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Biomarkers of Age-Related Frailty and Frailty Related to Diseases: An Exploratory, Cross-Sectional Analysis from the MAPT Study

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Abstract

BACKGROUND: Frailty may in most cases result from two main causes: the aging process (age-related frailty) and diseases (evolving chronic conditions or acute medical illnesses - disease-related frailty). The biological determinants characterizing these two main causes of frailty may be different.

OBJECTIVES: The aim of this study is to compare the biological and neuroimaging profile of people without frailty, those with age-related frailty, and subjects with disease-related frailty in community-dwelling older adults.

MATERIAL AND METHODS: We performed a secondary, cross-sectional analysis from the Multidomain Alzheimer Preventive Trial (MAPT). We included 1199 subjects without frailty throughout the 5-year follow-up, 82 subjects with incident age-related frailty, and 53 with incident disease-related frailty. Available blood biomarkers involved nutritional (eg, vitamin D, omega-3 fatty acids), inflammatory-related (IL-6, TNFR1, GDF15), neurodegenerative (eg, beta-amyloid, neurofilament light chain) and neuroimaging markers (MRI, Amyloid-PET).

RESULTS: Although not statistically significant, the results of the unadjusted model showed increasing gradients for inflammatory markers (GDF15, TNFR1) and decreasing gradients for nutritional and neuroimaging markers (omega 3 index, hippocampal volume) from age-related frailty participants to individuals with disease-related frailty. Considering the linear models we observed higher GDF15 values in disease-related frailty group compared to age-related frailty individuals [$\beta = 242.8$ (49.5, 436.2)]. We did not find any significant difference between subjects without frailty and those with age-related frailty. Subjects with disease-related frailty compared to subjects without frailty had lower values of DHA [$\beta = -2.42$ (-4.76, -0.08)], Omega 3 Index [$\beta = -0.50$ (-0.95, -0.06)] and hippocampal volume [$\beta = -0.22$ (-0.42, -0.02)]. They also had higher values of GDF15 [$\beta = 246.1$ (88.9, 403.4)] and TNFR1 [$\beta = 157.5$ (7.8, 307.2)].

CONCLUSION: Age-related frailty and disease-related frailty may represent different degrees of frailty severity on a biological level. Further research is needed to identify biomarkers potentially able to distinguish these classifications of frailty.

Key words: Frailty related to diseases, age-related frailty, biomarkers, geroscience.

Abbreviation: A β : amyloid-beta; ApoE: Apolipoprotein E; CRP: C-reactive protein; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; GDF15: growth differentiation factor 15; IL6: interleukin 6; MAPT: Multidomain Alzheimer Preventive Trial; MCP1: monocyte chemoattractant protein 1; SUVr: standard uptake value ratio; TNFR1: tumor necrosis factor receptor type 1; WF: without

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frailty, WMH: white matter hyperintensities.

Introduction

Although chronic diseases (1, 2) and acute medical events (3, 4) have been associated with physical frailty in cross-sectional and longitudinal studies, it is common to meet in clinical practice older adults becoming frail in the absence of significant medical events (5). For this reason, we have previously hypothesized that frailty in older adulthood could result from two main causes, the biological aging process itself (ie, age-related frailty) and evolving chronic conditions or acute illness (6) (ie, disease-related frailty).

Given the clinical relevance of frailty, there is an increasing interest to identify the markers for physical frailty (7). In the recent years, several markers such as nutritional (8), inflammatory (9), and neuroimaging markers (10) have been associated with incident frailty. However, as far as we know, no investigation examined differences in such biomarkers in people who became frail without overt disease (individuals rated as age-related frailty) and those with disease-related frailty. Since chronic conditions are often associated to a pro-inflammatory profile (11), nutritional deficiencies (12), and neurodegenerative markers (13), it is plausible to think that frail older adults with evolving diseases would cumulate the deleterious biological changes related to both aging and disease. If different biological profiles according to the main cause of frailty exist, this may ultimately inform different strategies to prevent/delay or reverse frailty.

The aim of this exploratory study is to compare the biological and neuro-imaging profile of people without frailty, those with age-related frailty, and subjects with disease-related frailty in community-dwelling older adults, from the Multidomain Alzheimer Preventive Trial.

