THE GERONTOLOGICAL SOCIETY OF AMERICA®

*Journals of Gerontology: Biological Sciences*
cite as: *J Gerontol A Biol Sci Med Sci*, 2023, Vol. 78, No. 4, 569–578
https://doi.org/10.1093/gerona/glac244
Advance Access publication December 12, 2022

OXFORD

Original Article

# TNFR-1 and GDF-15 Are Associated With Plasma Neurofilament Light Chain and Progranulin Among Community-Dwelling Older Adults: A Secondary Analysis of the MAPT Study

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Received: July 21, 2022; Editorial Decision Date: October 29, 2022

**Decision Editor:** David Le Couteur, MBBS, FRACP, PhD

## Abstract

There is growing evidence that cognitive decline can be affected by both nutritional aspects and inflammation. Plasma neurodegenerative biomarkers stand out as minimally invasive useful measures to monitor the potential risk of cognitive decline. This study aimed to investigate the associations between biomarkers of neurodegeneration, nutrition, and inflammation among community-dwelling older adults, and to verify if associations differed according to apolipoprotein E (*APOE*) ε4 status. This cross-sectional analysis included 475 participants ≥70 years old from the Multidomain Alzheimer Preventive Trial (MAPT), mean age 76.8 years (*SD* = 4.5), 59.4% women. Biomarkers of neurodegeneration (plasma amyloid-$\beta_{42/40}$—$A\beta_{42/40}$, neurofilament light chain—NfL, progranulin), nutrition (erythrocyte docosahexaenoic acid, eicosapentaenoic acid, omega-3 index; plasma homocysteine—Hcy, 25 hydroxyvitamin D), inflammation (plasma tumor necrosis factor receptor 1—TNFR-1, monocyte chemoattractant protein 1—MCP-1, interleukin 6—IL-6), and cellular stress (plasma growth differentiation factor 15—GDF-15) were assessed. Linear regression analyses were performed to investigate the associations between nutritional and inflammatory biomarkers (independent variables) and neurodegenerative biomarkers (dependent variables), with adjustments for age, sex, education, body mass index, physical activity, allocation to MAPT groups, and *APOE* ε4 status. After adjusting for confounders, $A\beta_{42/40}$ was not associated with nutritional or inflammatory markers. NfL was positively associated with GDF-15, TNFR-1, IL-6, and Hcy. Progranulin was positively associated with GDF-15, TNFR-1, and MCP-1. Analyses restricted to *APOE* ε4 carriers (*n* = 116; 26.9%) or noncarriers were mostly similar. Our cross-sectional study with community-dwelling older adults corroborates previous evidence that inflammatory pathways are associated to plasma markers of neurodegeneration.

**Clinical Trials Registration Number:** NCT00672685

**Keywords:** Amyloid-β, Cognitive decline, Inflammation, Neurodegeneration, Nutrition

In the context of increasing prevalence of Alzheimer's disease (AD) and other neurodegenerative diseases worldwide (1), there is growing evidence that cognitive decline can be affected by both nutritional aspects (2) and inflammatory processes (3). Peripheral and cerebral inflammatory processes affect cognitive function through several potential mechanisms, in a complex cross-talk between microglia (brain-resident macrophages), systemic immune cells, and circulating mediators such as cytokines and chemokines (4–6), which becomes more strongly triggered with the age-related immune dysfunction (immunosenescence) (6). Among the growing number of inflammation-related molecules, tumor necrosis factor receptor 1 (TNFR-1), monocyte chemoattractant protein 1 (MCP-1), interleukin 6 (IL-6), and growth differentiation factor 15 (GDF-15) emerge as biomarkers potentially related to neurodegeneration (4,7–9).

Nutrients such as vitamins B, vitamin D, and omega-3 (ω-3) polyunsaturated fatty acids (PUFAs) have been shown to protect against neurodegeneration (10–12). Moreover, adequate intake of the aforementioned nutrients also favors the fight against inflammation (13–15). In a scenario in which available evidence still does not allow reaching a consensus on blood biomarkers profiles for the early prediction of neurodegeneration and cognitive impairment (16–19), further efforts are needed to help define the best care protocols.

Considering that carriers of the apolipoprotein E (*APOE*) ε4 allele are at increased risk of AD and tend to present particularities in metabolic utilization of nutrients (20), the evaluation of *APOE* ε4 status would importantly contribute to elucidating the related mechanisms. This study aimed to investigate the associations between blood biomarkers of neurodegeneration, nutrition, and inflammation among community-dwelling older adults at risk of cognitive decline, and to verify if associations differed according to *APOE* ε4 status. We hypothesized that neurodegenerative biomarkers (plasma amyloid-$\beta_{42/40}$ ratio—$A\beta_{42/40}$, neurofilament light chain—NfL, and progranulin) would be associated with both nutritional and inflammatory biomarkers, and that associations might differ in the presence of the *APOE* ε4 allele.

## Participants and Methods

### Study Design and Population

This cross-sectional study used data from participants of the Multidomain Alzheimer Preventive Trial (MAPT), a 3-year randomized, multicenter placebo-controlled trial designed to test the effects of 2 interventions (ω-3 PUFA supplementation, and a multidomain intervention composed of nutritional counseling, physical activity advice, and cognitive training), together or alone, on cognitive function. Briefly, interventions were not able to reduce cognitive decline (21). Participants were observationally followed for 2 additional years after the end of the 3-year interventional phase. Inclusion started in May 2008 and ended in February 2011; follow-up ended in April 2016.

