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Research Article

Association Between Erythrocyte Levels of n-3 Polyunsaturated Fatty Acids and Risk of Frailty in Community-Dwelling Older Adults: The Korean Frailty and Aging Cohort Study

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Abstract

Background: Inflammation is a major risk factor for frailty, but n-3 polyunsaturated fatty acids (PUFA) has been suggested as an anti-inflammatory agent. The present study aimed to investigate the hypothesis that the higher erythrocyte levels of long-chain n-3 PUFA were associated with lower odds of frailty and frailty criterion.

Methods: Cross-sectional analysis from the Korean Frailty and Aging Cohort Study, a total of 1,435 people aged 70–84 years were included. Sex- and age-stratified community residents, drawn in urban and rural regions nationwide, were eligible for participation in the study. All participants were categorized as frail and nonfrail according to the Cardiovascular Health Study index.

Results: The likelihood of frailty was inversely associated with the erythrocyte levels of eicosapentaenoic acid (EPA; odds ratio [OR] per unit 0.33; 95% confidence interval [CI] 0.14–0.77; *p* for trend = .002) and docosahexaenoic acid (DHA; OR per unit 0.42; 95% CI 0.20–0.87; *p* for trend = .018). Among each frailty criterion, the likelihood of slow walking speed was associated with erythrocyte levels of EPA and DHA, and the likelihood of exhaustion was inversely associated with the erythrocyte levels of DHA.

Conclusions: The present study showed that the frailty and frailty criterion were significantly associated with lower erythrocyte levels of long-chain n-3 PUFA, suggesting that lower n-3 PUFA could be a marker for the risk of frailty.

Keywords: Long-chain n-3 polyunsaturated fatty acids, Nutrition, Frailty, Epidemiology

Frailty is a common geriatric syndrome characterized by unintentional weight loss, exhaustion, slowness, low physical activity, and weakness, which results in adverse health outcomes including subsequent falls, fractures, hospitalization, disability, and death (1). Korea is one of the most rapidly aging countries worldwide, and prevalence of frailty has been estimated as 13% among Korean older adults over 65 years old (2).

Although the pathophysiological changes underlying and preceding frailty are not fully understood, inflammation is one of the major causes for frailty (3). A meta-analysis showed that proinflammatory cytokines were associated with the risk of frailty (4). On the other hand, InCHIANTI study showed that proinflammatory cytokines such as tumor necrosis factor-α (TNF- α), interleukin-6 (IL-6), and C-reactive protein (CRP) were inversely associated with plasma levels of n-3 polyunsaturated fatty acids (PUFA), suggesting that n-3 PUFA as an anti-inflammatory agent could have beneficial effect against frailty (5).

Intake of fish rich in n-3 PUFA was associated with reduced incidence of frailty during 3.5 years follow-up in the Seniors-ENRICA study (6). Robinson and colleagues (7) also reported that intake

of fatty fish was positively associated with handgrip strength as a component of the frailty phenotype among older people in the Hertfordshire study. Blood levels of eicosapentaenoic acid (EPA; 20:5n3) and docosahexaenoic acid (DHA; 22:6n3), an objective biomarker of dietary intake of fish oil (8), were positively associated with walking speed (9,10). In addition, supplementation of EPA and DHA significantly improved walking speed in postmenopausal women (11), and thigh muscle volume, muscle strength, and handgrip strength in older people (12). Sarcopenia, loss of muscle mass and strength, is one of the major causes for frailty (13), and mortality was higher in frail older people with sarcopenia than without sarcopenia (14). Harris and colleagues (15) showed that older people with higher erythrocyte levels of EPA + DHA had lower risk for mortality during 11 years follow-up in the Framingham Heart Study. Fatty acid composition of erythrocyte membrane has been suggested to be superior than that of plasma due to reflect long-term (~16 weeks) dietary n-3 PUFA (16). To our knowledge, there is no study evaluated the association between the erythrocyte levels of n-3 PUFA and risk of frailty in older people. Therefore, the purpose of the present study was to investigate the hypothesis that the higher erythrocyte levels of long-chain n-3 PUFA such as EPA and DHA were associated with lower odds of frailty and each frailty criterion, using data from the Korean Frailty and Aging Cohort Study (KFACS).

Methods

Participants

This cross-sectional study was based on the data from the KFACS, a Korean multicenter longitudinal study that purposed to identify diverse risk and preventive factors for the progression of frailty in community-dwelling older people (17). Sex- and age-stratified community residents aged 70–84 years, drawn from 10 medical centers (8 hospitals and 2 public health centers) in urban and rural regions nationwide, were eligible for participation in the study. From the baseline data of 1,455 participants recruited during 2017, 1,435 participants were included in the final analysis after excluding 20 participants who had missing data for frailty index, consent withdrawal or had insufficient blood samples for analysis.

