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Plasma Polyunsaturated Fatty Acids and Age-Related Physical Performance Decline

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Abstract

Due to supporting evidence that dietary patterns may have a significant role in the maintenance of good physical performance with aging, we tested whether plasma fatty acids, saturated fatty acids (SFA), and polyunsaturated (PUFA) fatty acids are cross-sectionally associated with different physical performance and predict changes in physical performance over a 3-year period. Data were from the InCHIANTI study, a population-based study of older Italians. Plasma fatty acids were measured at enrollment (1998–2000), and outcome variables, Summary Physical Performance Battery (SPPB), and time to walk 7 meters (m) were measured at enrollment and after 3 years (2001–2004). At enrollment, 330 participants had significantly impaired lower extremity performance (defined as a SPPB score ≤9). Adjusting for age, participants with a SPPB score >9 had higher levels of total PUFA, *n*-3 PUFA, and *n*-6 PUFA, while significantly lower levels of SFA than those with a SPPB score <9. Baseline SPPB scores were also associated with *n*-3 PUFA ($\beta = 0.148$, $p = 0.031$), whereas the 7-m walk time was associated with total PUFA ($\beta = -0.068$, $p = 0.008$), after adjusting for potential confounders. Of the 884 participants with a SPPB score >9 at baseline, 114 (12.9%) developed impaired lower extremity performance (SPPB ≤9). In fully adjusted logistic models, baseline *n*-3 PUFA levels were inversely related to the risk of developing a decline in SPPB to ≤9 (odds ratio [OR] = 0.21; 95% confidence interval [CI] = 0.08–0.53), while the *n*-6/*n*-3 ratio was associated with a higher risk of SPPB decline to ≤9 (OR = 5.23; 95% CI = 2.02–13.51). In multivariate regression models, the *n*-6/*n*-3 ratio was associated with a longer time to walk 7 m ($\beta = 0.396$, $p = 0.037$). *n*-3 PUFA plasma levels, which most likely reflect dietary intake, seem to protect against accelerated decline of physical performance. A higher *n*-6/*n*-3 ratio was associated with higher risk of developing poor physical performance and slower walking speed.

Introduction

Disability is a common condition in older persons and, although a decline in age- and sex-specific rates of disability has been recently observed,[1] the absolute number of disabled older persons will continue to increase in the next decades due to aging of the population, causing massive increases of health-care costs.[2] A decline in physical performance often marks the early stage of the process leading to disability in older persons.[3] Therefore, understanding the mechanisms that are responsible for the age-associated decline in performance is paramount to design preventive interventions.

Several factors have been associated with maintenance of a good physical performance in older persons, including physical activity and exercise[4] as well as low levels of inflammatory markers.[5] Recently, diet has been evaluated as a potential protective factor against the risk of developing physical performance decline. Studies have shown that nutritional factors, such as carotenoids[6] and antioxidant vitamins C[7] and E[7,8] are associated with higher muscle strength,

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better physical performance, and/or reduced risk of physical function decline in older subjects.

Several lines of evidence suggest that polyunsaturated fatty acids of the *n*-3 family have strong anti-inflammatory activity[9] and therefore may be beneficial for the treatment of diseases associated with an increased inflammatory state and subsequent catabolic state, such as muscle mass loss and impairment of physical performance.[10] A member of the *n*-3 fatty acids, eicosapentanoic acid (EPA) was shown to prevent weight loss[11] and to increase total energy expenditure with a parallel improvement in the physical function in cancer patients.[12] In a small clinical trial, polyunsaturated fatty acids (PUFAs) improved exercise capacity in patients with chronic obstructive pulmonary disease.[13] However, it is not known whether levels of circulating fatty acids are significant predictors on the risk of physical function decline. If this hypothesis is confirmed, a role for a diet rich in PUFAs against age-related decline of lower extremity function may be hypothesized.

Plasma fatty acids are good markers of dietary intake,[14] and they also considered biomarkers for long-term essential fatty acid intake because their levels change in parallel with changes in fatty acid composition of adipose tissue.[15] Therefore, the aim of this study is to investigate whether plasma fatty acids (both saturated and polyunsaturated) are cross-sectionally associated with objectively measured lower extremity performance and predict accelerated decline of lower extremity performance in a representative sample of community-dwelling older persons.

