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Association between dietary omega-3 fatty acid intake and all-cause mortality in patients with osteoarthritis: a population-based prospective cohort study

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A correlation between omega-3 polyunsaturated fatty acids (omega-3 PUFAs) and osteoarthritis (OA) incidence has been established, but research on the long-term outlook of OA patients remains limited. This study investigates the association between omega-3 PUFA intake and the risk of all-cause and cardiovascular (CV) mortality in the U.S. OA population. A cohort of 3,467 OA patients from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2018 was studied. Cox proportional hazards regression models, Kaplan-Meier curves, and subgroup analyses were used to evaluate the relationship between omega-3 PUFA intake and mortality. The dose-response relationship was examined using a restricted cubic spline (RCS) model. Among the 3,467 OA patients, there were 459 all-cause deaths and 175 CV deaths. Omega-3 PUFAs were significantly negatively correlated with all-cause mortality (95% CI: 0.59–0.93, $p = 0.011$) but not with CV mortality (95% CI: 0.29–1.04, $p = 0.056$). Higher omega-3 PUFA intake was associated with a 49% decrease in all-cause mortality. Kaplan-Meier curves showed lower all-cause mortality rates in those with higher omega-3 PUFA intake. The inverse correlation was more pronounced among individuals living with a partner. The dose-response analysis indicated a linear negative relationship between omega-3 PUFA intake and all-cause mortality. Increased intake of omega-3 PUFAs is associated with a decreased risk of all-cause mortality in OA patients.

Keywords Omega-3 PUFAs, Osteoarthritis, NHANES, All-cause mortality

Osteoarthritis (OA) is a prevalent degenerative joint disease characterized by the deterioration of joint cartilage, leading to pain, joint dysfunction, and potential disability, thereby severely impacting patient health[1]. Epidemiological studies indicate that as of 2020, an estimated 595 million individuals across the globe are affected by OA, representing a 132.2% increase in prevalence since 1990[2]. In line with the rising prevalence, the mortality rate among OA patients has also been increasing annually[2]. Furthermore, research has shown that OA patients exhibit elevated rates of both all-cause and cardiovascular mortality in comparison to the average person[3,4]. Consequently, there is a pressing necessity to formulate efficient approaches for the avoidance of OA.

Recent guidelines pertaining to the management of OA emphasize the substantial impact of dietary adjustments on preventing and treating this disease[5]. Omega-3 polyunsaturated fatty acids (omega-3 PUFAs) have attracted substantial attention as key components of dietary supplements, known for their benefits in enhancing well-being and mitigating the risk of illness[6]. Omega-3 PUFAs include linolenic acids (18:3), stearidonic acids (18:4), eicosatetraenoic acids (20:5), clupanodonic acids (22:5), and docosahexaenoic acids (22:6). These compounds exhibit various physiological effects, including anti-inflammatory, antioxidant, anti-platelet aggregation, vasodilation, immune regulation, and apoptosis[7,8]. Increasing amounts of research indicate that omega-3 PUFAs intake can reduce not only the incidence of OA but also the risks of all-cause and cardiovascular mortality[9–11]. However, the precise correlation between the consumption of omega-3 PUFAs and

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the long-term prognosis of OA patients remains uncertain. Additional investigation is required to establish the correlation between the intake of omega-3 PUFAs and mortality from all causes and cardiovascular diseases in OA patients, as well as to determine the optimal dosage for achieving these benefits.

Therefore, this study utilizes the NHANES database to evaluate the impact of omega-3 PUFA on all-cause and cardiovascular disease mortality in patients with OA. By using data from a large national cohort, this study aims to fill significant knowledge gaps in osteoarthritis research, enhance understanding of the relationship between omega-3 PUFA and mortality in OA patients, and provide robust scientific support for clinical practice.

Methods

The National Health and Nutrition Examination Survey (NHANES) is a comprehensive health survey conducted jointly by the Centers for Disease Control and Prevention (CDC) and the National Center for Health Statistics (NCHS). Utilizing a sophisticated sampling design, NHANES employs a participant selection process and utilizes questionnaires, physical examinations, and laboratory tests to assess the health and nutritional well-being of individuals residing outside of institutional settings in the United States. NHANES, conducted by the National Center for Health Statistics, employs a stratified multistage probability sampling method to ensure data representativeness and accuracy. The target population includes the non-institutionalized civilian population of the United States. The sampling process involves selecting primary sampling units (PSUs), secondary sampling units (such as neighborhoods), households, and individual household members. To enhance statistical precision for specific subgroups, such as minorities, children, and the elderly, NHANES oversamples these groups. The survey methodology includes in-home interviews and physical examinations conducted at mobile examination centers, covering health status, dietary habits, and socioeconomic information. Laboratory tests analyze biological samples to assess nutritional indicators and chronic disease markers. NHANES is a continuous annual survey, with data released every two years. The study protocol has received approval from the Institutional Review Board, and all participants stipulated informed and written consent.

Study population

This study utilized data collected from the NHANES between 2005 and 2018, encompassing a total of 70,190 participants. Considering participants under the age of 20, their bodies are still in the developmental stage, and their metabolism and vital signs may differ significantly from those of adults[12], potentially leading to different responses to dietary intake and health outcomes. Additionally, factors such as dietary habits (e.g., snacking, skipping meals[13]) and activity levels in adolescents may significantly differ from those in adults, which could affect the applicability of the study's results. Furthermore, pregnant women experience a significant increase in nutritional needs and metabolic rate during pregnancy[14], and their dietary intake directly impacts the health of both the mother and fetus. Due to hormonal changes and different nutritional demands, pregnant women may have dietary intakes and health outcomes that differ markedly from non-pregnant women. Additionally, the use of medications and supplements during pregnancy could confound the study results. Therefore, this study excluded participants under the age of 20 and pregnant women. After excluding individuals under 20 years of age ($N=30,441$), pregnant women ($N=708$), individuals with missing omega-3 PUFAs and osteoarthritis data ($N=35,564$), and those without survival follow-up data ($N=10$), a final cohort of 3,467 subjects was included in the research (Fig. 1).