The KFACS protocol was approved by the Institutional Review Board (KHUH-2015-12-103-044 and HYI-18–166). Written informed consent was obtained from the all participants.

Frailty Assessment

Fried's frailty index consists of five components, with a score range of 0–5 (unintentional weight loss, self-reported exhaustion, low physical activity, slow walking speed, and weakness) (1). Participants who met three or more criteria were considered frail, otherwise they were considered nonfrail. Unintentional weight loss was defined as self-reported unintentional loss of ≥ 4.5 kg or 5% of the body weight during the last year. Self-reported exhaustion was evaluated using the questions from the Center for Epidemiological Studies Depression (CES-D) scale, and defined if either one of the questions "I felt that everything I did was an effort" or "I could not get going" was positive for three days or more a week (1). Low physical activity was calculated as the energy spent for a week by International Physical Activity Questionnaire (IPAQ) and defined as ≤ 494.65 kcal/wk for men and ≤ 283.50 kcal/wk for women (18). Slow walking speed was defined as < 1 m/s from the average of the walking speed for 4 m with 1.5 m before and after the walkway to allow for acceleration and deceleration (13). Low handgrip strength was defined as maximal grip strength < 26 kg for men and < 18 kg for women (19), measured twice for each and using a digital hand grip dynamometer (TKK-5401; Takei Scientific Instruments CO, Ltd., Tokyo, Japan).

Measurement of Erythrocyte Fatty Acid Composition

At the baseline visit, blood samples were drawn when the participant was in a fasting state and aliquots of erythrocyte samples were frozen immediately to −80°C until utilization in order to prevent cell lysis. The fatty acid composition of erythrocytes was performed as previously described (20). Briefly, the erythrocytes were methylated with boron trifluoride methanol benzene (Sigma–Aldrich, St. Louis, MO) and heated at 100°C for 10 minutes. Fatty acid methyl esters were extracted with hexane and analyzed by gas chromatography (Shimadzu 2010AF; Shimadzu Scientific Instrument, Kyoto, Japan), which was equipped with a 100 m × 0.25 mm inner diameter, with a 0.20 μm film capillary column (SP2560; Supelco, Bellefonte, PA). The content within erythrocytes of 27 fatty acids were identified by comparison with standards (GLC-727; Nu-Check Prep, Elysian, MN), and expressed as a weight present of total identified fatty acids. The gas chromatography evaluation was qualified by measuring the coefficient of variation of the sum of EPA and DHA composition in quality control material. The coefficient of variation for a quality control sample was 3.9%.

Covariates

Sociodemographic characteristics included age, sex, living alone, year of education (0–6, ≥ 7), economic status, and marital status (married, divorced/separated, widowed, single). Smoking status categorized never, former or current smoker, and alcohol drinking was classified as never or ever (servings per week). Comorbid status was determined by presence of 0, 1, and ≥ 2 of following diseases: hypertension, diabetes mellitus, cancer, chronic obstructive pulmonary disease, myocardial infarction, heart failure, angina, asthma, arthritis, cerebral ischemic, or renal disease (21). Participants were also asked about prescribed medications used in the past 3 months. Weight was measured in light clothing without shoes to the nearest 0.1 kg using a portable digital scale, and height was measured without shows to the nearest 0.1 cm using a measuring tape. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Cognitive impairment was measured using the Korean Mini-Mental State Examination (K-MMSE) score of less than 24 (22), and nutritional status was assessed using the Korean version of Mini-Nutritional Assessment Short Form (23). High-sensitivity (hs)-CRP concentration was analyzed and categorized as low (<1.0 mg/L), average (1.0–3.0 mg/L), and high (>3.0 mg/L) according to the statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association (24).

Statistical Analysis

The Kolmogorov–Smirnov test was used to check the normal distribution of variables. Continuous variables were presented as mean ± standard deviation (*SD*) value using the independent *t* test for normally distributed variables, and using the Mann–Whitney *U* test for skewed distributed variables. Proportions of nominal variables were presented as the number of participants (percentage distribution) using the chi-squared test. In the multivariate models, the covariates showing a *p*-value of < .20 were selected as confounding factors and included in the fully-adjusted model (25).

