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Original Article

Association between plasma docosahexaenoic acid levels and the incidence of frailty: A prospective analysis of the UK Biobank

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ABSTRACT

Objectives: The blood level of n-3 polyunsaturated fatty acids (PUFAs) has been associated cross-sectionally with frailty, but its relationship with incident frailty remains unclear. The present study investigates the hypothesis that plasma levels of n-3 PUFAs, particularly docosahexaenoic acid (DHA), are inversely associated with the incidence of frailty and individual frailty criteria.
Design: Prospective cohort study.
Setting: The UK Biobank cohort.
Participants: A total of 38,577 non-frail adults aged 40–69 years who enrolled between 2006 and 2010 were followed for a maximum of 13 years.
Measurements: Frailty was defined as meeting at least 3 of 5 separate criteria (low physical activity, exhaustion, slow walking speed, weight loss, and low grip strength), and plasma levels of total n-3 PUFAs, DHA, and non-DHA n-3 PUFAs were measured by nuclear magnetic resonance. Cox-proportional hazards models were used to predict incident frailty after adjusting for demographic, medical history and other potential confounding factors.
Results: After a median follow-up of 9.37 years, 1,024 individuals became frail. The incidence of frailty was inversely associated with plasma level of DHA (hazard ratio [HR] per inter-quintile range: 0.82, 95% confidence interval [CI] 0.69–0.97; $p = 0.019$) after adjusting for confounding factors. Plasma level of DHA was inversely associated with the incidence of two frailty criteria—low physical activity and exhaustion. On the other hand, neither plasma levels of non-DHA n-3 PUFAs (HR 0.98, 95% CI 0.83–1.16) nor those of total n-3 PUFAs (HR 0.91, 95% CI 0.77–1.07) was significantly associated with the incidence of frailty after adjusting for confounding factors.
Conclusions: The incidence of frailty was inversely associated with the plasma level of DHA but not with the levels of other n-3 PUFAs, suggesting that a low plasma DHA level could help identify individuals at high risk for developing frailty, enabling preventive measures to be initiated.

1. Introduction

Frailty is a geriatric syndrome characterized by low physical activity, exhaustion, slow walking speed, unintentional weight loss, and low grip strength, and is associated with an increased risk of mortality, falls, fractures, disability, and hospitalization [1]. Because frailty is highly associated with age, an increasingly old global population has led to commensurate increases in the prevalence of frailty, from 12% and 24% among older adults in 62 countries [2]. The factors that contribute to frailty are unclear, but chronic inflammation has been suggested as a major risk factor [3].

N-3 polyunsaturated fatty acids (PUFAs), including docosahexaenoic acid (DHA, 22:6n3), eicosapentaenoic acid (EPA, 20:5n3), and α-linolenic (ALA, 18:3n3), are known to have anti-inflammatory effects [4]. Epidemiological studies consistently report that the intake of oily fish, or fish rich in EPA and DHA is associated with a lower risk of frailty [5–12]. In addition, cross-sectional studies have reported that the use of fish oil is lower in frail (vs. non-frail) adults in Taiwan [13] and the UK [10].

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The intake of n-3 PUFAs was also inversely associated with the risk of frailty in American adults [14], but not in Spanish older adults [15]. Clinical trials reported that supplementation of >2 g/day of DHA and EPA improved grip strength in American older adults, suggesting that higher intake of n-3 PUFAs could have beneficial effect on the development of frailty [16].

In previous studies by our group, blood levels of DHA were inversely associated with the prevalence of frailty in British older adults from the UK Biobank [10] and Korean older adults from the Korean frailty and aging cohort study (KFACS) [17]. Our 6-year follow-up of the latter cohort found that the incidence of frailty was also inversely associated with the blood level of DHA in Korean older adults suggesting that the blood level of DHA could be a marker for the risk of frailty [18]. In addition, the blood level of DHA was associated with a lower prevalence and incidence of each frailty criteria, such as low physical activity, exhaustion, slow walking speed, weight loss, and low grip strength in British older adults [10], slow walking speed in Korean older adults [17, 18], low physical activity, low grip strength, and weight loss in Japanese older adults [19], and slow walking speed in French older adults [20].

Therefore, it is of interest to examine the associations between the incidence of frailty and the blood levels of n-3 PUFAs in the UK Biobank, which contains a population with lower, more typical blood levels as compared to Korean adults [21]. The present study investigated the hypothesis that higher blood levels of n-3 PUFAs, particularly DHA and possibly non-DHA n-3 PUFAs, would be associated with a lower incidence of frailty and each frailty component in middle aged and older adults in the UK Biobank.

2. Material and methods

2.1. Participants

This study utilized data from the UK Biobank, a large population-based cohort of participants aged 40–69 years who were recruited from 22 assessment centers in England, Scotland, and Wales between 2006 and 2010 [22]. The UK Biobank initially enrolled 502,366 participants. Among them, 82,725 individuals had at least one follow-up visit, and 51,527 had both fatty acid and follow-up data of maximum 13 years (Fig. 1). From that group, we excluded 5,929 participants with missing frailty measures and 2,149 participants who were classified as frail at baseline. Additional exclusions were made for missing covariate data, resulting in a final analytic sample of 23,147 robust and 14,416 pre-frail participants.