Assessment of omega-3 PUFAs and osteoarthritis

Dietary omega-3 PUFAs intake was estimated using data from two 24-hour dietary recall interviews. The primary interview was carried out at a mobile examination facility, while the subsequent interview took place over the telephone after a few days. Nutrient and micronutrient intake was calculated using the U.S. Department of Agriculture (USDA) database. Total omega-3 PUFAs intake was estimated by summing the intake of linolenic acids (18:3), stearidonic acids (18:4), eicosatetraenoic acids (20:5), clupanodonic acids (22:5), and docosahexaenoic acids (22:6)[15]. The average intake over the two interview days was used for analysis.

According to published studies[16,17], the NHANES codebook questionnaire "Has a doctor or other health professional ever told you that you have arthritis?" was used to measure osteoarthritis. There were two possible answers: "yes" or "no." The next phase of the questionnaire asked, "What type of arthritis is this?" to those who selected "yes." The study comprised those who chose the osteoarthritis option.

Mortality outcomes collection

To obtain mortality information for the study population, we utilized mortality data that was made available by the National Center for Health Statistics in the United States, with the final follow-up date being December 31, 2019. The survival outcomes of this study encompassed mortality from all causes and cardiovascular diseases, with cardiovascular deaths determined using International Classification of Diseases (ICD) codes. The calculation of individual follow-up time involved determining the duration between the interview date and either the date of death or the conclusion of the follow-up period.

Covariates

Relevant information regarding demographics and health factors was extensively gathered from the NHANES study, including age, gender, race, marital status, education level, poverty-to-income ratio (PIR), alcohol and smoking status, diabetes, hypertension, obesity, and physical activity. Detailed grouping information can be found in Table S1.

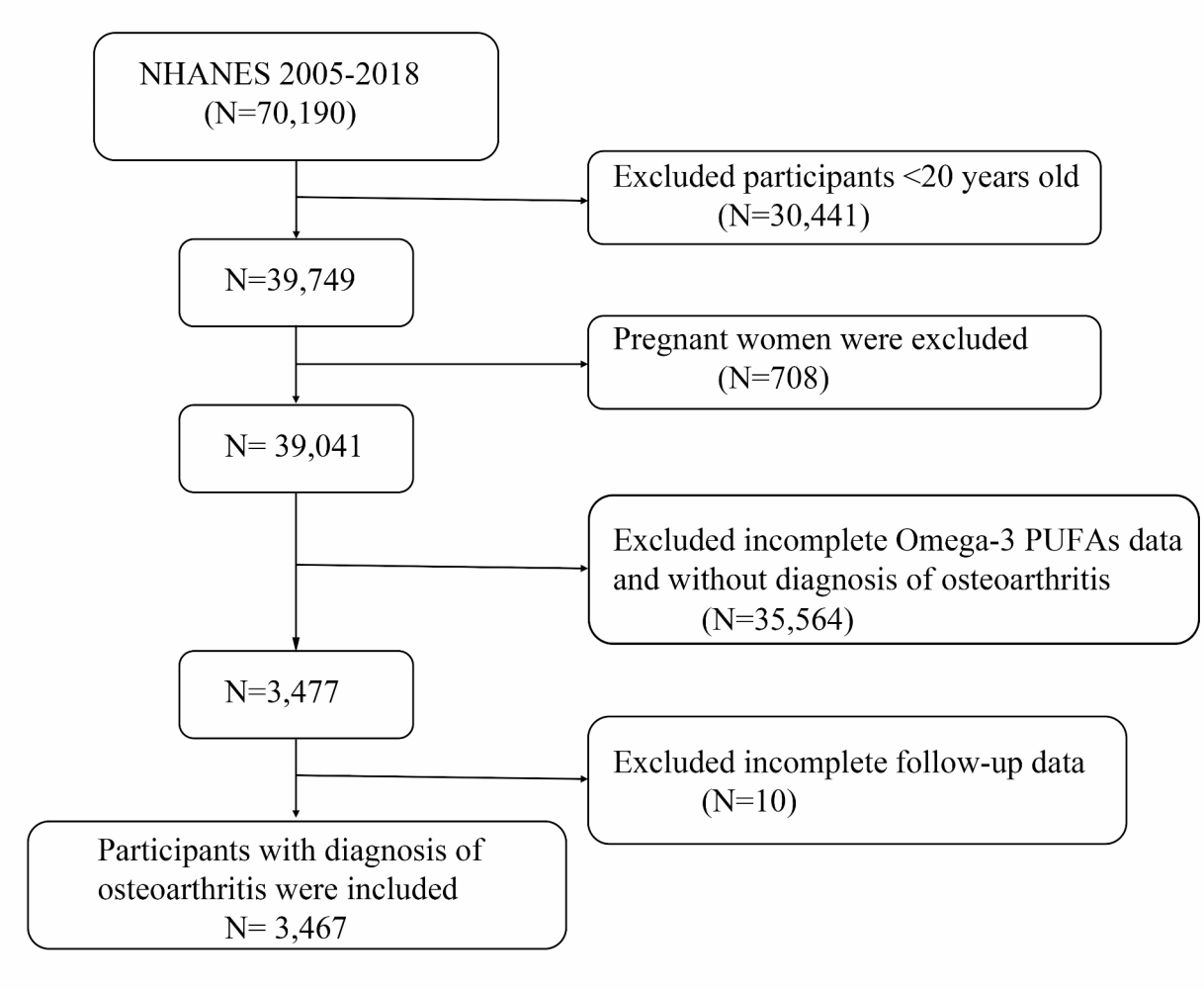

Fig. 1. A flow diagram of eligible participant selection in the National Health and Nutrition.