Erythrocyte levels of fatty acids were compared by analysis of covariance (ANCOVA) for normal distributed variables or rank ANCOVA for skewed variables between the groups after adjustment for the covariates. The Dunn-Bonferroni post hoc test was performed to assess differences of n-3 PUFA among three categories of hs-CRP. The erythrocyte levels of n-3 PUFA were analyzed both as a continuous variable for each 1-unit increase in erythrocyte levels of n-3 PUFA, and by quintiles for examination of nonlinear associations. The association between risk of frailty and the erythrocyte levels of n-3 PUFA was calculated with odds ratio (OR) and 95% confidence interval (CI) using multivariable logistic regression. In addition, the erythrocyte levels of fatty acids were divided into quintiles based on nonfrail participants as a reference, and trend test was performed by treating the median values of each quintile of the erythrocyte levels of fatty acids. Considering the type 1 error caused by multiple testing, *p*-values were adjusted by using Bonferroni correction, and thus divided by the number of subgroups. The SPSS version 24.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

Results

The characteristics of the participants are shown in Table 1. Prevalence of frailty was 7.4%, and frail participants were older, more likely women, lower educated, lower economic status, divorced/separated, and had more comorbidities than nonfrail participants. In addition, frail participants had higher number of medications, prevalence of malnutrition, and hs-CRP (>3.0 mg/dL), but lower cognitive ability than nonfrail participants. However, BMI, smoking, and alcohol drinking were not significantly different between frail and nonfrail participants. In addition, erythrocyte level of EPA was significantly higher in participants with low and normal categories of hs-CRP than those with high category of hs-CRP, but other fatty acids were not associated with hs-CRP (Table 2).

Frail participants had lower erythrocyte levels of EPA and DHA, and higher erythrocyte levels of 16:1n7 compared to nonfrail participants after adjusting covariates (Table 3). After accounting for multiple comparisons, only EPA was significantly different between frail and nonfail participants.

In the multivariable adjusted model, the likelihood of frailty was inversely associated with erythrocyte levels of EPA and DHA before and after accounting for multiple comparisons (Table 4). In addition, participants in the highest quintile of erythrocyte levels of EPA and DHA had lower likelihood of frailty than those in the lowest quintile.

Among each frailty criterion in the multivariable adjusted model, the likelihood of slow walking speed was inversely associated with EPA and DHA before and after accounting for multiple comparisons (Table 5). In addition, the likelihood of exhaustion was inversely associated with erythrocyte levels of DHA before and after accounting for multiple comparisons. In the multivariable adjusted model, the likelihood of low handgrip strength and low physical activity were inversely associated with erythrocyte levels of EPA before correcting for multiple comparisons.

Discussion

The present cross-sectional study showed that the erythrocyte levels of long-chain n-3 PUFA such as EPA and DHA were associated with lower odds of frailty, slow walking speed, and exhaustion in community-dwelling older people. There has been no previous study showing the association between risk of frailty and erythrocyte levels of n-3 PUFA. However, previous epidemiological studies consistently reported that intake of seafood including fish was inversely associated with risk of frailty in older Japanese (26), and the incidence of frailty in older people during 3.5-year follow-up of the Senior-ENRICA study (6). In particularly, Leon-Munoz and colleagues (6) showed that risk of frailty was lower in older Spanish people with intake of fish or seafood ≥ 3 servings/wk, which resulted in intake of 1.3–1.8 g/d of EPA + DHA in older people (27,28). Flock and colleagues (29) reported that supplementation of 1.8 g/d of EPA + DHA increased erythrocyte levels of EPA + DHA Index from 4.3% to 9.5% in older Western population. As a marker for fish intake, erythrocyte levels of EPA + DHA have been shown to be inversely associated with risk for all-cause mortality among older

Table 1. Baseline Characteristics of the Participants With and Without Frailty

	Nonfrail (*n* = 1,329)	Frail (*n* = 106)	*p*
Age (years)	75.6 ± 3.8	78.9 ± 3.5	<.001
Women, *n* (%)	680 (51.2)	65 (61.3)	.044
BMI (kg/m^2)	24.5 ± 3.0	24.4 ± 3.9	.946
Smoking status, *n* (%)			.642
Never	810 (60.9)	67 (63.2)	
Former	439 (33.0)	31 (29.2)	
Current	80 (6.0)	8 (7.5)	
Alcohol, *n* (%)[a]			.909
Never	1069 (80.7)	86 (81.1)	
Ever	256 (19.3)	20 (18.9)	
Education (year), *n* (%)			<.001
0–6	553 (41.6)	70 (66.0)	
≥7	776 (58.4)	36 (34.0)	
Low economic status, *n* (%)[b]	83 (6.3)	13 (12.4)	.016
Marital status, *n* (%)			.008
Married	946 (71.2)	59 (55.7)	
Divorced/separated	351 (26.4)	44 (41.5)	
Widowed	30 (2.3)	3 (2.8)	
Single	2 (0.2)	0 (0.0)	
Comorbidity, *n* (%)[c]			.001
0	334 (25.1)	14 (13.2)	
1	510 (38.4)	35 (33.0)	
≥2	485 (36.5)	57 (53.8)	
Number of medications[d]	3.7 ± 5.4	7.3 ± 13.2	<.001
Cognitive impairment, *n* (%)[e]	233 (17.5)	50 (47.2)	<.001
Nutritional status[f]			<.001
Normal	1131 (85.1)	64 (60.4)	
At risk of malnutrition	191 (14.4)	32 (30.2)	
Malnutrition	7 (0.5)	10 (9.4)	
hs-CRP mg/L, *n* (%)			.005
<1.0	862 (64.9)	63 (59.4)	
1.0–3.0	345 (26.0)	23 (21.7)	
>3.0	122 (9.2)	20 (18.9)	