2.2. Measurement of n-3 PUFAs

Nuclear magnetic resonance (Nightingale Health Plc, Helsinki, Finland) was used to measure the levels of total n-3 PUFAs and DHA in plasma, expressed as a percentage of total fatty acids [22]. The n-3 PUFAs included the sum of DHA, EPA, docosapentaenoic acid (22:5n3), ALA, and stearidonic acid (18:4n3), but only DHA was specifically quantified. Plasma level of non-DHA n-3 PUFA was computed by subtracting DHA from the plasma levels of total n-3 PUFAs using the directly measured values.

2.3. Assessment of frailty

The revised version of the Cardiovascular Health Study frailty phenotype was used to define frailty in any individual who simultaneously met three or more of the following five criteria: low physical activity, exhaustion, slow walking speed, weight loss, and low grip strength [1]. Physical activity levels were determined based on self-reported responses to “Types of physical activity and how many times in the last 4 weeks” and classified as none (no physical activity), low (light activity such as pruning or watering the lawn), medium (heavy activity like weeding, lawn mowing, carpentry, digging, walking for pleasure, or other exercises), and high (strenuous sports). Participants engaging in none or light activity with a frequency of once per week or less were classified as having low physical activity. Exhaustion was assessed by asking, “Over the past 2 weeks, how often have you felt tired or had little energy?” The response options were “more than half the days,” “nearly every day,” and “other,” and participants who responded more than half the days or nearly every day were classified as having exhaustion. Low grip strength was measured using a hydraulic hand dynamometer (Jamar J00105, Patterson Medical, Ashfield, United Kingdom). With the participants seated upright with their elbow by their side and fixed at 90°, handgrip strength was acquired from each hand, and the highest value from both hands was categorized using the sex and body mass index–adjusted cutoffs defined by Fried et al. [1]. Walking speed was self-reported in response to the question, “How would you describe your usual walking speed?” Participants who responded “slow” were classified as having slow walking speed. Weight loss was self-reported with the question, “Compared with 1 year ago, has your weight changed?” Participants who answered “reduced” were classified as having weight loss.

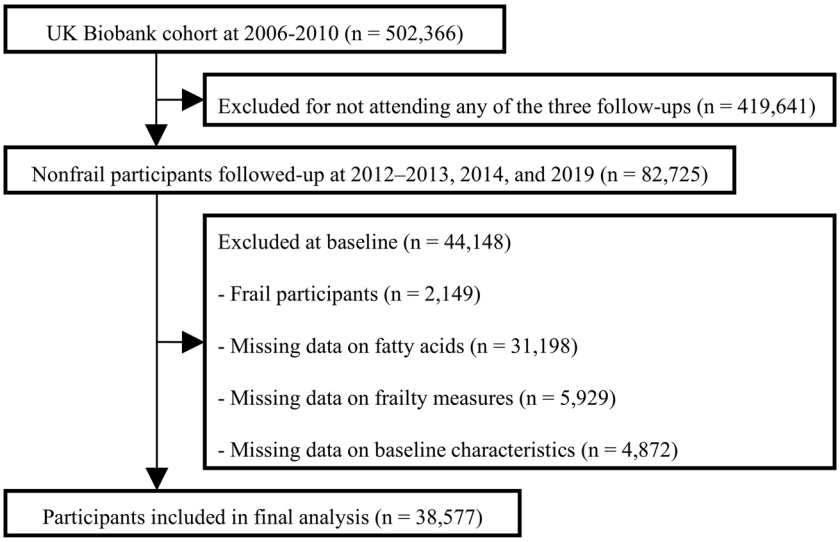


Fig. 1. Flowchart showing the inclusion and exclusion of participants.

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2.4. Covariates

Baseline values of numerous demographic and medical history variables were considered. Covariates such as age (years) and biological sex (male, female) were collected from National Health Service records and/or self-reported data from the touchscreen questionnaire. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (meters), and waist circumference (cm) was measured by a trained research assistant using a non-stretchable tape at the level of the umbilicus. Using a self-reported questionnaire administered on a touchscreen, participants provided their ethnicity (White, Asian, Black, or other), smoking history (never, previous, or current), alcohol intake (rarely, 1-2 per week, 3-4 per week, or daily), education level (less than high school, high school, or college), household income (<£18,000, £18,000-30,999, £31,000–51,999, £52,000-100,000, or >£100,000), employment (employed, retired, unemployed, disabled, or other), household size, frequency of friend and family visits (rarely, 1 per month, 1 per week, 2-4 per week, or daily) and duration of sleep (<7 h, 7–8 h, or ≥8 h).

2.5. Statistical analysis

All statistical analyses were conducted in R version 4.1.2, and statistical significance was set at $p < 0.05$. Continuous variables were evaluated using the independent sample *t*-test and are presented as the mean ± SD, and categorical variables were assessed with the chi-square test and are reported as frequencies and percentages. Death was treated as a censoring event. Person-years were calculated from the date of the last exposure assessment at baseline to the date of the incidence of frailty, death, or the end of follow-up, whichever occurred first. To assess the associations between frailty incidence and plasma levels of DHA, non-DHA n-3 PUFAs, and n-3 PUFAs, hazard ratios (HR) and 95% confidence intervals (CI) were calculated using multivariable Cox proportional hazards regression analyses adjusted for potential confounders and assessed for proportional hazards assumptions; strata were added to the models as needed. Model 1 was adjusted for age, sex, and ethnicity, and model 2 was adjusted for the covariates in model 1 and smoking status, alcohol drinking, BMI, waist circumference, education, income, employment, household size, frequency of friend and family visits, and sleep duration. Plasma levels were analyzed both as continuous variables using inter-quintile range (IQ5R) analysis, defined as the difference between the 90th and 10th percentiles of each exposure, and as quintiles, with the lowest quintile serving as the reference group. To explore nonlinear relationships between frailty incidence and the three plasma-based exposures, restricted cubic spline functions were applied to the Cox model, and a spline model was generated. The spline model and the original Cox models were compared to determine the presence of nonlinearity, using likelihood ratio test.