Statistical analysis

Given the intricate, multi-stage, probability sampling design of the NHANES database, data from various survey cycles were combined using sample weights to ensure that the results better represent the actual characteristics of the entire U.S. population. In this study, we used WTDRD2 (weights for participants who completed the second 24-hour dietary recall interview) as sample weights.

Firstly, we conducted descriptive statistical analyses of population characteristics, with continuous variables reported as mean ± standard deviation, while the categorical variables were presented as frequencies and percentages. Weighted t-tests were used to compare continuous variables, and weighted chi-square tests were used to compare categorical variables. We utilized Cox proportional hazards regression models to analyze the correlation between the intake of omega-3 PUFAs and mortality from all causes and cardiovascular diseases. Three regression models were utilized to adjust for potential confounding variables: Model 1 was left unadjusted, Model 2 was adjusted for age, gender, education level, marital status, and PIR, and Model 3 further accounted for alcohol and smoking status, diabetes, hypertension, obesity, and physical activity.

The dose-response relationship between intake of omega-3 PUFAs and the rate of mortality was analyzed by restricted cubic spline (RCS) models. The evaluation of survival outcomes was conducted using Kaplan-Meier methods, and the comparisons were performed using the log-rank test. Finally, subgroup analyses were conducted based on key covariates to explore potential interactions between consumption of omega-3 PUFAs and different stratified factors. In addition, to improve the reliability of the study, we excluded participants with extreme total energy intake (< 500 kcal/day or > 8000 calories/day for men and < 500 kcal/day or > 5000 calories/day for women) and missing other covariates for reanalysis. All statistical analyses were conducted using R software version 4.2.2. A significance level of $P < 0.05$ was used to determine statistical significance.

Ethical approval and consent to participate

All analyses were based on publicly shared databases and no additional ethical approvals were required.

Results

Characteristics of the participants

The demographic characteristics of the participants are presented in Table 1, which includes a total of 3,467 subjects included in this study. Throughout the follow-up period, 2,833 individuals survived, while 634 succumbed to mortality. The study cohort had a mean age exceeding 60 years (2,195 cases, 59%), with a higher representation of females compared to males (2,203 cases, 64% vs. 1,264 cases, 36%). The predominant demographic group consisted of individuals identified as non-Hispanic white (2,177 cases, 83%), with 65% cohabiting with a partner, 13% having education levels below high school, and 17% reporting poor household income.

In comparison to survivors, deceased individuals exhibited characteristics of advanced age, non-Hispanic white ethnicity, non-cohabitation with a partner, education levels at high school or above, moderate alcohol consumption, susceptibility to hypertension, and absence of diabetes ($p < 0.001$). Additionally, survivors demonstrated higher levels of omega-3 PUFAs intake (1.89 ± 1.20 vs. 1.56 ± 1.05, $p < 0.001$).

Omega-3 PUFAs intake and all-cause and cardiovascular mortality

We employed three Cox regression models to investigate the independent correlation between omega-3 PUFAs intake and mortality from all causes and cardiovascular diseases (Table 2). In Model 1, omega-3 PUFAs intake exhibited a significant negative correlation with all-cause mortality (HR: 0.81, 95% CI: 0.70–0.94), a correlation which remained significant in both the minimally adjusted Model 2 (HR: 0.74, 95% CI: 0.59–0.93) and the fully adjusted Model 3 (HR: 0.74, 95% CI: 0.59–0.93). Similarly, when further stratified by quartiles of omega-3 PUFAs consumption, comparable results were obtained. In all three models, individuals in the highest quartile of omega-3 PUFAs intake exhibited a decreased risk of all-cause mortality in comparison to those in the lowest quartile (Model 1: 0.62, 95% CI 0.44–0.86; Model 2: 0.63, 95% CI 0.44–0.90; Model 3: 0.51, 95% CI 0.26–0.99). However, there was no noteworthy correlation found between omega-3 PUFAs and CV mortality. Furthermore, the results remained robust after excluding participants with extreme total energy intake and missing other covariates (Table S2). Table 3 presents the association between the ingestion of omega-3 PUFAs and mortality, and after accounting for all confounders, the results indicate a significant and inverse correlation between linolenic acids and all-cause mortality (HR = 0.73, 95%Cl: 0.57,0.95). Kaplan-Meier curves demonstrated significant differences in survival patterns among participants with separate quartiles for the intake of omega-3 PUFAs ($p < 0.001$), indicating a lower risk of all-cause mortality with higher quartiles of omega-3 PUFAs consumption (Fig. 3). Restricted cubic spline (RCS) models depicted a linear negative association between omega-3 PUFAs intake and all-cause mortality (Fig. 2).

Subgroup analysis

In the subgroup analysis, we observed a negative correlation between consumption of omega-3 PUFAs and all-cause mortality across the majority of subgroups (Fig. 4). Apart from marital status (p-value for interaction with all-cause mortality = 0.015), no significant interactions were found among other subgroup variables. These findings suggest that the effect of omega-3 PUFAs intake on mortality from all causes in OA patients is consistent across different subgroups, with no significant influence from these stratification variables.

