Omega-3 fatty acid levels in red blood cell membranes and physical decline over 3 years: longitudinal data from the MAPT study

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Abstract Studies have shown that omega-3 polyunsaturated fatty acids (PUFAs) are associated with brain, cardiovascular, and immune function, as well as physical performance and bone health in older adults. So far, few studies have investigated the associations between PUFA status and performance-based tests of physical function. The objective of this study was to investigate the associations between omega-3 PUFA levels (eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA)) in red blood cell (RBC) membranes and physical performance, in a sample of community-dwelling older adults. This is a longitudinal observational study using data from the Multidomain Alzheimer's Disease Trial (MAPT), a randomized, placebo-controlled trial. Four hundred participants from MAPT placebo group with available PUFA data were included. Omega-3 PUFA levels in RBC membranes were measured at

baseline, and their percentage of total RBC membrane fatty acid content was calculated. We dichotomized the standardized omega-3 PUFA levels in RBC membranes as low (lowest quartile) vs. high (three upper quartiles). Gait speed (in m/s) and short physical performance battery (SPPB) score (range from 0 to 12, higher is better) were used to assess physical performance at baseline and after 6, 12, 24, and 36 months. Participants were 75.2 ($\pm$ 4.3) years old and 68% were female. Bivariate analyses found that the characteristic of the participants in the lowest quartile of omega-3 PUFA levels (Q1) and those in the three upper quartiles (Q2–Q4) was not different at baseline; only those in Q1 were slightly older. In an unadjusted model, the difference in gait speed after 3 years of follow-up was significant (-0.09 ± 0.03 m/s; $p = 0.008$) between participants in Q1 and those in Q2–Q4. In a model adjusted for age, gender, educational level, cognitive function, depressive status, body mass index, physical activity, grip strength, and their time interaction, this difference remained clinically relevant (-0.07 ± 0.04 m/s; $p = 0.075$). No difference between the two groups was found for the SPPB score development over 3 years. Older adults with subjective memory complaints and in the lower quartile of omega-3 have a faster decline on gait speed compared to people in the three upper quartiles. Other longitudinal studies are needed to explore this association and to examine mechanisms.

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Introduction

As the elderly population has been expanding rapidly, the growing prevalence of age-related diseases and disability is a major public concern. Aging is associated with loss of physical function (Fried et al. 2004). With the aging of the general population and the considerable prevalence of older persons with physical decline, identifying modifiable factors that might delay or prevent loss of physical function is important to promote independence and quality of life for older persons.

Nutrient intake is a modifiable factor that may be important for maintaining the health of aging individuals. Over the past three decades, there has been substantial interest in the therapeutic potential of fish oils, rich in omega-3 polyunsaturated fatty acids (PUFAs), for various inflammatory conditions such as rheumatoid arthritis, inflammatory bowel diseases, and asthma in humans. Omega-3 PUFAs, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been associated with improved muscle composition or muscle strength (Reinders et al. 2015a; Rousseau et al. 2009; Robinson et al. 2008). In addition, lower intakes of omega-3 PUFAs are cross-sectionally associated with worse physical function (Robinson et al. 2008; Takayama et al. 2013). Data from the InCHIANTI study showed that higher plasma omega-3 PUFA levels were associated with lower risk of poor performance after 3 years of follow-up (Abbatecola et al. 2009). In AGES-Reykjavik study, plasma omega-3 PUFAs, and in particular DHA, were associated with lower risk of mobility disability (Reinders et al. 2015a). Data on omega-3 PUFA supplementation (fish oil), although limited, suggest a benefit of 1.2 g of EPA and DHA on gait speed among post-menopausal women (Hutchins-Wiese et al. 2013).

As most previous studies were limited to cross-sectional measures of function and the majority of the studies estimated omega-3 PUFAs using questionnaires rather than measurements of circulating PUFA, further studies are needed. The aim of the present study is to determine the associations between omega-3 PUFAs in red blood cell (RBC) and physical performance over 3 years in a sample of community-dwelling older adults with subjective memory complaints. We hypothesized that participants with

higher omega-3 PUFAs in RBC would have lower risk of physical decline.