3. Results

Frail participants were older at baseline, had a higher BMI and waist circumference, and had a higher proportion of females, smokers, participants with comorbidities, and individuals with low income and single-person households (Table 1). Frail participants had lower education and alcohol drinking, a lower proportion of employment, friend and family visits, and sleep duration of 7–8 h than non-frail participants.

During a median follow-up of 9.37 years, 1024 cases of frailty were documented over 350,286.6 person-years of observation. The incidence of frailty was inversely associated with the plasma level of DHA in linear model 2 (HR 0.82, 95% CI 0.69–0.97, $p = 0.019$). There was significant non-linearity ($p = 0.022$), with the risk being lower in plasma DHA quintiles 2–5 than in quintile 1 (Table 2). The incidence of frailty was not associated with the plasma levels of non-DHA n-3 PUFAs and total n-3 PUFAs in the linear analyses, and there was no evidence of non-linearity for those exposures.

Table 1
Baseline characteristics of the study participants by incident frailty.

	Non-frail participants ($n = 37,553$)	Frail participants ($n = 1024$)	*p*-value
Age (years)	55.3 ± 7.6	57.4 ± 7.6	<0.001
Female, *n* (%)	18,275 (48.7)	561 (54.8)	<0.001
BMI (kg/m^2)	26.6 ± 4.1	30.8 ± 6	<0.001
Waist circumference (cm)	88.4 ± 12.5	98.3 ± 15.4	<0.001
Ethnicity, *n* (%)			0.170
White	36,632 (97.5)	995 (97.2)	
Asian	403 (1.1)	10 (1.0)	
Black	181 (0.5)	10 (1.0)	
Other	337 (0.9)	9 (0.9)	
Smoking status, *n* (%)			<0.001
Never	22,367 (59.6)	521 (50.9)	
Previous	12,766 (34)	400 (39.1)	
Current	2420 (6.4)	103 (10.1)	
Alcohol drinking, *n* (%)			<0.001
Rarely	8230 (21.9)	386 (37.7)	
1–2 per week	9727 (25.9)	251 (24.5)	
3–4 per week	10,820 (28.8)	208 (20.3)	
Daily	8776 (23.4)	179 (17.5)	
Education, *n* (%)			<0.001
Less than high school	2323 (6.2)	138 (13.5)	
High school	6847 (18.2)	238 (23.2)	
College	28,383 (75.6)	648 (63.3)	
Income, *n* (%)			<0.001
<£18,000	4465 (11.9)	238 (23.2)	
£18,000–30,999	8744 (23.3)	338 (33.0)	
£31,000–51,999	11,348 (30.2)	270 (26.4)	
£52,000–100,000	10,315 (27.5)	160 (15.6)	
>£100,000	2681 (7.1)	18 (1.8)	
Employment, *n* (%)			<0.001
Employed	26,457 (70.5)	574 (56.1)	
Retired	10,000 (26.6)	361 (35.3)	
Unemployed	375 (1.0)	9 (0.9)	
Disabled	315 (0.8)	66 (6.4)	
Other	406 (1.1)	14 (1.4)	
Living alone, *n* (%)	6088 (16.2)	218 (21.3)	<0.001
Frequency of friend and family visits, *n* (%)			<0.001
Rarely	2847 (7.6)	108 (10.5)	
1 per month	5657 (15.1)	131 (12.8)	
1 per week	14,242 (37.9)	352 (34.4)	
2–4 per week	11,342 (30.2)	304 (29.7)	
Daily	3465 (9.2)	129 (12.6)	
Sleep duration, *n* (%)			
<7 h	8019 (21.4)	271 (26.5)	<0.001
7–8 h	16,317 (43.5)	368 (35.9)	
≥8 h	13,217 (35.2)	385 (37.6)	

Notes: Data are presented as the mean ± SD or number of participants (percentage distribution), as appropriate.

With respect to the five frailty criteria that comprise the Cardiovascular Health Study Index, in the linear (i.e., per IQ5R) analyses, the incidence of low physical activity was inversely associated with the plasma level of DHA (HR 0.76, 95% CI 0.66–0.87, $p < 0.001$), non-DHA n-3 PUFAs (HR 0.82, 95% CI 0.72–0.93, $p = 0.002$), and total n-3 PUFAs (HR 0.78, 95% CI 0.68–0.89, $p < 0.001$) in model 2 (Table 3). Comparing quintile 5 with quintile 1 for this outcome and the three exposures, the risk for low physical activity was 27%, 21%, and 21% lower, respectively. For the incidence of exhaustion, there was an inverse association with DHA (HR 0.85, 95% CI 0.76–0.96, $p = 0.006$), with the quintile 5 vs. 1 risk being 22% lower. However, there were no significant associations between the plasma levels of non-DHA or total n-3 PUFAs and this criterion. There were no statistically significant relationships between any of the three n-3 PUFA metrics and low grip strength, slow walking speed, or weight loss. None of these analyses showed evidence of significant non-linearity.

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Table 2
Association between plasma level of n-3 PUFAs and the incidence of frailty.