Materials and Methods

Study population

This research is part of the InCHIANTI study, a prospective population-based study of older persons originally designed by the laboratory of Clinical Epidemiology of the Italian National Research Council of Aging, (INRCA, Florence, Italy) and carried out in the Chianti geographic area in Tuscany, Italy. The InCHIANTI database includes data from 1453 participants (between 22 and 104 years of age) randomly selected from the residents in the two municipalities of Greve in Chianti and Bagno a Ripoli using a multistage stratified sampling method.[16] Baseline data collection started in September, 1998, and was completed in March, 2000; the first follow up started in November, 2001, and was completed in April, 2003. All subjects gave their informed consent before participating in the study, which was approved by the ethical committee of our institutions. For participants who were unable to provide a full consent, because of cognitive or communication impairment, we obtained an assent and surrogate consent from a proxy.

The baseline population for this study included 1273 participants between 22 and 104 years of age, selected from the cohort from Greve and Bagno a Ripoli because they had complete data on fatty acids and lower extremity performance. At follow up, we considered only those participants having full data sets for study purposes ($n = 884$).

Laboratory analysis

Blood samples were collected in the morning after the participants had been fasting for at least 8 h. Aliquots of serum and plasma were immediately stored at −80°C. The samples used to measure cytokines and fatty acids had not been previously thawed. Fatty acids were measured using a fasting plasma sample.

A detailed description of the assay for fatty acids has been already described in detail.[9] A known amount of heptadecanoic acid (17:0) (Sigma Chemical Co., St. Louis) was added to each sample as an internal standard, and total lipids were extracted from 0.15 mL of plasma. In a pilot study, we found that no traces of heptadecanoic acid were detectable in 25 plasma samples from InCHIANTI participants. Fatty acid methyl esters (FAME) were prepared through transesterification. Separation of FAME was carried out on an HP-6890 gas chromatograph (Hewlett-Packard, Palo Alto, CA) with a 30-m fused silica column (HP-225 from Hewlett-Packard, Palo Alto, CA). FAMEs were identified by comparison with pure standards (NU Chek Prep Inc., Elysian, MA). For quantitative analysis of fatty acids as methyl esters, calibration curves for FAME (ranging from C14:0 to C24:1) were prepared by adding six increasing amounts of individual FAME standards to the same amount of internal standard (C17:0; 50 μg). The correlation coefficients for the calibration curves of 20 fatty acids were in all cases higher than 0.998 in the range of concentrations studied. Fatty acid concentration was expressed as a percentage of total fatty acids based on milligram per liter values. The coefficient of variation for all fatty acids was on average 1.6% for intraassay and 3.3% for interassay.

The amount of plasma fatty acids (ranging from C14:0 to C24:1) is expressed as percentages of total fatty acids based on mg/L values. In the present analysis, plasma saturated fatty acids (SFAs), monounsaturated fatty acids (MUFAs), total PUFAs, omega-3 fatty acid (*n*-3), omega-6 fatty acid (*n*-6), and the *n*-6/*n*-3 ratio were calculated. The *n*-3 and *n*-6 families of fatty acids account for more than 95% of total PUFAs and are named from the position of the first double bond, located on the third or sixth carbon, respectively from the terminal methyl group. The *n*-3 fatty acids included α-linolenic (ALA) (C18:3*n*3), EPA (C20:5*n*3), and docosahexenoic (DHA) (C22:6*n*-3) acids. The total *n*-6 fatty acids included: linoleic (LA) (C18:2*n*6), eicosadienoic (C20:2*n*6), and arachidonic (AA) (C20:4*n*6) acids.