Eligibility criteria for joining MAPT study included: age ≥ 70 years; absence of major neurocognitive disorders and Mini-Mental State Examination score ≥24; presenting at least one of the following: spontaneous memory complaint, inability to perform one instrumental activity of daily living (eg, shopping, cooking, housekeeping), or slow walking speed (<0.8 m/s in a 4-m usual walking test). Participants were not included if they declared to take ω-3 PUFA supplements over the last 6 months prior to inclusion. Detailed information about the MAPT protocol has been published elsewhere (21).

From the total of 1 680 participants randomized in the MAPT intervention, 475 individuals presented at least one of the neurodegenerative markers assessment at the 12-month visit and were included in the present study: 448 with plasma $A\beta_{42/40}$, 472 with NfL and progranulin, and 445 with all 3 biomarkers (Supplementary Figure S1). These biomarkers were not measured at baseline due to unavailability of plasma samples.

### Ethics

All participants signed an informed consent. The MAPT study (trial protocol NCT00672685, available at www.clinicaltrials.gov) was authorized by the French Health Authority and approved by the Advisory Committee for the Protection of Persons participating in Biomedical Research of Toulouse (CPP *Sud-Ouest et Outre-Mer I et II*).

### Nutritional Biomarkers

Venous blood samples were collected to evaluate biomarkers. Plasma 25 hydroxyvitamin D [25(OH)D] and homocysteine (Hcy) concentrations were assessed at baseline. 25(OH)D was measured in ng/mL by electrochemiluminescence competitive binding assay (Cobas, Roche), according to standard protocols, with higher levels of 25(OH)D indicating better vitamin D status. Total plasma Hcy was measured in μM/L using a commercially available enzymatic cycling assay (Cobas, Roche, Indianapolis, IN). Higher Hcy is an indicative of B-vitamins deficiency (22), and is also related to inflammation (23).

Lipids were extracted from red blood cells for determining erythrocyte membrane fatty acid composition at the 12-month visit, using a mixture of hexane and isopropanol after acidification. Margaric acid (Sigma, Saint Louis, MO) was added as an internal standard. Total lipid extracts were then saponified and methylated. Fatty acid methyl esters (FAME) were extracted with pentane and analyzed by gas chromatography. Identification of FAME was based on retention times obtained for FAME prepared from fatty acid standards. The area under the curve was determined using the Chem Station software (Agilent, Santa Clara, CA). Other specific details have been previously described (24). The ω-3 index was calculated as the sum of % docosahexaenoic acid (%DHA) and % eicosapentaenoic acid (%EPA), expressed as a percentage of total erythrocyte membrane fatty acids.

### Biomarkers of Inflammation and Cellular Stress

GDF-15, TNFR-1, MCP-1, and IL-6 concentrations were assessed at the 12-month visit. They were quantified using the fully automated immunoassay platform Ella (ProteinSimple/Bio-techne, San Jose, CA), using a single disposable microfluidic SimplePlexTM cartridge, and displayed as pg/mL. For GDF-15, higher levels are indicative of cellular stress (25). For the other markers, higher levels indicate higher inflammatory processes (4,8,26).

### Outcomes

Neurodegenerative biomarkers were assessed at the 12-month visit. Plasma samples were spiked with a known quantity of $^{15}N$-$A\beta_{42}$ and $^{15}N$-$A\beta_{40}$ for use as analytical internal standards. Immunoprecipitation of samples was performed as described elsewhere (27). Briefly, $A\beta_{42}$ and $A\beta_{40}$ isoforms were simultaneously immunoprecipitated from 0.45 mL of plasma via a monoclonal anti-Aβ mid-domain antibody (HJ5.1, anti-Aβ13–28) conjugated to M-270 Epoxy Dynabeads (Invitrogen, Waltham, MA). LysN endoprotease (Pierce, Waltham, MA) was used for protein digestion

into peptides. Liquid chromatography–mass spectrometry was performed as detailed by Schindler et al. (27). Plasma analyses were performed as targeted parallel reaction monitoring on an Orbitrap Fusion Lumos Tribrid mass spectrometer (Thermo Fisher, Waltham, MA) interfaced with an M-class nanoAcquity chromatography system (Waters, Milford, MA). The precursor and product ion pairs used for analysis of Aβ isoforms were chosen as described elsewhere (28,29). Derived integrated peak areas were analyzed using the Skyline software package. $A\beta_{42}$ and $A\beta_{40}$ were quantified by integrated peak area ratios to known concentrations of the internal standards. Plasma $A\beta_{42/40}$ ratio was then determined by dividing $A\beta_{42}$ by $A\beta_{40}$, and its normalized values were used. In the literature, lower $A\beta_{42/40}$ has been associated with cognitive decline (30,31).

Plasma NfL concentrations were assessed in pg/mL by an ECL-based assay using the R-PLEX human neurofilament L antibody set (Meso Scale Discovery, Rockville, MD, F217X). Samples were diluted twofold in diluent buffer and assayed in duplicate. Higher circulating NfL is a marker of neurodegeneration (32). Plasma progranulin concentrations were determined in ng/mL by a commercially available enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems, Minneapolis, MN, DPGRN0) according to the manufacturer's instructions. Samples were diluted fourfold in diluent buffer and assayed in duplicate. Intra-assay coefficients of variation were between 0.2% and 4.2% and inter-assay coefficient of variation between plates was 13.2%. Low progranulin levels caused by mutations in the progranulin gene (*GRN*) are associated with frontotemporal dementia and cognitive decline (33). However, its metabolic functions are complex, with the full-length form of the protein having anti-inflammatory activity, whereas its derived granulin peptides are pro-inflammatory (34).