	Cases/n	Person-years	Model 1 HR (95% CI)	*p*-value	Model 2 HR (95% CI)	*p*-value	Nonlinear *p*-value
DHA (per IQ5R)			0.35 (0.30, 0.42)	<0.001	0.82 (0.69, 0.97)	0.019	0.022
Q1 (<1.52%)	336/7715	69,974.3	1.0		1.0		
Q2 (1.52–1.83%)	210/7713	70,579.2	0.56 (0.47, 0.67)	<0.001	0.81 (0.67, 0.96)	0.016	
Q3 (1.83–2.13%)	180/7718	70,263.8	0.47 (0.39, 0.56)	<0.001	0.79 (0.65, 0.95)	0.012	
Q4 (2.13–2.53%)	159/7713	70,565.2	0.38 (0.31, 0.46)	<0.001	0.77 (0.63, 0.94)	0.010	
Q5 (>2.53%)	139/7718	68,904.1	0.32 (0.26, 0.39)	<0.001	0.79 (0.63, 0.98)	0.029	
Non-DHA (per IQ5R)			0.85 (0.72, 0.99)	0.036	0.98 (0.83, 1.16)	0.833	0.150
Q1 (<1.58%)	185/7714	71,576.4	1.0		1.0		
Q2 (1.58–2.08%)	216/7715	71,470.2	1.07 (0.87, 1.30)	0.534	1.05 (0.85, 1.28)	0.655	
Q3 (2.08–2.55%)	217/7717	70,063.3	1.06 (0.87, 1.30)	0.555	1.06 (0.86, 1.30)	0.574	
Q4 (2.55–3.15%)	213/7714	69,467.2	0.97 (0.79, 1.19)	0.789	1.03 (0.80, 1.26)	0.786	
Q5 (>3.15%)	193/7717	67,709.6	0.84 (0.68, 1.04)	0.107	0.99 (0.77, 1.23)	0.932	
N-3 PUFAs (per IQ5R)			0.59 (0.50, 0.69)	<0.001	0.91 (0.77, 1.07)	0.249	0.056
Q1 (<2.23%)	256/7716	71,004.8	1.0		1.0		
Q2 (2.23–3.91%)	196/7715	71,200.8	0.71 (0.59, 0.86)	<0.001	0.84 (0.69, 1.01)	0.064	
Q3 (3.91–4.58%)	215/7713	70,533.7	0.74 (0.62, 0.89)	0.001	0.95 (0.79, 1.15)	0.619	
Q4 (4.58–5.53%)	192/7717	69,496.0	0.62 (0.51, 0.75)	<0.001	0.85 (0.70, 1.04)	0.109	
Q5 (>5.53%)	165/7716	68,051.3	0.50 (0.41, 0.61)	<0.001	0.86 (0.69, 1.06)	0.144	

Notes: Data are presented as the hazard ratio [HR, 95% confidence interval (CI)]. IQ5R = inter-quintile range (defined as 90th minus 10th percentiles of DHA, Non-DHA, and N-3 PUFAs). Q = quintile. DHA = docosahexaenoic acid. PUFAs = polyunsaturated fatty acids. Model 1 was adjusted for age, sex, and ethnicity. Model 2 was adjusted for the covariates in Model 1 and smoking status, alcohol drinking, body mass index, waist circumference, education, income, employment, household size, frequency of friend and family visits, and sleep duration.

4. Discussion

The present study shows that higher plasma levels of DHA were associated with lower incidence of frailty in middle aged and older adults from UK Biobank during 13-year follow-up. This is consistent with our previous findings in a Korean older adults in KFACS [18]. The mean plasma levels of DHA were 9% in Korean older adults from KFACS [17,18], compared with 2% in this UK Biobank cohort [23]. These together suggest that the plasma level of DHA could be used to predict frailty risk.

Dupont et al. [24] showed that the erythrocyte levels of DHA, but not EPA, were positively associated with muscle mass in Belgian community-dwelling older adults with sarcopenia from the Exercise and Nutrition for Healthy AgeiNg study. The association of DHA consumption and muscle mass was associated negatively in Italian community-dwelling older adults [25], but positively in Belgian community-dwelling sarcopenic older adults [24], indicating that intake of DHA might not be an objective biomarker for the status of DHA. An *in vitro* study using muscle cells reported that treatment with DHA, but not EPA, prevented the myosteatosis induced by palmitic acid and restored the function of protein synthesis [26]. DHA is known to increase muscle protein synthesis by activating the mammalian target of rapamycin pathway and to decrease protein breakdown by reducing inflammatory signaling and inhibiting the ubiquitin–proteasome and autophagy–lysosome systems [27]. In the present study, the incidence of frailty was lower in participants with plasma level of Q2-Q5 (>1.52%) than Q1, indicating the threshold effect of DHA rather than linear association, suggesting saturation of anti-inflammatory effect on muscle protein synthesis. Previous study reported that mean plasma DHA level of 1.51% was observed in American adults consumed 130 mg/day of DHA [28].

In the present study, plasma levels of non-DHA n-3 PUFAs and total n-3 PUFAs were not associated with the incidence of frailty in the multivariable adjusted model. Our previous study of the same UK Biobank cohort showed that plasma levels of non-DHA n-3 PUFAs and total n-3 PUFAs were inversely associated with the prevalence of frailty [10]. Prevalence and incidence are used for different purposes and to answer different research questions, and thus direct comparison of prevalence and incidence of frailty may be inappropriate for conceptual, theoretical, and practical reasons [29].

