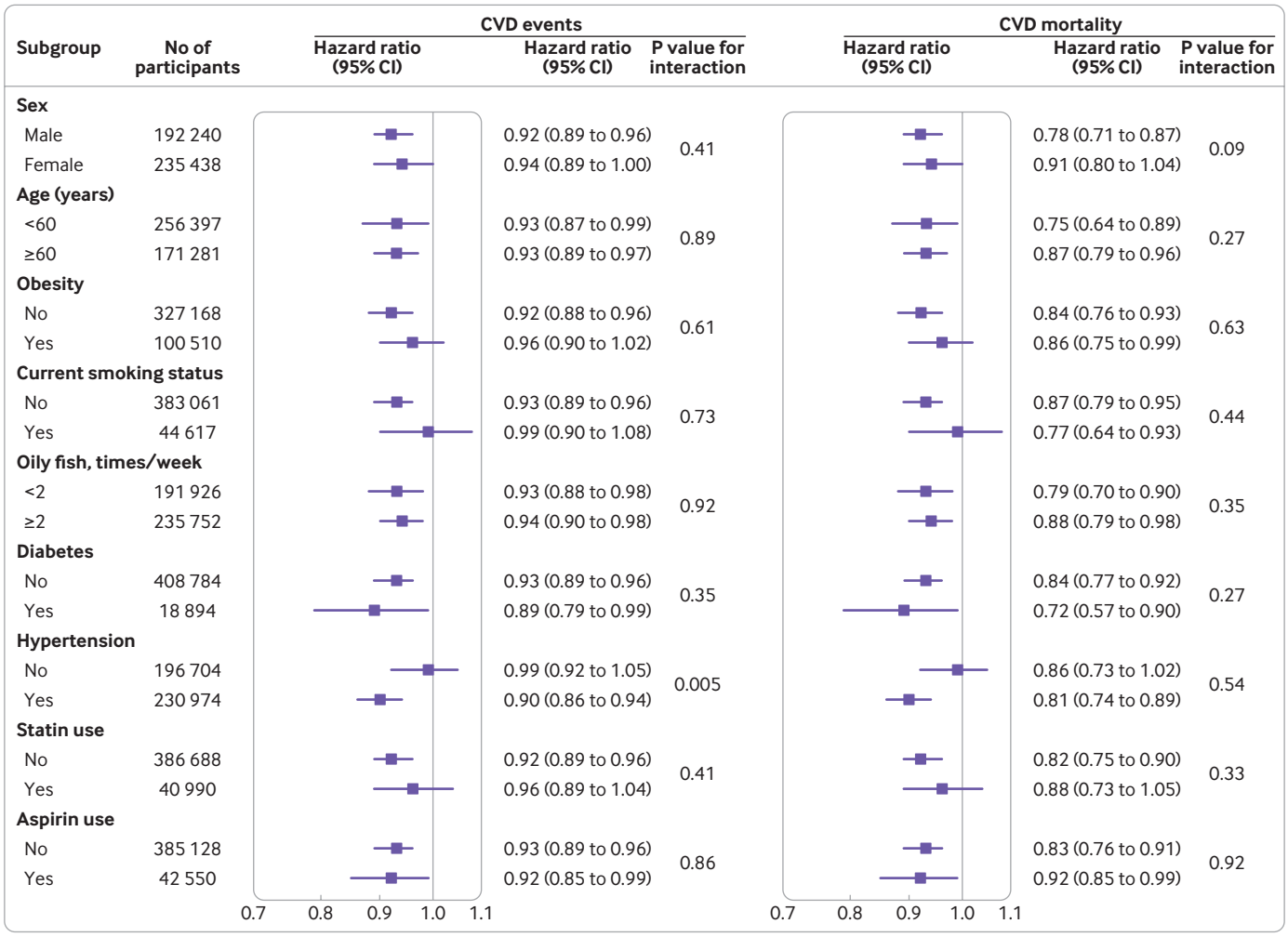

Fig 2 | Associations of fish oil supplement use and the risk of cardiovascular events and cardiovascular mortality stratified by potential risk factors. Results were adjusted for age, sex, Townsend Deprivation Index, assessment centre (22 categories), ethnicity (white, black, Asian, Chinese, mixed, or other ethnic group), household income (<£18 000 (€21 489; $23 253), £18 000-£30 999, £31 000-£51 999, £52 000-£100 000, or >£100 000), body mass index, fruit consumption (<2.0, 2.0-3.9, or ≥4.0 servings/day), vegetable consumption (<2.0, 2.0-3.9, or ≥4.0 servings/day), oily fish consumption (<2 or ≥2 times/week), smoking status (never, former, or current), alcohol consumption (never, 1-2, 3-4, or ≥5 times/week), physical activity (<150 or ≥150 min/week), diabetes (yes or no), hypertension (yes or no), longstanding illness (yes or no), antihypertensive drug use (yes or no), statin use (yes or no), insulin treatment use (yes or no), aspirin use (yes or no), vitamin supplementation (yes or no), and mineral and other dietary supplementation (yes or no)