### Potential Confounders

Potential confounders were: sex (male; female), age (in years), education (no diploma; primary school certificate; secondary education; high school diploma; university level), body mass index (BMI; calculated as weight in kg divided by height$^2$ in m$^2$), physical activity (assessed by the short form of the Minnesota Leisure Time Activities questionnaire and provided in metabolic equivalent task—MET-min/wk), allocation to MAPT groups (multidomain intervention with ω-3 supplementation; multidomain intervention with placebo; ω-3 supplementation alone; placebo alone) and *APOE* ε4 status (carrier; noncarrier).

### Statistics

Characterization of the study sample was presented with mean and standard deviation—*SD*, or frequencies and percentage, according to *APOE* ε4 status. The normality of the distribution of variables was tested with the Shapiro–Wilk test, and logarithmic transformation was applied when needed. Means were compared by Student's *t* test, and categorical variables were compared using the Chi-square test. Pearson's correlation test was performed to test the correlation between the biomarkers. All biomarkers were analyzed as continuous variables. Linear regression analyses were performed to investigate the associations between nutritional and inflammatory biomarkers (independent variables) and neurodegenerative biomarkers (dependent variables), with adjustments for potential confounders (sex, age, education, BMI, physical activity, allocation to MAPT groups, and *APOE* ε4 status). Each model included one nutritional or inflammatory marker as the independent variable. Considering the metabolic particularities involving *APOE* ε4 carriers (20), regression analyses were also performed among the subgroups of *APOE* ε4 carriers and noncarriers separately. Participants presenting biomarker levels above or below 4 *SD*s from the sample mean were considered as outliers, and such aberrant values were not included in the analyses. One participant was considered an outlier for $A\beta_{42/40}$, IL-6, TNFR-1, and %EPA; 2 participants for progranulin, 25(OH)D, and Hcy; 4 participants for NfL and GDF-15; and 6 participants for MCP-1. Analyses were performed using the Statistical Analysis Software version 9.4 (Cary, NC), and results were considered significant if $p < .05$.

## Results

### Characterization of the Sample

The main characteristics of the studied sample according to *APOE* ε4 status are presented in Table 1. From the 475 participants of the study (mean age 76.8 years, *SD* = 4.5), 282 (59.4%) were female and 116 (26.9%) were *APOE* ε4 carriers. Compared to noncarriers, *APOE* ε4 carriers presented lower $A\beta_{42/40}$ (0.106, *SD* = 0.013 vs 0.115, *SD* = 0.015; $p < .0001$).

### Associations Between Nutritional and Neurodegenerative Biomarkers

Correlations between nutritional and neurodegenerative biomarkers are presented in Table 2. Positive correlations were observed between NfL and Hcy. Plasma $A\beta_{42/40}$ and progranulin were not associated with any of the nutritional biomarkers in correlation analysis nor in adjusted regression models (Tables 2–4). In adjusted regression models, NfL was positively associated with Hcy in the total sample and also in subgroup analyses with *APOE* ε4 carriers and noncarriers separately. No other associations of nutritional markers with neurodegeneration markers according to *APOE* ε4 status were found (Table 5).

### Associations Between Inflammatory and Neurodegenerative Biomarkers

Correlations between inflammatory and neurodegenerative biomarkers are presented in Table 2. Progranulin was positively correlated with GDF-15, MCP-1, and TNFR-1. NfL was positively correlated with GDF-15, IL-6, and TNFR-1. Plasma $A\beta_{42/40}$ was not associated with any inflammatory biomarkers in correlation analysis nor in adjusted regression models (Tables 2 and 3). In adjusted regression models, progranulin was positively associated with GDF-15, TNFR-1, and MCP-1 in the total sample. In subgroup analysis among *APOE* ε4 carriers, only the association with TNFR-1 persisted; while among *APOE* ε4 noncarriers, associations with TNFR-1 and MCP-1 were observed (Table 4). For NfL, positive associations were found with GDF-15, TNFR-1, and IL-6 among the total sample, and similarly in subgroup analysis among *APOE* ε4 carriers. Among the subgroup of *APOE* ε4 noncarriers, only associations with GDF-15 and MCP-1 were observed (Table 5).

## Discussion

This study investigated the associations between plasma neurodegenerative markers ($A\beta_{42/40}$, NfL, and progranulin) and biomarkers of nutrition and inflammation among community-dwelling older adults with subjective memory complaints. We found that Hcy was the only nutritional biomarker associated with