Methods

Study population

The present study used data from the Multidomain Alzheimer Preventive Trial (MAPT) (14, 15). MAPT is a

randomized controlled trial (registration: NCT00672685) aiming to assess the effects of multidomain interventions (nutritional and physical activity counselling, and cognitive training), omega-3 supplementation, or their combination on cognitive function over 3 years. The trial found no effect of these interventions compared to placebo on a composite cognitive score (16). MAPT participants were additionally followed for 2 observational years (no intervention). MAPT participants were community-dwelling individuals aged ≥ 70 years and meeting at least one of the following criteria: limitation in executing ≥ 1 Instrumental Activity of Daily Living (eg, cooking, shopping, using the phone, housekeeping), spontaneous memory complaints, slow gait speed (≤ 0.8 m/s). MAPT methods and procedures have been described elsewhere (14-16). MAPT respected the Declaration of Helsinki and was approved by the ethics committee (CPP SOOM II) in Toulouse. After signing informed consent, participants underwent clinical assessments, including frailty, at baseline and at 6, 12, 24, 36, 48 and 60 months.

Frailty assessment

Physical Frailty status was assessed using Fried criteria (17): 1. Unintentional weight loss (more than 4.5 kg) in the past 12 months; 2. Fatigue measured by two questions from the Center for Epidemiologic Studies Depression Scale (CES-D); 3. Low handgrip strength based on the best of 3 measurements with preferred hand; 4. Slow walking speed based on the best of 2 measurements over 4 meters; 5. Low level of physical activity expressed in weekly energy expenditure considering time spent doing physical activities. Patients meeting 3 or more criteria were considered frail, those meeting 1 or 2 criteria pre-frail and those without any criterion robust. For the present study we considered:

- Subjects without frailty (WF): defined as robust or prefrail participants at baseline that did not become frail during the follow-up period;
- Subjects with incident frailty: robust or prefrail participants at baseline who became frail during the follow-up period. These subjects have been previously classified in age-related frailty, disease-related frailty, and frailty of uncertain origin. Given that the objective of the present work was to study the markers of age-related and disease-related frailty, we did not consider the subjects with frailty of uncertain origin in the current analysis. Classification methods and procedures have been described in our previous study (6). Summarily, clinical files were reviewed by two different clinicians using a standardized assessment method. Inconsistencies among the two raters and the cases of uncertain frailty were reconsidered by two more experienced raters in order to obtain the definitive classification.

Blood biomarkers

A full description of measurement procedures is presented in the supplementary materials. Baseline omega-3 PUFAs were assessed in erythrocyte membranes, by measuring

docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The omega-3 index was calculated as the sum of %DHA and %EPA (18). APOE $\epsilon 4$ carriers were defined by ApoE genotyping as having at least one $\epsilon 4$ allele.

All the other blood biomarkers were obtained from plasma samples. 25-hydroxyvitamin D (ng/mL) and homocysteine ($\mu\text{mol/L}$) were measured at baseline using a commercially available electro-chemiluminescence competitive binding assay (Cobas; Roche). Vitamin D status was classified into 3 groups (deficiency: <20 ng/mL; insufficiency: 20–29.9 ng/mL; sufficiency: ≥ 30 ng/mL) according to previous research (19). Hyperhomocysteinemia was defined as homocysteine concentrations of more than 15 $\mu\text{mol/L}$ (20). CRP levels (mg/L) were measured at baseline, 6 and 12 months by immunoturbidity according to standard protocols. Low-grade inflammation, according to previous research (21), was defined as having at least two CRP values within 3 to 10 mg/L in consecutive visits between baseline, 6- and 12-month visits. Acute inflammation was defined as having at least one CRP value >10 mg/L between baseline and the 12-month visit. At the 12-month, A β 42 and A β 40 levels were assayed by immunoprecipitation mass spectrometry. Progranulin (ng/mL) was measured at the 12-month visit by a Human Progranulin Quantikine ELISA kit (R&D Systems, DPGRN0) following the manufacturer's instructions. Neurofilament light chain (NfL) were assayed at the 12-month visit using the R-PLEX human neurofilament L antibody set (Meso Scale Discovery, F217X) at the 12-month visit. Growth differentiation factor 15 (GDF15) (pg/ml), Tumor Necrosis Receptor 1 (TNFR1) (pg/ml), Interleukin 6 (IL6) (pg/ml), and Monocyte chemoattractant protein 1 (MCP1) (pg/ml), were assayed using the fully automated immunoassay platform Ella (ProteinSimple/Bio-technique, San Jose, CA, USA) at the 12-month visit. For biomarkers measured at 12 months, only participants who did not become frail, or who were not lost to follow-up before the 12-month visit, were considered for the current analysis.

