Associations of plasma omega-6 and omega-3 fatty acids with overall and 19 site-specific cancers: a population-based cohort study in UK Biobank

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Abstract

Background

Previous epidemiological studies of the associations between polyunsaturated fatty acids (PUFAs) and cancer incidence have been inconsistent. We investigated the associations of plasma omega-3 and omega-6 PUFAs with the incidence of overall and 19 site-specific cancers in a large prospective cohort.

Methods

253,138 eligible UK Biobank participants were included in our study. With a mean follow-up of 12.9 years, 29,838 participants were diagnosed with cancer. The plasma levels of omega-3 and omega-6 PUFAs were expressed as percentages of total fatty acids (omega-3% and omega-6%).

Results

In our main models, both omega-6% and omega-3% were inversely associated with overall cancer incidence (HR per SD = 0.98, 95% CI = 0.96-0.99; HR per SD = 0.99, 95% CI = 0.97-1.00; respectively). Of the 19 site-specific cancers available, 14 were associated with omega-6% and five with omega-3%, all indicating inverse associations, with the exception that prostate cancer was positively associated with omega-3% (HR per SD = 1.03, 95% CI = 1.01 - 1.05).

Conclusions

Our population-based cohort study in UK Biobank indicates small inverse associations of plasma omega-6 and omega-3 PUFAs with the incidence of overall and most site-specific cancers, although there are notable exceptions, such as prostate cancer.

Keywords

Polyunsaturated fatty acids, Omega-6 fatty acids, Omega-3 fatty acids, Cancer incidence, Prospective cohort study

Background

Cancer is a leading cause of morbidity and mortality worldwide, with an estimated 18.1 million cancer cases globally in 2020. Breast, lung, and colorectal cancer account for over 30% of the total annual incidence [1]. Polyunsaturated fatty acids (PUFAs) have been postulated to influence cancer incidence and survival [2-4]. Potential mechanisms of PUFAs in cancer etiology include serving as precursors to lipid mediators regulating metabolic pathways and inflammatory responses [5], and altering membrane composition that could affect cell signaling pathways [6].

Despite extensive interest and research, the links between PUFAs and cancer remain inconclusive. An umbrella review of meta-analyses of observational studies of cancer incidence concluded that there was no convincing evidence regarding the effects of omega-3 PUFAs on the risk of any cancer, and that there was only weak evidence supporting inverse associations of omega-3 intake with liver, breast, and brain cancers [3]. A meta-analysis of observational studies of cancer survival found that the intake of fish or marine omega-3 PUFAs, but not total omega-3 PUFAs, was associated with lower mortality in cancer patients [7]. A meta-analysis of randomized trials showed that increasing marine omega-3 PUFAs had little or no effects on overall cancer diagnosis or cancer death, while the effects of increasing omega-6 PUFAs were unclear because the evidence was of very low quality [2]. These systemic reviews showcase the limitations of existing studies, which include large between-study heterogeneity, small study bias, insufficient case numbers, and short follow-up time. Moreover, most studies relied on self-reported fish oil supplementation or estimated dietary intake, which may suffer from recall errors, outdated food databases, and measurement inaccuracy [8]. Circulating biomarkers provide more objective measures of omega-3 and omega-6 PUFA status and are reflective of dietary intakes [9]. Indeed, a meta-analysis of prospective studies found that the blood level of omega-6 PUFAs, but not their intake, was inversely associated with overall cancer risk [10]. Similarly, another meta-analysis showed that the blood level of omega-3 PUFAs, but not their intake, was associated with a lower colorectal cancer risk [11]. Addressing the limitations of current studies and examining objective blood levels of PUFAs may offer clarity into the roles of omega-3 and omega-6 PUFAs in cancer risk.

UK Biobank is a large population-based prospective cohort that has followed over 500,000 participants since 2006 [12]. It is a large homogeneous cohort with a long follow-up time, offering an unprecedented opportunity to examine the effects of PUFAs on overall cancer and a comprehensive range of site-specific cancers. A few early studies have revealed that fish oil supplementation or dietary omega-3 PUFA intake was associated with lower incidence of colon cancer, lung cancer, or liver cancer [13-15]. Recently, UK Biobank obtained metabolomic measurements of baseline plasma samples for about 60% of the participants, a random subset of the full cohort [16]. Leveraging this valuable dataset, we previously showed that circulating levels of omega-3 and omega-6 PUFAs were both inversely associated with overall cancer mortality [17]. In this study, we aim to examine the associations of circulating omega-3 and omega-6 PUFAs, as well as their ratio (i.e., omega-6/omega-3), with the incidence of overall and 19 site-specific cancers in UK Biobank.

Methods

Study population

Between 2006 and 2010, UK Biobank recruited over half a million participants, aged 37-73, in 22 assessment centers across England, Wales and Scotland. During the baseline assessment visit, a wide variety of sociodemographic, lifestyle, and health-related data were acquired through self-administered touch-screen questionnaires, concise computer-assisted interviews, and physical and functional measures. Blood, urine, and saliva samples were also collected. Of the 502,366 participants, those who had cancer diagnoses at baseline (n=37,737, excluding nonmelanoma skin cancer with an ICD-10 code of C44), those who had withdrawn from UK Biobank (n=1,227), and those with missing data on the plasma polyunsaturated fatty acids (n=210,264) were excluded from our study. A total of 253,138 eligible participants were eventually included.

Ascertainment of exposures

The absolute concentrations of plasma polyunsaturated fatty acids (PUFAs) were assessed using nuclear magnetic resonance (NMR) in plasma samples obtained at the baseline visit from 2007 to 2010, and the corresponding percentages of total fatty acids were calculated [12, 16]. The omega-3 fatty acids to total fatty acids percentage (omega-3%) and the omega-6 fatty acids to

total fatty acids percentage (omega-6%) were the primary exposures of interest in this study. In addition, we conducted analyses on the ratio of plasma omega-6/omega-3 PUFAs, docosahexaenoic acid to total fatty acids percentage (DHA%), and linoleic acid to total fatty acids percentage (LA%). No other individual PUFAs, except DHA and LA, were measured by the NMR metabolomic platform.

Ascertainment of outcomes

The primary outcomes were the first incidence of overall and 19 site-specific cancers based on diagnostic records in cancer registers ascertained from National Health Service (NHS) central registers [12]. At the time of our analysis (15 August 2023), we had access to the most current health outcomes dataset (Version: July 2023), which contained cancer incidence records up to 19 December 2022. Consequently, follow-up time was calculated from the recruitment date until the aforementioned date, any cancer diagnosis or death, whichever came first. The incidence of cancer was coded according to the World Health Organization's International Statistical Classification of Diseases (ICD)-9 or ICD-10 codes. Participants who had cancer at baseline (excluding nonmelanoma skin cancer) were excluded. ICD-9 codes were only used for pre-existing cancer and thus excluded. New cancer incidence was defined based on ICD-10 codes for overall cancer (C00-C97, excluding nonmelanoma skin cancer, C44) and the following 19 site-specific cancers: head and neck (C00-C14), esophagus (C15), stomach (C16), colon (C18), rectum (C19-C20), hepatobiliary tract (C22-C24), pancreas (C25), lung (C33-C34), malignant melanoma (C43), connective soft tissue (C49), breast (C50), uterus (C54-C55), ovary (C56), prostate (C61), kidney (C64-C65), bladder (C66-C67), brain (C70-C72), thyroid (C73), and lymphoid and hematopoietic tissues (C81-C96).

Covariates

The initial questionnaire covered a comprehensive range of potential confounding factors: demographic characteristics (e.g., age, gender, ethnicity); socioeconomic status, as measured by the Townsend Deprivation Index (TDI); lifestyle behaviors (e.g., alcohol consumption, smoking status, body mass index (BMI), and physical activity); and history or family history of diseases (e.g., diabetes, gastroesophageal reflux disease and family history of cancer). Body mass index (BMI) was calculated from weight and height expressed in kg/m^2. Waist circumference and hip circumference were recorded at a central registry, and we calculated the corresponding waist-hip

ratio (waist circumference divided by hip circumference). The TDI, employed as a measure of socioeconomic deprivation, was directly obtained from the UK Biobank database, with a higher score indicating a higher level of socioeconomic deprivation.

Statistical analyses

We began by summarizing and comparing participant characteristics based on the quintiles of the plasma omega-6% and omega-3% at baseline using descriptive statistics. To assess the differences in demographic features across these quintiles, we employed Pearson's Chi-squared test for categorical variables and the ANOVA test for continuous variables.

To explore the associations with cancer incidence for plasma omega-6%, omega-3%, and their ratio, we utilized multivariable Cox proportional hazards regression models to estimate hazard ratios (HRs) along with their corresponding 95% confidence intervals (CIs). We developed three distinct models, namely, the simply adjusted model, the main model, and the additionally adjusted model. Within the simply adjusted model, age and sex were designed as stratification variables owing to their violation of the assumptions inherent to the proportional hazards model. The main model was additionally adjusted for ethnicity (classified into White, Black, Asian, Others), TDI (continuous), assessment center (categorical), BMI (kg/m2; continuous), smoking status (categorized as never, previous, current), alcohol intake status (categorized as never, previous, current), and physical activity (classified as low, moderate, high). In addition to investigating the overall cancer, we also performed separate analyses for each site-specific cancer. The analysis of prostate cancer was restricted to the male sample, whereas the investigation of breast cancer, ovarian cancer, and uterine cancer was limited to the female sample. Furthermore, to adjust for additional possible confounding variables, we incorporated additional covariates into the analysis for certain cancer types (i.e., additionally adjusted models), guided by previous literature and biological plausibility [15]. More details can be found in Table S1.

Our analysis treated the exposures of interest both in continuous (standardized to a mean of 0 and standard deviation of 1) and categorical (in quintiles) terms. When conducting trend tests, we used the median value of each quintile as a continuous variable within the models. Given 19 distinct cancer subtypes, we adopted the False Discovery Rate (FDR) approach to address the issue of increasing false positives arising from multiple testing and reported the adjusted p-

values for simply adjusted models and main models. We did not perform multiple testing correction for the additionally adjusted models because they were for the purpose of sensitivity analysis and were only performed for 10 site-specific cancers with site-specific covariates. We also evaluated potential nonlinear dose-response using a semi-parametric approach through the utilization of restricted cubic splines [18] (4 knots were used in regression splines). We considered there was evidence supporting the presence of an association between a PUFA exposure and a cancer outcome if the continuous exposure analysis or the trend across quintiles analysis was statistically significant in the main models or in the additionally adjusted models, if applicable. In addition to the two above-described analyses, we assessed if there were any differences among the HRs across the five quintiles by applying likelihood ratio tests.

In secondary analyses aiming at investigating potential variations in associations within distinct population subgroups, we replicated the aforementioned analyses for overall cancer while stratifying the data by the following factors: age (< vs. ≥ the median age of 58 years), sex (male vs. female), TDI (< vs. ≥ the population median of -2), BMI (< vs. ≥ 25), current smoking status (yes vs. no), current alcohol consumption status (yes vs. no) and level of physical activity (low and moderate vs. high). The exposures of interest (omega-6%, omega-3%, and their ratio) were categorized in quintiles. For each stratification variable, we conducted a likelihood ratio test to obtain the associated p-value for interaction. In the case of continuous stratification variables (i.e., age, TDI, and BMI), we calculated interaction p-values based on a one-unit alteration of the respective stratification variables.

Furthermore, we carried out a series of sensitivity analyses. First, to assess whether the association of plasma omega-6% with overall cancer risk would be altered by omega-3% or vice versa, we replicated the main analysis for overall cancer while involving both omega-6% and omega-3% as variables in the model. The correlation between omega-3% and omega-6% was assessed by the Pearson correlation. Second, to explore the effects of individual fatty acids, DHA and LA, on cancer incidence, we repeated the main analysis on DHA% and LA%. Third, to investigate the potential impact of reverse causation on the observed associations, individuals who experienced outcomes within the first year or the first three years of the follow-up period were excluded from the analysis. Last, to evaluate the representativeness of the study participants,

we conducted a comparative analysis of baseline characteristics between those individuals with exposure information and those without it. All p-values were assessed using a two-sided approach. Statistical significance was defined as a p-value less than 0.05 or a 95% confidence interval that did not include the value 1.0 for the corresponding HRs. We conducted all analyses using R (version: 4.0.3).