Methods

Participants

For this study, we used data from the Multidomain Alzheimer's Disease Trial (MAPT), a randomized, placebo-controlled trial with four groups: omega-3 PUFA supplementation, omega-3 PUFA supplementation plus a multidomain intervention (exercise advice, nutritional counseling, and cognitive training), a multidomain intervention alone, and a placebo group (Vellas et al. 2014). To rule out the effects of the interventions on physical performance, the present study was restricted to participants assigned to the placebo group with available information on baseline omega-3 PUFA levels (400 individuals).

The MAPT population included older adults aged 70 years and over, living in the community, and at risk of cognitive decline. Inclusion criteria were either a spontaneous memory complaint, a limitation in one instrumental activity of daily living (IADL) (Lawton and Brody 1969), or slow walking speed (i.e., lower or equal than 0.8 m/s). Exclusion criteria were a diagnosis of dementia (American Psychiatric Association 1994), a Mini Mental State Examination (MMSE) score lower than 24 out of 30 points (Folstein et al. 1975), dependency in at least one basic activity of daily living (ADL) (Katz et al. 1963), and the presence of any disease that could compromise the subject's participation in the multidomain intervention (e.g., Parkinson's disease). In addition, subjects who had taken omega-3 PUFA supplementation within the past 6 months were excluded (Andrieu et al. 2017).

The study protocol has been approved by the Ethical Committee in Toulouse (CPP SOOM II). Written informed consent was obtained from all participants. The protocol of the study is registered on a public-access clinical trial database (www.clinicaltrials.gov [NCT00672685]).

Measurements

RBC membrane PUFA analysis

At the baseline visit, participants underwent a blood drawing. RBCs were isolated from blood samples

drawn into heparin-containing tubes. RBC membrane PUFA composition was analyzed by gas chromatography with flame ionization (Harris and Von Schacky 2004). Briefly, unwashed packed RBCs were directly methylated with boron trifluoride and hexane at 100 °C for 10 min. The PUFA methyl esters thus generated were analyzed using a GC2010 gas chromatograph (Shimadzu Corporation) equipped with an SP2560 fused-silica capillary column (Supelco, Bellefonte, PA). PUFAs were identified by comparison with a standard mixture of fatty acids (FAs) characteristic of RBCs (GLC 727; NuCheck Prep).

The sum of the RBC membrane DHA plus EPA content was calculated and expressed as the percentage of total FAs in RBC membranes. We dichotomized the standardized omega-3 PUFA levels in low (lowest quartile, i.e., omega-3 index levels $\leq 4.89\%$) vs. high (three upper quartiles) levels (Andrieu et al. 2017).

Measures of physical performance

Gait speed assessment

Gait speed was measured by timing participants while they walked 4 m along a corridor at their usual walking pace (Gill 2010). The procedure was carried out twice, and the best performance (the faster gait speed) of the two walking trials was used to calculate gait speed in meters per second (m/s). These measures were done at baseline after 6, 12, 24, and 36 months.

Short physical performance battery

The short physical performance battery (SPPB) was used to assess physical performance at baseline after 6, 12, 24, and 36 months (Guralnik et al. n.d.). It consists of three lower extremity performance-based tests: gait speed, standing balance, and ability to rise from a chair. Gait speed was measured as described above. For standing balance, participants were asked to stand in three progressively more difficult positions for 10 s each: a position with feet side by side, a semi tandem 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 in a row without using their hands. Each physical performance test result was then categorized into a five-level score, with 0 points representing inability to complete the test and 4 points representing the highest level

of performance. A summary performance measure ranging from 0 (poorest) to 12 points (highest) was built by summing up the categorical scores of the individual performance tests.