Measures of lower extremity performance

The Summary Physical Performance Battery (SPPB) that was used to assess physical function at baseline and at follow up consists of three lower extremity performance tests: walking speed, standing balance, and ability to rise from a chair. Walking speed was measured as the best performance (shortest time in seconds) of two 4-m walks along a corridor. For standing balance, participants were asked to stand in three progressively more difficult positions for 10 sec each: a position with feet side by side, a semitandem position, and a full-tandem position. Performance was also timed for the chair-stand test, which consisted of asking participants to stand up from and sit down in a chair five times without using hands. Each physical performance test was categorized into a five-level score, with 0 representing inability to do the test and 4 representing the highest level of performance. A summary performance measure ranging from 0 (poorest) to 12 (highest) was developed by summing categorical scores

of the individual performance tests. Specific operational definitions and scoring procedures for the SPPB have been described in detail previously, and a cut-off score of ≤9 was used to define impaired lower extremity performance.[3,17] The 7-m walking task was performed at usual pace. Participants were instructed to walk at their usual pace and each subject wore comfortable shoes for the entire walk test. The use of aids was permitted if the subject normally used them and could not walk without. Global cognitive performance was assessed with the Mini-Mental State Examination (MMSE).

Covariates

Participants were classified as nonsmokers or former smokers versus current smokers based on self-report. Weight was measured using a high-precision mechanical scale. Standing height was measured to the nearest 0.1 cm. Body mass index (BMI) was calculated as weight (kg)/height^2 (m^2). Average daily intake of energy (kcal) was estimated by administering the European Prospective Investigation into Cancer and Nutrition (EPIC) food frequency questionnaire, which has been extensively validated in the Italian population.[18]

Habitual physical activity was assessed using a modified version of the EPIC physical activity questionnaire.[19] This test ranks the habitual level of physical activity on a scale of 1 to 7 (7 = highest level of physical activity) and in the statistical models represents the covariate physical activity.

A lower leg peripheral quantitative computerized tomography (pQCT) was performed in all participants using a recent generation device (XCT 2000; Stratec, Pforzheim, Germany) to evaluate calf muscle density and area. Data were derived from standard 2.5-mm-thick transverse scans obtained at 66% of the tibia length. The cross-sectional images obtained from the scans were analyzed using BonAlyse software (Jyvaskyla, Finland). Different tissues in the analysis were separated according to diverse density thresholds. The average density of muscle tissue was calculated and used in the analysis as a potential confounder.

A physical examination was performed on all participants by a specifically trained physician. Co-morbid chronic diseases were ascertained according to standard, pre-established criteria that combined information from self-reported physician diagnoses, current pharmacological treatment, medical records, clinical examinations, and blood tests. Co-morbid chronic conditions included in the analyses were the following diseases: dementia, heart failure, hypertension, diabetes, myocardial infarction, and stroke. Other covariates that could possibly affect circulating fatty acids and physical performance included sociodemographic variables (age, gender), plasma lipid concentrations (high-density lipoprotein cholesterol [HDL-C] and low-density lipoprotein cholesterol [LDL-C], triglycerides), and inflammatory marker (interleukin-6 [IL-6] and total insulin-like growth factor-1 [IGF-1]) plasma levels.

Calculation and statistical analysis

Descriptive results of continuous variables values are presented as means ± standard deviation or standard error. All variables were normally distributed with the exception of total *n*-3 fatty acid, ALA, EPA, DHA, PUFA, MUFA, SFA, *n*-6/*n*-3 ratio, IL-6, and triglycerides, which were log-transformed for analyses and back transformed for data presentation. Analysis of covariance (ANCOVA)-based tests were used to evaluate the differences in clinical characteristics according to level of physical performance after adjusting for age. Multivariate linear regression analyses were performed testing the independent associations between fatty acids (SFA, MUFA, PUFA, PUFA *n*-3, PUFA *n*-6) and physical performance measures (SPPB, time to complete a 7-m walk) after adjusting for age, gender, BMI, smoking status, daily caloric intake, physical activity, muscle density, number of chronic co-morbid conditions, and plasma concentrations of total IGF-1, IL-6, HDL-C, LDL-C, and triglycerides.