Note: BMI = body mass index; hs-CRP = high-sensitivity C-reactive protein. Data were presented as mean ± *SD* or number of the participants (percentage distribution), as appropriate. *p*-values were analyzed using the Mann–Whitney *U* test for continuous variables and chi-squared test for categorical variables.

[a]Servings per week; four nonfrail participants had missing values. [b]Recipients of the National Basic Livelihood Security System or Medical Beneficial System; three nonfrail participants and 1 frail participant had missing values. [c]Number of comorbid conditions (hypertension, diabetes mellitus, cancer, chronic obstructive pulmonary disease, myocardial infarction, heart failure, angina, asthma, arthritis, cerebral ischemic, renal disease). [d]Three nonfrail participants and two frail participants had missing values. [e]Korean Mini-Mental State Examination score of less than 24. [f]Mini-Nutritional Assessment Short Form.

Table 2. Erythrocyte Levels of n-3 Polyunsaturated Fatty Acids According to High-Sensitivity C-reactive Protein (hs-CRP) Categories

	hs-CRP, mg/L			
%	<1.0 (n = 925)	1.0–3.0 (n = 368)	>3.0 (n = 142)	p
20:5n3	2.27 ± 0.91[a]	2.08 ± 0.81[b]	2.04 ± 0.87[b]	.001
22:6n3	9.53 ± 1.44	9.54 ± 1.52	9.30 ± 1.59	.205

Note: Data were presented as mean ± *SD*, as appropriate.

p-values were determined by ranked-ANOVA for non-normally distributed continuous variables of 20:5n3, and ANCOVA for normally distributed continuous variables of 22:6n3 after adjusting for age, medications, cognitive impairment, and frailty. Different letters indicate a statistically significant difference between three categories by Dunn-Bonferroni post hoc test. *p*-value of < .025 was regarded as statistically significant by Bonferroni correction.

Table 3. Erythrocyte Fatty Acid Composition of Participants With and Without Frailty

%	Nonfrail (n = 1,329)	Frail (n = 106)	p
14:0	0.34 ± 0.09	0.33 ± 0.09	.212[b]
16:0	21.94 ± 1.00	22.06 ± 0.96	.586[b]
18:0	17.11 ± 0.73	17.19 ± 0.68	.245[a]
16:1n7t	0.12 ± 0.09	0.12 ± 0.04	.159[b]
18:1t	0.31 ± 0.09	0.29 ± 0.07	.241[b]
18:2n6t	0.09 ± 0.03	0.09 ± 0.03	.516[b]
16:1n7	0.44 ± 0.21	0.53 ± 0.23	.024[b]
18:1n9	13.80 ± 0.94	13.99 ± 0.87	.216[b]
18:3n3	0.37 ± 0.24	0.40 ± 0.26	.096[b]
20:5n3	2.22 ± 0.89	1.84 ± 0.74	.002[b]
22:5n3	3.41 ± 0.51	3.45 ± 0.57	.766[b]
22:6n3	9.55 ± 1.47	9.02 ± 1.48	.011[a]
18:2n6	9.73 ± 1.62	9.43 ± 1.66	.285[a]
20:4n6	13.75 ± 1.48	14.24 ± 1.36	.220[a]

Note: Data were presented as mean ± *SD*, as appropriate.

p-values were determined by [a]ANCOVA for normally distributed continuous variables or [b]ranked ANCOVA for non-normally distributed continuous variables after adjustment for sex, age, body mass index, smoking, alcohol drinking, medications, cognitive impairment, nutritional status, and high-sensitivity C-reactive protein. *p*-value of < .00357 was regarded as statistically significant by Bonferroni correction.

people (15). Fried and colleagues (1) showed that mortality was approximately threefold higher in frail than nonfrail older people during the 7 years' follow-up of the Cardiovascular Health Study. In present study, erythrocyte levels of EPA + DHA of > 13.4% were associated with lower likelihood of frailty (OR 0.31; 95% CI 0.13–0.73; *p* for trend = .008) in Korean older adults, whose usual intake of fish and shellfish has been known to be higher than those in the Western population (30). In addition, a clinical trial reported that supplementation of 1.2 g/d of EPA + DHA improved gait speed, but did not improve frailty status in older women aged ≥ 65 years (11). In the clinical study by Hutchins-Wiese and colleagues (11), supplementation of EPA + DHA did not increase erythrocyte levels of n-3 PUFA, suggesting that 1.2 g/d of EPA + DHA could not be enough to improve frailty status.