Discussion

This prospective cohort study explored the relationship between omega-3 PUFAs intake and mortality rates among adult OA patients in the United States. We found a robust negative correlation between omega-3 PUFAs consumption and all-cause mortality rates. Even in the fully adjusted Cox models, an association was identified between higher omega-3 PUFAs intake and lower mortality risk. Further subgroup analysis based on marital status revealed a synergistic effect of omega-3 PUFAs intake on mortality among participants cohabiting with partners compared to those not cohabiting.

Omega-3 PUFAs, as a class of essential fatty acids for human beings, have garnered widespread attention due to their unique structure and physiological functions[18]. They exert protective effects on health through various complex physiological mechanisms, including anti-inflammatory, antioxidant, cardiovascular protection, neuroprotection, immune modulation, and metabolic regulation. The synergistic interaction of these mechanisms endows omega-3 PUFAs with significant potential for the prevention and management of chronic diseases[19–22]. Increasing evidence suggests that omega-3 PUFAs and their major components can reduce the risk of all-cause and cardiovascular mortality[11,23]. O'Keefe et al.[23] analyzed data from 117,702 participants in the UK Biobank and found that, after adjusting for pertinent risk factors, the highest quintile of DHA consumption was linked to a 17% reduction in all-cause mortality risk (95% CI, 0.79–0.87; $P < 0.0001$) and a 21% reduction in cardiovascular disease mortality risk (95% CI, 0.73–0.87; $P < 0.001$). Similar results were obtained after pooling statistics from 17 prospective cohort studies, where the highest quintile of omega-3 PUFAs ingestion was correlated with a significantly decreased risk of all-cause mortality (15–18%, $p < 0.003$) after taking into account relevant risk factors[9]. Studies focused on specific populations[24,25] have also demonstrated the efficacy of omega-3 PUFAs in reducing the risk of mortality from all causes and cardiovascular diseases. These findings underscore the essential significance of omega-3 PUFAs in the long-term prognosis of patients.

As a severe degenerative joint disease, not only results in pain, deformity, and functional impairment in the joints, but also substantially elevates the likelihood of cardiovascular events and mortality from any cause[26,27]. With the aging population, the prevalence and mortality of OA are on the rise, highlighting the need for effective prevention and management strategies. Omega-3 PUFAs have been widely reported for their therapeutic effects on OA[28–30]. Supplementing with omega-3 PUFAs can effectively alleviate pain and improve joint function in OA patients. Additionally, these fatty acids are involved in cartilage metabolism and can slow the progression of

Characteristic	Total, $N = 3,467$ (100%)	Survivor, $N = 2,833$ (85%)	Non-survivors, $N = 634$ (15%)	*P* Value
Age (%)				< 0.001
20–40	212 (6.2%)	208 (7.2%)	4 (0.5%)	
41–60	1,060 (35%)	997 (39%)	63 (12%)	
> 60	2,195 (59%)	1,628 (54%)	567 (87%)	
Gender (%)				0.133
Male	1,264 (36%)	989 (35%)	275 (40%)	
Female	2,203 (64%)	1,844 (65%)	359 (60%)	
Race (%)				**< 0.001**
Non-Hispanic White	2,177 (83%)	1,704 (82%)	473 (88%)	
Non-Hispanic Black	560 (6.6%)	471 (6.7%)	89 (5.9%)	
Other	482 (7.6%)	431 (8.2%)	51 (4.5%)	
Mexican American	248 (2.6%)	227 (2.8%)	21 (1.2%)	
Married/live with partner (%)				**< 0.001**
No	1,433 (35%)	1,100 (33%)	333 (50%)	
Yes	2,034 (65%)	1,733 (67%)	301 (50%)	
Education level (%)				**< 0.001**
Below high school	675 (13%)	492 (11%)	183 (24%)	
High School or above	2,792 (87%)	2,341 (89%)	451 (76%)	
PIR (%)				**< 0.001**
Not Poor	2,376 (68.5%)	1,963 (69.3%)	413 (66.7%)	
poor	824 (23.8%)	655 (23.1%)	169 (25.1%)	
Unknown	267 (7.7%)	215 (7.6%)	52 (8.2%)	
Obesity (%)				**0.025**
No	1,744 (50.3%)	1,372 (48.4%)	372 (58.7%)	
Yes	1,665 (48%)	1,429 (50.5%)	236 (37.2%)	
Unknown	58 (1.7%)	32 (1.1%)	26 (4.1%)	
Smoking (%)				**0.001**
Never	1,666 (48%)	1,406 (50%)	260 (41%)	
Former	1,235 (36%)	940 (35%)	295 (46%)	
Current	566 (15%)	487 (16%)	79 (13%)	
Physical activity (%)				0.071
Inactive	604 (17.4%)	508 (17.9%)	96 (15.1%)	
Active	1,635 (47.2%)	1,451 (51.2%)	184 (29%)	
Unknown	1,228 (35.4%)	874 (30.9%)	354 (55.9%)	
Drinking (%)				**< 0.001**
Former	686 (19.8%)	486 (17.2%)	200 (31.5%)	
Heavy	296 (8.5%)	267 (9.4%)	29 (4.5%)	
Mild	1,304 (37.6%)	1,096 (38.7%)	208 (32.8%)	
Moderate	441 (12.7%)	400 (14.1%)	41 (6.5%)	
Never	442 (12.7%)	334 (11.7%)	108 (17%)	
Unknown	298 (8.6%)	250 (8.8%)	48 (7.6%)	
Hypertension (%)				**< 0.001**
No	1,098 (36%)	980 (39%)	118 (20%)	
Yes	2,344 (63.3%)	1,836 (60.4%)	508 (78.7%)	
Unknown	25 (0.7%)	17 (0.6%)	8 (1.3%)	
Diabetes (%)				**< 0.001**
No	1,201 (34.6%)	1,011 (35.7%)	190 (29.9%)	
Yes	920 (26.5%)	711 (25.1%)	209 (33%)	
Unknown	1,346 (38.9%)	1,111 (39.2%)	235 (37.1%)	
Cardiovascular mortality	175 (3.9%)	0 (0%)	175 (26%)	**< 0.001**
Omega-3 PUFAs (g) (mean (SD))	1.84 (1.18)	1.89 (1.20)	1.56 (1.05)	**< 0.001**