Logistic regression models were used to assess the predictive role of fatty acids on the development of impaired lower extremity performance (SPPB ≤ 9) at follow up both in unadjusted and fully adjusted analyses after excluding those with a baseline SPPB score ≤ 9. Statistical analyses were performed using the SPSS software package (Chicago, IL). Multivariate linear regressions were performed using the time to complete a 7-m walk at follow up as dependent variable to test the independent association of age, gender, BMI, smoking status, daily caloric intake, physical activity, muscle density, time to complete a 7-m walk at baseline, number of co-morbid chronic conditions, and plasma concentrations of total IGF-1, IL-6, HDL-C, LDL-C, and triglycerides.

Results

Cross-sectional analyses

The mean age of the participants was 68.8 ± 15.7 years and 55.7% were women. Age-adjusted characteristics of study participants according to impaired versus normal lower extremity performance are shown in Table 1. As expected, participants with a SPPB score >9 had on average a better MMSE score than those with a SPPB score ≤9. Participants in the higher-performance group also had higher levels of total PUFA, *n*-3 PUFA, *n*-6 PUFA, while the levels of SFA were significantly lower.

Linear multiple regression analyses testing the relationship between fatty acid levels and physical performance parameters after adjusting for multiple confounders are reported in Table 2. Total PUFA and *n*-3 fatty acid levels were associated with a shorter time to complete a 7-m walk independent of multiple confounders. A similar borderline significant trend was also found for *n*-6 fatty acid levels and the time to complete the 7-m walk. SFA levels were significantly associated with a longer 7-m walking time completion. PUFA and *n*-3 fatty acid levels were independently associated with better SPPB scores at baseline (Table 2).

Longitudinal analyses

At follow up, 12.9 % (n = 114 of the 884) participants who had a baseline SPPB score >9, developed impaired lower extremity physical performance (SPPB ≤ 9). Logistic regression models were used to test the hypothesis that the level of different fatty acids would be associated with different risks of developing poor lower extremity performance during 3 years of follow up. In unadjusted models, we found that higher total PUFA, *n*-3, and *n*-6 fatty acid levels were in-

Table 1. Baseline Characteristics of the Study Participants According to Physical Performance Level

	Summary physical performance battery score			
	Overall (n = *1273*)	≤*9* (n = *330*)	>*9* (n = *943*)	p[a]
BMI	27.2 ± 4.1	27.7 ± 4.5	27.0 ± 4.0	0.584
MMSE	25.4 ± 4.6	21.7 ± 6.3	26.7 ± 2.8	<0.001
IGF-1	129.3 ± 66.2	101.4 ± 49.8	138.9 ± 68.4	0.374
IL-6 (pg/mL)	2.03 ± 3.94	3.17 ± 6.93	1.63 ± 1.92	<0.001
LDL-C (mg/dL)	139.26 ± 35.54	136.87 ± 33.73	140.09 ± 36.13	<0.001
HDL-C (mg/dL)	55.72 ± 14.94	54.50 ± 16.61	56.14 ± 14.30	0.206
Triglycerides (mg/dL)	125.89 ± 76.60	138.30 ± 102.55	121.58 ± 64.74	0.323
Calf muscle density	71.5 ± 3.7	69.2 ± 3.9	72.2 ± 3.4	<0.001
Total PUFA[b]	38.35 ± 5.09	36.36 ± 5.56	39.05 ± 4.73	<0.001
Total MUFA[b]	31.05 ± 3.95	32.57 ± 3.81	30.52 ± 3.86	0.055
n-3 fatty acids[b]	3.35 ± 0.98	3.15 ± 0.98	3.43 ± 0.97	0.003
n-6 fatty acids	32.96 ± 4.66	31.14 ± 4.97	33.59 ± 4.37	0.002
Ratio *n*-6/*n*-3[b]	10.59 ± 3.23	10.74 ± 3.72	10.53 ± 3.04	0.194
SFA[b]	30.58 ± 2.84	31.09 ± 3.17	30.41 ± 2.69	0.004
Time to complete 7 m (sec)	6.55 ± 3.44	10.20 ± 5.65	5.49 ± 1.01	<0.001
Physical activity	3.36 ± 1.10	2.59 ± 1.12	3.63 ± 0.96	<0.001
Daily caloric intake (kcal/day)	2008 ± 616	1714 ± 485	2110 ± 624	<0.001
Number of co-morbidities	0.62 ± 0.78	1.05 ± 0.98	0.46 ± 0.63	<0.001