The possible explanation for the association of EPA and DHA with risk of frailty could be related with inflammation. Epidemiologic studies showed that inflammatory cytokines were positively associated with risk of frailty in older people (4). A meta-analysis of clinical trials reported that EPA + DHA had beneficial effect on reduction of inflammatory cytokines such as CRP, IL-6, and TNF-α, but EPA, not DHA negatively associated with hs-CRP (31). Moreover, it is well known that EPA competes with AA for cyclooxynase, and inhibits production of inflammatory eicosanoids (32), which reduce the secretion of inflammatory cytokines such as IL-6 and TNF-α (33). The present study also showed that erythrocyte levels of EPA were significantly higher in older adults with the low hs-CRP.

Consistent with the present study, slow walking speed among frailty criteria was inversely associated with blood levels of EPA and DHA in the Three-City-Bordeaux study (9) and InCHIANTI study (10). Clinical trial also showed that EPA + DHA supplementation improved walking speed in older women (11). In addition, among older people aged over 85 years, intake of EPA + DHA was negatively associated with risk of poor Timed Up and Go test (34), which has been shown to highly correlate with walking speed (35). Previous epidemiologic studies showed that handgrip strength was also positively associated with intake of n-3 PUFA (36) and fatty fish (7) in older people. Additionally, clinical study showed that supplementation of EPA + DHA resulted in improvement in handgrip strength in older people (12). Present study showed that the erythrocyte levels of EPA were inversely associated with the likelihood of low physical activity assessed by IPAQ. Stefan and colleagues (37) also showed that higher intake of fish and seafood was positively associated with physical activity assessed by IPAQ in older people aged ≥ 85 years.

Table 4. Logistic Regression of Erythrocyte Levels of n-3 Polyunsaturated Fatty Acids for Risk of Frailty

	Quintiles of Fatty Acid Levels						Fatty Acid Continuous[a]	
	Q1	Q2	Q3	Q4	Q5	p for Trend	OR (95% CI)	p
20:5n3								
Frail/nonfrail, n	32/266	33/265	20/266	12/266	9/266			
Cutoff, %	≤1.48	1.48<to≤1.90	1.90<to≤2.30	2.30<to≤2.86	>2.86			
OR (95% CI)	1.0	1.34 (0.74–2.42)	0.78 (0.40–1.50)	0.62 (0.30–1.30)	0.33 (0.14–0.77)*	.002	0.59 (0.44–0.80)	.001
22:6n3								
Frail/nonfrail, n	35/265	20/267	21/265	17/267	13/265			
Cutoff, %	≤8.30	8.30<to≤9.17	9.17<to≤9.87	9.87<to≤10.78	>10.78			
OR (95% CI)	1.0	0.83 (0.44–1.58)	0.58 (0.30–1.10)	0.74 (0.37–1.45)	0.42 (0.20–0.87)*	.018	0.81 (0.70–0.94)	.006

Note: OR (Odd ratios) and 95% CIs (confidence intervals) were presented. Estimates of *p* for trend values for linear trends were based on linear scores derived from the medians of quintiles of erythrocyte levels of n-3 PUFA among nonfrail participants. Logistic regression was adjusted for sex, age, body mass index, smoking, alcohol drinking, medications, cognitive impairment, nutritional status, and high-sensitivity C-reactive protein. *p*-value of < .025 was regarded as statistically significant by Bonferroni correction. *p < .025 compared to the first quintile by logistic regression analysis.

[a]Each point corresponds to a 1-unit increment in erythrocyte levels of n-3 PUFA.

Table 5. Logistic Regression of Erythrocyte Levels of n-3 Polyunsaturated Fatty Acids for Each Frailty Criterion

	Weight Loss/ Nonweight Loss		Exhaustion/ Nonexhaustion		Low PA/ Non-low PA		Slow WS/Non-slow WS		Low HGS/ Non-HGS	
	(*n* = 61/1,374)		(*n* = 445/990)		(*n* = 126/1,309)		(*n* = 340/1,095)		(*n* = 229/1,206)	
	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
20:5n3										
OR (95% CI)	1.05 (0.77–1.42)	.669	0.89 (0.77–1.03)	.101	0.78 (0.61–0.98)	.036	0.84 (0.72–0.99)	.022	0.83 (0.69–0.99)	.032
22:6n3										
OR (95% CI)	0.97 (0.81–1.16)	.729	0.89 (0.82–0.97)	.005	1.06 (0.93–1.20)	.382	0.86 (0.79–0.94)	.001	0.94 (0.85–1.04)	.197

Note: ORs (odds ratio) and 95% CIs (confidence intervals) were presented. Each point corresponds to a 1-unit increment in erythrocyte levels of n-3 PUFA. Logistic regression was adjusted for sex, age, body mass index, smoking, alcohol drinking, medications, cognitive impairment, nutritional status, and high-sensitivity C-reactive protein. *p*-value of < .025 was regarded as statistically significant by Bonferroni correction. PA = physical activity; WS = walking speed; HGS = handgrip strength.