Neuroimaging markers

All participants recruited in the MAPT study were invited to join the Magnetic Resonance Imaging-MAPT ancillary study, that was conducted in 9 centers (Toulouse, Bordeaux, Dijon, Foix, Limoges, Lyon, Montpellier, Nice, and Tarbes), using a standardized protocol designed by the CATI, the French national platform for multicenter neuroimaging (22). In the present study, we considered MRI data of gray matter volume (cm^3), hippocampal volume (cm^3), the volume of White Matter Hyperintensity lesions (cm^3) and global cortical thickness (mm). Global Cortical thickness was averaged from the two hemispheres. The hippocampal volume was calculated as the mean of the left and right hippocampal volume. For each measure, the imaging quality was scored and data with unreliable quality were excluded from our analysis. Only MRI data obtained before the date of incident frailty or the date of last frailty assessment were included.

All participants recruited in one of the 5 Positron Emission Tomography (PET) centers were invited to join the PET-MAPT

Table 1. Comparison of biomarkers according to frailty status

Median (IQR) or n (%)	N	Without frailty (n=1199)	N	Age-related frailty (n=82)	N	Disease-related frailty (n=53)	p-value
Age (years)	1199	74.0 (71.0, 77.0)	82	77.5 (74.0, 81.0)	53	78 (75.0, 81.0)	< 0.001
Sex (male)	1199	436 (36.4 %)	82	25 (30.5 %)	53	15 (28.3 %)	0.292
MAPT group	1199		82		53		0.718
Multidomain intervention + Omega 3		302 (25.2%)		21 (25.6 %)		10 (18.9%)	
Omega 3		287 (24.0 %)		23 (28.1 %)		17 (32.1 %)	
Multidomain intervention		317 (26.4 %)		17 (20.7 %)		13 (24.5 %)	
Placebo		293 (24.4 %)		21 (25.6 %)		13 (24.5 %)	
Biological markers							
25-hydroxyvitamin D (ng/mL)	515	23 (15, 32)	37	22 (14, 26)	36	18 (12, 35)	0.281
Deficiency (< 20 ng/mL)		197 (38.3%)		15 (40.6%)		21 (58.3%)	0.109
Insufficiency (20-29.9 ng/mL)		165 (32.0%)		13 (35.1%)		5 (13.9%)	
Sufficiency (≥ 30 ng/mL)		153 (29.7%)		9 (24.3%)		10 (27.8%)	
Homocysteine (μmol/L)	512	14.8 (12.0, 17.8)	38	16.2 (12.7, 20.7)	36	16.7 (12.6, 18.9)	0.150
Hyper-homocysteinemia (>15 μmol/L)		239 (46.7%)		21 (55.3%)		20 (55.6%)	0.373
Erythrocyte membrane fatty acid	1135		80		50		
DHA (μg/g)		25.5 (20.3, 31.2)		25.6 (20.6, 29.7)		23.0 (17.7, 28.2)	0.168
EPA (μg/g)		4.7 (3.6, 6.3)		4.4 (3.1, 6.4)		4.3 (3.3, 6.2)	0.306
Omega-3 index (%DHA+%EPA)		5.9 (4.9, 6.9)		5.5 (4.6, 6.6)		5.3 (4.4, 6.5)	0.009
CRP (mg/L)	971		64		37		< 0.001
Normal		771 (79.4%)		48 (75.0%)		22 (59.5%)	
Low-grade inflammation		104 (10.7%)		11 (17.2%)		9 (24.3%)	
Acute inflammation		96 (9.9%)		5 (7.8%)		6 (16.2%)	
