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ORIGINAL CONTRIBUTION

Associations of baseline use of fish oil with progression of cardiometabolic multimorbidity and mortality among patients with hypertension: a prospective study of UK Biobank

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Abstract

Purpose The role of fish oil in the prognosis of hypertensive patients is unknown. This study investigated the associations of fish oil supplementation with the progression of cardiometabolic multimorbidity (CMM) and mortality among patients with hypertension.

Methods Based on UK Biobank, we enrolled participants with hypertension and free of other cardiometabolic diseases. The exposure was baseline use of fish oil derived from questionnaires at baseline. The primary outcomes were the incidence of CMM and all-cause mortality. Competing risk models and flexible parametric proportion-hazards models were fitted to assess the adjusted hazard ratios (HRs) for the risk of CMM and mortality outcomes, respectively.

Results Among 81,579 participants involved [50.37%, men; mean age, 59.38 years (standard deviation, 7.23 years)], 15,990 CMM events and 6456 all-cause deaths were reported (median follow-up, 12.23 years). In multivariable-adjusted models, baseline use of fish oil was associated with 8% lower risk of CMM [95% confidence interval (95% CI) 0.89–0.96, $P < 0.001$] and 10% lower risk of all-cause mortality (95% CI 0.85–0.95, $P < 0.001$).

Conclusion In individuals with hypertension, baseline use of fish oil was associated with a reduced risk of CMM and all-cause mortality, and further clinical trials are needed to prove this hypothesis.

Keywords Fish oil · UK Biobank · Cardiometabolic multimorbidity · Mortality · Hypertension

Introduction

As the growing population is aging [1], the prevalence of multimorbidity, especially cardiometabolic multimorbidity (CMM), which means the concurrent occurrences of ≥ 2 cardiometabolic diseases (CMDs) in an individual, has been increasing rapidly, rising as a public health issue requiring attention [2, 3]. Studies based on global, U.K., and Chinese population suggested that CMM cumulatively increased the risk of all-cause mortality and reduced the life expectancy [4, 5]. Furthermore, hypertension, the most prevalent chronic disease and major risk factor for coronary heart disease (CHD), stroke, and chronic kidney disease (CKD), contributes to common comorbidities worldwide [6, 7]. It is an important component of the common CMM patterns. In UK Biobank, 70% patients with CKD also had hypertension, and the corresponding percentage for patients with diabetes was 64% [8]. In this way, developing cost-effective strategies against the progression of CMM among hypertensive patients is necessary. Existing evidence has indicated

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the crucial role of healthy lifestyles in the occurrence and prognosis of CMM [9–12]. However, the potential effects of nutritional supplements on the trajectory from single CMD to CMM and afterward death are unknown yet, since relevant clinical trials usually focused on conditions of a single disease.

Fish oil is a commonly used nutritional supplement. It provides marine long-chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) as the active ingredient, and eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are the most functionally important ones [13, 14]. In addition to marine fish and fish oil, other supplements including cod liver oil, krill oil, and pharmaceuticals such as icosapent ethyl (IPE) and lovaza also contain EPA and/or DHA [15]. During the past 2 decades, the use of fish oil supplements was increasingly prevalent in the U.S. and Europe [16–18]. For instance, its supplementation increased to 12% in 2012 among American adults, ten times higher than that in 2000 [18], and among community-dwelling old people in South East England, it was the most widely used supplement [16]. In general population, fish oil supplementation was associated with a decreased risk of all-cause, cardiac mortality, and myocardial infarction events [19–21], and the cardioprotective effects of the supplement were more substantial for people at high risk or with a history of cardiovascular diseases [22, 23]. Among hypertensive patients, it significantly improved cardiometabolic profiles including glycometabolism, lipid metabolism, and blood pressure levels [24–26]. However, the effect of fish oil supplementation on the progression of CMM and mortality of hypertensive patients is unknown.

Thus, this study aimed to investigate the role of fish oil supplements in the progression of CMM (hypertension plus diabetes, CHD, or stroke in this study) and mortality of hypertension. We assessed the associations of fish oil supplementation with the risk of CMM and mortality among hypertensive patients in the large prospective cohort, UK Biobank [27].