Results

Baseline characteristics

Within our analytical cohort of 253,138 participants, spanning an average follow-up period of 12.9 years, a total of 29,838 individuals were diagnosed with cancer during follow-up. The baseline characteristics of all participants distributed across quintiles of plasma omega-6% and omega-3% were summarized in Table 1 and Table S2, respectively. On average, study participants were approximately 56 years old, with 90% of them identifying as White. Those in the higher quintiles of plasma omega-6% tended to be younger, female, with lower BMI and more physically active, and were less likely to smoke or drink alcohol.

Associations of plasma omega-6, omega-3, and their ratio with cancer risk

The findings for the associations of plasma omega-6% and omega-3% with the incidence of overall and site-specific cancer are shown in Figure 1, with more detailed information in Tables 2 and 3. In the main models with continuous omega-6% and omega-3%, each standard deviation (SD) increase in the percentage was associated with a 2% (HR per SD = 0.98, 95% CI = 0.96-0.99, $p < 0.01$) and 1% (HR per SD = 0.99, 95% CI = 0.97 - 1.00, $p = 0.03$) decline in risk of overall cancer for omega-6% and omega-3%, respectively. Additionally, categorizing omega-6% and omega-3% into quintiles revealed that higher concentrations were linked to a decreased overall cancer risk, with a significant trend observed for both omega-6% and omega-3% ($p_{trend} < 0.05$).

We performed similar analyses for 19 site-specific cancers. In the main models with continuous exposure, omega-6% was inversely associated with the risk of 13 site-specific cancers (corrected $p < 0.05$, Figure 1). If considering the trend across the quintiles in the main models, all but two site-specific cancers had inverse associations with omega-6%. The two exceptions were prostate

cancer and malignant neoplasms of lymphoid and hematopoietic tissues (corrected $p_{trend} < 0.05$, Table 2). As for omega-3%, only five site-specific cancers had significant associations in the main analysis with continuous exposure (Figure 1), and the trend analysis across quintiles did not reveal additional significant associations (Table 3). Cancers at four sites, including stomach, colon, hepatobiliary tract, and lung, were inversely associated with both omega-6% and omega-3%. Only one site-specific cancer, prostate cancer, was associated with omega-3% (HR per SD = 1.03, 95% CI = 1.01 - 1.05, corrected p = 0.049) but not omega-6% (HR per SD = 1.01, 95% CI = 0.98 - 1.03, corrected p = 0.56). In the sensitivity analysis of 10 site-specific cancers by additionally adjusting for site-specific covariates, most of the above-mentioned significant associations remained, except the associations of omega-6% with cancers at breast, uterus, and ovary (Figure 2). In summary, we counted associations that were statistically significant in the main models with either continuous exposure analysis or trend analysis, and that remain significant after adjusting for additional site-specific covariates when appropriate. There were 14 site-specific cancers associated with omega-6% and five with omega-3%, with an overlap of four between these two groups. Only four site-specific cancers (i.e., ovary, breast, uterus, and lymphoid and hematopoietic tissues) were not associated with either omega-3% or omega-6%.

We also conducted analysis of the omega-6/omega-3 ratio (Table S3, Figure S1). A higher omega-6/omega-3 ratio was associated with a higher overall cancer risk ($p_{trend} = 0.038$). A total of three site-specific cancers showed evidence of positive associations with the ratio. Every SD increment in the ratio was associated with a 2% increase in the risk of rectum cancer, and the association remained unchanged after additionally controlling for site-specific covariates (per SD HR = 1.02, 95% CI = 1.01 - 1.03, p = 0.003). When examining trends across quintiles, lung cancer was significant in the main model (corrected $p_{trend} = 0.011$) and remained significant after adjusting for additional covariates ($p_{trend} < 0.001$). Colon cancer was significant in the additionally adjusted model ($p_{trend} = 0.015$).

In addition to the trend analysis across quintiles, we assessed if there were any differences across the association effect sizes of quintiles by applying likelihood ratio tests. Most of the PUFAs-cancer relationships with significant trends were also statistically significant in the overall likelihood ratio tests. On the other hand, there were two pairs of relationships whose trend

analyses were not significant, but their overall tests were. The most notable pair was omega-6% and prostate cancer (additionally adjusted model, p_{trend} = 0.72, $p_{overall}$ = 0.005). The association estimates across the quintiles support the presence of a nonlinear relationship: Quintile 2 (HR = 1.10, 95% CI = 1.02 - 1.18), Quintile 3 (HR = 1.09, 95% CI = 1.01 - 1.17), Quintile 4 (HR = 1.09, 95% = 1.00 - 1.17), and Quintile 5 (HR = 0.98, 95% CI = 0.90-1.06). The other pair was omega-6% and uterus cancer (additionally adjusted model, p_{trend} = 0.97, $p_{overall}$ = 0.022), and there was an inverse association in the Quintile 5 (HR = 0.81, 95% CI = 0.66-0.99).

Stratified analyses for plasma omega-6 and omega-3 fatty acids

Stratified analyses were conducted to assess potential effect modifications by age, sex, TDI, BMI, smoking status, alcohol consumption status, and physical activity, as shown in Table 4. The observed inverse associations of plasma omega-6% with overall cancer risk appeared to be notably more pronounced in the younger age group (p for interaction <0.001) and in females (p for interaction = 0.006), with no apparent modification by the remaining potential stratification variables. Moreover, the estimated inverse associations of plasma omega-3% with overall cancer risk demonstrated a tendency to be stronger in the older group (p for interaction < 0.001), in males (p for interaction = 0.002), and in current smokers (p for interaction = 0.017).

Restricted cubic spline analysis

In the restricted cubic spline analysis, it is noteworthy that significant inverse associations were observed for omega-6% and omega-3% with the overall cancer incidence ($p < 0.05$ for both variables, as shown in Figure S2). Moreover, potential nonlinearity was identified for the relationship between omega-3% and overall cancer incidence ($p < 0.05$). This finding suggests that the protective effect of omega-3 PUFAs may exhibit enhanced efficacy at the lower concentration level. Due to the possible presence of a nonlinear association between omega-6% and prostate cancer, we further performed cubic spline analysis for prostate cancer. We found evidence of nonlinearity between omega-6% and prostate cancer, with the intermediate level of omega-6% associated with the highest risk (p = 0.02, Figure S3).

Sensitivity analyses

In order to evaluate whether the associations between plasma omega-6% and overall cancer risk might undergo modification by omega-3%, or vice versa, both omega-6% and omega-3% were

simultaneously integrated into the same models (as detailed in Table S4 and Table S5). The correlation between plasma omega-6% and omega-3% was relatively low, with r = -0.12 ($p < 0.01$). After their inclusion in the same models, the associations of both plasma omega-6% and omega-3% with overall cancer risk remained statistically significant. The results for DHA% and LA% were consistent with those for omega-3% and omega-6%, respectively (as detailed in Table S6 and Table S7). Additionally, when we excluded participants who experienced cancer or death within the first year or the first three years of follow-up, the outcomes remained unchanged (as detailed in Table S8 and Table S9). It is worth noting that the baseline characteristics were comparable between participants with and without exposure information, as evidenced by Table S10.

Discussion

Our population-based prospective cohort study in UK Biobank revealed that higher plasma omega-6% and omega-3% were both associated with a lower incidence of overall cancer. The overall association effect sizes in the main model were 2% and 1% reductions per SD of omega-6% and omega-3%, respectively. The association of omega-6% with cancer risk was independent of most risk factors examined, including TDI, BMI, smoking status, alcohol status, and physical activity. The observed inverse associations of plasma omega-6% appeared to be notably more pronounced in the younger age group and in women. On the other hand, the inverse associations of plasma omega-3% with overall cancer incidence were stronger in the older age group, in men, and in current smokers. The inverse associations of omega-6% and omega-3% with overall cancer incidence were robust to a list of sensitivity analyses. In terms of the incidence of 19 site-specific cancers, 14 were associated with omega-6% and five with omega-3%, all exhibiting inverse associations (3% - 7% reduced risk per SD of omega-6%; 5% - 8% reduced risk per SD of omega-3%), with the exception that prostate cancer was positively associated with omega-3% (3% increased risk). Only four site-specific cancers (i.e., ovary, breast, uterus, and lymphoid and hematopoietic tissues) were not associated with either omega-3% or omega-6%.

Despite a large number of studies, the links between PUFAs, especially omega-6 PUFAs, and the incidence of overall cancer remain ill-defined. Most existing studies examined dietary PUFAs or

supplements, instead of circulating biomarkers. A 2019 prospective cohort study found no significant associations of omega-3 or omega-6 PUFA intakes with the overall cancer incidence [19]. A 2020 meta-analysis of randomized trials showed that increasing dietary long-chain omega-3 PUFAs had little or no effects on overall cancer diagnosis or cancer death, while the effects of increasing dietary omega-6 PUFAs were unclear because the evidence was of very low quality [2]. A 2022 meta-analysis of observational studies revealed that fish intake and marine omega-3 PUFA intake were associated with lower mortality in patients with overall cancer [7]. Of note, a 2020 meta-analysis of prospective studies showed that the blood level of omega-6 PUFAs (highest vs. lowest category RR = 0.92, 95% CI = 0.86 - 0.98), but not their intake, was inversely associated with overall cancer risk [10]. They also found that the protective association was stronger in women than in men, consistent with our findings. In the context of UK Biobank, a 2021 prospective study demonstrated that regular fish oil supplementation was associated with a lower incidence of overall cancer, but only in participants who consumed fatty fish less than two times per week (HR = 0.96, 95% CI = 0.94 - 0.99), not in those who consumed more than twice per week (HR = 1.01, 95% CI = 0.95 - 1.07). Their subgroup analysis further unraveled that men were more likely to gain benefits from fish oil supplementation than women [15]. Consistently, our study found that the plasma level of omega-3 PUFAs was inversely associated with overall cancer incidence and that the association was only significant in men. Moreover, a 2023 study of circulating PUFAs and cancer mortality by our group revealed that both plasma omega-3 and omega-6 PUFAs were inversely associated with cancer mortality (highest vs. lowest quintile HR = 0.75, 95% = 0.65 - 0.87; HR = 0.80, 95% CI = 0.68 - 0.92; respectively) [17]. Overall, our findings provide support for possible small net protective roles of omega-3 and omega-6 PUFAs in the development of new cancer incidence. Our study also suggests that the usage of circulating blood biomarkers captures different aspects of dietary intake, reduces measurement errors, and thus enhances statistical power. The differential effects of omega-6% and omega-3% in age and sex subgroups warrant future investigation.

In our study, we observed site-specific associations of omega-3 PUFAs with cancer incidence. A higher plasma level of omega-3 PUFAs was associated with a significant reduction in the incidence of digestive system cancers (including colon, stomach, and hepatobiliary tract) and lung cancer. However, it appeared to be linked to an increased risk of prostate cancer. The

observed protective associations between plasma omega-3 PUFAs and the incidence of digestive system cancers and lung cancer are consistent with recent studies of fish oil supplementation and dietary intake in UK Biobank [13-15]. Regular fish oil supplementation was associated with lower incidence of colon cancer (HR = 0.88, 95% CI = 0.8-0.98), hepatobiliary cancer (HR = 0.72, 95% CI = 0.58-0.91), and lung cancer (HR = 0.87, 95% CI = 0.78-0.96) [15]. Another independent analysis of UK Biobank data revealed a 44% lower risk of liver cancer incidence among fish oil users [14]. Dietary intake of omega-3 PUFAs was associated with an 18% decreased risk in lung cancer incidence (HR=0.82, 95% CI= 0.73-0.93; per 1g/d) [13]. Notably, some studies and meta-analyses did not find significant associations of dietary omega-3 PUFAs and fish oil supplementation with colorectal cancer [3, 20, 21]. However, a recent meta-analysis showed that while the dietary intake of omega-3 PUFAs was not associated with the colorectal cancer risk (relative risk, RR = 0.97, 95% CI = 0.90 - 1.04 for the highest versus lowest category), the blood level of omega-3 PUFAs was associated with a lower risk (RR = 0.79, 95% CI = 0.64 - 0.98) [11]. Regarding prostate cancer, most studies did not find significant associations with dietary intake or blood level of omega-3 PUFAs [3, 15, 22-24]. However, the few statistically significant findings suggest that dietary intake of alpha-linolenic acid (ALA) was associated with a lower prostate cancer risk, while both dietary intake and blood level of DHA were associated with a higher risk [3, 23, 25]. Our study found that plasma omega-3% and DHA% were both positively associated with the risk of prostate cancer. Further studies are warranted to explore the roles of individual omega-3 PUFAs in the etiology of prostate cancer.