The prevalence of frailty was consistently and inversely associated with the intake of oily fish in British older adults from UK Biobank [10], and with the intake of fish in Korean older adults from KFACS [6], Japanese older women [7,8], and Brazilian middle aged and older adults from the Brazilian Longitudinal Study of Aging [30]. In addition, the intake of fish was inversely associated with the incidence of frailty in Chinese older adults from Chinese Longitudinal Healthy Longevity Survey during 3-year follow-up [9] and in Spanish older adults from the ENRICA cohort during 3.5-year follow-up [11]. The frailty score was also inversely correlated with the intake of oily fish in older Ecuadorian older adults [12], and with the intake of fish in Irish older adults [5].

The prevalence of frailty was inversely associated with the intake of n-3 PUFAs in American adults from National Health and Nutrition Examination Survey (NHANES) 2005–2014 [14]. However, the intake of n-3 PUFAs was not associated with the prevalence of frailty in American adults from NHANES 2003–2006 [31] and the incidence of frailty in Spanish older adults from ENRICA cohort during 3.5-year follow-up [15]. The major form of dietary n-3 PUFAs is ALA, which is found in plant sources such as flaxseed and canola oil, rather than fish [32]. The intake of ALA was not significantly associated with the prevalence of frailty in Americans [31] and the incidence of frailty in Spanish older adults [15]. A meta-analysis of clinical trials showed that the supplementation of > 2 g/day of DHA and EPA increased muscle mass in older adults [33], suggesting that higher doses of n-3 PUFAs could be beneficial on the progress of frailty.

Consistent with the present study, previous studies showed that the blood level of DHA was inversely associated with the incidence of low physical activity in Korean older adults from KFACS [18], and the prevalence of low physical activity in Japanese older adults [19] and UK older adults from UK Biobank [10]. In addition, the plasma levels of n-3 PUFAs were inversely associated with the prevalence of low physical activity in UK older adults from UK Biobank [10], and with the incidence of low physical activity in the present study. In our previous study using UK Biobank data, the prevalence of low physical activity was also inversely associated with the intake of oily fish and the use of fish oil supplementation in UK older adults [10]. The present study suggested that anti-inflammatory effect of n-3 PUFA, particularly DHA could be associated with low physical activity, since lower physical activity and increased inflammation were often observed in frail older adults [34,35].

The blood level of DHA was inversely associated with the prevalence of exhaustion in Korean older adults from KFACS [17], UK older adults from UK Biobank [10]. The present study also found that the blood level

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Table 3
Association between the plasma level of n-3 PUFAs and the incidence of the frailty criteria.