**Table 1.** Characteristics of the Studied Sample According to *APOE* ε4 Status

| | Total | *APOE* ε4 Carriers | *APOE* ε4 Noncarriers | |
|---|---|---|---|---|
| | *n* = 475 | *n* = 116 | *n* = 315 | |
| | Mean (*SD*)* | Mean (*SD*)* | Mean (*SD*)* | *p* Value |
| Sex (female) | 282 (59.4%) | 65 (56.0%) | 192 (61.0%) | .356 |
| Age (years) | 76.8 (4.5) | 76.7 (4.6) | 76.9 (4.6) | .646 |
| Education (*n* = 468) | | | | |
| No diploma or primary school | 115 (24.6%) | 31 (27.0%) | 76 (24.4%) | .261 |
| Secondary education | 152 (32.5%) | 35 (30.4%) | 104 (33.4%) | |
| High school diploma | 70 (15.0%) | 11 (9.6%) | 51 (16.4%) | |
| University level | 131 (28.0%) | 38 (33.0%) | 80 (25.7%) | |
| Body mass index (kg/m²; *n* = 472) | 26.4 (4.0) | 26.7 (3.9) | 26.2 (3.9) | .214 |
| Physical activity (MET-min/wk; *n* = 474) | 1 558.6 (2 019.0) | 1 327.0 (1 205.0) | 1 603.0 (2 185.6) | .098 |
| Biomarkers** | | | | |
| $A\beta_{42/40}$ (*n* = 447) | 0.113 (0.015) | 0.106 (0.013) | 0.115 (0.015)† | **<.0001** |
| NfL (pg/mL; *n* = 468) | 81.4 (35.3) | 85.4 (38.4) | 79.1 (33.5) | .141 |
| Progranulin (ng/mL; *n* = 470) | 45.3 (9.3) | 44.4 (8.5) | 45.6 (9.3) | .216 |
| GDF-15 (pg/mL; *n* = 450) | 1 260.8 (480.6) | 1 255.8 (496.9) | 1 262.4 (479.6) | .867 |
| TNFR-1 (pg/mL; *n* = 454) | 1 361.0 (414.5) | 1 357.3 (464.2) | 1 347.0 (398.2) | .934 |
| MCP-1 (pg/mL; *n* = 449) | 239.0 (77.9) | 234.3 (73.5) | 241.3 (76.4) | .395 |
| IL-6 (pg/mL; *n* = 454) | 3.9 (4.0) | 3.5 (2.3) | 3.9 (4.1) | .616 |
| Omega-3 index (%; *n* = 427) | 7.5 (2.4) | 7.3 (2.3) | 7.5 (2.4) | .487 |
| Erythrocyte DHA (%; *n* = 427) | 6.3 (2.1) | 6.1 (2.0) | 6.4 (2.1) | .391 |
| Erythrocyte EPA (%; *n* = 426) | 1.1 (0.5) | 1.2 (0.5) | 1.1 (0.5) | .916 |
| 25(OH)D (ng/mL; *n* = 320) | 23.9 (12.5) | 23.9 (12.7) | 24.2 (12.6) | .924 |
| Homocysteine (μM/L; *n* = 316) | 15.3 (4.3) | 15.7 (4.5) | 15.1 (4.3) | .364 |

*Notes*: Bold values indicate $p < .05$. 25(OH)D = 25 hydroxyvitamin D; $A\beta_{42/40}$ = amyloid-$\beta_{42/40}$ ratio; *APOE* = apolipoprotein E gene; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GDF-15 = growth differentiation factor 15; IL-6 = interleukin 6; MCP-1 = monocyte chemoattractant protein 1; MET = metabolic equivalent task; NfL = neurofilament light chain; TNFR-1 = tumor necrosis factor receptor 1.

*Except where indicated other.

**All biomarkers concentrations were measured in plasma, except for erythrocyte omega-3 index, %DHA, and %EPA.

†$p < .05$ based on Student's *t* test or Chi-square test.

a neurodegenerative biomarker (NfL). Among the other group of markers, MCP-1, IL-6, TNFR-1, and GDF-15 were positively associated with NfL and/or progranulin, while no associations were observed with $A\beta_{42/40}$. Findings were mostly similar in subgroup analyses among *APOE* ε4 carriers and noncarriers separately.

Inflammation is believed to activate toll-like receptors and receptors for advanced glycation end products, impair blood–brain barrier (BBB) function, reduce cerebral blood flow, and accelerate neuronal damage, increasing the risk of cognitive decline (4–6,35). NfL is a protein that represents axonal damage, being released in cerebrospinal fluid (CSF) and blood upon neurodegeneration (32). Analyzing the relationship between plasma NfL and several inflammatory markers, Delaby et al. (36) recently reported, for the first time, strong correlations with TNFR-1, a proapoptotic molecule involved in amyloid precursor protein (APP) processing and formation of Aβ plaques (7). In addition to a positive association between NfL and TNFR-1, our study also found associations with GDF-15 (a marker of cellular stress which is responsive to inflammation (25)) and IL-6 (a pro-inflammatory cytokine (4)). Progranulin, a growth factor protein whose gene haploinsufficiency relates to frontotemporal lobar degeneration (37), was also associated with TNFR-1 and GDF-15, and additionally with MCP-1 (a marker of microglial inflammatory reaction also known as CC motif chemokine ligand 2 (8)). Progranulin was shown to associate with TNFR-1 in multiple experimental and animal studies, but the direction of interactions (if inhibitory or stimulatory) are still to be elucidated (38). In addition, in murine mature 3T3-L1 adipocytes, IL-6 significantly increased progranulin secretion (39). To our knowledge, no studies have evaluated the other observed relationships with progranulin so far. The fact that progranulin is secreted by adipocytes (34) suggests that obesity may partially contribute to explain its link with inflammation, but in our analysis, this association was independent of BMI. These cross-sectional associations support that inflammation contributes to neurodegeneration; however, the absence of associations with $A\beta_{42/40}$ highlights the need of additional research on the topic.

Our findings corroborate previous evidence that GDF-15 and TNFR-1 relate with neurodegeneration and neurodegenerative diseases (7,9,40–42). So far, a number of mechanisms have been proposed to explain how TNFR-1 promotes neurotoxicity and neurodegeneration (7,40–42). They include rapid impairment of mitochondrial function leading to nerve cell loss (40), the ability to trigger necroptosis (42), and the capacity to cause morphological damage of choroid plexus epithelial cells leading to blood–CSF barrier impairment (41), in addition to the involvement in APP processing and Aβ plaque formation (7). GDF-15, in turn, responds to cellular stress in inflammatory conditions, but enhances Aβ clearance and promotes hippocampal neurogenesis and synaptic activity (9). In spite of its increased levels observed with aging (43) and inflammation (44), how GDF-15 mediates specific signaling pathways in brain disorders such as AD have not been fully elucidated yet (9).