ApoE ε4 carrier	981	234 (23.9%)	73	14 (19.2%)	38	7 (18.4%)	0.506
Aβ42/40 ratio	332	0.110 (0.100, 0.120)	22	0.110 (0.100, 0.120)	20	0.110 (0.100, 0.120)	0.529
Aβ42/40 positive (≤0.107)		113 (34.0%)		7 (31.8%)		8 (40.0%)	0.836
Neurofilament light chain (pg/mL)	329	73.0 (55.4, 91.8)	22	79.3 (68.3, 93.0)	20	74.8 (63.7, 135.9)	0.210
Progranulin (ng/mL)	329	44.5 (38.3, 50.0)	22	44.0 (40.2, 48.5)	20	50.1 (42.9, 61.1)	0.047
GDF15 (pg/mL)	857	985 (795, 1264)	53	1009 (810, 1304)	33	1422 (1069, 1612)	< 0.001
TNFR1 (pg/mL)	858	1125.5 (947, 1364)	53	1256 (922, 1456)	33	1469 (1055, 1754)	0.002
IL6 (pg/mL)	857	2.5 (1.8, 3.6)	53	2.6 (1.7, 4.1)	33	3.6 (2.3, 4.5)	0.111
MCP1 (pg/mL)	858	202.5 (170, 246)	53	224 (176, 293)	32	213 (180, 288)	0.228
Imaging markers							
Cortical SUVR	203	1.13 (1.05, 1.28)	15	1.10 (0.95, 1.20)	5	1.35 (1.12, 1.39)	0.146
% SUVR positive (≥ 1.17)		80 (39.4%)		5 (33.3%)		3 (60.0%)	0.545
Gray matter volume (cm ³)	392	638.4 (599.5, 685.3)	20	633.4 (598.0, 664.9)	15	604.0 (558.8, 656.9)	0.079
Hippocampal volume (cm ³)	395	3.5 (3.3, 3.8)	20	3.3 (3.2, 3.6)	15	3.2 (2.9, 3.5)	0.003
WMH volume (cm ³)	379	9.7 (6.5, 15.8)	17	13.2 (8.6, 19.6)	15	12.5 (11.2, 21.6)	0.033
Cortical thickness, whole brain (mm)	383	2.36 (2.28, 2.43)	20	2.34 (2.23, 2.44)	13	2.34 (2.31, 2.40)	0.735

P-value determined using Chi-square/Fisher exact test for categorical variables or using Kruskal-Wallis test for continuous variables; Bold p-values indicate statistically significant differences ($p < 0.05$); Abbreviation: Aβ, amyloid-beta; ApoE, Apolipoprotein E; BMI, body mass index; CRP, C-reactive protein; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GDF15, growth differentiation factor 15; IL6, interleukin 6; MAPT, Multidomain Alzheimer Preventive Trial; MCP1, monocyte chemoattractant protein 1; SUVR, standard uptake value ratio; TNFR1, tumor necrosis factor receptor type 1; WMH, white matter hyperintensities.

ancillary study. [18F]-Florbetapir PET scans were performed for measuring brain amyloid-β load. In line with previous studies, significant brain amyloid-β deposits (ie, cortical SUVR positive) were defined as cortical SUVR ≥ 1.17 (23). Regional standard uptake value ratios (SUVRs) were obtained using semi-automated quantitative analysis with the whole cerebellum as the reference region. Cortical-to-cerebellar SUVRs were generated from the mean signal of six regions (frontal, parietal, temporal, precuneus, anterior cingulate, and posterior cingulate cortical regions). In the current analysis, we only considered participants, whose PET results were obtained before the date of frailty onset or their last frailty assessment visit.