In the present study, the erythrocyte levels of DHA were inversely associated with the likelihood of exhaustion assessed by two questions from the CES-D scale used to assess depressive symptoms (38). To our knowledge, there has been no previous study showing an inverse association between n-3 PUFA and risk of exhaustion. Glise and colleagues (39) reported that patients with stress-related exhaustion had high levels of mental symptoms such as burnout, anxiety, and depression. Epidemiologic studies showed that the blood levels of EPA and DHA were inversely associated with risk of depression (40). Our previous study showed that CES-D scores were negatively correlated with erythrocyte levels of EPA and DHA in Korean (41). In addition, a meta-analysis of clinical study showed that EPA + DHA supplementation had beneficial effect on depression (42).

In the present study, ALA and DPA, but not EAP and DHA were not significantly different between frail and nonfrail older adults. Epidemiologic studies reported that blood levels of ALA and DPA were not associated with risk of disability (43) and mortality (15) in older people. Burdge and colleagues (44) showed that ALA supplementation did not increase plasma levels of EPA and DHA in older men. Additionally, it has been showed that intake of fish and n-3 PUFA was not correlated with erythrocyte levels of ALA and also DPA (45). In particular, DPA is originated from meat and poultry not from fish and seafood (46).

This present study has a few limitations. Frist, the relatively small number of frailty older people might have attenuated the strength of or underestimated our results. Second, this study was the cross-sectional design, so that only associations rather than causal relationships between erythrocyte fatty acid composition and frailty could be inferred. Third, since Koreans are known to have higher erythrocyte levels of n-3 PUFA than the Western populations, the generalizability of our findings to other populations may be limited. Last, although adjustments were made for confounders, it is possible that unmeasured factors affected the results of this study.

This study was the first to show that erythrocyte levels of long-chain n-3 PUFA were inversely associated with the likelihood of frailty, slow walking speed, low handgrip strength, exhaustion, and low physical activity in older people. Further study is needed to investigate whether erythrocyte levels of EPA and DHA are associated with incidence of frailty in large population-based longitudinal studies of diverse ethnic origins.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. Fried LP, Tangen CM, Walston J, et al.; Cardiovascular Health Study Collaborative Research Group. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56:M146–M156. doi: 10.1093/gerona/56.3.m146
2. Jung HW, Kim SW, Ahn S, et al. Prevalence and outcomes of frailty in Korean elderly population: comparisons of a multidimensional frailty index with two phenotype models. *PLoS One*. 2014;9:e87958. doi: 10.1371/journal.pone.0087958
3. Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging*. 2014;9:433–441. doi: 10.2147/CIA.S45300
4. Soysal P, Stubbs B, Lucato P, et al. Inflammation and frailty in the elderly: a systematic review and meta-analysis. *Ageing Res Rev*. 2016;31:1–8. doi: 10.1016/j.arr.2016.08.006
5. Ferrucci L, Cherubini A, Bandinelli S, et al. Relationship of plasma polyunsaturated fatty acids to circulating inflammatory markers. *J Clin Endocrinol Metab*. 2006;91:439–446. doi: 10.1210/jc.2005-1303
6. León-Muñoz LM, Guallar-Castillón P, López-García E, Rodríguez-Artalejo F. Mediterranean diet and risk of frailty in community-dwelling older adults. *J Am Med Dir Assoc*. 2014;15:899–903. doi: 10.1016/j.jamda.2014.06.013
7. Robinson SM, Jameson KA, Batelaan SF, et al.; Hertfordshire Cohort Study Group. Diet and its relationship with grip strength in community-dwelling older men and women: the Hertfordshire cohort study. *J Am Geriatr Soc*. 2008;56:84–90. doi: 10.1111/j.1532-5415.2007.01478.x
8. Brenna JT, Plourde M, Stark KD, Jones PJ, Lin YH. Best practices for the design, laboratory analysis, and reporting of trials involving fatty acids. *Am J Clin Nutr*. 2018;108:211–227. doi: 10.1093/ajcn/nqy089
9. Frison E, Boirie Y, Peuchant E, Tabue-Teguo M, Barberger-Gateau P, Féart C. Plasma fatty acid biomarkers are associated with gait speed in community-dwelling older adults: the Three-City-Bordeaux study. *Clin Nutr*. 2017;36:416–422. doi: 10.1016/j.clnu.2015.12.008
10. Abbatecola AM, Cherubini A, Guralnik JM, et al. Plasma polyunsaturated fatty acids and age-related physical performance decline. *Rejuvenation Res*. 2009;12:25–32. doi: 10.1089/rej.2008.0799
11. Hutchins-Wiese HL, Kleppinger A, Annis K, et al. The impact of supplemental n-3 long chain polyunsaturated fatty acids and dietary antioxidants