Materials and methods

Study population and design

This study utilized data from UK Biobank, a large-population-based, long-term, and prospective cohort. The detailed design and population of UK Biobank have been previously described [27, 28]. In brief, from 2006 to 2010, the UK Biobank recruited more than 500,000 people across UK from general population, aged 40–69 years. With written informed consents, extensive information on demography, lifestyles, anthropometry, other clinical-related aspects, and biological samples (blood, urine, and saliva) of participants were collected. The information in their health-related outcomes such as inpatient diagnoses, COVID-19 tests, and death records was then accessed via linkages to a range of health-related records. Biological assays, imaging measurements, and gene sequencing were also conducted in a subset of participants. UK Biobank was approved by the North West Multi-center Research Ethics Committee (approval letter dated 17th June 2011, Ref 11/NW/0382) [29]. This study was approved by the UK Biobank (ID: 76,118).

In the current research, we enrolled UK Biobank participants with hypertension ($n = 149{,}148$) at baseline. Participants who reported other CMDs combined with hypertension ($n = 40{,}514$) at baseline, or had missing data on the use of fish oil and covariates ($n = 1222$ in fish oil use, $n = 19$ in the dates of outcome occurrences, $n = 23{,}511$ in physical activity, and $n = 2303$ in other covariates) were excluded. Finally, 81,579 participants were enrolled in our analyses.

Ascertainment of CMDs

The detailed definitions of CMDs are summarized in Table S1. Briefly, the occurrences of these diseases were ascertained according to self-reported information derived from verbal interviews at baseline and repeated visits afterward (diagnoses by physicians, medication history, and operation history) and medical outcomes derived from health-related records [inpatient diagnoses coded by the International Classification of Diseases, 9th revision (ICD-9), ICD-10, and operations coded by the Office of Population Censuses and Surveys Classification of Interventions and Procedures, version 4 (OPCS-4)]. For an individual with an ascertained disease, the diagnosed date was compared with the date at recruitment. If the available earliest date of its diagnosis was prior to the date at recruitment, he or she was believed to have this disease at baseline, otherwise get it during follow-up. The information in CMDs were used to screen participants with hypertension at baseline and ascertain the occurrence of CMM outcomes during follow-up.

Assessment of exposure

Our exposure of interest was the baseline use of fish oil. At baseline, relevant information was collected via touchscreen questionnaires at the assessment center. Participants were asked, "Do you regularly take any of the following?" They could select more than one answer from the listed mineral and dietary supplements, with "Fish oil (including cod liver oil)" as an option. Participants who selected "Prefer not to answer" option were thought to have missing data in this information, and others were classified into fish oil users and non-users according to their selections.

Ascertainment of outcomes

The primary outcomes in our study were CMM and all-cause mortality, and the secondary outcomes were the incidence of specific CMDs, cardiac, and cancer death.

For participants with hypertension at baseline, they were defined as having CMM during follow-up if other CMDs occurred after recruitment. The occurrences of other CMDs during follow-up were assessed by aggregating the information in self-reported medical history and inpatient records, as mentioned above. For mortality outcomes, information on death date and cause (categorized by ICD-10 codes) were derived via linkages to the National Health Service (NHS) Information Centre in England, Wales, and the NHS Central Register in Scotland [27]. Cardiac and cancer death was defined by ICD-10 codes I00–I99 and C00–C97, respectively.

Assessment of other covariates

Touchscreen questionnaires, verbal interview records, and physical measures of participants at baseline were used to derive information in other covariates: demographic variables (age, sex, ethnicity, and Townsend Deprivation Index), clinical variables (BMI, number of multimorbidity, use of antihypertensive drug, cholesterol-lowering medication, aspirin, and other dietary supplements), and lifestyles (diet, oily fish consumption, current smoking status, alcohol consumption, and physical activity).

The Townsend Deprivation Index was provided directly by UK Biobank. Calculated from participants' home postcodes, it is an integrated indicator of socioeconomic status [30]. BMI (kg/m^2) was calculated as the body weight (kg) divided by the square of height (m^2). Number of multimorbidity was the sum of self-reported cancers and non-cancer illnesses at baseline. To assess the diet condition at baseline, we applied a healthy diet score adapted from the American Heart Association (AHA) Guidelines [31], and the computational method is presented in Table S2. Involving total fruit and vegetable, total fish, processed, and red meat consumption, the diet score generated dichotomous values: 1 (more advisable) and 0 (less advisable). In terms of physical activity, participants were dichotomized according to whether they met the 2017 UK Physical Activity Guidelines (150 min of walking or moderate activity or 75 min of vigorous activity per week) [32].