Table 1. The demographic characteristics of the osteoarthritis population in the present study were stratified by survival status, weighted. Mean (SD) for continuous variables: the P value was calculated by the weighted linear regression model. Percentages (weighted N, %) for categorical variables: the P value was calculated by the weighted chi-square test. Abbreviation: Omega-3 PUFAs, Omega-3 polyunsaturated fatty acids; PIR, poverty income ratio. Significant values are in bold.

Omega-3 PUFAs (g)	Model 1 [HR (95% CI)]	*p*-value	Model 2 [HR (95% CI)]	*p*-value	Model 3 [HR (95% CI)]	*p*-value
All-cause mortality						
Continuous	0.81 (0.70, 0.94)	**0.005**	0.84 (0.73, 0.97)	***0.017***	0.74 (0.59, 0.93)	**0.011**
Quartile						
Q1	1 (ref.)		1 (ref.)		1 (ref.)	
Q2	0.94 (0.73, 1.22)	0.600	0.83 (0.65, 1.06)	0.140	0.77 (0.45, 1.32)	0.300
Q3	0.64 (0.50, 0.84)	**< 0.001**	0.67 (0.51, 0.89)	***0.006***	0.66 (0.36, 1.20)	0.200
Q4	0.62 (0.44, 0.86)	**0.005**	0.63 (0.44, 0.90)	***0.012***	0.51 (0.26, 0.99)	**0.048**
P for trend	< 0.001		0.006		0.039	
Cardiovascular mortality						
Continuous	0.81 (0.65, 1.01)	0.059	0.83 (0.66, 1.04)	0.100	0.50 (0.29, 1.04)	0.056
Quartile						
Q1	1 (ref.)		1 (ref.)		1 (ref.)	
Q2	0.73 (0.47, 1.14)	0.200	0.66 (0.43, 1.01)	0.056	0.31 (0.10, 1.06)	0.055
Q3	0.88 (0.52, 1.50)	0.600	0.91 (0.53, 1.55)	0.700	0.60 (0.22, 1.59)	0.300
Q4	0.53 (0.29, 0.97)	**0.041**	0.53 (0.27, 1.02)	0.056	0.05 (0.01, 1.33)	0.152
P for trend	0.077		0.130		0.152	

Table 2. HRs (95% CIs) for all-cause mortality and cardiovascular mortality according to the Omega-3 PUFAs intake in the osteoarthritis population, weighted. Model 1: no covariates were adjusted. Model 2: age, gender, education level, marital, PIR, and race were adjusted. Model 3: age, gender, education level, marital status, PIR, race, obesity, smoking, drinking, Physical activity, hypertension, and diabetes were adjusted. Abbreviation: PIR, poverty income ratio; Omega-3 PUFAs, Omega-3 polyunsaturated fatty acids; HR, hazard ratio; CI, confidence interval. Significant values are in bold.

Components (g)	All-cause mortality [HR (95% CI)]	*p*-value	Cardiovascular mortality [HR (95% CI)]	*p*-value
Linolenic acids (g)	0.73 (0.57, 0.95)	**0.019**	0.50 (0.25, 1.00)	0.053
Stearidonic acids (g)	0.03 (0.01, 307)	0.400	0.01 (0.01,1.25)	0.300
Eicosatetraenoic acids (g)	0.08 (0.01, 2.38)	0.140	0.01 (0.01,1.25)	0.500
Clupanodonic acids (g)	0.02 (0.01, 130)	0.400	0.01 (0.01,1.33)	0.100
Docosahexaenoic acids (g)	0.36 (0.06, 2.14)	0.300	0.04 (0.01, 21.7)	0.300

Table 3. Effects of Omega-3 PUFAs components on all-cause and Cardiovascular mortality by multivariate cox proportional hazards regression analysis in the osteoarthritis population, weighted. Fully adjusted for age, gender, education level, marital status, PIR, race, obesity, smoking, drinking, Physical activity, hypertension, and diabetes were adjusted. Abbreviation: PIR, poverty income ratio; Omega-3 PUFAs, Omega-3 polyunsaturated fatty acids; HR, hazard ratio; CI, confidence interval. Significant values are in bold.

OA. However, a limited amount of research has examined the benefits of omega-3 PUFAs in reducing premature mortality among OA patients.

Our study demonstrates that the consumption of omega-3 PUFAs significantly reduces the risk of all-cause mortality in patients with OA. This effect is likely due to the anti-inflammatory, antioxidant, gut microbiota regulatory, and immune-modulating properties of omega-3 PUFAs. Aging is the most significant risk factor for OA[31]. During aging, cells secrete various inflammatory factors, chemokines, and growth factors, leading to chronic inflammation. This chronic inflammation accelerates aging and increases mortality risk by causing oxidative damage, DNA telomere attrition, loss of protein homeostasis, and stem cell depletion[32]. Omega-3 fatty acids can effectively modulate inflammatory responses and reduce the risk of severe inflammatory reactions. They inhibit inflammation-related transcription factor activity and disrupt the production of pro-inflammatory mediators, thereby lowering mortality risk[33,34].