Confounders

Sociodemographic information recorded at baseline included sex, age, and educational level. The educational level of participants was defined in four classes: 1—no diploma or primary school certificate, 2—secondary education, 3—high school diploma, 4—university level. Body mass index (BMI) [computed as measured weight (kg)/height² (m)] was measured to assess nutritional status. Depressive symptoms were assessed with the Geriatric Depression Scale (GDS, max 15 points) (Clément et al. 1997), cognitive function with the Mini Mental State Examination (MMSE, max 30 points) (Folstein et al. 1975), leisure-time physical activity (LTPA) was measured as metabolic equivalent task-minutes per week (Plouvier et al. 2016), and hand grip strength in kilograms was measured using a Collins dynamometer (Adult Size, 12.7 × 5.7 cm, Witte GMBH Chirurgische Instrumente, Solingen, Germany) with participants seated, their elbows by their side and flexed at right angles, and a neutral wrist position (Massy-Westropp et al. 2011). The participants were asked to perform the task twice with each hand. The average of the best results obtained for each side was used for the present analyses.

Statistical analyses

To describe the baseline characteristics according to the levels of omega-3, categorical variables are expressed in frequencies and percentages and continuous variables are reported as means and standard deviations (SD). To compare the baseline characteristics according to the levels of omega-3 (or between the 2 groups), we used *t* tests for parameters with Gaussian distribution (in some cases after transforming the variable of interest) or Wilcoxon rank-sum tests for quantitative variables and chi-square tests for qualitative variables.

To estimate (or to study) the change of physical performance (gait speed, SPPB total score) over the time according to the levels of omega-3, we used linear mixed models at three levels to take into account two types of correlation. We included a center specific random intercept to take into account the correlation center

and a subject-specific random intercept and slopes to take into account the correlation intra-subject.

For each physical performance (gait speed, SPPB total score), we performed an unadjusted linear mixed model with the following fixed effects: omega-3 group, time, interaction between omega-3 group, and time. We included time² and time³ terms because the trajectory forms were not linear.

A second adjusted linear mixed model was performed in which we added potential confounders: age, gender, educational level, cognitive function [MMSE score], depressive symptoms [GDS score], BMI, leisure-time physical activity, hand grip strength, and their time interaction.

As there is no standard cutoff to define “low omega-3 level” and “high omega-3 level,” we have done analyses by using the four omega-3 quartiles in our population. We have observed the same change from baseline in all three upper quartiles (results not shown). So, we dichotomized these standardized omega-3 PUFA levels in low (lowest quartile, i.e., omega-3 index levels $\leq 4.89\%$) vs. high (three upper quartiles) levels (Andrieu et al. 2017).

Statistical significance was set at a p value < 0.05 . All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Cross-sectional analyses

Baseline characteristics of the study sample are detailed in Table 1. More than half of the study group was female (68%), with a mean age of about 75 years. The education level of participants was rather high (29% with university level), as was the mean MMSE score (28/30 points), and the mean GDS (about 3/15 points). Regarding physical functional performance, mean gait speed was about 1.1 m/s and mean SPPB score was 10.7/12 points.

At baseline, there was no significant difference between participants in the lowest omega-3 quartile (Q1) and those in the three upper quartiles (Q2–Q4) except for age (those in Q1 were older).

Longitudinal analyses

Linear mixed models were used to test the hypothesis that lower levels of omega-3 PUFAs would be associated with the risk of developing poorer lower extremity performance

during 3 years of follow-up. In an unadjusted model, we found that participants in Q1 had lower physical performances than participants in Q2–Q4 quartiles regarding SPPB score and gait speed, but this difference was significant only for gait speed (-0.09 ± 0.03 m/s; $p = 0.008$; see Figs. 1 and 2). In the fully adjusted model regarding gait speed, this difference did not remain statistically significant ($p = 0.075$). Regarding the results of both unadjusted and fully adjusted models for the SPPB score, participants in Q1 had a lower score than participants in Q2–Q4, but this difference was not statistically significant (Table 2).