Statistical analysis

Participants were categorized according to the use of fish oil (fish oil users vs. fish oil non-users), and their characteristics at baseline were presented as number (percentage) for categorical variables and mean value [standard deviation (SD)] for continuous variables. Student's *t* tests and Chi-square tests were used to compare the characteristics of participants between two groups.

The associations of baseline fish oil supplementation with the occurrences of CMM and specific CMDs were assessed with Fine-Gray sub-distribution hazard models, which accounted for competing risk of death. Flexible parametric Royston–Parmar proportion-hazards models [33] were fitted to estimate the associations of fish oil supplements with all-cause and cause-specific death, with age as the time scale. In our analyses, three sets of models were fitted. The model 1 was adjusted for age, sex, and ethnicity. The model 2 was further adjusted for Townsend Deprivation Index, healthy diet score, oily fish consumption, current smoking status, alcohol consumption, and physical activity. And the full model 3 was further adjusted for BMI, number of multimorbidity, the use of antihypertensive drug, statin, aspirin, and other dietary supplements.

To assess the potential modification effects of other covariates, the main analysis was further stratified by sex (male or female), age (<60 or ≥ 60 years), ethnicity (white or non-white), Townsend Deprivation Index (≤ 0 or >0), obesity [yes (BMI ≥ 30 kg/m^2) or no (BMI < 30 kg/m^2)], current smoking status (yes or no), alcohol consumption (≤ 2 or >2 times/week), oily fish consumption (<2 or ≥ 2 servings/week), healthy diet score (0 or 1), and meeting physical activity recommendation (yes or no).

We then performed sensitivity analyses to test the robustness of our results. First, we excluded participants who died during the first 2 years of follow-up. Second, we excluded participants who had a diagnosis of hypertension for <1 year at baseline. Third, we adjusted the calculation of physical activity to partly offset the exclusion of participants with missing data in physical activity questionnaires. For those who answered their frequency of walking/moderate/vigorous physical activity 10+ minutes but did not record duration, we substituted the corresponding duration with 10 min and re-performed the analysis. Finally, to compensate for the potential measurement errors caused by alterations in exposure and covariates during a long follow-up period, we truncated the follow-up periods to 9.0 years, since the reproducibility of fish-oil using conditions in UK Biobank has been observed to be more reliable during the first 9.0 follow-up years [34]. Analyses were conducted with R software (version 4.1.0) and Stata (version 17.0). R packages *tableone* (version 0.12.0), *survival* (version 3.2.11), *cmprsk* (version 2.2.10), and *forestplot* (version 1.10.1) were used. All *P* values in our analyses were two-sided, and it was considered statistically significant when *P* values <0.05.

Results

Baseline characteristics

The baseline characteristics of participants according to the use of fish oil are presented in Table 1. Of 81,579 participants, 41,090 (50.37%) were male, with a mean age of 59.38 years. 27,815 (34.10%) reported regular use of fish oil at baseline. Compared with non-users, fish oil users were older, more likely to be female, physically active, and current non-smokers. They tended to have higher socioeconomic status, oily fish and alcohol consumption, lower BMI, more comorbidities, and healthier diet. They were also more likely to use cardiometabolic-relevant medications and other supplements.

Fish oil use and outcomes

The median follow-up duration was 12.22 years. During follow-up, 15,990 CMM events (5662 cases of diabetes, 8718 cases of CHD, and 4109 cases of stroke) and 6456 all-cause deaths (1308 cardiac deaths and 3307 cancer deaths) were reported. Table 2 shows the associations of baseline use of fish oil supplements with outcomes. In model 1 adjusted for age, sex, and ethnicity, fish-oil use was inversely associated with the incidence of all outcomes (all $P < 0.05$) except for the occurrences of stroke [hazard ratio (HR) 0.94, 95% confidence interval (95% CI) 0.88–1.00, $P = 0.062$] and cancer death (HR 0.94, 95% CI 0.88–1.00, $P = 0.090$). The inverse associations remained significant after further adjustments for lifestyles and clinical features. In model 3, fish oil supplementation was associated with 8% reduction in the risk of CMM (95% CI 0.89–0.96, $P < 0.001$), and 10% reduction in the risk of all-cause mortality (95% CI 0.85–0.95, $P < 0.001$). For other secondary outcomes, participants who used fish oil had a lower risk of diabetes, CHD, and cardiac death by 9%, 11%, and 14%, respectively (all $P < 0.05$).