Furthermore, omega-3 PUFAs act as antioxidants, increasing superoxide dismutase activity, enhancing mitochondrial antioxidant capacity, and reducing oxidative stress and inflammation[35]. Dysbiosis of the gut microbiota is crucial in OA pathogenesis. It disrupts the balance of gut microbes, induces immune responses, and activates the "gut-joint axis," thereby worsening OA progression[36]. Omega-3 PUFAs can improve gut microecology by regulating the gut microbiota, their metabolites, and gut barrier function[37]. Studies indicate that omega-3 PUFAs restore the ratio of Bacteroidetes to Firmicutes, correct dysbiosis, and reduce intestinal inflammation by increasing short-chain fatty acid synthesis[38]. Additionally, omega-3 PUFAs modulate autoimmunity through gut microbiota by promoting the process of differentiating naïve CD4+T cells into

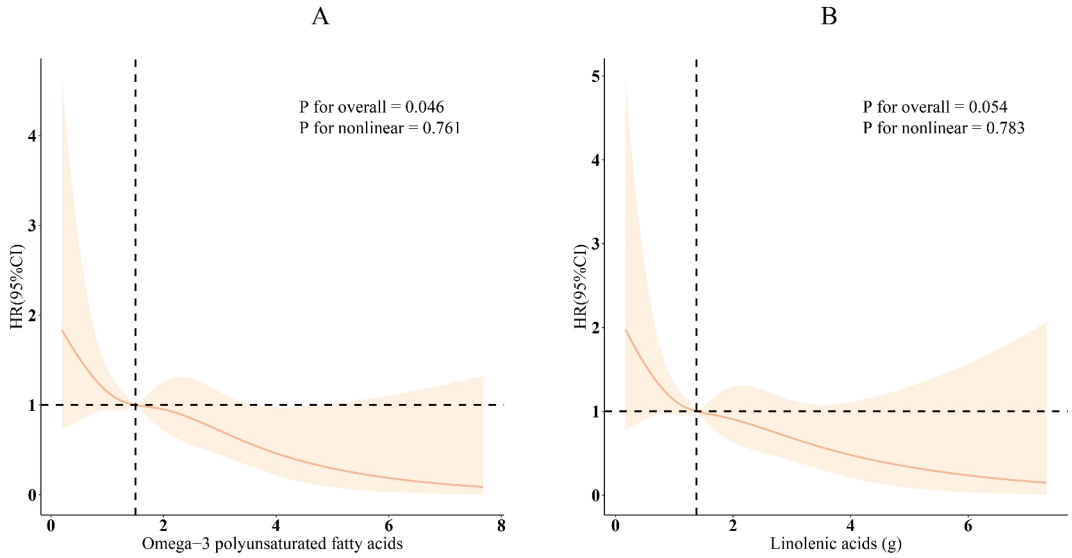

Fig. 2. The smooth curve fitting analysis of Omega-3 PUFAs intake (**A**) and Linolenic acids (**B**) and All-cause mortality. HR (solid lines) and 95% confidence levels (shaded areas) were adjusted for age, gender, education level, marital status, PIR, race, obesity, smoking, drinking, Physical activity, hypertension, and diabetes. Abbreviation: PIR, poverty income ratio; Omega-3 PUFAs, Omega-3 polyunsaturated fatty acids; HR, hazard ratio; CI, confidence interval.

either effector T cells or regulatory T cells, enhancing immune cell activity and function, thus maintaining immune system balance and strengthening the body's defense mechanisms[39].

Notably, our stratified analysis revealed that omega-3 PUFAs provide a more pronounced protective effect against mortality in individuals cohabiting with partners, likely related to the human microbiome. A recent study published in Nature found that cohabiting individuals share approximately 12% of their gut microbiota and 32% of their oral microbiota. These shared strains may significantly impact microbiome-related diseases[40]. Omega-3 PUFAs effectively regulate the gut microbiota, establish a stable and healthy gut microecology, and reduce mortality risk[41]. However, the specific mechanisms underlying these effects require further research and exploration.

This study utilized nationally representative large sample follow-up data, after controlling for demographic, clinical, and laboratory covariates, to examine the correlation between dietary consumption of omega-3 PUFAs and mortality rates related to all causes and cardiovascular events in participants diagnosed with OA. Firstly, previous studies have largely focused on the benefits of omega-3 PUFA on skeletal muscle health[42], joint pain[43], and mobility improvement[29]. This study, however, extends the potential benefits of omega-3 PUFA to include the reduction of overall mortality risk in OA patients, filling an important knowledge gap in osteoarthritis research. Additionally, by analyzing the effects of omega-3 PUFA on inflammatory markers and immune responses, this study explores the possible biological mechanisms underlying its role in improving the survival rate of OA patients, in conjunction with previous research. Secondly, although previous studies have examined the effects of omega-3 PUFA on cardiovascular health and other chronic diseases[44,45], its impact on mortality in OA patients has not been fully understood. By utilizing a large patient cohort and long-term follow-up data, this study provides new scientific evidence on the interface between omega-3 PUFA and osteoarthritis. Thirdly, advanced biostatistical methods, such as the restricted cubic spline (RCS) model and Kaplan-Meier curves, were employed with multivariable adjustments to eliminate the influence of potential confounding factors, ensuring the reliability and scientific rigor of the findings. These innovative approaches enhance the understanding of the relationship between omega-3 PUFA and mortality in OA patients, providing robust scientific support for clinical practice. Finally, the effect of omega-3 PUFAs on mortality risk across various subgroups was examined, confirming the robustness and applicability of our findings. Overall, our research underscores the critical role of omega-3 PUFAs ingestion in reducing all-cause mortality in OA patients, offering valuable insights for OA management and prevention.