In our investigation of omega-6 PUFAs, we observed inverse associations of plasma omega-6 PUFAs with 14 site-specific cancers at head and neck, esophagus, stomach, colon, rectum, hepatobiliary tract, pancreas, lung, malignant melanoma, connective soft tissue, kidney, bladder, brain, and thyroid. Moreover, an increased omega-6/omega-3 PUFAs ratio was associated with elevated risks of rectum, colon, and lung cancer. Notably, the evidence on the associations between omega-6 PUFAs, the omega-6/omega-3 ratio, and site-specific cancers was limited and exhibited varying results. Two prospective cohort studies did not establish significant links between dietary omega-6 PUFAs and colorectal cancer [20, 21]. However, in agreement with our findings, another prospective cohort study observed that omega-6 PUFA intake was inversely associated with the risk of digestive cancer (including esophagus, liver, stomach, pancreas, and

388 colorectal) (highest vs. lowest quintile HR = 0.56, 95% CI = 0.32 - 0.97) or colorectal cancer
389 alone (HR = 0.43, 95% CI = 0.22 - 0.83)(19). Also consistent with our results, a prospective
390 cohort study based on UK Biobank indicated a modest protective effect of dietary omega-6
391 PUFAs against lung cancer (HR = 0.98, 95% CI = 0.96-0.99; per 1g/d) [13]. A systematic review
392 and meta-analysis of eight previous studies also found no apparent association between dietary
393 omega-6 PUFAs and prostate cancer [23], in line with our findings from trend analysis.
394 However, we did find evidence for the possible presence of a nonlinear relationship, with
395 intermediate levels of omega-6% associated with the highest risk of prostate cancer. There were
396 three site-specific cancers at breast, uterus, and ovary that were inversely associated with plasma
397 omega-6% in our main models, but these associations disappeared after controlling for site-
398 specific covariates, such as age of menarche, hormone replacement therapy use, oral
399 contraceptive use, number of live births, menopausal status, and hysterectomy status. A previous
400 meta-analysis of prospective studies did observe an inverse association of the blood omega-6
401 level with breast cancer (highest vs. lowest category RR = 0.87; 95% CI: 0.77–0.98) [10]. Our
402 study indicated that the consideration of site-specific covariates is critical in interpreting
403 associations.
404
405 This study has several strengths. The major strength was the prospective population-based study
406 design in UK Biobank, which provides a large sample size, long duration of follow-up, and
407 detailed information on potential confounding variables. We used the objective measurements of
408 PUFA biomarkers in plasma instead of the estimated dietary intakes from self-reported
409 questionnaires, which increases the accuracy of exposure assessment. Moreover, the cancer
410 incidence data were acquired through cancer registries to reduce selection bias. This approach
411 ensures a more representative sample, as these registries comprehensively cover a wide range of
412 demographics and cancer types, and adhere to standardized data collection protocols, thereby
413 enhancing the reliability and generalizability of our findings [26]. Furthermore, we adopted the
414 FDR approach when investigating site-specific cancers, to address the issue of increasing false
415 positives from multiple comparisons. In several sensitivity analyses, most of the associations
416 remain materially unchanged, indicating the robustness of our results.
417

Some potential limitations warrant consideration in the interpretation of our findings. First, despite previous indications of the representativeness of UK Biobank in sociodemographic and health-related characteristics of the UK population, the potential for selective bias persists [27, 28]. Notably, the participant sample skewed heavily toward European ancestry and White ethnicity, necessitating caution in generalizing results across diverse ancestral backgrounds and ethnicities. Secondly, while we adjusted for multiple potential confounding variables in our model, the inherent limitations of observational studies preclude the complete elimination of inaccuracies in measurements, unmeasured variables, and interdependencies among factors. Thirdly, the number of events was small for some specific cancer sites, which may lead to the limited statistical power of our study. Fourthly, our study focused on total omega-3 and omega-6 PUFAs. There are only two individual PUFAs measured in the UK Biobank cohort, LA and DHA. We showed that the associations of LA% mirrored those of omega-6%, while DHA% mirrored omega-3%. Future studies into other individual PUFAs are needed. Lastly, despite the relative homogeneity of the sample, individual genetics have not been taken into account. Future studies are warranted to examine if specific genetic variants or composite genetic scores modify the associations of circulating PUFAs with overall or site-specific cancers.

Conclusion

In our UK Biobank prospective cohort study, elevated levels of plasma omega-6 and omega-3 PUFAs were linked to reduced overall cancer risk, while a higher omega-6/omega-3 ratio was associated with increased risk. The associations of omega-6 PUFAs were stronger in the younger age group and in women, while the associations of omega-3 PUFAs were more prominent in the older group, in men, and in current smokers. Our findings extended to the inverse associations of plasma omega-6 and omega-3 PUFAs with 14 site-specific cancers. One notable exception to this trend of protective association was between omega-3 PUFAs and prostate cancer. Our study laid a solid foundation for future mechanistic studies into the roles of PUFAs in the etiology of various cancers. It also provided insights into the development of cancer prevention strategies by managing circulating PUFAs.

Figure Legends

Figure 1. Risk estimates of the incidence of overall cancer and 19 cancer sites for 1-SD increase of plasma omega-6% and omega-3%, for simply adjusted and main models. The results from simply adjusted models revealed the associations stratified by age and sex in the general cohort. The main models were adjusted for general covariates, including ethnicity (classified into White, Black, Asian, Others), Townsend deprivation index (continuous), assessment Center, BMI (kg/m2; continuous), smoking status (categorized as never, previous, current), alcohol intake status (categorized as never, previous, current), and physical activity (classified as low, moderate, high). P values were corrected for the multiple testing of 19 site-specific cancers.

Figure 2. Risk estimates of the incidence of overall cancer and specific cancer sites for 1-SD increase of plasma omega-6% and omega-3%, for additionally adjusted models. For esophagus cancer, additionally adjusted for gastroesophageal reflux disease at baseline and waist-hip ratio. For colon cancer and rectum cancer, additionally adjusted for diabetes at baseline, aspirin use, processed meat intake, waist-hip ratio, and family history. For pancreas cancer, additionally adjusted for diabetes at baseline. For lung cancer, additionally adjusted for family history. For malignant melanoma cancer, additionally adjusted for skin color, ease of skin tanning, use of sun/UV protection, childhood sunburn occasions, frequency of solarium/sunlamp use. For breast cancer, restricted to female, and additionally adjusted for age when menarche started, hormone replacement therapy use, oral contraceptive use, number of live births, menopausal status, hysterectomy status, and family history. For uterus and ovary cancer, restricted to female, and additionally adjusted for age when menarche started, hormone replacement therapy use, oral contraceptive use, number of live births, menopausal status, hysterectomy status. For prostate cancer, restricted to male, and additionally adjusted for family history.

Additional Information

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Authors' contributions

YZ performed data analysis, prepared visualizations, and wrote the original draft of the manuscript. YS and SS contributed to the data analysis. NKK and JTB contributed to the interpretations of results. YS (yeshen@uga.edu) and KY (kaixiong.ye@uga.edu) contributed equally to this project and should be considered co-corresponding authors. They jointly designed and supervised the project. All authors critically edited the manuscript for important intellectual content. The corresponding author (KY) attests that all listed authors meet the authorship criteria and that no others meeting the criteria were omitted.

Ethics approval and consent to participate

The UK Biobank received ethical approval from the research ethics committee (reference ID: 11/NW/0382). Written informed consent was obtained from participants.

Consent for publication

Not applicable.

Data availability

The datasets analyzed during the current study are available from the UK Biobank through an application process (www.ukbiobank.ac.uk/).

Competing interests

The authors declare no competing interests.

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References

1. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.

2. Hanson S, Thorpe G, Winstanley L, Abdelhamid AS, Hooper L, Abdelhamid A, et al. Omega-3, omega-6 and total dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials. British Journal of Cancer. 2020;122(8):1260-70.

3. Lee KH, Seong HJ, Kim G, Jeong GH, Kim JY, Park H, et al. Consumption of Fish and ω-3 Fatty Acids and Cancer Risk: An Umbrella Review of Meta-Analyses of Observational Studies. Advances in Nutrition. 2020;11(5):1134-49.

4. Shahidi F, Ambigaipalan P. Omega-3 Polyunsaturated Fatty Acids and Their Health Benefits. Annu Rev Food Sci Technol. 2018;9:345-81.

5. Gleissman H, Johnsen JI, Kogner P. Omega-3 fatty acids in cancer, the protectors of good and the killers of evil? Exp Cell Res. 2010;316(8):1365-73.

6. Diggle CP. In vitro studies on the relationship between polyunsaturated fatty acids and cancer: tumour or tissue specific effects? Prog Lipid Res. 2002;41(3):240-53.

7. Wang YP, Liu K-J, Long T, Long J, Li Y, Li J, Cheng L. Dietary fish and omega-3 polyunsaturated fatty acids intake and cancer survival: A systematic review and meta-analysis. Critical Reviews in Food Science and Nutrition. 2022;63:6235 - 51.

8. Shim JS, Oh K, Kim HC. Dietary assessment methods in epidemiologic studies. Epidemiol Health. 2014;36:e2014009.

9. Hodson L, Skeaff CM, Fielding BA. Fatty acid composition of adipose tissue and blood in humans and its use as a biomarker of dietary intake. Prog Lipid Res. 2008;47(5):348-80.

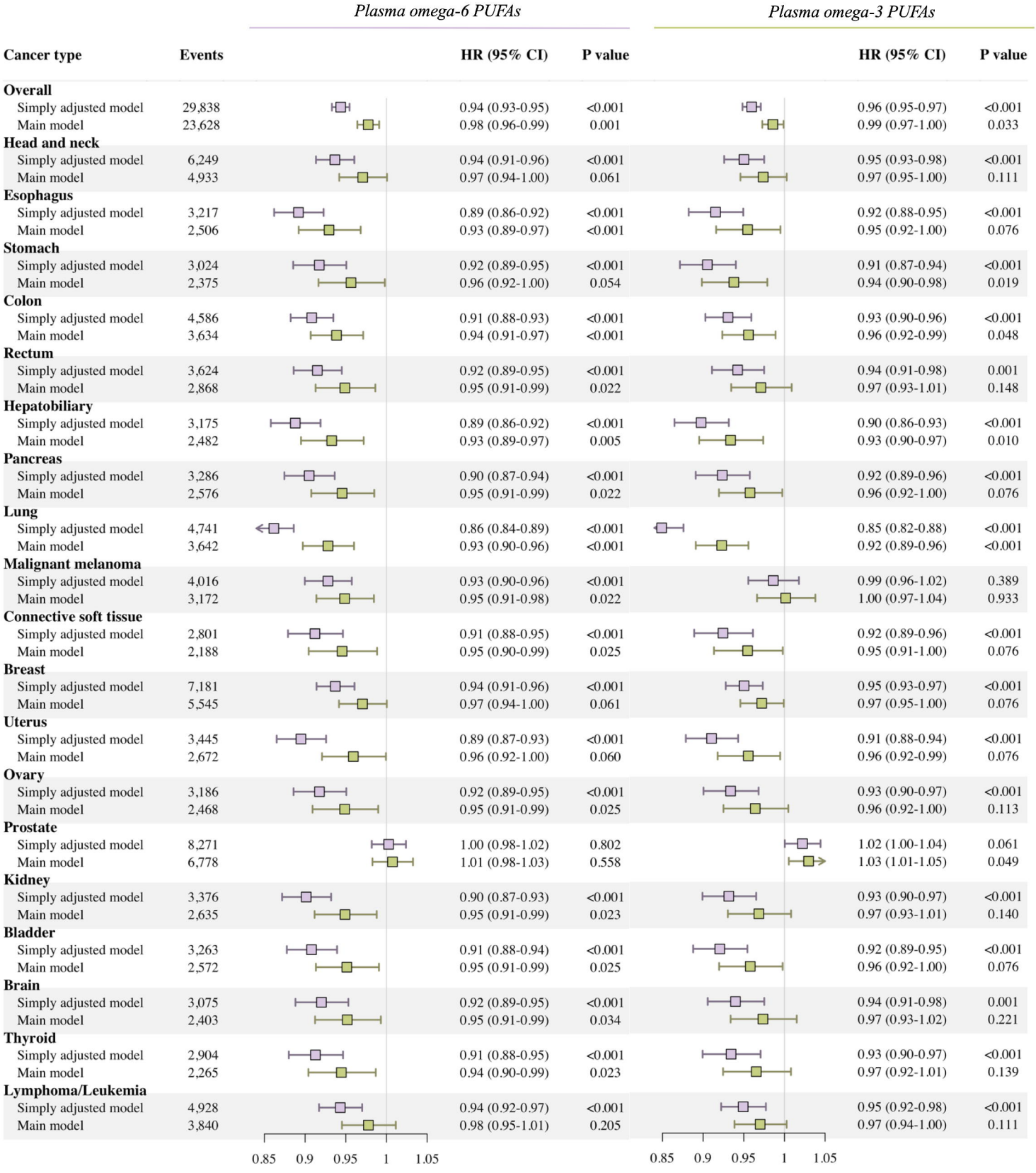
10. Kim Y, Kim J. N-6 Polyunsaturated Fatty Acids and Risk of Cancer: Accumulating Evidence from Prospective Studies. Nutrients. 2020;12(9).