		Cases/n	Person-years	Model 1 HR (95% CI)	*p*-value	Model 2 HR (95% CI)	*p*-value	Nonlinear *p*-value
Low Physical Activity	DHA (per IQ5R)			0.45 (0.40, 0.52)	<0.001	0.76 (0.66, 0.87)	<0.001	0.921
	Q1 (<1.52%)	438/7120	64,281.0	1.0		1.0		
	Q2 (1.52–1.83%)	359/7290	66,607.3	0.74 (0.64, 0.86)	<0.001	0.92 (0.80, 1.06)	0.256	
	Q3 (1.83–2.13%)	315/7327	66,495.8	0.64 (0.55, 0.74)	<0.001	0.90 (0.77, 1.05)	0.175	
	Q4 (2.13–2.53%)	296/7387	67,362.3	0.56 (0.48, 0.65)	<0.001	0.90 (0.77, 1.05)	0.180	
	Q5 (>2.53%)	221/7457	66,497.3	0.41 (0.35, 0.49)	<0.001	0.73 (0.61, 0.87)	<0.001	
	Non-DHA (per IQ5R)			0.75 (0.66, 0.85)	<0.001	0.82 (0.72, 0.93)	0.002	0.058
	Q1 (<1.58%)	345/7225	66,769.4	1.0		1.0		
	Q2 (1.58–2.08%)	328/7267	67,154.8	0.90 (0.78, 1.06)	0.196	0.89 (0.76, 1.04)	0.126	
	Q3 (2.08–2.55%)	352/7351	66,604.3	0.98 (0.84, 1.14)	0.756	0.97 (0.83, 1.13)	0.645	
	Q4 (2.55–3.15%)	332/7348	66,023.6	0.89 (0.76, 1.04)	0.136	0.93 (0.79, 1.09)	0.343	
	Q5 (>3.15%)	272/7390	64,691.6	0.72 (0.61, 0.85)	<0.001	0.79 (0.67, 0.94)	0.005	
	N-3 PUFAs (per IQ5R)			0.59 (0.52, 0.67)	<0.001	0.78 (0.68, 0.89)	<0.001	0.381
	Q1 (<2.23%)	395/7154	65,560.8	1.0		1.0		
	Q2 (2.23–3.91%)	341/7291	67,045.3	0.82 (0.71, 0.95)	0.007	0.90 (0.78, 1.05)	0.164	
	Q3 (3.91–4.58%)	341/7322	66,904.0	0.79 (0.68, 0.92)	0.002	0.93 (0.80, 1.08)	0.314	
	Q4 (4.58–5.53%)	292/7394	66,440.8	0.65 (0.56, 0.77)	<0.001	0.83 (0.70, 0.97)	0.015	
	Q5 (>5.53%)	260/7420	65,292.8	0.57 (0.48, 0.67)	<0.001	0.79 (0.67, 0.94)	0.006	
Exhaustion	DHA (per IQ5R)			0.65 (0.58, 0.72)	<0.001	0.85 (0.76, 0.96)	0.006	0.632
	Q1 (<1.52%)	549/6914	62,310.9	1.0		1.0		
	Q2 (1.52–1.83%)	491/7012	63,722.3	0.81 (0.71, 0.91)	<0.001	0.91 (0.80, 1.03)	0.142	
	Q3 (1.83–2.13%)	454/7081	64,255.4	0.72 (0.64, 0.82)	<0.001	0.89 (0.78, 1.01)	0.067	
	Q4 (2.13–2.53%)	420/7118	64,709.2	0.64 (0.56, 0.73)	<0.001	0.83 (0.72, 0.95)	0.006	
	Q5 (>2.53%)	366/7228	64,224.6	0.57 (0.50, 0.65)	<0.001	0.78 (0.68, 0.91)	0.001	
	Non-DHA (per IQ5R)			0.89 (0.80, 1.00)	0.037	0.94 (0.84, 1.05)	0.254	0.647
	Q1 (<1.58%)	530/7020	64,697.8	1.0		1.0		
	Q2 (1.58–2.08%)	466/7010	64,449.3	0.91 (0.80, 1.03)	0.138	0.91 (0.80, 1.04)	0.156	
	Q3 (2.08–2.55%)	429/7070	63,973.8	0.88 (0.77, 1.00)	0.044	0.88 (0.77, 1.00)	0.048	
	Q4 (2.55–3.15%)	445/7103	63,633.7	0.92 (0.81, 1.05)	0.221	0.95 (0.83, 1.08)	0.422	
	Q5 (>3.15%)	410/7150	62,467.8	0.88 (0.77, 1.00)	0.053	0.93 (0.81, 1.06)	0.277	
	N-3 PUFAs (per IQ5R)			0.77 (0.69, 0.86)	<0.001	0.90 (0.81, 1.00)	0.054	0.539
	Q1 (<2.23%)	532/6949	63,422.4	1.0		1.0		
	Q2 (2.23–3.91%)	495/7033	64,599.1	0.90 (0.80, 1.02)	0.098	0.96 (0.84, 1.08)	0.469	
	Q3 (3.91–4.58%)	450/7084	64,431.6	0.84 (0.74, 0.95)	0.006	0.92 (0.81, 1.05)	0.219	
	Q4 (4.58–5.53%)	420/7094	63,588.2	0.78 (0.69, 0.90)	<0.001	0.90 (0.79, 1.03)	0.110	
	Q5 (>5.53%)	383/7193	63,181.1	0.73 (0.64, 0.84)	<0.001	0.88 (0.76, 1.01)	0.057	
Low Grip Strength	DHA (per IQ5R)			0.79 (0.74, 0.83)	<0.001	0.97 (0.92, 1.03)	0.377	0.237
	Q1 (<1.52%)	1756/6989	62,101.2	1.0		1.0		
	Q2 (1.52–1.83%)	1623/7114	63,713.5	0.85 (0.80, 0.92)	<0.001	0.95 (0.89, 1.02)	0.152	
	Q3 (1.83–2.13%)	1601/7195	64,074.4	0.82 (0.77, 0.88)	<0.001	0.95 (0.89, 1.02)	0.169	
	Q4 (2.13–2.53%)	1612/7154	63,995.9	0.78 (0.73, 0.83)	<0.001	0.97 (0.90, 1.04)	0.418	
	Q5 (>2.53%)	1550/7164	62,431.9	0.73 (0.68, 0.78)	<0.001	0.95 (0.89, 1.03)	0.241	
	Non-DHA (per IQ5R)			0.99 (0.94, 1.04)	0.675	1.02 (0.97, 1.08)	0.430	0.354
	Q1 (<1.58%)	1507/7205	65,567.1	1.0		1.0		
	Q2 (1.58–2.08%)	1540/7143	64,828.0	0.94 (0.88, 1.01)	0.108	0.93 (0.86, 1.00)	0.037	
	Q3 (2.08–2.55%)	1645/7125	63,316.9	0.99 (0.92, 1.06)	0.738	0.98 (0.91, 1.05)	0.488	
	Q4 (2.55–3.15%)	1685/7078	62,320.2	0.95 (0.89, 1.03)	0.199	0.95 (0.89, 1.02)	0.175	
	Q5 (>3.15%)	1765/7065	60,284.8	0.98 (0.91, 1.05)	0.548	1.01 (0.94, 1.08)	0.793	
	N-3 PUFAs (per IQ5R)			0.90 (0.85, 0.95)	<0.001	1.00 (0.95, 1.06)	0.886	0.369
	Q1 (<2.23%)	1620/7149	64,495.6	1.0		1.0		
	Q2 (2.23–3.91%)	1559/7115	64,279.6	0.91 (0.85, 0.98)	0.007	0.95 (0.88, 1.02)	0.116	
	Q3 (3.91–4.58%)	1612/7145	63,946.8	0.89 (0.83, 0.96)	<0.001	0.94 (0.88, 1.01)	0.099	
	Q4 (4.58–5.53%)	1652/7093	62,502.2	0.87 (0.81, 0.93)	<0.001	0.95 (0.88, 1.02)	0.142	
	Q5 (>5.53%)	1699/7114	61,092.8	0.86 (0.80, 0.92)	<0.001	0.99 (0.99, 1.06)	0.755	
Slow Walking Speed	DHA (per IQ5R)			0.54 (0.47, 0.62)	<0.001	1.02 (0.89, 1.17)	0.786	0.708
	Q1 (<1.52%)	381/7425	67,601.1	1.0		1.0		
	Q2 (1.52–1.83%)	338/7480	68,721.0	0.81 (0.69, 0.94)	0.004	1.09 (0.94, 1.27)	0.241	
	Q3 (1.83–2.13%)	267/7527	68,662.3	0.63 (0.54, 0.74)	<0.001	0.94 (0.80, 1.11)	0.488	
	Q4 (2.13–2.53%)	266/7557	69,371.7	0.57 (0.49, 0.68)	<0.001	1.05 (0.89, 1.24)	0.571	
	Q5 (>2.53%)	221/7589	67,829.6	0.46 (0.39, 0.55)	<0.001	0.99 (0.82, 1.18)	0.888	
	Non-DHA (per IQ5R)			0.88 (0.77, 1.00)	0.048	0.96 (0.84, 1.10)	0.556	0.263
	Q1 (<1.58%)	279/7525	70,018.9	1.0		1.0		
	Q2 (1.58–2.08%)	298/7506	69,635.0	0.96 (0.81, 1.13)	0.595	0.93 (0.78, 1.10)	0.370	
	Q3 (2.08–2.55%)	294/7500	68,397.0	0.93 (0.78, 1.10)	0.367	0.87 (0.73, 1.03)	0.092	
	Q4 (2.55–3.15%)	293/7512	67,873.3	0.85 (0.72, 1.01)	0.063	0.87 (0.73, 1.03)	0.095	
	Q5 (>3.15%)	309/7535	66,261.6	0.87 (0.73, 1.03)	0.094	0.95 (0.80, 1.13)	0.567	
	N-3 PUFAs (per IQ5R)			0.71 (0.62, 0.81)	<0.001	0.98 (0.86, 1.12)	0.785	0.414
	Q1 (<2.23%)	334/7490	69,127.4	1.0		1.0		
	Q2 (2.23–3.91%)	293/7492	69,337.1	0.82 (0.70, 0.96)	0.013	0.89 (0.76, 1.04)	0.139	
	Q3 (3.91–4.58%)	294/7,513	68,991.8	0.77 (0.65, 0.90)	<0.001	0.90 (0.76, 1.05)	0.172	
	Q4 (4.58–5.53%)	274/7518	67,828.5	0.68 (0.57, 0.80)	<0.001	0.86 (0.72, 1.01)	0.062	
	Q5 (>5.53%)	278/7565	66,900.9	0.64 (0.54, 0.76)	<0.001	0.96 (0.81, 1.14)	0.631	
Weight Loss	DHA (per IQ5R)			0.78 (0.73, 0.83)	<0.001	0.98 (0.92, 1.04)	0.495	0.688