Statistical analysis

Descriptive statistics were presented as median and IQR, or frequencies and percentages. Chi-square/Fisher exact test and Kruskal-Wallis test were used to compare baseline characteristics and biomarkers according to the frailty status (without frailty, age-related frailty, disease-related frailty). We applied multivariate linear regressions to examine associations between biological markers (as the dependent variables) and the frailty status adjusted for age, sex and MAPT groups. For MRI variables, linear mixed-effect models (with random effect on study center) were conducted with adjustment for age, sex,

Table 2. Multivariate linear regression* evaluating associations between biomarkers (dependent variables) and frailty status

	Age-related frailty vs. without frailty β (95% CI); p-value	Disease-related frailty vs. without frailty β (95% CI); p-value	Disease-related frailty vs. age-related frailty β (95% CI); p-value
Biological markers			
25-hydroxyvitamin D (ng/mL)	-1.52 (-5.74, 2.69); 0.478	-1.44 (-5.76, 2.87); 0.512	0.08 (5.60, 5.77); 0.977
Homocysteine ($\mu\text{mol/L}$)	0.70 (-1.09, 2.49); 0.442	0.10 (-1.75, 1.96); 0.913	-0.60 (-3.03, 1.83); 0.629
DHA ($\mu\text{g/g}$)	-0.35 (-2.23, 1.52); 0.713	-2.42 (-4.76, -0.08); 0.043	-2.07 (-4.95, 0.82); 0.160
EPA ($\mu\text{g/g}$)	-0.20 (-0.76, 0.35); 0.470	-0.28 (-0.97, 0.41); 0.431	-0.07 (-0.93, 0.78); 0.865
Omega-3 index (%DHA+%EPA)	-0.31 (-0.67, 0.04); 0.085	-0.50 (-0.95, -0.06); 0.026	-0.19 (-0.74, 0.35); 0.493
Plasma A β 42/40	0.002 (-0.004, 0.008); 0.573	-0.003 (-0.010, 0.003); 0.341	-0.005 (-0.014, 0.004); 0.262
Neurofilament light chain (pg/mL) ²	0.02 (-0.06, 0.09); 0.693	0.03 (-0.05, 0.12); 0.423	0.02 (-0.09, 0.13); 0.740
Progranulin (ng/mL)	-0.62 (-5.91, 4.67); 0.818	5.43 (-0.27, 11.14); 0.062	6.05 (-1.44, 13.54); 0.113
GDF15 (pg/mL)	3.3 (-120.5, 127.1); 0.958	246.1 (88.9, 403.4); 0.002	242.8 (49.5, 436.2); 0.014
TNFR1 (pg/mL)	14.9 (-102.9, 132.8); 0.804	157.5 (7.8, 307.2); 0.039	142.6 (-41.5, 326.7); 0.129
IL6 (pg/mL) ²	-0.005 (-0.079, 0.070); 0.902	0.050 (-0.044, 0.144); 0.299	0.055 (-0.061, 0.171); 0.356
MC1P1 (pg/mL)	15.5 (-8.3, 39.4); 0.201	-3.3 (-33.5, 27.0); 0.833	-18.8 (-56.0, 18.4); 0.322
Imaging markers			
Cortical SUVR	-0.05 (-0.14, 0.04); 0.303	0.12 (-0.04, 0.28); 0.133	0.17 (-0.01, 0.35); 0.057
Gray matter volume (cm ³)	-3.78 (-9.11, 1.54); 0.163	-0.86 (-7.06, 5.33); 0.784	2.92 (-4.91, 10.75); 0.464
Hippocampal volume (cm ³)	-0.06 (-0.24, 0.12); 0.505	-0.22 (-0.42, -0.02); 0.035	-0.16 (-0.42, 0.10); 0.224
WMH volume (cm ³)	-1.37 (-5.78, 3.04); 0.542	2.47 (-2.27, 7.22); 0.306	3.84 (-2.36, 10.05); 0.224
Cortical thickness, whole brain (mm)	-0.03 (-0.08, 0.02); 0.234	-0.01 (-0.08, 0.05); 0.686	0.02 (-0.06, 0.10); 0.650

* Models using biomarkers as dependent variables with adjustment for age, sex and Multidomain Alzheimer Preventive Trial (MAPT) group. For MRI variables (gray matter, hippocampus, WMH and cortical thickness), mixed-effect model (with random effect on study center) was applied with adjustment for age, sex, MAPT groups, and total intracranial volume; 2. Value of biomarker was log transformed; Bold lines indicate statistically significant differences at $p < 0.05$; Abbreviation: A β , amyloid-beta; CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; GDF15, growth differentiation factor 15; IL6, interleukin 6; MC1P1, monocyte chemoattractant protein 1; SUVR, standard uptake value ratio; TNFR1, tumor necrosis factor receptor 1; WMH, white matter hyperintensities.