11. Kim Y, Kim J. Intake or Blood Levels of n-3 Polyunsaturated Fatty Acids and Risk of Colorectal Cancer: A Systematic Review and Meta-analysis of Prospective Studies. Cancer Epidemiol Biomarkers Prev. 2020;29(2):288-99.

12. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS Med. 2015;12(3):e1001779.

538 13. Chen T, Song L, Zhong X, Zhu Q, Huo J, Chen J, et al. Dietary polyunsaturated fatty
539 acids intake, air pollution, and the risk of lung cancer: A prospective study in UK biobank.
540 Science of The Total Environment. 2023;882:163552.
541 14. Jiang W, Li F-R, Yang H-H, Chen G-C, Hua Y-F. Relationship between fish oil use and
542 incidence of primary liver cancer: findings from a population-based prospective cohort study.
543 Frontiers in Nutrition. 2021;8:771984.
544 15. Liu Z, Luo Y, Ren J, Yang L, Li J, Wei Z, et al. Association between fish oil
545 supplementation and cancer risk according to fatty fish consumption: A large prospective
546 population-based cohort study using UK Biobank. International Journal of Cancer.
547 2022;150(4):562-71.
548 16. Julkunen H, Cichońska A, Tiainen M, Koskela H, Nybo K, Mäkelä V, et al. Atlas of
549 plasma NMR biomarkers for health and disease in 118,461 individuals from the UK Biobank.
550 Nature Communications. 2023;14(1):604.
551 17. Zhang Y, Sun Y, Yu Q, Song S, Brenna JT, Shen Y, Ye K. Higher ratio of plasma omega-
552 6/omega-3 fatty acids is associated with greater risk of all-cause, cancer, and cardiovascular
553 mortality: a population-based cohort study in UK Biobank. eLife Sciences Publications, Ltd;
554 2023.
555 18. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med.
556 1989;8(5):551-61.
557 19. Sellem L, Srour B, Guéraud F, Pierre FHF, Kesse□Guyot E, Fiolet T, et al. Saturated,
558 mono- and polyunsaturated fatty acid intake and cancer risk: results from the French prospective
559 cohort NutriNet-Santé. European Journal of Nutrition. 2019;58:1515-27.
560 20. Nguyen SM, Li H-L, Yu D, Cai H, Gao J, Gao Y-T, et al. Dietary fatty acids and
561 colorectal cancer risk in men: A report from the Shanghai Men's Health Study and a
562 meta□analysis. International Journal of Cancer. 2020;148:77 - 89.
563 21. Song M, Chan AT, Fuchs CS, Ogino S, Hu FB, Mozaffarian D, et al. Dietary intake of
564 fish, ω-3 and ω-6 fatty acids and risk of colorectal cancer: A prospective study in U.S. men and
565 women. International Journal of Cancer. 2014;135(10):2413-23.
566 22. Aucoin M, Cooley K, Knee C, Fritz H, Balneaves LG, Breau R, et al. Fish-Derived
567 Omega-3 Fatty Acids and Prostate Cancer: A Systematic Review. Integr Cancer Ther.
568 2017;16(1):32-62.

569 23. Chua ME, Sio MCD, Sorongon MC, Dy JS. Relationship of Dietary Intake of Omega-3
570 and Omega-6 Fatty Acids with Risk of Prostate Cancer Development: A Meta-Analysis of
571 Prospective Studies and Review of Literature. Prostate Cancer. 2012;2012:826254.
572 24. Farrell SW, DeFina LF, Tintle NL, Leonard D, Cooper KH, Barlow CE, et al. Association
573 of the Omega-3 Index with Incident Prostate Cancer with Updated Meta-Analysis: The Cooper
574 Center Longitudinal Study. Nutrients. 2021;13(2):384.
575 25. Fu Y-Q, Zheng J-S, Yang B, Li D. Effect of Individual Omega-3 Fatty Acids on the Risk
576 of Prostate Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective
577 Cohort Studies. Journal of Epidemiology. 2015;25(4):261-74.
578 26. Allen NE, Lacey B, Lawlor DA, Pell JP, Gallacher J, Smeeth L, et al. Prospective study
579 design and data analysis in UK Biobank. Sci Transl Med. 2024;16(729):eadf4428.
580 27. Batty GD, Gale CR, Kivimäki M, Deary IJ, Bell S. Comparison of risk factor
581 associations in UK Biobank against representative, general population based studies with
582 conventional response rates: prospective cohort study and individual participant meta-analysis.
583 Bmj. 2020;368:m131.
584 28. Fry A, Littlejohns TJ, Sudlow C, Doherty N, Adamska L, Sprosen T, et al. Comparison of
585 Sociodemographic and Health-Related Characteristics of UK Biobank Participants With Those
586 of the General Population. Am J Epidemiol. 2017;186(9):1026-34.
587


Plasma omega-6 PUFAs
Plasma omega-3 PUFAs
Cancer type
Events
HR (95% CI)
P value
HR (95% CI)
P value
Overall
Simply adjusted model 29,838 0.94 (0.93-0.95) <0.001 0.96 (0.95-0.97) <0.001
Main model 23,628 0.98 (0.96-0.99) 0.001 0.99 (0.97-1.00) 0.033
Head and neck
Simply adjusted model 6,249 0.94 (0.91-0.96) <0.001 0.95 (0.93-0.98) <0.001
Main model 4,933 0.97 (0.94-1.00) 0.061 0.97 (0.95-1.00) 0.111
Esophagus
Simply adjusted model 3,217 0.89 (0.86-0.92) <0.001 0.92 (0.88-0.95) <0.001
Main model 2,506 0.93 (0.89-0.97) <0.001 0.95 (0.92-1.00) 0.076
Stomach
Simply adjusted model 3,024 0.92 (0.89-0.95) <0.001 0.91 (0.87-0.94) <0.001
Main model 2,375 0.96 (0.92-1.00) 0.054 0.94 (0.90-0.98) 0.019
Colon
Simply adjusted model 4,586 0.91 (0.88-0.93) <0.001 0.93 (0.90-0.96) <0.001
Main model 3,634 0.94 (0.91-0.97) <0.001 0.96 (0.92-0.99) 0.048
Rectum
Simply adjusted model 3,624 0.92 (0.89-0.95) <0.001 0.94 (0.91-0.98) 0.001
Main model 2,868 0.95 (0.91-0.99) 0.022 0.97 (0.93-1.01) 0.148
Hepatobiliary
Simply adjusted model 3,175 0.89 (0.86-0.92) <0.001 0.90 (0.86-0.93) <0.001
Main model 2,482 0.93 (0.89-0.97) 0.005 0.93 (0.90-0.97) 0.010
Pancreas
Simply adjusted model 3,286 0.90 (0.87-0.94) <0.001 0.92 (0.89-0.96) <0.001
Main model 2,576 0.95 (0.91-0.99) 0.022 0.96 (0.92-1.00) 0.076
Lung
Simply adjusted model 4,741 0.86 (0.84-0.89) <0.001 0.85 (0.82-0.88) <0.001
Main model 3,642 0.93 (0.90-0.96) <0.001 0.92 (0.89-0.96) <0.001
Malignant melanoma
Simply adjusted model 4,016 0.93 (0.90-0.96) <0.001 0.99 (0.96-1.02) 0.389
Main model 3,172 0.95 (0.91-0.98) 0.022 1.00 (0.97-1.04) 0.933
Connective soft tissue
Simply adjusted model 2,801 0.91 (0.88-0.95) <0.001 0.92 (0.89-0.96) <0.001
Main model 2,188 0.95 (0.90-0.99) 0.025 0.95 (0.91-1.00) 0.076
Breast
Simply adjusted model 7,181 0.94 (0.91-0.96) <0.001 0.95 (0.93-0.97) <0.001
Main model 5,545 0.97 (0.94-1.00) 0.061 0.97 (0.95-1.00) 0.076
Uterus
Simply adjusted model 3,445 0.89 (0.87-0.93) <0.001 0.91 (0.88-0.94) <0.001
Main model 2,672 0.96 (0.92-1.00) 0.060 0.96 (0.92-0.99) 0.076
Ovary
Simply adjusted model 3,186 0.92 (0.89-0.95) <0.001 0.93 (0.90-0.97) <0.001
Main model 2,468 0.95 (0.91-0.99) 0.025 0.96 (0.92-1.00) 0.113
Prostate
Simply adjusted model 8,271 1.00 (0.98-1.02) 0.802 1.02 (1.00-1.04) 0.061
Main model 6,778 1.01 (0.98-1.03) 0.558 1.03 (1.01-1.05) 0.049
Kidney
Simply adjusted model 3,376 0.90 (0.87-0.93) <0.001 0.93 (0.90-0.97) <0.001
Main model 2,635 0.95 (0.91-0.99) 0.023 0.97 (0.93-1.01) 0.140
Bladder
Simply adjusted model 3,263 0.91 (0.88-0.94) <0.001 0.92 (0.89-0.95) <0.001
Main model 2,572 0.95 (0.91-0.99) 0.025 0.96 (0.92-1.00) 0.076
Brain
Simply adjusted model 3,075 0.92 (0.89-0.95) <0.001 0.94 (0.91-0.98) 0.001
Main model 2,403 0.95 (0.91-0.99) 0.034 0.97 (0.93-1.02) 0.221
Thyroid
Simply adjusted model 2,904 0.91 (0.88-0.95) <0.001 0.93 (0.90-0.97) <0.001
Main model 2,265 0.94 (0.90-0.99) 0.023 0.97 (0.92-1.01) 0.139
Lymphoma/Leukemia
Simply adjusted model 4,928 0.94 (0.92-0.97) <0.001 0.95 (0.92-0.98) <0.001
Main model 3,840 0.98 (0.95-1.01) 0.205 0.97 (0.94-1.00) 0.111
0.85 0.9 0.95 1 1.05
0.85 0.9 0.95 1 1.05