Values are expressed as means ± standard deviation.
[a]Adjusted for age.
[b]Logarithm of % based on mg/L of total plasma fatty acids; see Methods section.
BMI, Body mass index; MMSE, Mini Mental State Examination; IGF-1, insulin-like growth factor-1; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

versely associated with the development of low physical performance (Table 3a). On the contrary, higher MUFA and *n*-6/*n*-3 ratio levels were associated with a higher risk of developing poor performance (Table 3a). However, in fully adjusted models, only *n*-3 fatty acid levels continued to be inversely associated with the development of impaired physical performance, while the *n*-6/*n*-3 ratio continued to be associated with a higher risk of poor physical performance (Table 3a).

In further logistic regression models that included the individual *n*-3 and *n*-6 fatty acids, we found that all *n*-3 fatty acids were individually associated with lower probability of developing lower extremity performance during the 3-year follow up, whereas there were no significant associations for the *n*-6 fatty acids (Table 3b).

Finally, we tested whether fatty acids concentrations were associated with lower versus higher 7-m walking speed at follow up. Interestingly, we found that the ratio *n*-6/*n*-3 was associated with longer speed of the 3-year follow up, independent of multiple confounders and baseline walking speed (Table 4).

Discussion

Using data from a representative sample of the general population, we found that in participants with better func-

Table 2. Linear Regression Models Testing the Relationship of Baseline Fatty Acid Levels with Walking Speed and SPPB Score (*n* = 1273)

	Time to complete 7-m walk			*SPPB*		
Fatty acids[a]	*Beta*	*SE*	p	*Beta*	*SE*	p
Total PUFA	−2.957	0.929	0.002	1.714	0.721	0.018
Total MUFA	0.556	0.859	0.518	−0.334	0.667	0.616
SFA	2.647	1.062	0.013	−1.271	0.832	0.127
n-3 fatty acids	−0.724	0.304	0.018	0.524	0.237	0.027
n-6 fatty acids	−0.054	0.028	0.051	0.025	0.021	0.252
Ratio *n*-6/*n*-3	0.463	0.304	0.128	−0.379	0.236	0.109

All models were adjusted for age, sex, BMI, smoking, triglycerides , HDL-C, LDL-C, IL-6, total IGF-1, daily energy intake, physical activity, skeletal muscle density, and number of chronic co-morbid diseases.
[a]Logarithm was used for all fatty acids except n-6 fatty acids.
PUFA, Polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids.

Table 3a. Logistic Regression Modeling the Effect of the Fatty Acid Levels on Subsequent Physical Performance Decline (n = 884)

	Model a		*Model b*	
Fatty acid[c]	*Odds ratio (95% CI)*	p *value*	*Odds ratio (95% CI)*	p *value*
Total PUFA	0.126 (0.025–0.625)	0.011	0.510 (0.034–7.686)	0.626
Total MUFA	18.276 (3.160–105.707)	0.001	1.484 (0.091–24.137)	0.781
SFA	1.472 (0.135–16.070)	0.751	3.274 (0.128–83.975)	0.474
n-3 fatty acids	0.275 (0.130–0.584)	0.001	0.207 (0.081–0.530)	0.001
n-6 fatty acids	0.949 (0.904–0.996)	0.033	1.025 (0.943–1.114)	0.565
Ratio *n*-6/*n*-3	2.543 (1.181–5.474)	0.017	5.228 (2.023–13.514)	0.001

Table 3b. Logistic Regression Analyses Modeling the Effect of Each Fatty Acid Concentration on Subsequent Physical Performance Decline (n = 884)