However, this study has several limitations: (1) Given that this study is an observational one, establishing causal relationships is inherently challenging. To address this limitation, future research will focus on employing Mendelian Randomization (MR) analysis as a key statistical approach; (2) The estimation of omega-3 PUFAs intake during dietary data collection may not accurately reflect actual intake and individual dietary habits could change over the long follow-up period; (3) Despite extensive adjustments for confounding factors, residual confounding may still be present; (4) The majority of participants in this study were female and non-Hispanic white, which could introduce potential selection bias. Therefore, results related to this study should be interpreted with caution; (5) This study on the relationship between omega-3 fatty acid intake and the risk of all-cause and cardiovascular (CV) mortality in arthritis patients is limited to an American cohort, and differences across populations may exist. The lack of data from other populations restricts the generalizability of the findings.

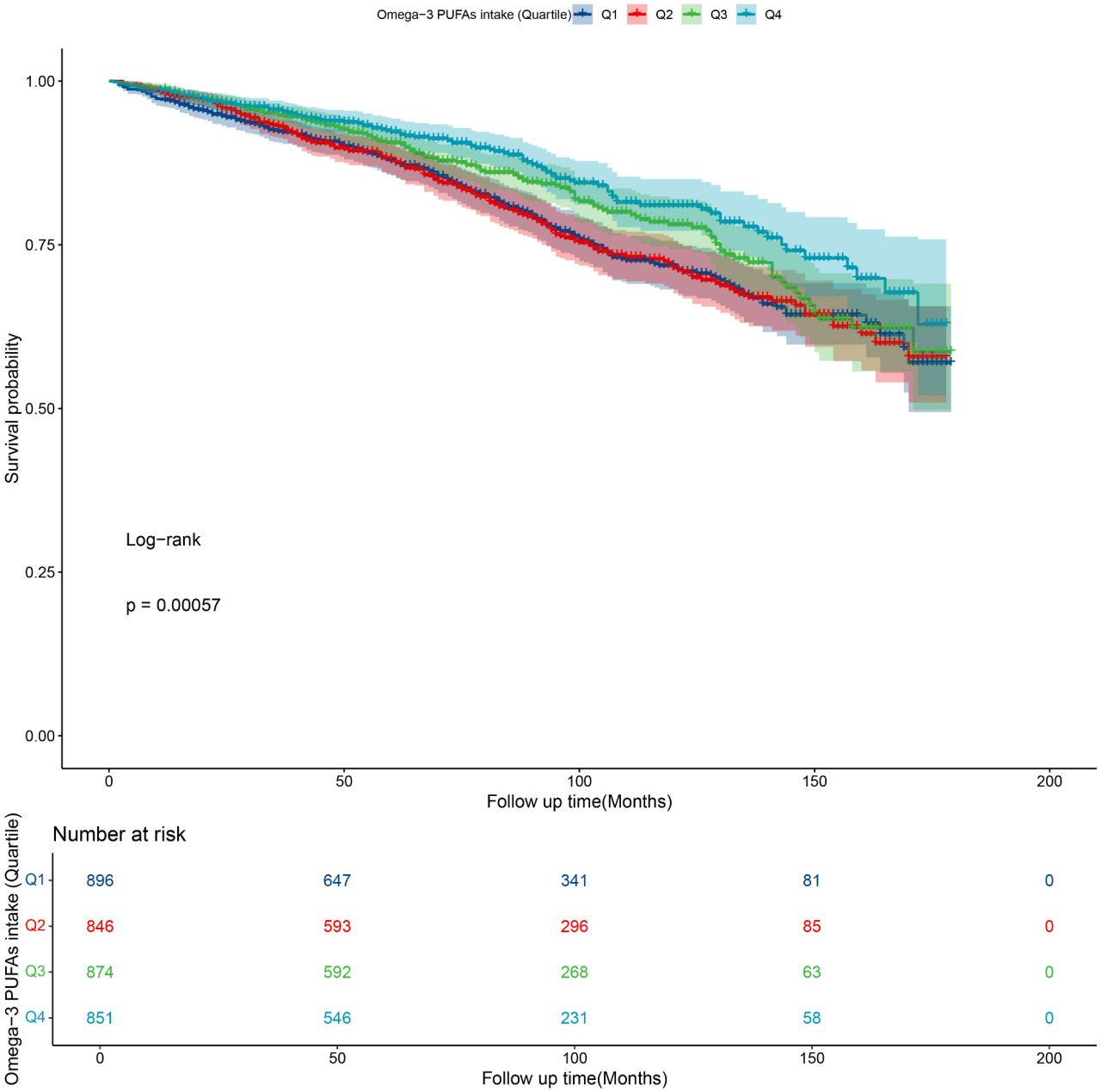

Fig. 3. Kaplan–Meier analysis of all-cause mortality.

Future research should focus on designing multinational, multi-population, and multicenter cohort studies to improve the applicability of these results to a broader range of populations. (6) The use of questionnaires related to self-reported definitions of osteoarthritis may bias the results, as they may not accurately reflect the participants' diagnoses. Therefore, the results of this study should be interpreted with caution. (7) Since elderly patients with advanced OA are often associated with limited daily activities, this may lead to the progression of cardiovascular disease. Therefore, it is important to analyze the correlation between OA (early or late) and all-cause mortality. In future studies with self-constructed databases, we will carefully analyze the relationship between patients with early or late OA and all-cause mortality.