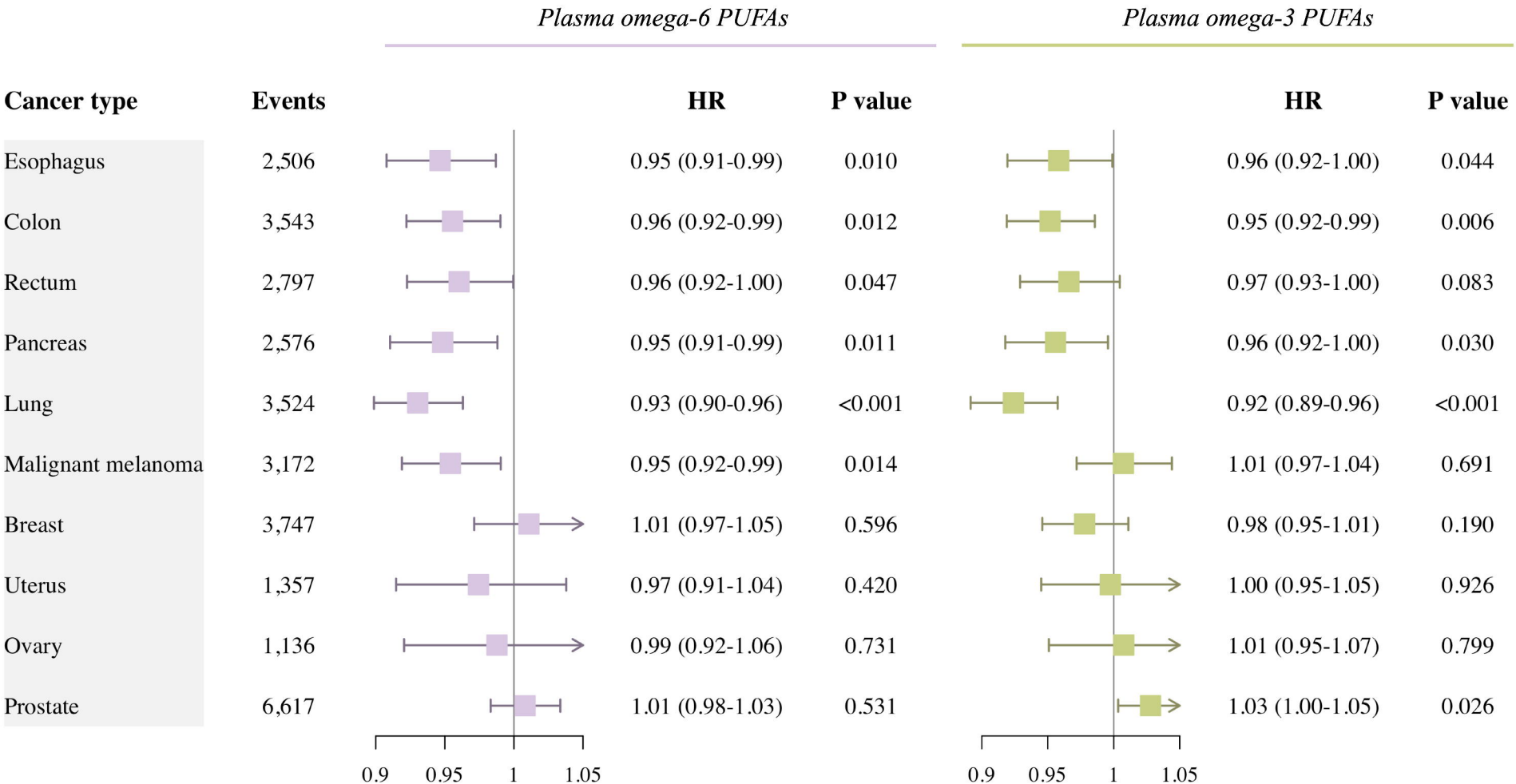

Plasma omega-6 PUFAs
Plasma omega-3 PUFAs
Cancer type
Events
HR
P value
HR
P value
Esophagus
2,506
0.95 (0.91-0.99)
0.010
0.96 (0.92-1.00)
0.044
Colon
3,543
0.96 (0.92-0.99)
0.012
0.95 (0.92-0.99)
0.006
Rectum
2,797
0.96 (0.92-1.00)
0.047
0.97 (0.93-1.00)
0.083
Pancreas
2,576
0.95 (0.91-0.99)
0.011
0.96 (0.92-1.00)
0.030
Lung
3,524
0.93 (0.90-0.96)
<0.001
0.92 (0.89-0.96)
<0.001
Malignant melanoma
3,172
0.95 (0.92-0.99)
0.014
1.01 (0.97-1.04)
0.691
Breast
3,747
1.01 (0.97-1.05)
0.596
0.98 (0.95-1.01)
0.190
Uterus
1,357
0.97 (0.91-1.04)
0.420
1.00 (0.95-1.05)
0.926
Ovary
1,136
0.99 (0.92-1.06)
0.731
1.01 (0.95-1.07)
0.799
Prostate
6,617
1.01 (0.98-1.03)
0.531
1.03 (1.00-1.05)
0.026
0.9
0.95
1
1.05
0.9
0.95
1
1.05

Table 1. Baseline characteristics of included participants by quintiles of the plasma omega-6% (n = 253,138)

Characteristics[a]	Omega-6% quintiles					p-value
	1 (median = 32.9) (n = 50,628)	**2** (median = 36.4) (n = 50,628)	**3** (median = 38.4) (n = 50,628)	**4** (median = 40.0) (n = 50,627)	**5** (median = 42.1) (n = 50,627)	
Age (years)	57.6 (7.7)	57.7 (7.8)	57.1 (7.9)	55.9 (8.1)	53.6 (8.2)	<0.001[a]
Gender (male%)	61.8	49.8	42.9	39.6	41.9	<0.001[b]
Ethnicity(n%)						
White	46,982 (93.2%)	46,868 (92.9%)	46,597 (92.4%)	45,918 (91.1%)	43,857 (87.2%)	<0.001[b]
Black	196 (0.4%)	229 (0.5%)	237 (0.5%)	256 (0.5%)	459 (0.9%)	
Asian	1,387 (2.8%)	1,514 (3.0%)	1,663 (3.3%)	1,948 (3.9%)	2,467 (4.9%)	
Others	1,831 (3.6%)	1,836 (3.6%)	1,933 (3.8%)	2,282 (4.5%)	3,530 (7.0%)	
Missing (n)	232	181	198	223	314	
TDI	-1.2 (3.2)	-1.4 (3.0)	-1.5 (3.0)	-1.5 (3.0)	-1.2 (3.2)	<0.001[a]
Missing (n)	55	59	63	60	74	
BMI (kg/m2)	29.8 (4.8)	28.4 (4.8)	27.3 (4.6)	26.4 (4.3)	25.4 (4.1)	<0.001[a]
Missing (n)	225	192	172	153	207	
Smoking status (n%)						<0.001[b]
Never	22,714 (45.1%)	26,033 (51.7%)	27,887 (55.3%)	29,650 (58.8%)	32,321 (64.2%)	
Previous	20,225 (40.2%)	18,554 (36.8%)	17,442 (34.6%)	16,228 (32.2%)	14,274 (28.3%)	
Current	7,392 (14.7%)	5,806 (11.5%)	5,080 (10.1%)	4,537 (9.0%)	3,778 (7.5%)	
Missing (n)	297	235	219	212	254	
Alcohol status (n%)						<0.001[b]
Never	1,816 (3.6%)	1,893 (3.7%)	1,857 (3.7%)	2,169 (4.3%)	3,234 (6.4%)	
Previous	1,896 (3.8%)	1,665 (3.3%)	1,615 (3.2%)	1,636 (3.2%)	2,085 (4.1%)	
Current	46,786 (92.6%)	46,957 (93.0%)	47,063 (93.1%)	46,722 (92.5%)	45,139 (89.5%)	
Missing (n)	130	113	93	100	169	
Physical activity (n%)						<0.001[b]
Low	9,713 (23.9%)	8,146 (20.1%)	7,398 (18.2%)	6,850 (16.7%)	6,576 (15.8%)	
Moderate	16,280 (40.1%)	16,700 (41.1%)	16,484 (40.5%)	16,564 (40.4%)	16,506 (39.7%)	
High	14,630 (36.0%)	15,739 (38.8%)	16,798 (41.3%)	17,614 (42.9%)	18,522 (44.5%)	
Missing (n)	10,005	10,043	9,948	9,599	9,023	

Abbreviations: omega-6%, omega-6 fatty acids to total fatty acids percentage; TDI, Townsend deprivation index; BMI, body mass index.
[a] All variables measured at baseline are presented as mean (SD) unless otherwise specified.
[b] From the ANOVA test for continuous variables.
[c] From the Pearson's Chi-squared test for categorical variables.

Table 2. Associations of the plasma omega-6% with the incidence of overall cancer and 19 cancer sites in the UK Biobank

Cancer Type	Per 1-SD	Quintiles										P for overall[i]	Adjusted P for overall[j]	P for trend[k]	Adjusted P for trend[j]
	HR (95% CI)	1		2		3		4		5					
		Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)				
Overall															
Simply adjusted model	0.94 (0.93-0.95)	6,787	1.00 (ref)	6,427	0.96 (0.93-0.99)	6,118	0.94 (0.90-0.97)	5,579	0.89 (0.86-0.92)	4,927	0.84 (0.81-0.88)	<0.001	--	<0.001	--
Main model	0.98 (0.96-0.99)	5,356	1.00 (ref)	5,064	0.99 (0.95-1.03)	4,804	0.98 (0.94-1.02)	4,420	0.95 (0.91-0.99)	3,984	0.94 (0.90-0.98)	0.018	--	0.002	--
Head and neck															
Simply adjusted model	0.94 (0.91-0.96)	1,344	1.00 (ref)	1,363	1.00 (0.93-1.08)	1,297	0.96 (0.89-1.04)	1,227	0.93 (0.86-1.00)	1,018	0.81 (0.75-0.88)	<0.001	<0.001	<0.001	<0.001
Main model	0.97 (0.94-1.00)	1,062	1.00 (ref)	1,066	1.02 (0.94-1.11)	998	0.98 (0.89-1.07)	971	0.98 (0.89-1.07)	836	0.90 (0.81-0.99)	0.099	0.111	0.042	0.046
Esophagus															
Simply adjusted model	0.89 (0.86-0.92)	784	1.00 (ref)	743	0.97 (0.87-1.07)	641	0.86 (0.78-0.96)	608	0.86 (0.77-0.96)	441	0.68 (0.61-0.77)	<0.001	<0.001	<0.001	<0.001
Main model	0.93 (0.89-0.97)	619	1.00 (ref)	575	0.99 (0.88-1.11)	491	0.90 (0.80-1.02)	477	0.94 (0.83-1.06)	344	0.75 (0.66-0.87)	0.001	0.010	<0.001	0.003
Additionally adjusted[a]	0.95 (0.91-0.99)	619	1.00 (ref)	575	1.01 (0.90-1.13)	491	0.93 (0.82-1.05)	477	0.98 (0.87-1.11)	344	0.79 (0.69-0.91)	0.006	--	0.009	--
Stomach															
Simply adjusted model	0.92 (0.89-0.95)	703	1.00 (ref)	696	1.00 (0.90-1.11)	608	0.90 (0.81-1.01)	573	0.90 (0.80-1.00)	444	0.76 (0.67-0.86)	<0.001	<0.001	<0.001	<0.001
Main model	0.96 (0.92-1.00)	556	1.00 (ref)	545	1.04 (0.92-1.17)	469	0.95 (0.83-1.07)	450	0.97 (0.85-1.10)	355	0.85 (0.73-0.98)	0.057	0.068	0.031	0.037
Colon															
Simply adjusted model	0.91 (0.88-0.93)	1,107	1.00 (ref)	1,016	0.92 (0.85-1.01)	906	0.85 (0.78-0.93)	866	0.85 (0.78-0.93)	691	0.75 (0.68-0.83)	<0.001	<0.001	0.000	<0.001
Main model	0.94 (0.91-0.97)	890	1.00 (ref)	798	0.94 (0.85-1.04)	709	0.88 (0.80-0.98)	688	0.92 (0.83-1.02)	549	0.81 (0.73-0.91)	0.006	0.023	0.001	0.003
Additionally adjusted[b]	0.96 (0.92-0.99)	868	1.00 (ref)	773	0.95 (0.86-1.05)	692	0.91 (0.82-1.01)	670	0.95 (0.85-1.06)	540	0.86 (0.76-0.97)	0.105	--	0.018	--
Rectum															
Simply adjusted model	0.92 (0.89-0.95)	864	1.00 (ref)	814	0.96 (0.88-1.06)	727	0.89 (0.81-0.98)	680	0.88 (0.79-0.97)	539	0.75 (0.68-0.84)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.91-0.99)	684	1.00 (ref)	642	0.99 (0.89-1.11)	571	0.93 (0.83-1.04)	534	0.92 (0.82-1.04)	437	0.83 (0.73-0.94)	0.034	0.053	0.004	0.015
Additionally adjusted[b]	0.96 (0.92-1.00)	667	1.00 (ref)	627	1.01 (0.90-1.13)	555	0.94 (0.84-1.06)	519	0.94 (0.84-1.06)	429	0.86 (0.75-0.98)	0.125	--	0.024	--
Hepatobiliary															
Simply adjusted model	0.89 (0.86-0.92)	775	1.00 (ref)	738	0.96 (0.87-1.07)	637	0.86 (0.77-0.95)	575	0.82 (0.73-0.91)	450	0.70 (0.62-0.79)	<0.001	<0.001	<0.001	<0.001
Main model	0.93 (0.89-0.97)	611	1.00 (ref)	580	1.01 (0.90-1.13)	489	0.91 (0.80-1.02)	445	0.89 (0.78-1.01)	357	0.79 (0.69-0.91)	0.003	0.019	<0.001	0.003
Pancreas															
Simply adjusted model	0.90 (0.87-0.94)	777	1.00 (ref)	748	0.97 (0.87-1.07)	664	0.88 (0.79-0.98)	631	0.88 (0.79-0.98)	466	0.72 (0.64-0.81)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.91-0.99)	613	1.00 (ref)	590	1.01 (0.90-1.13)	511	0.92 (0.82-1.04)	491	0.95 (0.84-1.08)	371	0.81 (0.70-0.93)	0.011	0.030	0.005	0.015
Additionally adjusted[c]	0.95 (0.91-0.99)	613	1.00 (ref)	590	1.02 (0.91-1.14)	511	0.93 (0.82-1.05)	491	0.96 (0.85-1.09)	371	0.81 (0.71-0.93)	0.012	--	0.007	--