Subgroup and sensitivity analyses

We performed stratified analyses according to potential confounding factors. For CMM (Fig. 1) and all-cause mortality (Fig. 2), their association with baseline use of fish oil were not significantly modified by all included factors including sex, age, ethnicity, Townsend Deprivation Index, obesity, current smoking status, alcohol consumption, oily fish consumption, healthy diet, and physical activity (all $P_{interaction} > 0.05$). And fish oil-related improvement in the progression of CMM tended to be stronger among patients who consumed oily fish < 2 times per week ($P_{interaction} = 0.073$). For all-cause mortality, the association tended to be modified by sex ($P_{interaction} = 0.079$). In sensitivity analyses (Table 3), there was no substantial alteration in the results when we excluded participants who died during the first 2 years of follow-up (excluded: $n = 449$), who had hypertension for < 1 year at baseline (excluded: $n = 5,020$), or adjusted the assessment method of physical activity (added: $n = 16,741$). After truncation of follow-up periods to 9.0 years, the protective role of fish oil was also observed.

Table 1 Baseline characteristics

Characteristics	Fish oil users	Fish oil non-users	*P*
Participants, No. (%)	27,815 (34.10)	53,764 (65.90)	
Age (years), mean (SD)	60.94 (6.47)	58.56 (7.47)	< 0.001
Male, No. (%)	13,334 (47.9)	27,756 (51.6)	< 0.001
White ethnicity, No. (%)	26,550 (95.5)	51,203 (95.2)	0.173
Townsend Deprivation Index, mean (SD)	− 1.56 (2.96)	− 1.28 (3.10)	< 0.001
Body mass index (kg/m^2), mean (SD)	28.40 (4.69)	28.96 (5.03)	< 0.001
Number of multimorbidity, mean (SD)	2.77 (1.74)	2.67 (1.73)	< 0.001
Antihypertensive drug use, No. (%)	18,246 (65.6)	33,744 (62.8)	< 0.001
Cholesterol lowering medication use, No. (%)	7891 (28.4)	13,631 (25.4)	< 0.001
Aspirin use, No. (%)	5637 (20.3)	8314 (15.5)	< 0.001
Other dietary supplementation, No. (%)[1]	20,163 (72.5)	15,113 (28.1)	< 0.001
Healthy diet, No. (%)	18,053 (64.9)	28,761 (53.5)	< 0.001
Oily fish consumption (servings/week) ≥ 2, No. (%)	6866 (24.7)	9809 (18.2)	< 0.001
Current smoking, No. (%)	1947 (7.0)	5199 (9.7)	< 0.001
Alcohol consumption frequency (times/week) ≥ 3, No. (%)	13,326 (47.9)	25,032 (46.6)	< 0.001
Meeting physical activity meeting guidelines[2], No. (%)	23,248 (83.6)	42,677 (79.4)	< 0.001

[1]The use of vitamin, mineral, and other dietary supplements except for fish oil at baseline

[2]Indicates whether a person met the 2017 UK Physical activity guidelines of 150 min of walking or moderate activity per week or 75 min of vigorous activity

Table 2 Associations of baseline use of fish oil with CMM, specific CMDs, and mortality

Outcomes	Events during follow-up n (%)		Model 1 [1]		Model 2 [2]		Model 3 [3]	
	Fish oil users	Fish oil non-users	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
CMM	5330 (19.16%)	10,660 (19.83%)	0.89 (0.86–0.92)	< 0.001	0.92 (0.89–0.95)	< 0.001	0.92 (0.89–0.96)	< 0.001
Diabetes	1755 (6.38%)	3907 (7.27%)	0.84 (0.80–0.89)	< 0.001	0.89 (0.84–0.94)	< 0.001	0.91 (0.86–0.97)	0.004
Coronary heart disease	2891 (10.40%)	5827 (10.84%)	0.88 (0.84–0.92)	< 0.001	0.90 (0.86–0.94)	< 0.001	0.89 (0.85–0.94)	< 0.001
Stroke	1480 (5.32%)	2629 (4.89%)	0.94 (0.88–1.00)	0.062	0.97 (0.91–1.03)	0.350	0.94 (0.88–1.01)	0.110
All-cause mortality	2233 (8.03%)	4223 (7.85%)	0.87 (0.83–0.92)	< 0.001	0.92 (0.87–0.97)	0.002	0.90 (0.85–0.95)	< 0.001
Cardiac mortality	432 (1.55%)	876 (1.63%)	0.82 (0.73–0.93)	0.001	0.88 (0.78–0.99)	0.036	0.86 (0.76–0.98)	0.027
Cancer mortality	1197 (4.30%)	2110 (3.92%)	0.94 (0.88–1.00)	0.090	0.98 (0.91–1.05)	0.614	0.99 (0.91–1.07)	0.742