	Model a		*Model b*	
Fatty acid[d]	*Odds ratio (95% CI)*	p *value*	*Odds ratio (95% CI)*	p *value*
ALA (C18:3*n*3)	0.632 (0.403–0.991)	0.046	0.563 (0.330–0.960)	0.035
EPA (C20:5*n*3)	0.409 (0.196–0.851)	0.017	0.213 (0.081–0.557)	0.002
DHA (C22:6*n*-3)	0.370 (0.198–0.688)	0.002	0.378 (0.176–0.809)	0.012
LA (C18:2*n*6)	0.337 (0.096–1.188)	0.091	3.141 (0.398–24.799)	0.278
Eicosadienoic (C20:2*n*6)	0.972 (0.834–1.134)	0.718	0.937 (0.781–1.124)	0.486
AA (C20:4*n*6)	0.579 (0.243–1.381)	0.218	0.605 (0.201–1.817)	0.370

[a]Unadjusted models.
[b]Fully adjusted that included the following independent variables: age, sex, BMI, smoking, triglycerides , HDL cholesterol, LDL cholesterol, IL-6, total IGF-1, daily energy intake, physical activity, skeletal muscle density, and number of chronic co-morbid diseases.
[c]Logarithm was used for all fatty acids except *n*-6 fatty acids.
[d]Logarithm was used for ALA, EPA, and DHA.
CI, confidence interval; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; ALA, α-linolenic acid; EPA, eicosapentanoic acid; DHA, docosahexenoic acid; LA, linolenic acid; AA, arachidonic acid.

tional status, baseline plasma concentrations of PUFAs were significantly higher, while SFA and MUFA concentrations were significantly lower, independent of age. Concentrations of *n*-3 fatty acids, which probably reflect dietary intake, were also associated with a lower probability of developing impaired lower extremity performance during the follow up. Interestingly, an imbalance between *n*-6 and *n*-3 fatty acids was associated with an increased risk of functional decline and accelerated decline of walking speed after 3 years of follow up. Overall, our findings support the notion that the maintenance of high PUFA levels may prevent physical function decline in older persons.

The preventive role of PUFAs on several negative health outcomes (especially *n*-3 fatty acids), which is probably attributable to the positive effects on circulating lipids, blood pressure, and inflammation, have been confirmed in many

Table 4. Adjusted[a] and Fully Adjusted[b] Linear Models Testing the Relationship of Baseline Fatty Acids with Walking Speed (n = 884)

	Time to complete 7-m walk[a]			*Time to complete 7-m walk*[b]		
Fatty acids[c]	*Beta*	*SE*	p	*Beta*	*SE*	p
Total PUFA	−1.198	0.488	0.014	−0.744	0.653	0.255
Total MUFA	1.147	0.476	0.016	0.459	0.555	0.409
SFA	0.068	0.678	0.920	−0.140	0.688	0.839
n-3 fatty acids	−0.554	0.211	0.009	−0.439	0.199	0.028
n-6 fatty acids	−0.029	0.014	0.040	−0.009	0.019	0.639
Ratio *n*-6/*n*-3	0.064	0.020	0.050	0.396	0.199	0.037

[a]Adjusted for time to complete 7 m at baseline.
[b]Fully adjusted included the following independent variables: age, sex, BMI, time to complete 7-m walk at baseline, smoking, triglycerides, HDL-C, LDL-C, IL-6, total IGF-1, daily energy intake, physical activity, skeletal muscle density, and number of chronic co-morbid diseases.
[c]Logarithm was used for all fatty acids except *n*-6 fatty acids.
SE, Standard error; PUFA, polyunsaturated fatty acids; MUFA, monounsaturated fatty acids; SFA, saturated fatty acids; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; IL-6, interleukin-6; IGF-1, insulin-like growth factor-1.

clinical and epidemiological trials.[20,21] By suggesting that concentrations of PUFAs may be protective against the deterioration of lower extremity function in middle-aged and older persons, our study expands this knowledge. It is particularly important to note that the class of fatty acids with the most beneficial effect on physical performance is the same that had been found inversely related to the circulating levels of proinflammatory markers in the same population.[9]