Discussion

We found that older adults with subjective memory complaints with high levels of baseline RBC omega-3 PUFAs, compared to those with low levels, had a slower decline on gait speed over a 3-year follow-up; this difference was not statistically significant after adjustment for confounders.

One of the reasons for our negative findings regarding the SPPB was probably the good health status of the participants, characterized by no functional impairment (exclusion criteria ADL score < 6 points) and no cognitive dysfunction (mean MMSE score 28 out of 30 points). The mean SPPB score at baseline was also particularly high (10.7 out of 12 points). Such a high mean SPPB score is also associated with a narrower range of distribution, which may generate a ceiling effect; thus, the predictive capacity for the outcome is lower.

In an unadjusted model, the difference in gait speed after 3 years of follow-up was significant and in an adjusted model, this difference did not reach statistical significance, but remained clinically relevant (-0.07 m/s) according to the smallest meaningful change estimate by Perera et al. (-0.05 m/s) (Perera et al. 2006).

The preventive role of omega-3 PUFA supplementation on several negative health outcomes, which is probably attributable to its positive effects on circulating lipids, blood pressure, and inflammation, have been confirmed in many clinical and epidemiological trials (Ascherio et al. 1995; Kromhout et al. 1985). By indicating that higher concentrations of omega-3 PUFAs may be protective against the deterioration of physical performance in older persons, our study expands the knowledge on the fundamental role of omega-3 PUFAs status. A potential mechanism for the observed association between

Table 1 Baseline characteristics of participants according to quartile (Q) of omega-3 PUFA levels in RBC membranes ($n = 400$)

	All ($n = 400$) Mean $\pm$ SD or n (%)	DHA + EPA Q1 ($n = 100$) Mean $\pm$ SD or n (%)	DHA + EPA Q2–Q4 ($n = 300$) Mean $\pm$ SD or n (%)	p
Gender (female)	272 (68.0%)	61 (61.0%)	211 (70.3%)	0.08
Age (years old)	75.2 $\pm$ 4.3	75.9 $\pm$ 4.3	74.9 $\pm$ 4.3	0.04
Education (university level)	113 (28.8%)	27 (27.8%)	86 (29.1%)	0.12
BMI (kg/m ²)	26.0 $\pm$ 3.94	26.4 $\pm$ 3.5	25.8 $\pm$ 4.0	0.20
MMSE/30	28.1 $\pm$ 1.5	27.9 $\pm$ 1.4	28.2 $\pm$ 1.6	0.11
GDS/15	3.3 $\pm$ 2.7	3.2 $\pm$ 2.7	3.3 $\pm$ 2.7	0.65
SPPB/12	10.7 $\pm$ 1.5	10.6 $\pm$ 1.7	10.7 $\pm$ 1.5	0.75
Gait speed (m/s)	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	1.1 $\pm$ 0.3	0.59
Grip strength (kg)	26.9 $\pm$ 9.0	27.0 $\pm$ 8.9	26.9 $\pm$ 9.0	0.93
LTPA, MET-min/week	419.6 $\pm$ 411.1	460.8 $\pm$ 454.5	405.8 $\pm$ 395.1	0.79

BMI body mass index, DHA docosahexaenoic acid, EPA eicosapentaenoic acid, GDS Geriatric Depression Scale, LTPA leisure-time physical activity, MET metabolic equivalent task, MMSE Mini Mental State Examination, PUFA polyunsaturated fatty acids, Q quartile, RBC red blood cells, SD standard deviation, SPPB short physical performance battery

omega-3 PUFAs in relation to physical performance is the RBC deformability. Indeed, RBC deformability decreases with exercise (van der Brug et al. 1995) and this is associated with increased aggregation and transit time through micropores (Yalcin et al. 2000), which may reduce the efficacy of oxygen delivery through the microcirculation. This increased deformability of RBCs was found to be a consequence of the incorporation of omega-3 PUFAs into RBC membrane phospholipids (Andersson

et al. 2002). Omega-3 PUFAs have also been shown to facilitate the transport of RBCs through the capillary bed (Bruckner et al. 1987), which could lead to enhanced oxygen delivery to skeletal muscle and a subsequent improvement in exercise performance. Other mechanism to consider is the omega-3 PUFAs' role in nervous system activity. They improve cognitive development and reference memory-related learning, increase neuroplasticity of nerve membranes, contribute to