CMM means cardiometabolic multimorbidity, *CMDs* means cardiometabolic diseases, *HR* means hazard ratio, *95% CI* means 95% confidence interval

[1]Model 1: adjusted for age, sex, and ethnicity

[2]Model 2: further adjusted for Townsend Deprivation Index, healthy diet score, oily fish consumption, current smoking status, alcohol consumption, and physical activity

[3]Model 3: further adjusted for body mass index, number of multimorbidity, use of antihypertensive drug, cholesterol-lowering medication, aspirin, and other dietary supplementation

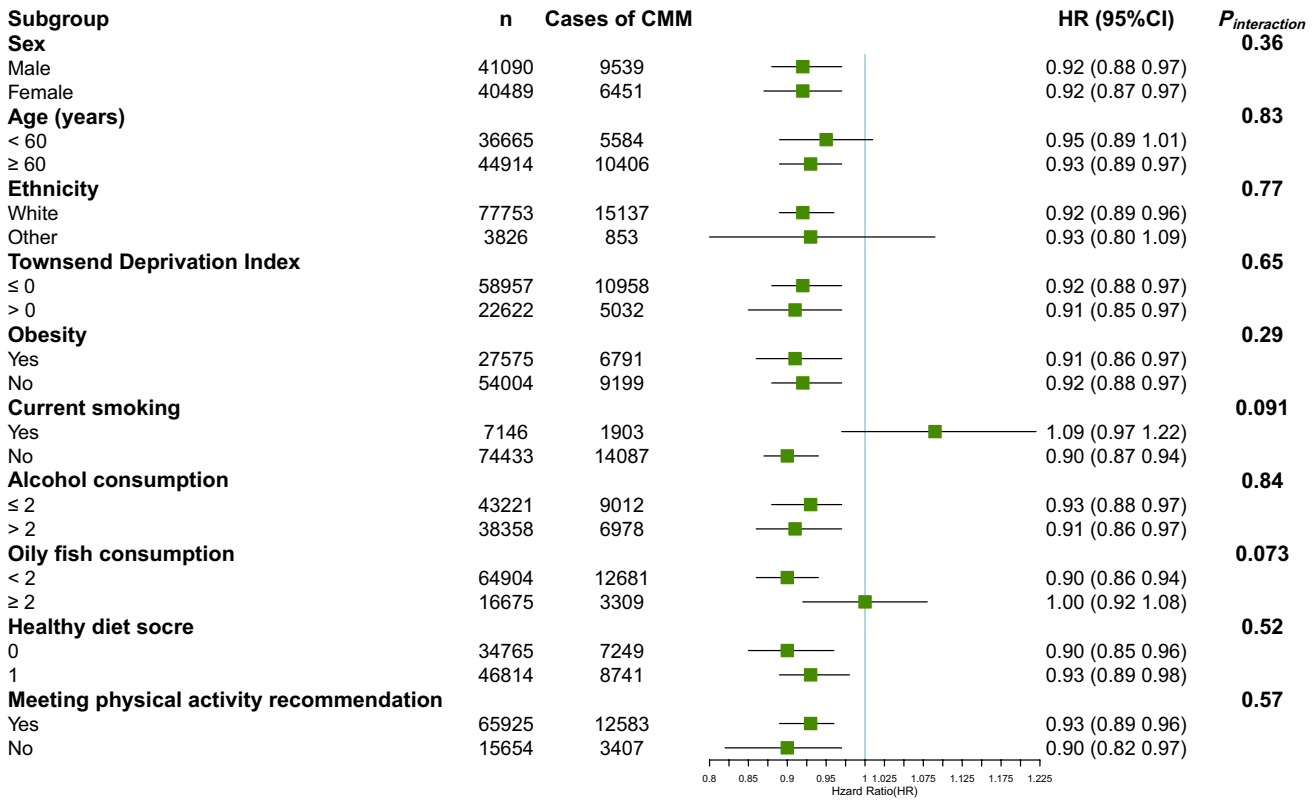

Fig.1 Associations of Fish Oil Supplements with Risk of CMM Stratified by Potential Risk Factors. The HRs for the risk of CMM were derived from Fine-Gray sub-distribution hazard models. Results were adjusted for age, sex, ethnicity, Townsend Deprivation Index, healthy diet score, oily fish consumption (servings/week), current smoking status, alcohol consumption (times/week), physical