Lung															
Simply adjusted model	0.86 (0.84-0.89)	1,241	1.00 (ref)	1,066	0.86 (0.79-0.94)	945	0.79 (0.72-0.86)	856	0.75 (0.69-0.82)	633	0.62 (0.56-0.69)	<0.001	<0.001	<0.001	<0.001
Main model	0.93 (0.90-0.96)	947	1.00 (ref)	815	0.93 (0.84-1.02)	715	0.87 (0.79-0.96)	664	0.88 (0.79-0.97)	501	0.76 (0.68-0.85)	<0.001	<0.001	<0.001	<0.001
Additionally adjusted[d]	0.93 (0.90-0.96)	912	1.00 (ref)	788	0.93 (0.85-1.03)	691	0.87 (0.78-0.96)	647	0.88 (0.79-0.98)	486	0.76 (0.68-0.86)	<0.001	--	<0.001	--
Malignant melanoma															
Simply adjusted model	0.93 (0.90-0.96)	874	1.00 (ref)	904	1.04 (0.94-1.14)	849	1.00 (0.90-1.09)	788	0.96 (0.87-1.06)	601	0.78 (0.71-0.87)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.91-0.98)	695	1.00 (ref)	710	1.05 (0.94-1.16)	663	1.01 (0.91-1.13)	615	0.98 (0.88-1.10)	489	0.85 (0.75-0.96)	0.008	0.025	0.021	0.033
Additionally adjusted[e]	0.95 (0.92-0.99)	695	1.00 (ref)	710	1.05 (0.94-1.17)	663	1.02 (0.92-1.14)	615	0.98 (0.88-1.10)	489	0.86 (0.76-0.98)	0.014	--	0.043	--
Connective soft tissue															
Simply adjusted model	0.91 (0.88-0.95)	645	1.00 (ref)	644	1.00 (0.90-1.12)	569	0.91 (0.81-1.02)	539	0.90 (0.80-1.01)	404	0.74 (0.65-0.84)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.90-0.99)	512	1.00 (ref)	498	1.02 (0.90-1.15)	438	0.94 (0.82-1.07)	419	0.95 (0.83-1.09)	321	0.81 (0.70-0.94)	0.022	0.044	0.010	0.022
Breast															
Simply adjusted model	0.94 (0.91-0.96)	1,323	1.00 (ref)	1,516	0.98 (0.91-1.06)	1,555	0.94 (0.87-1.01)	1,485	0.89 (0.82-0.96)	1,302	0.84 (0.77-0.91)	<0.001	<0.001	<0.001	<0.001
Main model	0.97 (0.94-1.00)	1,025	1.00 (ref)	1,153	0.99 (0.91-1.07)	1,176	0.95 (0.88-1.04)	1,149	0.93 (0.85-1.02)	1,042	0.92 (0.83-1.01)	0.292	0.308	0.032	0.037
Additionally adjusted[f]	1.01 (0.97-1.05)	523	1.00 (ref)	726	1.01 (0.91-1.14)	836	1.02 (0.91-1.14)	855	1.00 (0.89-1.12)	807	1.01 (0.90-1.14)	0.991	--	0.927	--
Uterus															
Simply adjusted model	0.89 (0.87-0.93)	772	1.00 (ref)	788	0.97 (0.88-1.08)	722	0.89 (0.80-0.98)	673	0.86 (0.77-0.95)	490	0.69 (0.61-0.77)	<0.001	<0.001	<0.001	<0.001
Main model	0.96 (0.92-1.00)	602	1.00 (ref)	602	1.02 (0.91-1.14)	557	0.98 (0.87-1.10)	526	0.99 (0.88-1.12)	385	0.82 (0.72-0.94)	0.018	0.043	0.026	0.037
Additionally adjusted[g]	0.97 (0.91-1.04)	220	1.00 (ref)	286	1.00 (0.84-1.19)	328	1.07 (0.90-1.26)	314	1.00 (0.88-1.25)	209	0.81 (0.66-0.99)	0.022	--	0.971	--
Ovary															
Simply adjusted model	0.92 (0.89-0.95)	697	1.00 (ref)	731	1.02 (0.92-1.13)	647	0.90 (0.81-1.01)	630	0.91 (0.82-1.02)	481	0.77 (0.68-0.86)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.91-0.99)	552	1.00 (ref)	558	1.02 (0.90-1.15)	492	0.92 (0.81-1.04)	489	0.96 (0.85-1.09)	377	0.82 (0.72-0.95)	0.023	0.044	0.011	0.022
Additionally adjusted[g]	0.99 (0.92-1.06)	164	1.00 (ref)	239	1.06 (0.87-1.29)	263	1.06 (0.87-1.29)	274	1.11 (0.91-1.35)	196	0.89 (0.71-1.11)	0.151	--	0.554	--
Prostate															
Simply adjusted model	1.00 (0.98-1.02)	1,962	1.00 (ref)	1,853	1.08 (1.01-1.15)	1,640	1.08 (1.01-1.15)	1,532	1.09 (1.02-1.16)	1,284	0.96 (0.90-1.03)	0.001	0.001	0.902	0.902
Main model	1.01 (0.98-1.03)	1,600	1.00 (ref)	1,524	1.09 (1.02-1.17)	1,347	1.08 (1.01-1.17)	1,253	1.09 (1.01-1.17)	1,054	0.97 (0.90-1.06)	0.005	0.023	0.765	0.765
Additionally adjusted[h]	1.01 (0.98-1.03)	1,555	1.00 (ref)	1,488	1.10 (1.02-1.18)	1,321	1.09 (1.01-1.17)	1,219	1.09 (1.00-1.17)	1,034	0.98 (0.90-1.06)	0.005	--	0.719	--
Kidney															
Simply adjusted model	0.90 (0.87-0.93)	813	1.00 (ref)	758	0.95 (0.86-1.05)	686	0.89 (0.80-0.98)	636	0.86 (0.78-0.96)	483	0.71 (0.64-0.80)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.91-0.99)	638	1.00 (ref)	591	0.99 (0.88-1.11)	523	0.93 (0.83-1.05)	495	0.95 (0.84-1.07)	388	0.83 (0.72-0.95)	0.051	0.065	0.011	0.022
Bladder															
Simply adjusted model	0.91 (0.88-0.94)	781	1.00 (ref)	746	0.98 (0.88-1.08)	652	0.89 (0.80-0.99)	623	0.90 (0.81-1.00)	461	0.73 (0.65-0.82)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.91-0.99)	613	1.00 (ref)	586	1.02 (0.91-1.15)	512	0.95 (0.85-1.08)	489	0.98 (0.87-1.11)	372	0.84 (0.73-0.96)	0.040	0.054	0.028	0.037

Brain															
Simply adjusted model	0.92 (0.89-0.95)	704	1.00 (ref)	705	1.01 (0.91-1.12)	621	0.92 (0.82-1.02)	594	0.92 (0.82-1.02)	451	0.76 (0.67-0.86)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.91-0.99)	555	1.00 (ref)	547	1.03 (0.91-1.16)	481	0.95 (0.84-1.08)	458	0.96 (0.84-1.09)	362	0.83 (0.72-0.96)	0.036	0.053	0.017	0.029
Thyroid															
Simply adjusted model	0.91 (0.88-0.95)	668	1.00 (ref)	653	0.97 (0.87-1.09)	591	0.90 (0.80-1.01)	561	0.89 (0.79-0.99)	431	0.74 (0.65-0.84)	<0.001	<0.001	<0.001	<0.001
Main model	0.94 (0.90-0.99)	529	1.00 (ref)	506	0.99 (0.88-1.12)	457	0.93 (0.82-1.06)	434	0.93 (0.82-1.07)	339	0.80 (0.69-0.93)	0.026	0.045	0.006	0.015
Lymphoid and Hematopoietic Tissues															
Simply adjusted model	0.94 (0.92-0.97)	1,113	1.00 (ref)	1,105	1.01 (0.93-1.09)	1,007	0.95 (0.87-1.03)	916	0.91 (0.83-0.99)	787	0.86 (0.78-0.94)	0.003	0.003	<0.001	<0.001
Main model	0.98 (0.95-1.01)	873	1.00 (ref)	854	1.03 (0.93-1.13)	783	0.99 (0.90-1.10)	717	0.97 (0.88-1.08)	613	0.93 (0.83-1.03)	0.446	0.446	0.174	0.183

Abbreviations: omega-6%, omega-6 fatty acids to total fatty acids percentage; SD, standard deviation; CI, confidence interval; HR, hazards ratio; ref, reference.
The results from simply adjusted models revealed the associations of plasma omega-6% with cancer risk stratified by age and sex in general cohort. The main models were adjusted for general covariates including ethnicity (classified into White, Black, Asian, Others), Townsend deprivation index (continuous), assessment Center, BMI (kg/m2; continuous), smoking status (categorized as never, previous, current), alcohol intake status (categorized as never, previous, current), and physical activity (classified as low, moderate, high). The additionally adjusted models were adjusted for extra covariates for some specific types of cancer.

[a] Additionally adjusted for gastroesophageal reflux disease at baseline and waist-hip ratio.
[b] Additionally adjusted for diabetes at baseline, aspirin use, processed meat intake, waist-hip ratio, and family history.
[c] Additionally adjusted for diabetes at baseline.
[d] Additionally adjusted for family history.
[e] Additionally adjusted for skin color, ease of skin tanning, use of sun/UV protection, childhood sunburn occasions, frequency of solarium/sunlamp use.
[f] Restricted to female, and additionally adjusted for age when menarche started, hormone replacement therapy use, oral contraceptive use, number of live births, menopausal status, hysterectomy status, and family history.
[g] Restricted to female, and additionally adjusted for age when menarche started, hormone replacement therapy use, oral contraceptive use, number of live births, menopausal status, hysterectomy status.
[h] Restricted to male, and additionally adjusted for family history.
[i] Used likelihood ratio test to compare the full model with reduced model.
[j] Based on False Discovery Rate (FDR) to calculate the adjusted p-values for simply adjusted models and main models among 19 cancer sites.
[k] Used the median value of each quintile as a continuous variable within the models.