MAPT groups, and total intracranial volume. For all linear models, the distribution of the residuals was assessed by visual inspection and the value of biomarker was log-transformed if the residuals deviated from a normal distribution. Logistic regressions (adjusted for age, sex and MAPT groups) were performed to evaluate associations of the frailty status with biomarkers in categorical measures. Statistical significance was defined as $p < 0.05$; data were analyzed by using SAS, version 9.4 (SAS Institute, Inc., Cary, NC).

Results

Among 1679 subjects enrolled in MAPT study, 91 and 143 participants were excluded due to missing data from baseline and post-baseline frailty assessment respectively. Fifty-one participants with frailty at baseline were excluded. Among the remaining 1394, 1199 (86%) subjects did not become frail during the 5-year follow-up period, 82 (6%) subjects were rated as incident age-related frailty, and 53 (4%) as incident disease-related frailty. Sixty individuals with incident frailty were excluded from our analysis because it was not possible to classify them according to the main cause of frailty (ie, either age- or disease-related). Finally, a total of 1334 participants was included in this study. Subjects without frailty were younger at baseline when compared with other groups. We did not find any significant difference regarding sex and MAPT group between

the three frailty groups (Table 1).

Comparison of biomarkers between the three groups (without frailty, age-related frailty, disease-related frailty) with bivariate analysis are detailed in the Table 1. In the disease-related frailty group, we observed lower values of omega-3 index and hippocampal volume compared to both individuals without frailty and age-related frailty participants. Low-grade inflammation and acute inflammation were more common among participants with disease-related frailty compared to the two other groups. Significantly higher values of Progranulin, GDF15 and TNFR1 were found in the group frailty related to diseases compared to individuals without frailty and age-related frailty participants.

The results of the adjusted models are presented in the Table 2 (for continuous variables) and Table 3 (for binary variables). Subjects with disease-related frailty had higher GDF15 values compared with age-related frailty individuals. We did not find any significant difference between participants with age-related frailty and subjects without frailty. Subjects with disease-related frailty presented lower values of DHA, omega-3 Index, and hippocampal volume and higher values of GDF15 and TNFR1 compared to subjects without frailty.

Discussion

This is the first study aimed to compare the biological characteristics of subjects with incident age-related frailty,

Table 3. Logistic regression* evaluating association between biomarkers (dependent variables) and frailty status

	N	Age-related frailty vs. without frailty OR (95% CI); p-value	Disease-related frailty vs. without frailty OR (95% CI); p-value	Disease-related frailty vs. age-related frailty OR (95% CI); p-value
25-hydroxyvitamin D deficiency (< 20 ng/mL)	588	1.15 (0.48, 2.78); 0.750	1.33 (0.59, 3.01); 0.491	1.16 (0.37, 3.58); 0.803
Hyper-homocysteinemia ($\geq 15 \mu\text{mol/L}$)	586	1.18 (0.58, 2.39); 0.653	1.13 (0.55, 2.32); 0.748	0.96 (0.37, 2.49); 0.928
Low-grade inflammation	1072	1.71 (0.85, 3.44); 0.135	3.10 (1.35, 7.11); 0.008	1.82 (0.66, 5.04); 0.251
ApoE $\epsilon 4$ carrier	1092	0.79 (0.43, 1.46); 0.456	0.78 (0.33, 1.81); 0.555	0.98 (0.36, 2.68); 0.966
Low plasma A β 42/40 (≤ 0.107)	374	0.71 (0.28, 1.80); 0.472	1.05 (0.40, 2.72); 0.928	1.47 (0.41, 5.28); 0.555
SUVR positive (≥ 1.17)	223	0.92 (0.28, 3.02); 0.893	2.26 (0.33, 15.50); 0.407	2.45 (0.28, 21.12); 0.415