activity, body mass index, number of multimorbidity, use of antihypertensive drug, cholesterol-lowering medication, aspirin, and other dietary supplementation. *CMM* cardiometabolic multimorbidity, *HR* hazard ratio, *95% CI* 95% confidence interval

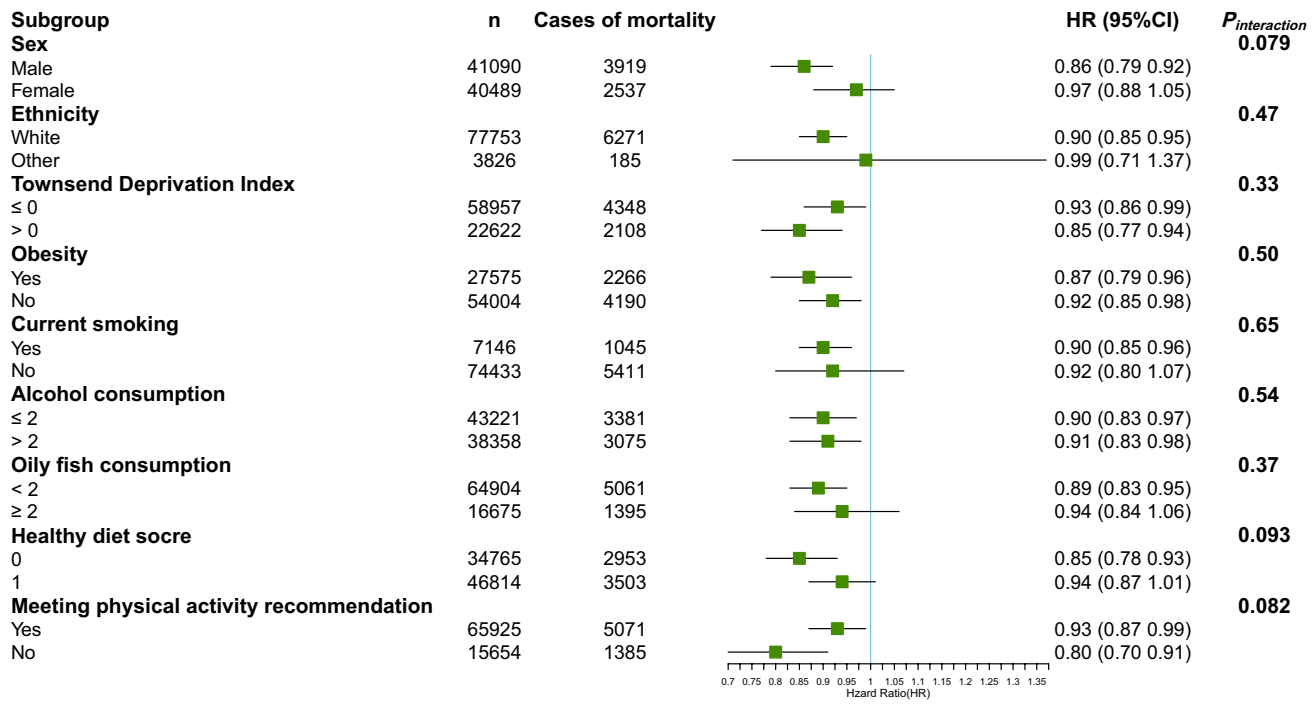

Fig.2 Associations of fish oil supplements with risk of all-cause mortality stratified by potential risk factors. The HRs for the risk of all-cause mortality were derived from flexible parametric Royston–Parmar proportion-hazards models, setting age as the time scale. Results were adjusted for sex, ethnicity, Townsend Deprivation Index, healthy diet score, oily fish consumption (servings/week), current smoking status, alcohol consumption (times/week), physical activity, body mass index, number of multimorbidity, use of antihypertensive drug, cholesterol-lowering medication, aspirin, and other dietary supplementation. *HR* means hazard ratio, and *95% CI* means 95% confidence interval