Hcy, a marker of B-vitamins deficiency (22), was the only nutritional biomarker associated with NfL in our study. Elevated Hcy is a condition that increases the risk of AD in older ages, as shown in a recent meta-analysis (45), probably by promoting oxidative stress,

**Table 2.** Correlations Between Nutritional, Inflammatory, and Neurodegenerative Biomarkers Among Community-Dwelling Older Adults

| | | 25(OH)D | Hcy | Omega-3 Index | %DHA | %EPA | GDF-15 | MCP-1 | IL-6 | TNFR-1 | $A\beta_{42/40}$ | NfL | Progranulin |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25(OH)D | *r* | 1 | −0.045 | 0.139 | 0.115 | 0.210 | −0.037 | −0.039 | −0.121 | −0.083 | −0.089 | 0.015 | 0.067 |
| | *p* value | | .422 | **.016** | **.046** | **.0002** | .517 | .503 | **.034** | .148 | .124 | .796 | .234 |
| | *n* | 320 | 314 | 302 | 302 | 302 | 303 | 303 | 306 | 307 | 303 | 315 | 316 |
| Hcy | *r* | | 1 | 0.048 | 0.048 | 0.021 | 0.354 | 0.000 | 0.167 | 0.348 | −0.083 | 0.255 | 0.018 |
| | *p* value | | | .405 | .413 | .721 | **<.0001** | .998 | **.004** | **<.0001** | .153 | **<.0001** | .757 |
| | *n* | | 316 | 298 | 298 | 298 | 300 | 299 | 302 | 303 | 299 | 311 | 312 |
| Omega-3 index | *r* | | | 1 | 0.987 | 0.725 | 0.003 | −0.085 | −0.137 | −0.031 | 0.052 | 0.070 | 0.013 |
| | *p* value | | | | **<.0001** | **<.0001** | .954 | .088 | **.006** | .530 | .300 | .152 | .797 |
| | *n* | | | 427 | 427 | 426 | 404 | 404 | 408 | 408 | 405 | 420 | 422 |
| %DHA | *r* | | | | 1 | 0.613 | 0.000 | −0.069 | −0.137 | −0.024 | 0.061 | 0.059 | 0.014 |
| | *p* value | | | | | **<.0001** | .995 | .165 | **.006** | .631 | .222 | .224 | .782 |
| | *n* | | | | 427 | 426 | 404 | 404 | 408 | 408 | 405 | 420 | 422 |
| %EPA | *r* | | | | | 1 | 0.014 | −0.117 | −0.099 | −0.047 | −0.034 | 0.085 | 0.012 |
| | *p* value | | | | | | .779 | **.018** | **.046** | .344 | .490 | .082 | .805 |
| | *n* | | | | | 426 | 403 | 403 | 407 | 407 | 404 | 419 | 421 |
| GDF-15 | *r* | | | | | | 1 | 0.299 | 0.363 | 0.591 | −0.075 | 0.332 | 0.124 |
| | *p* value | | | | | | | **<.0001** | **<.0001** | **<.0001** | .123 | **<.0001** | **.009** |
| | *n* | | | | | | 450 | 444 | 449 | 450 | 423 | 445 | 447 |
| MCP-1 | *r* | | | | | | | 1 | 0.244 | 0.355 | −0.003 | −0.004 | 0.105 |
| | *p* value | | | | | | | | **<.0001** | **<.0001** | .958 | .940 | **.026** |
| | *n* | | | | | | | 449 | 448 | 448 | 422 | 444 | 446 |
| IL-6 | *r* | | | | | | | | 1 | 0.383 | 0.016 | 0.139 | 0.064 |
| | *p* value | | | | | | | | | **<.0001** | .747 | **.003** | .175 |
| | *n* | | | | | | | | 454 | 453 | 427 | 449 | 451 |
| TNFR-1 | *r* | | | | | | | | | 1 | 0.038 | 0.348 | 0.169 |
| | *p* value | | | | | | | | | | .430 | **<.0001** | **.0003** |
| | *n* | | | | | | | | | 454 | 427 | 449 | 451 |
| $A\beta_{42/40}$ | *r* | | | | | | | | | | 1 | −0.071 | 0.071 |
| | *p* value | | | | | | | | | | | .137 | .137 |
| | *n* | | | | | | | | | | 447 | 440 | 442 |
| NfL | *r* | | | | | | | | | | | 1 | 0.083 |
| | *p* value | | | | | | | | | | | | .074 |
| | *n* | | | | | | | | | | | 468 | 466 |
| Progranulin | *r* | | | | | | | | | | | | 1 |
| | *p* value | | | | | | | | | | | | |
| | *n* | | | | | | | | | | | | 470 |

*Notes*: Bold values indicate $p < .05$. 25(OH)D = 25 hydroxyvitamin D; $A\beta_{42/40}$ = amyloid-$\beta_{42/40}$ ratio; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GDF-15 = growth differentiation factor 15; Hcy = homocysteine; IL-6 = interleukin 6; MCP-1 = monocyte chemoattractant protein 1; NfL = neurofilament light chain; TNFR-1 = tumor necrosis factor receptor 1. All biomarkers concentrations were measured in plasma, except for erythrocyte omega-3 index, %DHA, and %EPA. Correlation coefficients ≥0.3 or ≤−0.3 are highlighted in gray.