supplements in the UK[6]; another study also showed that 32.6% of the participants (aged more than 45) self-reported use of fish oil supplements in Australia.[4] Owing to its low cost, lack of fishy taste or smell, convenience of use, and mild side effects,[27-29] fish oil supplementations could be an inexpensive, quick, and safe way of increasing an individual's omega 3 fatty acid intake.

Our findings are in accordance with the results of several previous studies that found that fish oil supplementation is associated with a lower risk of CVD outcomes. For instance, several studies, including randomised controlled trials and prospective cohort studies,[15 30-33] reported that omega 3 fatty acid products had a significant protective effect against CVD events. In a meta-analysis of 402 127 individuals, a greater intake of fish was associated with a decreased risk of stroke.[34] Other studies, however, have shown that omega 3 fatty acids have no effect, or only a weak effect, on the prevention of CVD.[16-18 35] One possible explanation is that those studies could have lacked sufficient sample sizes or sufficient events. For example, in a recent large trial (VITAL),[16] which included 25 871 participants, major CVD events occurred in 386 participants in the group receiving omega 3 fatty acids and in 419 participants in the placebo group (hazard ratio 0.92, 95% confidence interval 0.80 to 1.06), suggesting that omega 3 fatty acids had no preventive effect against major CVD events. However, the post hoc study power for major CVD events in the VITAL study was only 0.78. By point estimation, our results (hazard ratio 0.93) were relatively similar to those of the VITAL study (hazard ratio 0.92). The confidence interval estimation (0.90 to 0.96) in our study suggests that omega 3 fatty acids have a significant association with CVD events. Therefore, we postulate a marginal inverse association between fish oil supplementation and CVD events.

Another possible explanation is that the lack of protection from omega 3 fatty acids reported in previous trials could be due to the dose.[30] For instance, two recent large randomised controlled trials[16 30] reported conflicting results for the effect of omega 3 fatty acids on the risk of CVD, but the daily doses of these fatty acids given in the two studies differed by a factor of 4.75: 840 mg versus 3992 mg. Similarly, the Alpha Omega Trial[36] and ASCEND (A Study of Cardiovascular Events in Diabetes)[35] reported that supplementation with low dose omega 3 fatty acids was ineffective at reducing CVD events. By increasing the sample size and carrying out dose-response analyses, a recent meta-analysis,[10] which incorporated data from 13 randomised controlled trials, showed that greater benefits for CVD outcomes were achieved with higher doses of omega 3 fatty acid supplements. This finding indicates that the conflicting results from the randomised controlled trials could be due to sample sizes and the doses of fish oil supplements. This meta-analysis strongly supports our findings as it provides the best evidence for an effect of the intervention. Furthermore, for mortality, several studies have reported findings that are consistent with our results, suggesting that habitual use of fish oil supplements is associated with a lower risk of all cause mortality.[37 38] Our study also indicates that the association seemed stronger for CVD mortality than for the incidence of CVD, implying that fish oils could have a stronger effect among individuals with established CVD events.

Previous reports have suggested that the effects of omega 3 fatty acids vary according to a patient's previous use of statins.[1 39] Our study, however, showed no heterogeneity in the effects of fish oil use on CVD events. In addition, inverse associations of fish oil use with CVD events seemed to be somewhat stronger in participants with hypertension than in those without hypertension, which was consistent with a meta-regression analysis showing a more favourable effect of fish oil on blood pressure in those with hypertension.[40]

To date, there is insufficient evidence to show which component of omega 3 fatty acids (docosahexaenoic acid, eicosapentaenoic acid, or docosahexaenoic acid and eicosapentaenoic acid) could be beneficial for CVD outcomes or all cause mortality.[10 41] Although the recent randomised controlled trial REDUCE-IT (Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial)[30] showed that supplementation with eicosapentaenoic acid ethyl ester reduced the risk of CVD events, the dose of the supplement (4 g/day) was significantly higher than in other randomised controlled trials,[16 32 35] and the participants were at a high risk of CVD events (eg, those using statins with raised triglyceride levels). The trial left unanswered whether a normal dose of eicosapentaenoic acid ethyl ester is effective in the general population, whether the effects of eicosapentaenoic acid and docosahexaenoic acid on CVD events are independent, and the optimal ratio of eicosapentaenoic acid to docosahexaenoic acid in fish oil supplements. These subjects need to be examined in future studies.