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Table 3 (*continued*)

	Cases/n	Person-years	Model 1 HR (95% CI)	*p*-value	Model 2 HR (95% CI)	*p*-value	Nonlinear *p*-value
Q1 (<1.52%)	1608/6723	59,535.4	1.0		1.0		
Q2 (1.52–1.83%)	1491/6690	59,765.0	0.91 (0.85, 0.98)	0.009	1.01 (0.94, 1.09)	0.767	
Q3 (1.83–2.13%)	1353/6607	58,913.0	0.84 (0.78, 0.91)	<0.001	0.98 (0.91, 1.06)	0.598	
Q4 (2.13–2.53%)	1333/6624	59,297.2	0.80 (0.75, 0.87)	<0.001	1.01 (0.93, 1.09)	0.893	
Q5 (>2.53%)	1210/6528	57,232.4	0.75 (0.70, 0.82)	<0.001	0.99 (0.92, 1.08)	0.889	
Non-DHA (per IQ5R)			1.05 (0.99, 1.12)	0.090	1.04 (0.98, 1.11)	0.162	0.247
Q1 (<1.58%)	1310/6585	59,555.4	1.0		1.0		
Q2 (1.58–2.08%)	1418/6696	60,741.9	1.04 (0.96, 1.12)	0.362	0.99 (0.91, 1.06)	0.695	
Q3 (2.08–2.55%)	1424/6689	59,443.8	1.07 (0.99, 1.16)	0.071	1.01 (0.94, 1.09)	0.770	
Q4 (2.55–3.15%)	1489/6629	58,440.7	1.12 (1.04, 1.21)	0.003	1.05 (0.97, 1.14)	0.193	
Q5 (>3.15%)	1354/6573	56,561.2	1.06 (0.98, 1.14)	0.161	1.03 (0.95, 1.12)	0.438	
N-3 PUFAs (per IQ5R)			0.93 (0.88, 0.99)	0.015	1.02 (0.96, 1.08)	0.527	0.372
Q1 (<2.23%)	1407/6654	59,747.7	1.0		1.0		
Q2 (2.23–3.91%)	1454/6656	59,963.9	1.01 (0.94, 1.09)	0.703	1.04 (0.97, 1.12)	0.282	
Q3 (3.91–4.58%)	1450/6661	59,717.7	1.01 (0.94, 1.09)	0.786	1.05 (0.97, 1.13)	0.226	
Q4 (4.58–5.53%)	1405/6667	58,805.2	0.99 (0.91, 1.06)	0.724	1.04 (0.96, 1.12)	0.301	
Q5 (>5.53%)	1279/6534	56,508.5	0.93 (0.86, 1.01)	0.062	1.04 (0.96, 1.13)	0.289	