Fig. 1 Unadjusted model assessing the relationship between baseline omega-3 PUFA (DHA and EPA) levels and gait speed development ($n = 400$). DHA docosahexaenoic acid, EPA

eicosapentaenoic acid, PUFA polyunsaturated fatty acid, Q Quartile. DHA + EPA high = Q2–Q4. DHA + EPA low = Q1. The asterisk indicates $p \leq 0.05$

Fig. 2 Unadjusted model assessing the relationship between baseline omega-3 PUFA (DHA and EPA) levels and short physical performance battery score development ($n = 400$). DHA

docosahexaenoic acid, EPA eicosapentaenoic acid, PUFA polyunsaturated fatty acid, Q quartile, SPPB short physical performance battery. DHA + EPA high = Q2–Q4. DHA + EPA low = Q1

synaptogenesis, and are involved in synaptic transmission (Fontani et al. 2005). Low plasma omega-3 PUFAs levels were associated with accelerated decline of peripheral nerve function with aging (Lauretani et al. 2007).

So far, only limited data exists 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 (Ruf et al. 2006; Ayre and Hulbert 1996), and some, but not all, existing studies found that a deficiency in both omega-6 and omega-3 PUFAs was associated with reduced performance in skeletal muscle in rats (Ayre and Hulbert 1996). In a

Table 2 Adjusted and unadjusted model assessing the relationship between baseline omega-3 PUFA (DHA and EPA) levels and gait speed and short physical performance battery score development ($n = 400$)

Time point	Change between baseline and follow-up visit or within-group change from baseline		Unadjusted difference of change between baseline and follow-up visit		Adjusted difference of change between baseline and follow-up visit	
	DHA + EPA Q1 ($n = 100$)	DHA + EPA Q2–Q4 ($n = 300$)	DHA + EPA Q1 vs. Q2–Q4	p value	DHA + EPA Q1 vs. Q2–Q4	p value
Gait speed (mean m/s $\pm$ SE)						
M6	-0.05 ± 0.02	-0.01 ± 0.01	-0.04 ± 0.02	0.06	-0.04 ± 0.02	0.07
M12	-0.07 ± 0.02	-0.02 ± 0.01	-0.05 ± 0.03	0.04	-0.06 ± 0.03	0.05
M24	-0.08 ± 0.03	-0.03 ± 0.01	-0.06 ± 0.03	0.07	-0.06 ± 0.03	0.09
M36	-0.15 ± 0.03	-0.06 ± 0.02	-0.09 ± 0.03	0.01	-0.07 ± 0.04	0.07
SPPB (mean/12 points $\pm$ SE)						
M6	-0.11 ± 0.08	0.12 ± 0.04	-0.23 ± 0.09	0.01	-0.17 ± 0.10	0.08
M12	-0.21 ± 0.13	0.17 ± 0.07	-0.39 ± 0.15	0.01	-0.28 ± 0.16	0.08
M24	-0.38 ± 0.17	0.11 ± 0.09	-0.49 ± 0.20	0.01	-0.32 ± 0.20	0.11
M36	-0.51 ± 0.18	-0.20 ± 0.10	-0.31 ± 0.20	0.13	-0.13 ± 0.20	0.51

Adjusted for age, gender, educational level, GDS score, BMI, MMSE score, grip strength, leisure-time physical activity, and their time interaction