**Table 3.** Linear Regression Analyses for Associations Between Plasma Amyloid-$\beta_{42/40}$ and Other Biomarkers in Total Sample and According to *APOE* ε4 Status

| | Total Sample* | | | | | *APOE* ε4 Carriers** | | | | | *APOE* ε4 Noncarriers** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | β | *SE* | *p* Value | Adjusted $R^2$ | *n* | β | *SE* | *p* Value | Adjusted $R^2$ | *n* | β | *SE* | *p* Value | Adjusted $R^2$ |
| 25(OH)D | 273 | −0.011 | 0.016 | .476 | 0.204 | 65 | −0.011 | 0.039 | .786 | 0.193 | 208 | −0.010 | 0.018 | .586 | 0.152 |
| Homocysteine | 269 | −0.027 | 0.032 | .394 | 0.202 | 64 | 0.133 | 0.101 | .194 | 0.213 | 205 | −0.055 | 0.035 | .122 | 0.154 |
| Omega-3 index | 368 | 0.000 | 0.025 | .982 | 0.167 | 99 | 0.046 | 0.055 | .410 | 0.166 | 269 | −0.014 | 0.029 | .628 | 0.119 |
| %DHA | 368 | 0.004 | 0.025 | .869 | 0.167 | 99 | 0.060 | 0.054 | .269 | 0.171 | 269 | −0.014 | 0.028 | .612 | 0.120 |
| %EPA | 368 | −0.019 | 0.016 | .242 | 0.171 | 99 | −0.016 | 0.033 | .628 | 0.162 | 269 | −0.020 | 0.019 | .300 | 0.122 |
| GDF-15 | 376 | −0.013 | 0.020 | .540 | 0.148 | 102 | −0.026 | 0.044 | .550 | 0.178 | 274 | −0.008 | 0.023 | .730 | 0.105 |
| MCP-1 | 375 | −0.003 | 0.022 | .908 | 0.153 | 101 | 0.024 | 0.047 | .612 | 0.174 | 274 | −0.008 | 0.025 | .741 | 0.105 |
| IL-6 | 379 | 0.008 | 0.012 | .496 | 0.150 | 102 | 0.013 | 0.026 | .616 | 0.177 | 277 | 0.009 | 0.014 | .524 | 0.108 |
| TNFR-1 | 379 | 0.025 | 0.022 | .241 | 0.150 | 102 | 0.034 | 0.043 | .430 | 0.181 | 277 | 0.027 | 0.025 | .284 | 0.108 |

*Notes*: 25(OH)D = 25 hydroxyvitamin D; *APOE* = apolipoprotein E gene; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GDF-15 = growth differentiation factor 15; IL-6 = interleukin 6; MCP-1 = monocyte chemoattractant protein 1; TNFR-1 = tumor necrosis factor receptor 1.

*Models adjusted by age, sex, education, body mass index, physical activity, allocation to MAPT groups, and *APOE* ε4 status, after log transformation of all continuous variables.

**Models adjusted by age, sex, education, body mass index, physical activity, and allocation to MAPT groups, after log transformation of all continuous variables; All biomarkers concentrations were measured in plasma, except for erythrocyte omega-3 index, %DHA, and %EPA.

**Table 4.** Linear Regression Analyses for Associations Between Plasma Progranulin and Other Biomarkers in Total Sample and According to *APOE* ε4 Status

| | Total Sample* | | | | | *APOE* ε4 Carriers** | | | | | *APOE* ε4 Noncarriers** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | β | *SE* | *p* Value | Adjusted $R^2$ | *n* | β | *SE* | *p* Value | Adjusted $R^2$ | *n* | β | *SE* | *p* Value | Adjusted $R^2$ |
| 25(OH)D | 285 | 0.028 | 0.023 | .227 | 0.099 | 68 | −0.040 | 0.055 | .470 | 0.231 | 217 | 0.040 | 0.026 | .121 | 0.117 |
| Homocysteine | 281 | 0.012 | 0.045 | .796 | 0.089 | 67 | −0.182 | 0.122 | .141 | 0.264 | 214 | 0.045 | 0.050 | .369 | 0.110 |
| Omega-3 index | 384 | −0.072 | 0.040 | .074 | 0.087 | 105 | 0.004 | 0.092 | .962 | 0.136 | 279 | −0.084 | 0.045 | .060 | 0.107 |
| %DHA | 384 | −0.070 | 0.039 | .077 | 0.087 | 105 | −0.024 | 0.091 | .795 | 0.136 | 279 | −0.074 | 0.044 | .095 | 0.104 |
| %EPA | 384 | −0.018 | 0.026 | .492 | 0.080 | 105 | 0.060 | 0.052 | .247 | 0.148 | 279 | −0.046 | 0.030 | .140 | 0.102 |
| GDF-15 | 399 | 0.082 | 0.031 | **.007** | 0.110 | 110 | 0.114 | 0.062 | .072 | 0.166 | 289 | 0.069 | 0.036 | .056 | 0.122 |
| MCP-1 | 398 | 0.080 | 0.034 | **.020** | 0.103 | 109 | 0.067 | 0.068 | .329 | 0.166 | 289 | 0.092 | 0.040 | **.021** | 0.120 |
| IL-6 | 402 | 0.020 | 0.018 | .275 | 0.092 | 110 | −0.004 | 0.039 | .921 | 0.138 | 292 | 0.025 | 0.021 | .215 | 0.109 |
| TNFR-1 | 402 | 0.125 | 0.033 | **.0002** | 0.124 | 110 | 0.135 | 0.062 | **.031** | 0.179 | 292 | 0.118 | 0.040 | **.004** | 0.135 |

*Notes*: Bold values indicate $p < .05$. 25(OH)D = 25 hydroxyvitamin D; *APOE* = apolipoprotein E gene; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GDF-15 = growth differentiation factor 15; IL-6 = interleukin 6; MCP-1 = monocyte chemoattractant protein 1; TNFR-1 = tumor necrosis factor receptor 1.