Notes: Data are presented as the hazard ratio [HR, 95% confidence interval (CI)]. IQ5R = inter-quintile range (defined as 90th minus 10th percentiles of DHA, Non-DHA, and N-3 PUFAs). Q = quintile. DHA = docosahexaenoic acid. PUFAs = polyunsaturated fatty acids. Model 1 was adjusted for age, sex, and ethnicity. Model 2 was adjusted for the covariates in Model 1 and smoking status, alcohol drinking, body mass index, waist circumference, education, income, employment, household size, frequency of friend and family visits, and sleep duration.

of DHA was inversely associated with the incidence of exhaustion in middle aged and older adults from UK Biobank. In addition, the intake of oily fish and fish was inversely associated with the prevalence of exhaustion in older adults from UK Biobank [10] and KFACS [6]. The use of fish oil supplementation was also inversely associated with the prevalence of exhaustion in older adults from UK Biobank [10]. The exhaustion was assessed by a question from Recent Depressive Symptoms-4 in UK Biobank [36]. Previous studies reported that the blood level of DHA was significantly lower in patients with depression than in those without depression [37] and also inversely associated with the incidence of depression and anxiety in UK adults from UK Biobank [38]. A meta-analysis of clinical studies showed that supplementation with n-3 PUFAs had beneficial impacts on depression in depressive patients [39].

Previous studies reported that the blood level of DHA was not associated with the prevalence and incidence of low grip strength in Korean older adults [17,18], Icelandic older adults [40], and American older adults [41,42], which is consistent with the present study. In addition, the intake of fish was not associated with grip strength in Korean older adults [6,43], Finnish older adults [44], British older adults [45], and European older adults [46].

Furthermore, the plasma level of DHA was not associated with the incidence of slow walking speed in UK middle aged and older adults from UK Biobank during 13-year follow-up in the present study. The intake of DHA was not associated with walking speed in older Finnish women [47], and older Australians with subjective memory complaints [48]. On the other hand, the blood level of DHA was significantly associated with the prevalence of slow walking speed in Korean older adults from KFACS [17], British adults from UK Biobank [10], and French older adults from the Three-City-Bordeaux study [20], and with the incidence of slow walking speed in Korean older adults from KFACS during 6-year follow-up [18]. The intake of oily fish was also inversely associated with the prevalence of slow walking speed in British older adults [10] and the incidence of slow walking speed in Korean older adults during 6-year follow-up [49]. In the UK Biobank, walking speed was self-reported rather than objectively measured, which could be affected by reporting bias. The incidence of slow walking speed was 4% in middle age and older adults the present study, but the prevalence of slow walking speed was 10% in UK older adults from UK Biobank [10]. The inconsistent results between the present study and the previous UK Biobank study could partly be due to the difference on the rate of slow walking speed by different mean age of the study populations. Specifically, average age was 55.3 ± 7.6 years old at baseline; therefore, these findings might not be directly applied in older adults.

The plasma level of DHA was not associated with the incidence of weight loss in middle aged and older adult from UK Biobank in the present study. The erythrocyte level of DHA was also not associated with the prevalence of weight loss in Korean older adults from KFACS [17]. On the other hand, the erythrocyte level of DHA was inversely associated with the prevalence of weight loss in Japanese older adults [19] and the incidence of weight loss in Korean older adults from KFACS [18], while positively associated with the prevalence of weight loss in UK older adults from UK Biobank [10]. Previous clinical trials reported that n-3 PUFA supplementation had no effect on body weight [50] or reduced body weight [51] in overweight and obese participants, while had no effect on weight [52] or significantly increased body weight [53] in normal weight participants, suggesting that effect of n-3 PUFAs on weight change depending on the BMI of the participants.

The strengths of the present study include the use of a large sample and long follow-up, the use of objective biomarkers for n-3 PUFA status, and the exploration of not only frailty per se but also the multiple components of frailty. Nonetheless, the present study has a few limitations. First, walking pace was self-reported rather than measured, and weight loss was not specified as unintentional, which could lead to inaccurate estimates. In the UK Biobank, weight loss as part of the malnutrition diagnosis since malnutrition is an important risk factor for frailty, but intentional and unintentional weight loss does not differentiate and degree of weight loss is not reported either. Second, the participants of UK Bank were primarily middle aged adults, and thus the results might not be directly generalized to the older population. Finally, despite controlling for confounding factors, there remains a potential for unobserved variables to have impacted the outcomes of the study.

5. Conclusions

This study shows that plasma level of DHA was inversely associated with the incidence of frailty in middle aged and older adults from the UK Biobank, suggesting that DHA could be used as a predictor of high frailty risk. Future clinical trials are needed to determine the extent to which DHA supplementation can reduce the risk of frailty.

CRediT authorship contribution statement

Y.A.: Writing - Original draft. N.T. and J.W.: Data Curation; Formal analysis. W.S.H.: Writing – Review & Editing. Y.P.: Supervision, Writing – Review & Editing.

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Ethics approval

The UK Biobank received ethical approval from the Northwest Multicenter Research Ethics Committee (Ref. 11/NW/0382). Use of these de-identified, publicly available data for research was approved by the University of South Dakota Institutional Review Board (IRB-21-147). Additionally, the Institutional Review Board of Hanyang University reviewed and approved the study protocol (HYUIRB-202509-015).

Declaration of Generative AI and AI-assisted technologies in the writing process

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Data availability

The UK Biobank data can be accessed online at https://www.ukbiobank.ac.uk. Researchers registered with UK Biobank can request access to the database by completing an application.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Yongsoon Park reports financial support was provided by National Research Foundation of Korea. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

WSH owns stock in OmegaQuant Analytics, LLC, a laboratory that offers blood fatty acid testing. The other authors have nothing to disclose.

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