on physical performance in postmenopausal women. *J Nutr Health Aging*. 2013;17:76–80. doi: 10.1007/s12603-012-0415-3
12. Smith GI, Julliand S, Reeds DN, Sinacore DR, Klein S, Mittendorfer B. Fish oil-derived n-3 PUFA therapy increases muscle mass and function in healthy older adults. *Am J Clin Nutr*. 2015;102:115–122. doi: 10.3945/ajcn.114.105833
13. Fielding RA, Vellas B, Evans WJ, et al. Sarcopenia: an undiagnosed condition in older adults. Current consensus definition: prevalence, etiology, and consequences. International working group on sarcopenia. *J Am Med Dir Assoc*. 2011;12:249–256. doi: 10.1016/j.jamda.2011.01.003
14. Landi F, Cruz-Jentoft AJ, Liperoti R, et al. Sarcopenia and mortality risk in frail older persons aged 80 years and older: results from ilSIRENTE study. *Age Ageing*. 2013;42:203–209. doi: 10.1093/ageing/afs194
15. Harris WS, Tintle NL, Etherton MR, Vasan RS. Erythrocyte long-chain omega-3 fatty acid levels are inversely associated with mortality and with incident cardiovascular disease: the Framingham Heart Study. *J Clin Lipidol*. 2018;12:718–727.e6. doi: 10.1016/j.jacl.2018.02.010
16. Cao J, Schwichtenberg KA, Hanson NQ, Tsai MY. Incorporation and clearance of omega-3 fatty acids in erythrocyte membranes and plasma phospholipids. *Clin Chem*. 2006;52:2265–2272. doi: 10.1373/clinchem.2006.072322
17. Won CW, Lee Y, Choi J, et al. Starting construction of frailty cohort for elderly and intervention study. *Ann Geriatr Med Res*. 2016;20:114–117. doi: 10.4235/agmr.2016.20.3.114
18. Jeon SY, Won CW, Choi HR, Kim BS, Kin SY, Hur JH. Physical frailty predicts cognitive decline in elderly people: prospective findings from the living profiles of older people survey in Korea. *Korean J Fam Pract*. 2015;5:S702–S707.
19. Chen LK, Liu LK, Woo J, et al. Sarcopenia in Asia: consensus report of the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc*. 2014;15:95–101. doi: 10.1016/j.jamda.2013.11.025
20. Harris W, von Schacky C, Park Y. *The Omega-3 Fatty Acid Deficiency Syndrome: Opportunities for Disease Prevention. Standardizing Methods for Assessing Omega-3 Fatty Acid Biostatus*. Hauppauge, NY: Nova Science Publishers; 2013:385–398.
21. Morley JE, Malmstrom TK, Miller DK. A simple frailty questionnaire (FRAIL) predicts outcomes in middle aged African Americans. *J Nutr Health Aging*. 2012;16:601–608. doi: 10.1007/s12603-012-0084-2
22. Kang Y, Na DL, Hahn S. A validity study on the Korean Mini-Mental State Examination (K-MMSE) in dementia patients. *J Korean Neurol Assoc*. 1997;15:300–308.
23. Nestlé Nutrition Institute. Mini Nutritional Assessment (MNA). https://www.mna-elderly.com/mna_forms.html. Accessed October 14, 2019.
24. Pearson TA, Mensah GA, Alexander RW, et al. Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. *Circulation*. 2003;107:499–511. doi: 10.1161/01.cir.0000052939.59093.45
25. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health*. 1989;79:340–349. doi: 10.2105/ajph.79.3.340
26. Yamaguchi M, Yamada Y, Nanri H, et al. Association between the frequency of protein-rich food intakes and Kihon-Checklist frailty indices in older Japanese adults: the Kyoto-Kameoka study. *Nutrients*. 2018;10:84. doi: 10.3390/nu10010084
27. Levitan EB, Wolk A, Mittleman MA. Fish consumption, marine omega-3 fatty acids, and incidence of heart failure: a population-based prospective study of middle-aged and elderly men. *Eur Heart J*. 2009;30:1495–1500. doi: 10.1093/eurheartj/ehp111
28. Levitan EB, Wolk A, Mittleman MA. Fatty fish, marine omega-3 fatty acids and incidence of heart failure. *Eur J Clin Nutr*. 2010;64:587–594. doi: 10.1038/ejcn.2010.50
29. Flock MR, Skulas-Ray AC, Harris WS, Etherton TD, Fleming JA, Kris-Etherton PM. Determinants of erythrocyte omega-3 fatty acid content in response to fish oil supplementation: a dose-response randomized controlled trial. *J Am Heart Assoc*. 2013;2:e000513. doi: 10.1161/JAHA.113.000513