Table 3 Sensitivity analysis of primary outcomes

Sensitivity analysis	CMM		All-cause mortality	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Sensitivity 1 [1]	0.92 (0.89–0.95)	< 0.001	0.90 (0.85–0.96)	0.001
Sensitivity 2 [2]	0.93 (0.90–0.97)	0.002	0.90 (0.85–0.96)	0.001
Sensitivity 3 [3]	0.91 (0.88–0.95)	< 0.001	0.90 (0.86–0.95)	< 0.001
Sensitivity 4 [4]	0.91 (0.87–0.95)	< 0.001	0.89 (0.83–0.96)	0.003

CMM means cardiometabolic multimorbidity, *HR* means hazard ratio, *95% CI* means 95% confidence interval

[1]Participants who died during the first 2 years of follow-up were excluded (excluded: $n = 449$)

[2]Participants who had been diagnosed with hypertension for < 1 year at baseline were excluded (excluded: $n = 5{,}020$)

[3]Assessment of physical activity was adjusted. For those who answered their frequency of walking/moderate/vigorous physical activity 10 + minutes but did not record duration, we conservatively substituted the corresponding duration with 10 min and re-performed the analysis (added: $n = 16{,}741$)

[4]Follow-up periods were truncated to 9.0 years, and participants who reported outcome events after 9.0 follow-up years were considered as censored during the 9-year follow-up period

Discussion

Main findings

In this prospective study involving 81,579 participants with hypertension at baseline from UK Biobank, the use of fish oil at baseline was associated with 8% reduction in the risk of CMM and 10% reduction in the risk of all-cause mortality. The associations were independent of sex, age, ethnicity, Townsend Deprivation Index, BMI, smoking status, physical activity, consumption of alcohol, oily fish, or a healthy diet.

Comparison with previous studies

For hypertensive patients, fish oil supplementation has been reported to reduce blood pressure levels by ~ 2.5 mmHg for systolic and ~ 1.5 mmHg for diastolic blood pressure [24, 25, 35, 36]. It has been estimated that a decrease of SBP by 2 mmHg lowered the risk of stroke and cardiac death by ~ 10% and 7%, respectively [37], while the further implications of fish oil-related hypotensive effects on clinical outcomes of hypertensive patients are unknown yet. Based on the high prevalence of hypertension [38], its tight association with other CMDs [39, 40], and substantial burden, our results hint at the protective role of fish oil in the progression of CMDs and prognosis among hypertensive patients, which are in line with the results of previous studies in conditions of single disease.

In the literature, the protective effects of fish oil or *n*-3 PUFAs supplementation against CHD and diabetes were indicated by a series of clinical trials [22, 41–43]. A recent meta-analysis incorporating 13 randomized controlled trials (RCTs) suggested that fish oil significantly lowered the risk of CHD and cardiac death [44]. For the primary prevention of diabetes, an observation study observed that regular use of fish oil supplements was associated with 9% lower risk of type 2 diabetes [45], and several RCTs revealed that *n*-3 PUFAs supplementation improved glycemic control and insulin sensitivity among patients with the metabolic disorder [46–48]. Collectively, the existing evidence of the beneficial effects of fish oil was restricted with the prevention and prognosis of single diseases, and our results filled in the gap of CMM. In our study, baseline use of fish oil supplements was associated with 8% lower risk of developing CMM overall ($P < 0.001$) among patients with hypertension, and the implication on CHD outcomes was most outstanding (HR 0.89, 95% CI 0.85–0.94, $P < 0.001$), slightly stronger than its effects in the general population [20]. For the risk of diabetes, we observed 9% reduction associated with baseline use of fish oil (95% CI 0.86–0.97, $P = 0.004$), which was similar to that in the primary prevention of type 2 diabetes [45]. Besides, we did not observe a significant association between fish oil and stroke, as previous trials did [49], even though *n*-3 PUFAs and their metabolites exhibited protective effects against stroke via multiple pathways in experimental studies [50]. It is possible that the boundary effect of fish oil on stroke was too subtle to be detected with statistical significance.