*Models adjusted by age, sex, education, body mass index, physical activity, allocation to MAPT groups, and *APOE* ε4 status, after log transformation of all continuous variables.

**Models adjusted by age, sex, education, body mass index, physical activity, and allocation to MAPT groups, after log transformation of all continuous variables. All biomarkers concentrations were measured in plasma, except for erythrocyte omega-3 index, %DHA, and %EPA.

**Table 5.** Linear Regression Analyses for Associations Between Plasma Neurofilament Light Chain and Other Biomarkers in Total Sample and According to *APOE* ε4 Status

| | Total Sample* | | | | | *APOE* ε4 Carriers** | | | | | *APOE* ε4 Noncarriers** | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *n* | β | *SE* | *p* Value | Adjusted $R^2$ | *n* | β | *SE* | *p* Value | Adjusted $R^2$ | *n* | β | *SE* | *p* Value | Adjusted $R^2$ |
| 25(OH)D | 285 | −0.020 | 0.044 | .658 | 0.185 | 68 | −0.126 | 0.113 | .272 | 0.185 | 217 | 0.001 | 0.049 | .981 | 0.199 |
| Homocysteine | 281 | 0.281 | 0.082 | **.001** | 0.221 | 67 | 0.570 | 0.245 | **.024** | 0.242 | 214 | 0.289 | 0.091 | **.002** | 0.240 |
| Omega-3 index | 383 | −0.041 | 0.072 | .570 | 0.176 | 105 | 0.028 | 0.182 | .879 | 0.169 | 278 | −0.053 | 0.079 | .498 | 0.194 |
| %DHA | 383 | −0.060 | 0.071 | .401 | 0.177 | 105 | −0.074 | 0.180 | .685 | 0.1716 | 278 | −0.049 | 0.077 | .5259 | 0.194 |
| %EPA | 383 | 0.031 | 0.046 | .499 | 0.176 | 105 | 0.160 | 0.102 | .121 | 0.191 | 278 | −0.016 | 0.053 | .765 | 0.193 |
| GDF-15 | 398 | 0.287 | 0.056 | **<.0001** | 0.204 | 110 | 0.523 | 0.117 | **<.0001** | 0.306 | 288 | 0.214 | 0.065 | **.001** | 0.181 |
| MCP-1 | 397 | −0.046 | 0.064 | .479 | 0.151 | 109 | −0.001 | 0.139 | .996 | 0.161 | 288 | −0.049 | 0.073 | .503 | 0.161 |
| IL-6 | 401 | 0.087 | 0.034 | **.010** | 0.164 | 110 | 0.172 | 0.078 | **.029** | 0.203 | 291 | 0.058 | 0.038 | .124 | 0.162 |
| TNFR-1 | 401 | 0.386 | 0.060 | **<.0001** | 0.233 | 110 | 0.561 | 0.114 | **<.0001** | 0.330 | 291 | 0.321 | 0.072 | **<.0001** | 0.210 |

*Notes*: Bold values indicate $p < .05$. 25(OH)D = 25 hydroxyvitamin D; *APOE* = apolipoprotein E gene; DHA = docosahexaenoic acid; EPA = eicosapentaenoic acid; GDF-15 = growth differentiation factor 15; IL-6 = interleukin 6; MCP-1 = monocyte chemoattractant protein 1; TNFR-1 = tumor necrosis factor receptor 1.

*Models adjusted by age, sex, education, body mass index, physical activity, allocation to MAPT groups, and *APOE* ε4 status, after log transformation of all continuous variables.

**Models adjusted by age, sex, education, body mass index, physical activity, and allocation to MAPT groups, after log transformation of all continuous variables. All biomarkers concentrations were measured in plasma, except for erythrocyte omega-3 index, %DHA, and %EPA.

endothelial dysfunction (22), and BBB disruption (46). In addition, Hcy is also considered an inflammatory marker, because it promotes leukocyte adhesion, expression of adhesion molecules, production of reactive oxygen species and C-reactive protein, and impairs nitric oxide release (23). Moreover, the absence of other associations between nutritional and neurodegenerative markers suggests that the potential impact of nutrients on neurodegeneration and cognitive decline may occur mainly through modulation of inflammation, and may also depend on the nutritional status of the studied population. Our analyses did not discriminate deficiencies, and most participants of MAPT were not deficient for these nutrients (47,48), so it is possible that findings could vary under conditions of nutrients deficits. Further studies exploring these relationships among individuals presenting vitamin D deficiency, low ω-3 index, and hyperhomocysteinemia are encouraged.

Given that the presence of the *APOE* ε4 allele is importantly related with increased amyloid burden, tau pathology, and neurodegeneration (49,50), our study also explored if associations would differ when *APOE* ε4 carriers were analyzed separately, but findings remained similar. This is curious, because there is evidence that expression of the *APOE* ε4 allele is related to greater levels of pro-inflammatory cytokines and neurotoxicity in response to lipopolysaccharide in both human and animal models, compared to those presenting the *APOE* ε3 allele (51).