* Adjusted for age, sex and Multidomain Alzheimer Preventive Trial (MAPT) group; Bold lines indicate statistically significant differences at $p < 0.05$; Abbreviation: A β , amyloid-beta; APOE, Apolipoprotein E; OR, odds ratio; SUVR, standard uptake value ratio.

incident disease-related frailty, and subjects who did not become frail during a follow-up period of 5 years. GDF15 was the only marker for which we found a significant difference between the subjects with age-related frailty and those with disease-related frailty. Subjects without frailty did not differ from individuals with age-related frailty from a biological point of view. Subjects with disease-related frailty had worse levels of several inflammatory, nutritional and neuroimaging markers compared to people without frailty.

The higher GDF15 values in the group disease-related frailty, compared with age-related frailty, could be due to the higher comorbidity burden in the former group. In physiological conditions, GDF15 is a peptide expressed in multiple tissues at low concentrations. Nevertheless, this protein is overexpressed in several pathological conditions, such as cancer, systemic inflammation, metabolic and cardiovascular diseases (24). The role of GDF15 during diseases is few defined. GDF15 may play a protective role in several tissues, following inflammation, by mitigating the extent of damage (25). Moreover, GDF15 leads to appetite suppression, being potentially responsible for weight loss (26). Weight loss is a hallmark of frailty especially prevalent in the context of several chronic and acute medical conditions (27). Indeed, in our previous paper, we showed that the criterion weight loss was more common in people with disease-related frailty, compared to those with age-related frailty (6). Further studies are needed to clarify if GDF15 can distinguish these classifications of frailty in other populations.

Although not statistically significant, our results showed increasing gradients for inflammatory markers (CRP, GDF15, TNFR1) and decreasing gradients for nutritional (omega 3 index) and neuroimaging (hippocampal volume) markers from age-related frailty participants to individuals with disease-related frailty. This could suggest that, rather than opposite concepts, age-related frailty and disease-related frailty could represent different stratifications of frailty severity. Participants who became frail due to diseases are probably frailer than age-related frail subjects. This could be due to the fact that, in addition to the progressive effect of the aging process, they are weakened by the deleterious pathophysiological process linked to chronic comorbidities and acute diseases. In the future, a better knowledge of the hallmarks of aging (28) (ie, cellular senescence, epigenetic alterations, telomere attrition, etc.) and

their biomarkers could help understand the pathophysiological mechanisms of these different classifications of frailty (ie, age-related and disease-related). This could ultimately permit identifying different strategies of prevention and treatment.

As expected, subjects with frailty related to diseases presented lower values of omega 3 and higher levels of inflammatory biomarkers than subjects without frailty. Low levels of omega 3 have been associated with several pathophysiological mechanisms (such as atherosclerosis, hypercoagulability, bone and muscle degeneration) and chronic diseases potentially leading to frailty (29-31). Low-grade inflammation is a common denominator of cardiovascular, metabolic, neurologic and systemic diseases (32). Furthermore, low-grade inflammation represents one of the most promising biological pathways that have been studied in the context of frailty pathogenesis (33).

This study extends the knowledge of the biological profile of individuals characterized as having developed age-related frailty and those with frailty related to diseases. Nevertheless, some limitations should be acknowledged. Firstly, this work is a secondary analysis of the MAPT study that was not specifically designed to measure the biomarkers of frailty. Frailty subtypes (ie, age-related or disease-related) classification was performed from clinical files in a retrospective manner. Furthermore, we investigated only biomarkers available in MAPT database. A non-biased approach is therefore needed to provide a comprehensive view of biological differences according to the main cause leading to frailty. We planned to implement this approach in the ongoing cohorts of the CogFrail (34) and INSPIRE Projects (35-39).

Conclusion

At a biological level, age-related frailty and disease-related frailty may represent different degrees of frailty severity, with the latter cumulating the deleterious biological mechanisms leading to aging and disease development/progression. Further research is needed to identify biomarkers potentially able to distinguish these classifications of frailty at a biological level.

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