DHA docosahexaenoic acid, EPA eicosapentaenoic acid, m/s meters per second, Q quartile, SE standard error, SPPB short physical performance battery

cross-sectional study among French community-dwelling older adults, a higher proportion of the omega-3 PUFAs EPA and DHA in plasma was associated with a higher gait speed (Frison et al. 2017). These associations were independent of many potential confounders (sex, age, educational level, energy and protein intakes, physical activity, and comorbidities). Another study reported similar cross-sectional results (Abbatecola et al. 2009): among 1273 older adults involved in the InCHIANTI study, higher total PUFA and omega-3 PUFA plasma concentrations were significantly associated with the faster completion of a 7-m walking test. In a Japanese study, higher intake of omega-3 PUFAs was associated with shorter timed up and go tests (Takayama et al. 2013). In contrast, another study showed no associations between self-reported omega-3 PUFAs and physical performance measures such as chair rise, grip strength, and gait speed, casting doubt over the role of omega-3 PUFAs in physical function (Rousseau et al. 2009). In AGES-Reykjavik study, a population-based study of risk factors for disease and disability in old age, higher concentrations of omega-3 PUFAs and, particularly, DHA may protect women from impaired mobility but does not appear to have such an effect in men (Reinders et al. 2015b).

Several limitations of this study need to be mentioned. Most important, this is a secondary analysis using data from a randomized controlled trial designed to prevent cognitive decline. We tried to compensate for this issue by including only the placebo group into the analyses. Secondly, the study participants were recruited among community-dwelling older persons with a subjective memory complaint as main inclusion criterion. This may introduce a representativeness bias. Our findings may therefore not be applicable to community-dwelling older adults without any memory complaint.

However, there are also several strengths of this study. First, the sample size is large; second, we controlled the analysis for many potential confounders. Finally, some difference between other studies and our study should be underlined. The first and major difference is that while many studies were cross-sectional, with the MAPT study, we were able to perform a longitudinal study on the association of omega-3 PUFA levels and gait speed decline, as gait speed measurements were repeated under a protocol at the 3-year follow-up. As a second difference, many studies used plasma omega-3 PUFA concentrations to estimate PUFA exposure, whereas we measured the omega-3 PUFA content in RBC membranes. Plasma PUFA concentrations are indicative of PUFA intake over

a few days to weeks prior to sample collection only, and are more promptly affected by any PUFA intake within the 24 h prior to collection than the concentrations in RBC membranes (Hodson et al. 2009; Harris et al. 2013). This means that the plasma levels of PUFAs are more prone to reflect only the short-term fluctuations in the diet than the RBC membrane PUFA concentration (Harris et al. 2013). Information on RBC membrane PUFA levels can therefore be considered as more accurate because it reflects PUFA intake over a period of several months, with less biological variability than plasma PUFAs (Harris 2007; Harris and Thomas 2010).

Conclusion

In this longitudinal study, we found that participants with low omega-3 PUFA levels in the red blood cell membranes had worse performance-based test scores of physical function than people with higher omega-3 PUFA levels. For gait speed, the difference between the two groups remained clinically relevant over 3-year follow-up once confounders were controlled for. For the SPPB, this association did not reach statistical significance. Other longitudinal studies are needed to explore these associations and to examine mechanisms.

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Author contributions BF has made substantial contributions to conception and design of the manuscript and carried out the data collection. BF and CC performed the statistical analyses. BF wrote the manuscript. BF, SG, CC, GS, SG, PdB, MC, SA, and BV have made substantial contributions to the final manuscript. All authors have read and approved the final manuscript.

Compliance with ethical standards

Clinical trial registry number and website

The study protocol has been approved by the Ethical Committee in Toulouse (CPP SOOM II). Written informed consent was obtained from all participants. The protocol of the study is registered on a public-access clinical trial database (www.clinicaltrials.gov [NCT00672685]).

Conflict of interest The authors declare that they have no conflict of interest.

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