Conclusion

In summary, our study found that increased intake of omega-3 PUFAs is linked to a reduction in all-cause mortality among OA patients. This suggests that enhancing dietary omega-3 PUFAs consumption may lower the mortality risk associated with OA. Our findings offer valuable guidance for the dietary health management of OA patients.

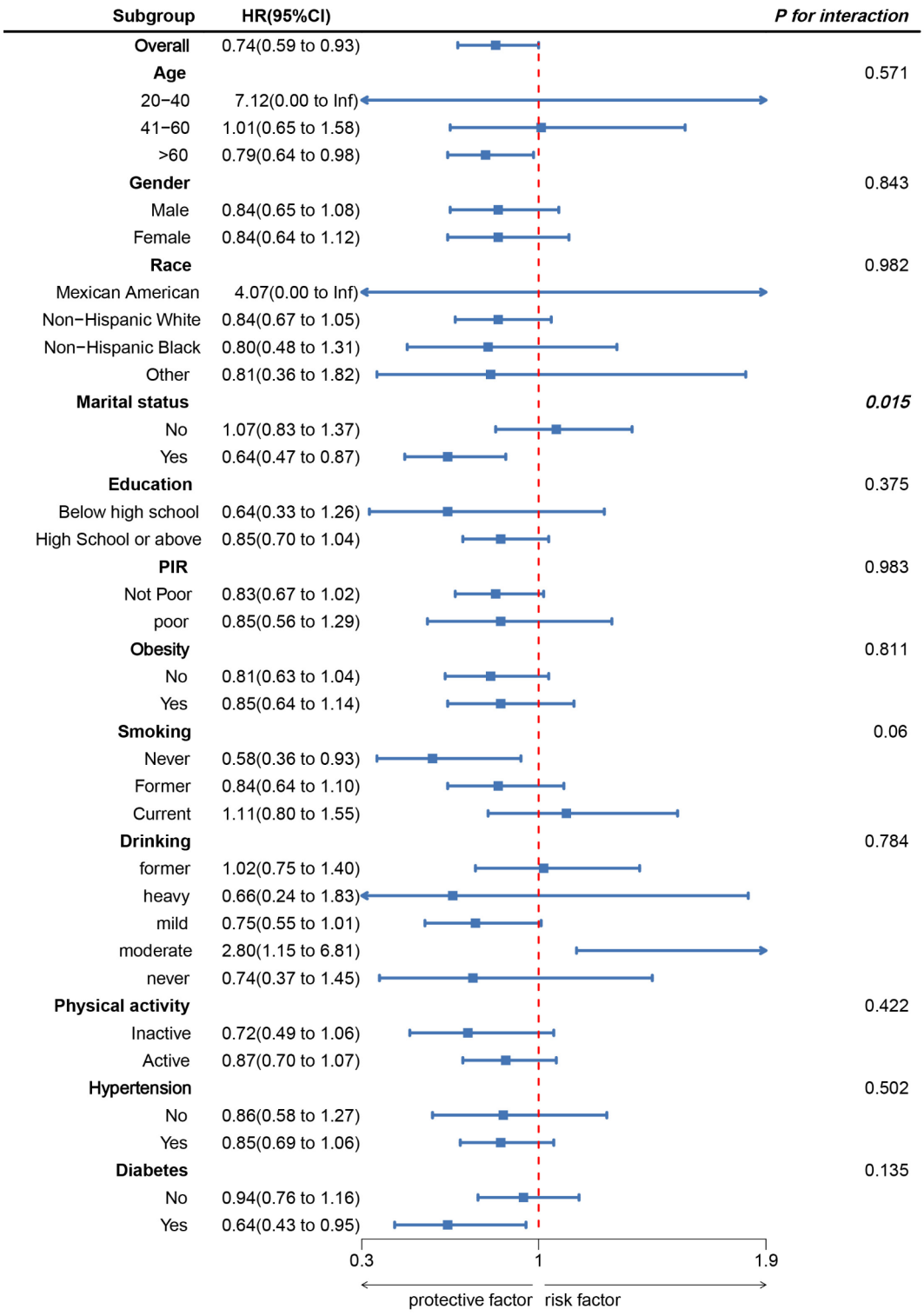

Fig. 4. Subgroup analysis between Omega-3 PUFAs intake and All-cause mortality. ORs were calculated as each unit increased in Omega-3 PUFAs intake. Analyses were adjusted for age, gender, education level, marital status, PIR, race, obesity, smoking, drinking, Physical activity, hypertension, and diabetes. Abbreviation: PIR, poverty income ratio; Omega-3 PUFAs, Omega-3 polyunsaturated fatty acids; HR, hazard ratio; CI, confidence interval.

Data availability

The study involved the analysis of publicly available datasets. The data can be accessed at the following URL: https://www.cdc.gov/nchs/nhanes/.

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Author contributions
S.H. contributed to the Conceptualization, Methodology, Software, Validation, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Visualization. J.J. contributed to the original draft, Methodology, Supervision, Project administration, and Formal analysis. H.G. was involved in Writing – review & editing, Supervision, Project administration, and Investigation.

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Declarations

Competing interests
The authors declare no competing interests.

Institutional review board statement
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Informed consent
Waiver of consent was obtained for this study. The need for informed consent was waived by Domain Specific Review Board.

Consent for publication
Prior to their involvement in the study, all participants provided informed consent.

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