The consumption of fish, the major source of EPA and DHA, is low in the Chianti area and causes low variability in long-chain *n*-3 fatty acids plasma levels. Considering that there is such a low intake of fish consumption from the InCHIANTI study population, the concentrations of EPA and DHA most likely reflect a transformation from ALA. The finding that the protective effect on physical performance was found for ALA is reassuring. Indeed, it has been shown that ALA, a source of DHA and EPA, provides similar health benefits to longer-chain *n*-3 fatty acids, e.g., with respect to neuronal function in animals,[22] inflammation, and cardiovascular disease in humans.[23]

An interesting finding that deserves discussion is that both *n*-3 and *n*-6 concentrations were significantly higher in the better functional status group at baseline. However, in linear models testing the independent association between diverse fatty acids and the SPPB, the *n*-3 plasma levels continued to be associated with better physical performance status. Furthermore, after testing the quality of polyunsaturated fatty acids, as seen by the *n*-6/*n*-3 ratio, we found that the *n*-6/*n*-3 ratio was cross-sectionally associated with poor gait performance as well as with an increased risk of developing poor lower extremity performance over a 3-year follow-up period. Indeed, an extensive literature search suggests that *n*-6 fatty acids exert positive effects on diverse health outcomes,[24–26] although the importance of quality of fatty acid intake as seen by the *n*-6/*n*-3 ratio remains controversial. Nevertheless, the overall consensus is that an unbalanced intake with a greater consumption of *n*-6 fatty acids should be avoided.[27] Indeed, our findings add insight to those from a preclinical study demonstrating that the *n*-6/*n*-3 ratio was significantly lower in animals with improved leg muscle functioning.[28] However, the role of fatty acids and the impact of the *n*-6/*n*-3 ratio on physical decline should be confirmed in intervention studies of fatty acid supplementation.

The potential mechanisms by which *n*-3 fatty acids may positively affect cardiovascular health have been investigated intensively in large epidemiological studies, which have shown that a diet rich in *n*-3 fatty acid was associated with lower-risk cardiovascular events and mortality. It has been hypothesized that *n*-3 fatty acids favorably influence the traditional cardiovascular risk factors, including lowering plasma triglycerides and high blood pressure, as well as reducing neuro-cardiac instability and risk of arrhythmias.[29,30]

Limited data exist on the effects of PUFAs on skeletal muscle composition and function. There is evidence that a deficiency in dietary PUFAs impair skeletal muscle performance in animals,[31,32] and some but not all studies found that a deficiency in both *n*-6 and *n*-3 fatty acids was associated with reduced performance in skeletal muscles.[32] In addition, it has been also demonstrated that fatty acid profiles from skeletal muscle biopsies are strongly associated with diverse locomotor function in animals.[32] Our findings also substantiate findings from an animal study demonstrating that diet exerted a greater effect on fatty acid skeletal muscle composition independently of exercise.[33] Unfortunately the InCHIANTI protocol did not use muscle biopsies; however *n*-3 fatty acids were inversely associated with a decline in physical function independently of physical activity.

Another possible mechanism by which *n*-3 fatty acids may be acting on physical performance may be linked to metabolic or respiratory response, and it may be hypothesized that PUFAs may have a positive effect on the mitochondrial biogenesis. Unfortunately, blood lactate concentrations or oxygen consumption were not measured in the InCHIANTI population.

Indeed our data suggest that *n*-3 fatty acids protect against physical performance decline and that an imbalance of the *n*-6/*n*-3 ratio is correlated with an increased risk on developing poor physical performance in humans. However, because of the observational nature of our study, it remains to be clarified whether the preventive affect of PUFAs on physical function decline is due to their anti-inflammatory properties, their positive activity in chronic disease, or a direct effect on locomotor function.

To the best of our knowledge, this is the first investigation to test the relationship between plasma levels of fatty acids and physical performance measures in middle-aged and older persons. It is important to underline that fatty acids were measured directly from plasma and not estimated from dietary reports or dietary supplementation. Only future trials testing the role of fatty acid supplementation on physical performance and gait speed will determine whether the supplementation of specific fatty acids in the diet may prevent the development of physical impairment and disability in older individuals.

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Authors Disclosure Statement

No competing financial interests exist.

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