Several mechanisms could explain the benefits for clinical outcome derived from fish oil supplementation. Firstly, the results of several studies have indicated that supplementation with omega 3 fatty acids has beneficial effects on blood pressure,[40] plasma triglycerides,[42] and heart rate,[43] all of which would exert a protective effect against the development of CVD. Secondly, several trials have shown that omega 3 fatty acids can improve flow mediated arterial dilatation, which is a measure of endothelial function and health.[44 45] Thirdly, omega 3 fatty acids have been shown to possess antiarrhythmic properties that could be clinically beneficial.[46] Finally, studies have reported that fish oil can reduce thrombosis.[47] Additionally, studies have reported that the anti-inflammatory properties of fish oil could have a preventive role in the pathophysiology of CVD outcomes.[11 48] Other mechanisms could also be involved to explain the effect of fish oil on CVD outcomes.

Strengths and limitations

Our study has a number of strengths. Firstly, a major strength is its population based cohort, which shows the effectiveness of fish oil supplementation in a real-life setting. Secondly, it included nearly half a million of participants, which provided a large number of outcome events and adequate statistical power to explore important outcomes related to supplement intake over an 8 to 12 year follow-up period. Finally, detailed information was available on socioeconomic characteristics, lifestyle habits, disease prevalence, drug use, and other covariates, enabling us to perform comprehensive sensitivity analyses and subgroup analyses that could help to minimise confounding factors.

Several potential limitations should also be considered. Firstly, the study did not record detailed information on the use of fish oil supplements, such as the dose, formulation, and duration of use. The lack of such information precluded us from evaluating dose-response associations between fish oil supplementation and outcomes, the independent effects and best ratio of the individual components of fish oil supplements, and the optimal duration of fish oil supplementation. Importantly, from the published studies, it is also difficult to comment on the dose of fish oil supplements needed to achieve a clinically meaningful effect. Secondly, the possibility of residual confounding factors due to imprecise measurements or unknown factors cannot be excluded. Moreover, in an observational study, it is difficult to separate the effects of a healthy lifestyle from the habitual use of fish oil supplements. Therefore, although we carefully adjusted for a series of confounders in our analyses, the observed associations could have been affected by healthy lifestyle or other factors. Finally, reverse causality might exist in our study, although the results remained unchanged when we excluded participants with outcome events that occurred during the first two years of follow-up.

Conclusions

The results of this large scale prospective study show that a considerable proportion (31.2%) of the 427 678 participants reported habitual use of fish oil supplements. Moreover, we found that habitual fish oil supplementation was inversely associated with the risk of CVD outcomes and all cause mortality. These findings indicate that habitual use of fish oils is associated with a marginal benefit for CVD events in the general population, supporting their use for the prevention of mortality from all causes and CVD. Future studies are needed to examine the extent to which the dose of fish oil supplements influences the ability to achieve a clinically meaningful effect.

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Contributors: Z-HL and W-FZ are joint first authors, contributed to the statistical analyses, and had primary responsibility for writing the manuscript. Z-HL and W-FZ contributed equally to this article. CM, DW, X-MS, and X-BW directed the study. Y-JZ, Y-BL, DS, X-RZ, and QC contributed to the data cleaning. CM, SL, VBK, XG, P-DZ, and Q-MH contributed to the analysis or interpretation of the data. CM (maochen9@smu.edu.cn) and DW (dongw96@smu.edu.cn) contributed equally to this work and should be considered co-corresponding authors. All authors critically reviewed the manuscript for important intellectual content. CM is the study guarantor. The corresponding author (CM) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Data sharing: The UK Biobank data are available from the UK Biobank on request (www.ukbiobank.ac.uk/).

The lead author (CM) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Dissemination to participants and related patient and public communities: The results of the research will be disseminated to the public through broadcasts, popular science articles, and newspapers.

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Web appendix: Supplementary materials