30. Choi E, Park Y. The Association between the consumption of fish/shellfish and the risk of osteoporosis in men and postmenopausal women aged 50 years or older. *Nutrients*. 2016;8:113. doi: 10.3390/nu8030113
31. Li K, Huang T, Zheng J, Wu K, Li D. Effect of marine-derived n-3 polyunsaturated fatty acids on C-reactive protein, interleukin 6 and tumor necrosis factor alpha: a meta-analysis. *PLoS ONE*. 2014;9:e88103. doi: 10.1371/journal.pone.0088103.
32. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutr Rev*. 2010;68:280–289. doi: 10.1111/j.1753-4887.2010.00287.x
33. Tilley SL, Coffman TM, Koller BH. Mixed messages: modulation of inflammation and immune responses by prostaglandins and thromboxanes. *J Clin Invest*. 2001;108:15–23. doi: 10.1172/JCI13416
34. Takayama M, Arai Y, Sasaki S, et al. Association of marine-origin n-3 polyunsaturated fatty acids consumption and functional mobility in the community-dwelling oldest old. *J Nutr Health Aging*. 2013;17:82–89. doi: 10.1007/s12603-012-0389-1
35. Podsiadlo D, Richardson S. The timed "Up & Go": a test of basic functional mobility for frail elderly persons. *J Am Geriatr Soc*. 1991;39:142–148. doi: 10.1111/j.1532-5415.1991.tb01616.x
36. Barrea L, Muscogiuri G, Di Somma C, et al. Association between Mediterranean diet and hand grip strength in older adult women. *Clin Nutr*. 2019;38:721–729. doi: 10.1016/j.clnu.2018.03.012
37. Stefan L, Petrinovic L, Sporis G, Vrgoc G. Frequency of dietary intake and physical activity in older adults: a cross-sectional study. *Nutrients*. 2018;10:1960. doi: 10.3390/nu10121960
38. Orme JG, Reis J, Herz EJ. Factorial and discriminant validity of the center for epidemiological studies depression (CES-D) scale. *J Clin Psychol*. 1986;42:28–33. doi: 10.1002/1097-4679(198601)42:1<28::aid-jclp2270420104>3.0.co;2-t
39. Glise K, Ahlborg G Jr, Jonsdottir IH. Course of mental symptoms in patients with stress-related exhaustion: does sex or age make a difference? *BMC Psychiatry*. 2012;12:18. doi: 10.1186/1471-244X-12-18
40. Lin PY, Huang SY, Su KP. A meta-analytic review of polyunsaturated fatty acid compositions in patients with depression. *Biol Psychiatry*. 2010;68:140–147. doi: 10.1016/j.biopsych.2010.03.018
41. Park Y, Kim M, Baek D, Kim SH. Erythrocyte n-3 polyunsaturated fatty acid and seafood intake decrease the risk of depression: case-control study in Korea. *Ann Nutr Metab*. 2012;61:25–31. doi: 10.1159/000339264
42. Grosso G, Pajak A, Marventano S, et al. Role of omega-3 fatty acids in the treatment of depressive disorders: a comprehensive meta-analysis of randomized clinical trials. *PLoS One*. 2014;9:e96905. doi: 10.1371/journal.pone.0096905
43. Reinders I, Murphy RA, Song X, et al. Polyunsaturated fatty acids in relation to incident mobility disability and decline in gait speed; the Age, Gene/Environment Susceptibility-Reykjavik Study. *Eur J Clin Nutr*. 2015;69:489–493. doi: 10.1038/ejcn.2014.277
44. Burdge GC, Finnegan YE, Minihane AM, Williams CM, Wootton SA. Effect of altered dietary n-3 fatty acid intake upon plasma lipid fatty acid composition, conversion of [^{13}C]α-linolenic acid to longer-chain fatty acids and partitioning towards beta-oxidation in older men. *Brit J Nutr*. 2003;90:311–321. doi: 10.1079/bjn2003901
45. Sun Q, Ma J, Campos H, et al. Blood concentrations of individual long-chain n-3 fatty acids and risk of nonfatal myocardial infarction. *Am J Clin Nutr*. 2008;88:216–223. doi: 10.1093/ajcn/88.1.216
46. Howe P, Meyer B, Record S, Baghurst K. Dietary intake of long-chain omega-3 polyunsaturated fatty acids: contribution of meat sources. *Nutrition*. 2006;22:47–53. doi: 10.1016/j.nut.2005.05.009