The present study evaluated several biomarkers considered as useful and minimally invasive measures to monitor the potential risk of future cognitive decline. In spite of our focus on plasma biomarkers related to cognitive decline, we must mention that results of the present study may also potentially be driven to other characteristics of the aging process, as mobility impairment (52) and the onset of chronic diseases (53), once neurodegeneration and inflammation affect the aging phenotype at a broader spectrum beyond cognition (54,55). As additional strengths, we may mention the use of a recently improved measurement technique for assessing plasma Aβ (with high precision and lower variability compared to previous methods) (56), and the assessment of *APOE* ε4 status in our sample. The cross-sectional design of the study is, however, a limitation, because it does not allow the inference of causality. The use of data from participants of a randomized controlled trial is another limitation, because most biomarkers were assessed at the study 12-month visit (ie, 1 year after the beginning of interventions); thus, it is not excluded that MAPT interventions may have affected some biomarkers. However, allocation to MAPT intervention groups was considered as a variable of adjustment. Finally, biomarkers were not measured for all participants of MAPT study, and Hcy and vitamin D were assessed 12 months before the other biomarkers.

## Conclusion

With technological advance, biomarkers of neurodegeneration erstwhile assessed with invasive or costly techniques (such as positron emission tomography—PET scan and CSF measurements) are becoming increasingly feasible in blood, providing reliable information (32,56). Our cross-sectional study with older adults corroborates previous evidence that inflammatory pathways are associated with plasma biomarkers of neurodegeneration (NfL and progranulin). On the other hand, we were not able to find associations with plasma $A\beta_{42/40}$. Except for an association between NfL and Hcy, no other associations were observed between plasma neurodegenerative markers and nutritional biomarkers (and, as discussed, Hcy is also considered an inflammatory marker). Analyses performed with *APOE* ε4 carriers and noncarriers

separately provided similar findings. Recent evidence on how nutrients and bioactive compounds are able to reduce inflammatory responses and have the ability to modulate the risk of cognitive decline and AD (13–15) reinforces the importance of further exploring the potential relationship between nutritional biomarkers and neurodegeneration in large studies with longitudinal approaches, by testing if long-term dietary interventions may lead to better nutritional biomarkers profile and then affect inflammatory processes and cognitive decline.

## Supplementary Material

Supplementary data are available at *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences* online.

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## Funding

The MAPT study was supported by grants from the French Ministry of Health (PHRC 2008, 2009), University Hospital Center of Toulouse/Gérontopôle, Pierre Fabre Research Institute (manufacturer of the ω-3 supplement), ExonHit Therapeutics (biological sample collection), and Avid Radiopharmaceuticals (PET-amyloid measurement). The promotion of this study was supported by the University Hospital Center of Toulouse. The data sharing activity was supported by the Association Monegasque pour la Recherche sur la maladie d'Alzheimer (AMPA) and the UMR 1027 Unit INSERM-University of Toulouse III. The plasma measures of amyloid-β in this study was supported by institutional gift funds (R. J. Bateman, PI) and National Institute on Aging grants NIH R56AG061900 and RF1AG061900 (R. J. Bateman, PI). The plasma measures of NfL and progranulin was supported by institutional funds from Saint Louis University. The present work was performed in the context of the Inspire Program, a research platform supported by grants from the Region Occitanie/Pyrénées-Méditerranée (Reference number: 1901175) and the European Regional Development Fund (Project number: MP0022856), and received funds from Alzheimer Prevention in Occitania and Catalonia (APOC Chair of Excellence – Inspire Program). No sponsor placed any restriction on this work or had any role in the design of the study, data collection, data analyses or interpretation, or in the preparation, review, or approval of the manuscript.

## Conflict of Interest

Washington University and R.J.B. have equity ownership interest in C2N Diagnostics and receive income based on technology (blood plasma assay) licensed by Washington University to C2N Diagnostics. R.J.B. receives income from C2N Diagnostics for serving on the scientific advisory board. Washington University, with R.J.B. as co-inventor, has submitted the U.S. nonprovisional patent application "Plasma Based Methods for Determining A-Beta Amyloidosis." R.J.B. has received honoraria as a speaker/consultant/advisory board member from Amgen, Eisai, Hoffmann-LaRoche, and Janssen; and reimbursement of travel expenses from Hoffmann-La Roche and Janssen. The other authors declare no conflict of interest.

## Acknowledgments

We would like to thank the investigators from CHU de Toulouse, Centre Hospitalier Lyon-Sud, Hôpital de Tarbes, Hôpital de Foix, Hôpital de Castres, CHU de Limoges, CHU de Bordeaux, Hôpital de Lavaur, CHU de Montpellier, Hôpital Princesse Grace, Hôpital de Montauban, CHU de Nice, and CHU de Dijon for their participation in this study.

## Author Contributions

K.V.G. designed and conceptualized the research, performed the analyses, interpreted the data, and drafted the manuscript. P.S.B. designed and conceptualized the research, interpreted the data, and revised the draft critically for intellectual content. J.E.M., A.D.N., and G.A. managed data of plasma NfL and progranulin, interpreted the data, and revised the draft critically for important intellectual content. Y.L. and R.J.B. managed data of plasma amyloid-β, interpreted the data, and revised the draft critically for important intellectual content. S.G. and A.P. interpreted the data and revised the draft critically for intellectual content. B.V. conceived the MAPT study, interpreted the data, and revised the draft critically for intellectual content. All authors have read and approved the final manuscript submitted for publication.

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