Table 3. Associations of the plasma omega-3% with the incidence of overall cancer and 19 cancer sites in the UK Biobank

Cancer Type	Per 1-SD	Quintiles										P for overall[i]	Adjusted P for overall[j]	P for trend[k]	Adjusted P for trend[j]
	HR (95% CI)	1		2		3		4		5					
		Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)	Events	HR (95% CI)				
Overall															
Simply adjusted model	0.96 (0.95-0.97)	5,864	1.00 (ref)	5,837	0.95 (0.92-0.99)	5,935	0.92 (0.89-0.96)	6,086	0.91 (0.88-0.95)	6,116	0.88 (0.85-0.91)	<0.001	--	<0.001	--
Main model	0.99 (0.97-1.00)	4,546	1.00 (ref)	4,603	0.97 (0.93-1.01)	4,688	0.95 (0.91-0.99)	4,838	0.95 (0.91-0.99)	4,953	0.95 (0.91-0.99)	0.080	--	0.022	--
Head and neck															
Simply adjusted model	0.95 (0.93-0.98)	1,267	1.00 (ref)	1,185	0.89 (0.83-0.97)	1,252	0.90 (0.84-0.98)	1,275	0.89 (0.82-0.96)	1,270	0.84 (0.78-0.91)	0.001	0.001	<0.001	<0.001
Main model	0.97 (0.95-1.00)	985	1.00 (ref)	928	0.91 (0.83-1.00)	1,004	0.95 (0.87-1.04)	988	0.91 (0.83-1.00)	1,028	0.92 (0.84-1.01)	0.205	0.493	0.150	0.192
Esophagus															
Simply adjusted model	0.92 (0.88-0.95)	685	1.00 (ref)	600	0.83 (0.75-0.93)	664	0.87 (0.78-0.97)	626	0.79 (0.71-0.88)	642	0.77 (0.69-0.86)	<0.001	<0.001	<0.001	<0.001
Main model	0.95 (0.92-1.00)	510	1.00 (ref)	468	0.88 (0.78-1.00)	523	0.95 (0.84-1.07)	494	0.87 (0.77-0.99)	511	0.88 (0.78-1.00)	0.163	0.493	0.089	0.188
Additionally adjusted[a]	0.96 (0.92-1.00)	510	1.00 (ref)	468	0.88 (0.78-1.00)	523	0.95 (0.84-1.08)	494	0.88 (0.77-0.99)	511	0.89 (0.79-1.02)	0.187	--	0.128	--
Stomach															
Simply adjusted model	0.91 (0.87-0.94)	648	1.00 (ref)	561	0.82 (0.73-0.92)	622	0.86 (0.77-0.96)	603	0.80 (0.71-0.89)	590	0.74 (0.66-0.83)	<0.001	<0.001	<0.001	<0.001
Main model	0.94 (0.90-0.98)	494	1.00 (ref)	442	0.86 (0.76-0.98)	491	0.92 (0.81-1.04)	476	0.86 (0.76-0.98)	472	0.83 (0.73-0.95)	0.051	0.242	0.015	0.076
Colon															
Simply adjusted model	0.93 (0.90-0.96)	952	1.00 (ref)	848	0.84 (0.77-0.92)	938	0.88 (0.80-0.96)	906	0.81 (0.74-0.89)	942	0.79 (0.72-0.87)	<0.001	<0.001	<0.001	<0.001
Main model	0.96 (0.92-0.99)	727	1.00 (ref)	675	0.88 (0.79-0.98)	759	0.94 (0.85-1.04)	718	0.86 (0.77-0.95)	755	0.87 (0.78-0.97)	0.021	0.152	0.016	0.076
Additionally adjusted[b]	0.95 (0.92-0.99)	710	1.00 (ref)	659	0.86 (0.78-0.96)	735	0.91 (0.82-1.01)	703	0.84 (0.75-0.93)	736	0.85 (0.76-0.95)	0.009	--	0.006	--
Rectum															
Simply adjusted model	0.94 (0.91-0.98)	726	1.00 (ref)	676	0.89 (0.80-0.99)	751	0.94 (0.85-1.04)	744	0.90 (0.81-1.00)	727	0.84 (0.76-0.93)	0.017	0.019	0.003	0.004
Main model	0.97 (0.93-1.01)	552	1.00 (ref)	536	0.93 (0.83-1.05)	605	1.01 (0.90-1.14)	591	0.97 (0.86-1.09)	584	0.93 (0.82-1.05)	0.494	0.575	0.343	0.383
Additionally adjusted[b]	0.97 (0.93-1.00)	538	1.00 (ref)	524	0.92 (0.82-1.04)	584	0.98 (0.87-1.10)	580	0.95 (0.84-1.07)	571	0.91 (0.80-1.03)	0.475	--	0.198	--
Hepatobiliary															
Simply adjusted model	0.90 (0.86-0.93)	695	1.00 (ref)	593	0.81 (0.72-0.90)	647	0.83 (0.75-0.93)	619	0.76 (0.68-0.85)	621	0.72 (0.65-0.81)	<0.001	<0.001	<0.001	<0.001
Main model	0.93 (0.90-0.97)	519	1.00 (ref)	470	0.87 (0.77-0.98)	513	0.91 (0.80-1.03)	488	0.84 (0.74-0.95)	492	0.82 (0.72-0.94)	0.024	0.152	0.005	0.047
Pancreas															
Simply adjusted model	0.92 (0.89-0.96)	671	1.00 (ref)	611	0.86 (0.77-0.96)	665	0.88 (0.79-0.97)	672	0.84 (0.75-0.94)	667	0.78 (0.70-0.87)	<0.001	<0.001	<0.001	<0.001
Main model	0.96 (0.92-1.00)	507	1.00 (ref)	475	0.89 (0.79-1.01)	528	0.95 (0.84-1.07)	531	0.92 (0.81-1.04)	535	0.89 (0.79-1.01)	0.351	0.493	0.152	0.192
Additionally adjusted[c]	0.96 (0.92-1.00)	507	1.00 (ref)	475	0.89 (0.79-1.01)	528	0.94 (0.83-1.07)	531	0.90 (0.81-1.03)	535	0.89 (0.78-1.00)	0.312	--	0.126	--

Lung															
Simply adjusted model	0.85 (0.82-0.88)	1,067	1.00 (ref)	941	0.82 (0.76-0.90)	959	0.78 (0.72-0.86)	904	0.70 (0.64-0.76)	870	0.63 (0.57-0.69)	<0.001	<0.001	<0.001	<0.001
Main model	0.92 (0.89-0.96)	789	1.00 (ref)	720	0.90 (0.82-1.00)	744	0.92 (0.83-1.01)	698	0.84 (0.76-0.93)	691	0.81 (0.73-0.91)	0.001	0.019	<0.001	0.002
Additionally adjusted[d]	0.92 (0.89-0.96)	759	1.00 (ref)	695	0.90 (0.81-1.00)	721	0.91 (0.82-1.01)	676	0.83 (0.75-0.93)	673	0.81 (0.73-0.91)	0.001	--	<0.001	--
Malignant melanoma															
Simply adjusted model	0.99 (0.96-1.02)	768	1.00 (ref)	735	0.91 (0.83-1.01)	810	0.96 (0.87-1.06)	846	0.97 (0.88-1.07)	857	0.94 (0.85-1.03)	0.477	0.477	0.467	0.467
Main model	1.00 (0.97-1.04)	590	1.00 (ref)	583	0.94 (0.84-1.06)	650	1.00 (0.90-1.12)	677	1.01 (0.90-1.13)	672	0.97 (0.87-1.09)	0.699	0.699	0.998	0.998
Additionally adjusted[e]	1.01 (0.97-1.04)	590	1.00 (ref)	583	0.94 (0.84-1.06)	650	1.01 (0.90-1.13)	677	1.02 (0.91-1.14)	672	0.99 (0.88-1.11)	0.686	--	0.758	--
Connective soft tissue															
Simply adjusted model	0.92 (0.89-0.96)	581	1.00 (ref)	517	0.84 (0.75-0.95)	577	0.89 (0.79-1.00)	565	0.83 (0.74-0.94)	561	0.78 (0.70-0.88)	0.001	0.001	<0.001	<0.001
Main model	0.95 (0.91-1.00)	436	1.00 (ref)	407	0.90 (0.78-1.03)	456	0.96 (0.84-1.10)	445	0.91 (0.80-1.04)	444	0.88 (0.77-1.01)	0.323	0.493	0.118	0.192
Breast															
Simply adjusted model	0.95 (0.93-0.97)	1,295	1.00 (ref)	1,341	0.95 (0.88-1.02)	1,405	0.92 (0.85-0.99)	1,540	0.92 (0.85-0.99)	1,600	0.87 (0.80-0.93)	0.004	0.005	<0.001	<0.001
Main model	0.97 (0.95-1.00)	965	1.00 (ref)	1,048	0.99 (0.91-1.08)	1,076	0.95 (0.87-1.04)	1,194	0.96 (0.88-1.05)	1,262	0.94 (0.86-1.02)	0.545	0.575	0.118	0.192
Additionally adjusted[f]	0.98 (0.95-1.01)	620	1.00 (ref)	705	1.00 (0.90-1.12)	677	0.89 (0.80-0.99)	845	0.98 (0.88-1.09)	900	0.93 (0.84-1.03)	0.108	--	0.194	--
Uterus															
Simply adjusted model	0.91 (0.88-0.94)	678	1.00 (ref)	647	0.89 (0.79-0.99)	714	0.91 (0.82-1.01)	710	0.84 (0.76-0.94)	696	0.76 (0.68-0.85)	<0.001	<0.001	<0.001	<0.001
Main model	0.96 (0.92-0.99)	507	1.00 (ref)	501	0.92 (0.82-1.05)	552	0.96 (0.85-1.09)	556	0.92 (0.82-1.04)	556	0.89 (0.78-1.00)	0.376	0.493	0.079	0.188
Additionally adjusted[g]	1.00 (0.95-1.05)	210	1.00 (ref)	234	0.97 (0.81-1.16)	259	0.96 (0.80-1.15)	323	1.05 (0.88-1.25)	331	0.97 (0.82-1.16)	0.817	--	0.971	--
Ovary															
Simply adjusted model	0.93 (0.90-0.97)	646	1.00 (ref)	576	0.83 (0.74-0.93)	631	0.85 (0.76-0.95)	664	0.84 (0.75-0.94)	669	0.79 (0.71-0.88)	0.001	0.001	<0.001	<0.001
Main model	0.96 (0.92-1.00)	485	1.00 (ref)	452	0.88 (0.78-1.00)	487	0.90 (0.80-1.02)	519	0.91 (0.81-1.04)	525	0.88 (0.77-1.00)	0.287	0.493	0.147	0.192
Additionally adjusted[g]	1.01 (0.95-1.07)	187	1.00 (ref)	184	0.86 (0.70-1.05)	193	0.80 (0.66-0.98)	276	0.99 (0.82-1.19)	296	0.92 (0.76-1.11)	0.105	--	0.888	--
Prostate															
Simply adjusted model	1.02 (1.00-1.04)	1,605	1.00 (ref)	1,637	1.01 (0.94-1.08)	1,723	1.04 (0.97-1.12)	1,635	1.02 (0.95-1.09)	1,671	1.07 (1.00-1.14)	0.337	0.356	0.065	0.069
Main model	1.03 (1.01-1.05)	1,276	1.00 (ref)	1,332	1.02 (0.94-1.10)	1,419	1.06 (0.98-1.14)	1,360	1.04 (0.96-1.12)	1,391	1.08 (1.00-1.17)	0.275	0.493	0.041	0.154
Additionally adjusted[h]	1.03 (1.00-1.05)	1,239	1.00 (ref)	1,302	1.02 (0.95-1.10)	1,389	1.06 (0.98-1.15)	1,331	1.04 (0.96-1.12)	1,356	1.08 (1.00-1.17)	0.346	--	0.060	--
Kidney															
Simply adjusted model	0.93 (0.90-0.97)	701	1.00 (ref)	647	0.88 (0.79-0.98)	680	0.88 (0.79-0.97)	677	0.84 (0.75-0.93)	671	0.79 (0.71-0.88)	0.001	0.001	<0.001	<0.001
Main model	0.97 (0.93-1.01)	527	1.00 (ref)	512	0.93 (0.83-1.06)	525	0.92 (0.82-1.04)	532	0.91 (0.81-1.03)	539	0.90 (0.80-1.02)	0.526	0.575	0.133	0.192
Bladder															
Simply adjusted model	0.92 (0.89-0.95)	680	1.00 (ref)	614	0.86 (0.77-0.95)	663	0.87 (0.78-0.97)	661	0.83 (0.75-0.93)	645	0.77 (0.69-0.86)	<0.001	<0.001	<0.001	<0.001
Main model	0.96 (0.92-1.00)	518	1.00 (ref)	482	0.89 (0.79-1.01)	526	0.93 (0.83-1.06)	526	0.91 (0.80-1.03)	520	0.88 (0.77-0.99)	0.269	0.493	0.080	0.188