For mortality outcomes, the use of fish oil was related to a reduction in the risk of all-cause mortality by 10%, and cardiac mortality by 14%, while no significant association was observed for cancer mortality. Our findings were partly consistent with the results of VITAL trial in the general population (HR 0.50, 95% CI 0.26–0.97 for death from myocardial infarction, HR 0.97, 95% CI 0.79–1.20 for death from cancer) [21]. And the cardioprotective effects of fish oil supplements predominantly contributed to its protection against death [51]. It has been reported that a history of CMM accumulatively increased the risk of all-cause mortality and reduced life expectancy. Our results indicated that fish oil supplementation was associated with a reduced risk of CMM by 8%, which might mediate its inverse association with mortality outcomes, and needs to be further proved in the future with multi-state models, for instance.

Up to date, the effects of fish oil supplements on the incidence of CMM have not been reported. Our results suggested that among hypertensive patients, baseline use of fish oil was significantly associated with a reduced risk of CMM, all-cause mortality, and cardiac mortality. Even though the associations seemed moderate, the use of fish oil might benefit public health greatly, based on the increasing disease burden of hypertension. And most commercially accessible supplements of fish oil contain both EPA and DHA in moderate doses (< 600 mg per g of oil) [15], while highly purified and easily absorbed pharmaceuticals of *n*-3 PUFAs have risen, made a great coup in RCTs, and have been introduced by European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) guidelines for the management of dyslipidaemias [22, 43, 52, 53]. Thus, our results tend to underestimate the protective role of fish oil, and further clinical trials are needed to prove the causality of our findings, and find feasible doses and formulations of fish-oil supplements with stronger effects.

Strengths and limitations

Our study has several strengths. First, UK Biobank, a prospective cohort with long follow-up periods, enabled us to conduct analyses in a real-world setting. Second, a large sample size and number of events made it possible to concentrate on the progression of CMM among patients with hypertension and estimate the role of fish oil. Third, with the detailed information in participants' characteristics, we were able to account for confounding factors, and conduct stratified and sensitivity analyses.

Nevertheless, our study has limitations. First, participants in UK Biobank were volunteers mainly from European descent. They were healthier and less socioeconomically deprived than the general population of U.K. [54]. It needs caution to extend our results to other populations and areas. Second, the exposure in our study was a self-reported, binary variable derived at recruitment. The detailed information on its brand, formulation, doses, and duration was unclear. It hindered us from assessing the dose/time-dependent role of fish oil supplements and identifying specific roles of its ingredients. Third, we have carefully adjusted for covariables in multiple aspects, but there are other residual confounding factors which were

not involved in our analyses. The existence of these factors may also modify the results of our study. Fourth, we used information in exposure and covariates collected at baseline in our analyses. During a long follow-up period, these variables were prone to change, contributing to potential dilution bias and measurement errors. Nevertheless, the reproducibility of fish oil using conditions in UK Biobank has been proved to be stable and reliable (especially during the first 9.0 follow-up years) [34]. To compensate for the potential alterations in exposure and covariates, we also verified our results in sensitivity analyses by truncating the follow-up periods to 9.0 years. Finally, reverse causality cannot be eliminated in this observational research, although we have excluded the participants who died within the first 2 years of follow-up or had new-onset hypertension in sensitivity analyses.

Conclusion

Baseline use of fish oil supplements was associated with a reduced risk of CMM occurrence and all-cause mortality. Further clinical trials are needed to prove this hypothesis and provide evidence to support the use of fish oil among patients with hypertension, for greater clinical benefits.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00394-022-02889-w.

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Author contributions Conceptualization: TM, XC, and YB; methodology: XC and JL; formal analysis and investigation: TM, LH, YL, and XC; writing—original draft preparation: TM; writing—review and editing: LH, YL, GZ, XC, and YB; funding acquisition: XC and YB; resources: JL; supervision: YB. All authors approved the final version to be published.

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Availability of data and materials Restrictions apply to the availability of these data. Data were obtained from UK Biobank (approved project number 76118) and are available at https://www.ukbiobank.ac.uk/ with the permission of UK Biobank.

Code availability Available if required.

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval This study was performed under generic ethical approval obtained by the UK Biobank from the National Health Service National Research Ethics Service (ref 11/NW/0382, 17 June 2011).

Consent to participate All participants provided their written informed consents for participating in the UK Biobank.

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