Brain															
Simply adjusted model	0.94 (0.91-0.98)	634	1.00 (ref)	560	0.84 (0.75-0.94)	634	0.90 (0.81-1.01)	621	0.85 (0.76-0.95)	626	0.81 (0.72-0.91)	0.003	0.004	0.001	0.002
Main model	0.97 (0.93-1.02)	473	1.00 (ref)	434	0.88 (0.77-1.01)	506	0.99 (0.87-1.12)	488	0.92 (0.81-1.05)	502	0.92 (0.81-1.05)	0.286	0.493	0.407	0.430
Thyroid															
Simply adjusted model	0.93 (0.90-0.97)	593	1.00 (ref)	534	0.85 (0.76-0.96)	599	0.91 (0.81-1.01)	585	0.84 (0.75-0.95)	593	0.81 (0.72-0.91)	0.005	0.006	0.001	0.002
Main model	0.97 (0.92-1.01)	445	1.00 (ref)	415	0.89 (0.78-1.02)	473	0.98 (0.86-1.11)	461	0.92 (0.80-1.05)	471	0.91 (0.79-1.04)	0.389	0.493	0.268	0.318
Lymphoid and Hematopoietic Tissues															
Simply adjusted model	0.95 (0.92-0.98)	980	1.00 (ref)	942	0.91 (0.83-1.00)	1,009	0.92 (0.84-1.01)	989	0.86 (0.79-0.94)	1,008	0.83 (0.76-0.91)	0.001	0.001	<0.001	<0.001
Main model	0.97 (0.94-1.00)	747	1.00 (ref)	725	0.92 (0.83-1.02)	789	0.95 (0.86-1.06)	782	0.91 (0.82-1.01)	797	0.9 (0.81-0.99)	0.249	0.493	0.055	0.175

Abbreviations: omega-3%, omega-3 fatty acids to total fatty acids percentage; SD, standard deviation; CI, confidence interval; HR, hazards ratio; ref, reference.
The results from simply adjusted models revealed the associations of plasma omega-3% with cancer risk stratified by age and sex in general cohort. The main models were adjusted for general covariates including ethnicity (classified into White, Black, Asian, Others), Townsend deprivation index (continuous), assessment Center, BMI (kg/m2; continuous), smoking status (categorized as never, previous, current), alcohol intake status (categorized as never, previous, current), and physical activity (classified as low, moderate, high). The additionally adjusted models were adjusted for extra covariates for some specific types of cancer.

[a] Additionally adjusted for gastroesophageal reflux disease at baseline and waist-hip ratio.
[b] Additionally adjusted for diabetes at baseline, aspirin use, processed meat intake, waist-hip ratio, and family history.
[c] Additionally adjusted for diabetes at baseline.
[d] Additionally adjusted for family history.
[e] Additionally adjusted for skin color, ease of skin tanning, use of sun/UV protection, childhood sunburn occasions, frequency of solarium/sunlamp use.
[f] Restricted to female, and additionally adjusted for age when menarche started, hormone replacement therapy use, oral contraceptive use, number of live births, menopausal status, hysterectomy status, and family history.
[g] Restricted to female, and additionally adjusted for age when menarche started, hormone replacement therapy use, oral contraceptive use, number of live births, menopausal status, hysterectomy status.
[h] Restricted to male, and additionally adjusted for family history.
[i] Used likelihood ratio test to compare the full model with reduced model.
[j] Based on False Discovery Rate (FDR) to calculate the adjusted p-values for simply adjusted models and main models among 19 cancer sites.
[k] Used the median value of each quintile as a continuous variable within the models.

Table 4. Risk estimates[a] of plasma omega-6% and omega-3% with incidence of overall cancer, stratified by potential risk factors, in the UK Biobank Study (n = 253,138)

Stratified variables			Overall Cancer											
			Continuous P for interaction	Events & HR (95% CI) across quintiles									P for trend	Categorical P for interaction
				1		2		3		4		5		
Age, years	ω-6	< 58	*< 0.001*	1,873	1.00 (ref)	1,718	0.94 (0.88-1.01)	1,872	0.95 (0.88-1.02)	2,026	0.90 (0.83-0.97)	2,343	0.89 (0.83-0.96)	*0.001*	*0.093*
		≥ 58		4,914	1.00 (ref)	4,709	1.01 (0.96-1.06)	4,246	0.99 (0.95-1.04)	3,553	0.97 (0.92-1.02)	2,584	0.92 (0.87-0.97)	*0.006*	
	ω-3	< 58	*< 0.001*	2,474	1.00 (ref)	2,243	1.01 (0.94-1.07)	1,944	0.97 (0.91-1.04)	1,732	1.01 (0.94-1.08)	1,439	1.03 (0.96-1.11)	*0.421*	*< 0.001*
		≥ 58		3,390	1.00 (ref)	3,594	0.95 (0.90-1.00)	3,991	0.95 (0.90-1.00)	4,354	0.95 (0.90-1.00)	4,677	0.95 (0.90-1.00)	*0.106*	
Sex	ω-6	Male	--	4,299	1.00 (ref)	3,463	1.01 (0.96-1.06)	2,930	1.01 (0.95-1.06)	2,531	0.97 (0.91-1.02)	2,304	0.94 (0.89-1.00)	*0.048*	*0.006*
		Female		2,488	1.00 (ref)	2,964	0.95 (0.89-1.01)	3,188	0.94 (0.89-1.00)	3,048	0.92 (0.87-0.98)	2,623	0.91 (0.85-0.98)	*0.006*	
	ω-3	Male	--	3,554	1.00 (ref)	3,260	0.95 (0.90-1.00)	3,175	0.95 (0.90-1.00)	2,885	0.93 (0.88-0.98)	2,653	0.94 (0.89-0.99)	*0.03*	*0.002*
		Female		2,310	1.00 (ref)	2,577	1.00 (0.94-1.07)	2,760	0.96 (0.90-1.03)	3,201	0.99 (0.93-1.05)	3,463	0.97 (0.91-1.03)	*0.337*	
TDI	ω-6	< -2	*0.346*	3,381	1.00 (ref)	3,461	1.01 (0.95-1.06)	3,333	1.00 (0.95-1.06)	3,026	0.96 (0.91-1.02)	2,587	0.96 (0.90-1.02)	*0.101*	*0.732*
		≥ -2		3,400	1.00 (ref)	2,962	0.97 (0.92-1.03)	2,780	0.96 (0.91-1.02)	2,548	0.94 (0.89-1.00)	2,333	0.91 (0.86-0.97)	*0.005*	
	ω-3	< -2	*0.030*	2,606	1.00 (ref)	2,934	0.98 (0.93-1.04)	3,185	0.96 (0.91-1.02)	3,466	1.01 (0.95-1.07)	3,597	0.99 (0.93-1.05)	*0.942*	*0.094*
		≥ -2		3,251	1.00 (ref)	2,894	0.95 (0.90-1.01)	2,750	0.94 (0.88-0.99)	2,613	0.89 (0.84-0.94)	2,515	0.91 (0.86-0.97)	*< 0.001*	
BMI, kg/m^2	ω-6	< 25	*0.228*	838	1.00 (ref)	1,381	0.95 (0.87-1.05)	1,876	0.96 (0.88-1.06)	2,190	0.93 (0.85-1.02)	2,357	0.88 (0.81-0.96)	*0.003*	*0.446*
		≥ 25		5,924	1.00 (ref)	5,019	0.98 (0.94-1.03)	4,213	0.97 (0.92-1.01)	3,371	0.93 (0.88-0.97)	2,558	0.94 (0.89-0.99)	*0.001*	
	ω-3	< 25	*0.756*	1,740	1.00 (ref)	1,517	0.95 (0.88-1.03)	1,588	0.95 (0.88-1.02)	1,710	0.93 (0.86-1.01)	2,087	0.91 (0.85-0.98)	*0.018*	*0.439*
		≥ 25		4,107	1.00 (ref)	4,301	0.98 (0.93-1.02)	4,316	0.95 (0.90-1.00)	4,355	0.96 (0.91-1.00)	4,006	0.96 (0.91-1.01)	*0.105*	
Current smoking status	ω-6	Yes	--	1,166	1.00 (ref)	863	0.95 (0.86-1.05)	764	0.96 (0.86-1.07)	574	0.85 (0.76-0.96)	471	0.95 (0.83-1.07)	*0.07*	*0.380*
		No		5,574	1.00 (ref)	5,535	0.99 (0.95-1.03)	5,327	0.98 (0.94-1.02)	4,969	0.96 (0.92-1.00)	4,430	0.93 (0.88-0.97)	*0.001*	

Current alcohol status	ω-3	Yes	--	1,311	1.00 (ref)	902	0.90 (0.81-0.99)	708	0.84 (0.76-0.94)	536	0.84 (0.75-0.95)	381	0.78 (0.69-0.89)	*< 0.001*	*0.017*
		No		4,520	1.00 (ref)	4,902	0.99 (0.95-1.04)	5,191	0.98 (0.93-1.02)	5,518	0.98 (0.94-1.03)	5,704	0.98 (0.94-1.03)	*0.48*	
	ω-6	Yes	--	6,243	1.00 (ref)	5,957	1.00 (0.96-1.04)	5,676	0.99 (0.95-1.03)	5,147	0.96 (0.92-1.00)	4,398	0.94 (0.90-0.99)	*0.007*	*0.408*
		No		529	1.00 (ref)	459	0.90 (0.77-1.04)	429	0.92 (0.79-1.07)	418	0.87 (0.74-1.02)	515	0.86 (0.74-1.01)	*0.055*	
	ω-3	Yes	--	5,210	1.00 (ref)	5,364	0.97 (0.93-1.01)	5,499	0.95 (0.91-0.99)	5,652	0.95 (0.91-0.99)	5,696	0.95 (0.91-0.99)	*0.019*	*0.974*
		No		638	1.00 (ref)	462	0.97 (0.84-1.11)	417	0.95 (0.82-1.10)	426	0.95 (0.82-1.10)	407	1.00 (0.86-1.16)	*0.93*	
Physical activity	ω-6	Low or moderate	--	3,551	1.00 (ref)	3,204	0.99 (0.95-1.04)	2,888	0.98 (0.93-1.03)	2,589	0.95 (0.90-1.00)	2,290	0.93 (0.88-0.99)	*0.007*	*0.974*
		High		1,875	1.00 (ref)	1,909	0.98 (0.92-1.05)	1,972	0.99 (0.93-1.06)	1,882	0.96 (0.90-1.03)	1,741	0.94 (0.88-1.01)	*0.089*	
	ω-3	Low or moderate	--	2,750	1.00 (ref)	2,876	0.99 (0.94-1.04)	2,893	0.96 (0.91-1.01)	3,026	0.96 (0.91-1.01)	2,977	0.96 (0.91-1.01)	*0.099*	*0.844*
		High		1,848	1.00 (ref)	1,780	0.94 (0.88-1.00)	1,848	0.94 (0.88-1.00)	1,870	0.94 (0.88-1.00)	2,033	0.93 (0.87-1.00)	*0.089*	

Abbreviations: omega-6%, omega-6 fatty acids to total fatty acids percentage; omega-3%, omega-3 fatty acids to total fatty acids percentage; CI, confidence interval; HR, hazards ratio; ref, reference.

[a] From Cox proportional hazards regression; results were based on the main models, stratified by age and sex, and adjusted for ethnicity (classified into White, Black, Asian, Others), Townsend deprivation index (continuous), assessment Center, BMI (kg/m2; continuous), smoking status (categorized as never, previous, current), alcohol intake status (categorized as never, previous, current), and physical activity (classified as low, moderate, high).