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► To cite this version:

Wan-hsuan Lu, Emmanuel Gonzalez Bautista, Sophie Gillette-Guyonnet, Alexandre Lucas, Angelo Parini, et al.. Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults. *Journal of Cachexia, Sarcopenia and Muscle*, 2023, 14 (2), pp.930-939. 10.1002/jcsm.13163 . hal-04765965

HAL Id: hal-04765965

<https://hal.science/hal-04765965v1>

Submitted on 4 Nov 2024

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Plasma inflammation-related biomarkers are associated with intrinsic capacity in community-dwelling older adults

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Abstract

Background How inflammation relates to intrinsic capacity (IC), the composite of physical and mental capacities, remains undefined. Our study aimed to investigate the cross-sectional and longitudinal associations between plasma inflammation-related biomarkers and IC in older adults.

Methods This secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT) included 1238 community-dwelling older individuals with IC assessments from 12 to 60 months. Plasma C-reactive protein (CRP), interleukin-6 (IL-6), tumour necrosis factor receptor-1 (TNFR-1), monocyte chemoattractant protein-1 (MCP-1) and growth differentiation factor-15 (GDF-15) were measured at 12 months. IC was operationalized as a score ranging from 0 to 100, derived from four domains: cognition, *Mini-Mental State Examination*; locomotion, *Short Physical Performance Battery*; psychological, *Geriatric Depression Scale*; and vitality, *handgrip strength*. A five-domain IC score (plus sensory) was investigated in a subsample ($n = 535$) with a 1-year follow-up as an exploratory outcome.

Results The mean age of the 1238 participants was 76.2 years (SD = 4.3); 63.7% were female. Their initial four-domain IC scores averaged 78.9 points (SD = 9.3), with a yearly decline of 1.17 points (95% CI = -1.30 to -1.05 ; $P < 0.001$). We observed significant associations of lower baseline IC with higher CRP, IL-6, TNFR-1 and GDF-15, after controlling age, sex, MAPT group allocation and educational level [CRP: adjusted β (95% CI) = -1.56 (-2.64 to -0.48); $P = 0.005$; IL-6: adjusted $\beta = -3.16$ (-4.82 to -1.50); $P < 0.001$; TNFR-1: adjusted $\beta = -6.86$ (-10.25 to -3.47); $P < 0.001$; GDF-15: adjusted $\beta = -7.07$ (-10.02 to -4.12); $P < 0.001$]. Higher TNFR-1, MCP-1 and GDF-15 were associated with faster decline in four-domain IC over 4 years [TNFR-1: adjusted β (95% CI) = -1.28 (-2.29 to -0.27); $P = 0.013$; MCP-1: adjusted $\beta = -1.33$ (-2.24 to -0.42); $P = 0.004$; GDF-15: adjusted $\beta = -1.42$ (-2.26 to -0.58); $P = 0.001$]. None of the biomarkers was significantly associated with the five-domain IC decline.

Conclusions Inflammation was associated with lower IC in older adults. Among all plasma biomarkers, TNFR-1 and GDF-15 were consistently associated with IC at the cross-sectional and longitudinal levels.

Keywords Biological ageing; Geroscience; Functional decline; TNFR-1; MCP-1; GDF-15

Received: 26 April 2022; Revised: 27 September 2022; Accepted: 25 November 2022

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Members are listed in the acknowledgments.

Introduction

Intrinsic capacity (IC) is the composite of physical and mental capacities that individuals can draw upon as they age, encompassing the domains of cognition, locomotion, psychological, vitality and sensory.^{1,2} Overall, an individual's IC reaches a peak in early adulthood and then declines gradually with age.¹ Thus, monitoring and enhancing IC is useful to prevent functional impairment and promote healthy ageing.⁵¹ Indeed, a lower IC predicts the onset of disability,^{3,52} institutionalization³ and mortality⁴ in older adults. Despite the fact that IC shows an overall declining trend, there is a wide variation in IC levels and decline rates among older individuals.^{3,5} Heterogeneity in IC trajectories is possibly explained by individuals' variability in biological ageing. Yet, the link between biological ageing and IC is not fully understood.

Inflammation is one of the hallmarks of ageing^{53,54} and has been implicated in several age-related diseases, including dementia⁵⁵ and depression.^{56,57} In the skeletal muscle, inflammation can directly trigger muscle catabolism or inhibit growth factors,^{6,7} resulting in declined muscle strength⁸ and mobility disability.^{9,10} In addition, inflammation has been associated with the incidence of age-related sensory impairments.^{58,59} Previous epidemiologic studies have measured circulating pro-inflammatory factors—including acute-phase proteins, cytokines and chemokines—to quantify the inflammatory status in older adults.¹¹ Plasma markers like growth differentiation factor-15 (GDF-15), which is induced by age-related inflammation¹² and strongly predicts adverse health outcomes,^{13,510} are also promising candidates in recent research. Although the link between inflammation-related biomarkers and individual IC domains has been extensively explored,^{8,14-17,58,511-513} the association with the IC composite remains poorly investigated. To the best of our knowledge, only three observational studies investigated the association between inflammation-related biomarkers with IC.^{4,18,19} However, their findings were inconsistent, probably due to their cross-sectional approach,^{4,19} categorical measures of IC,^{4,19} small sample size¹⁹ and a focus on pro-inflammatory markers.^{4,18,19}

Considering the limitations in the literature, we aimed to investigate the cross-sectional and longitudinal associations between IC and five plasma inflammation-related biomarkers: C-reactive protein (CRP, acute-phase protein), interleukin-6 (IL-6, cytokine), tumour necrosis factor receptor-1 (TNFR-1, soluble cytokine receptor), monocyte chemoattractant protein-1 (MCP-1, chemokine) and GDF-15. Moreover, we compared the inflammatory biological profiles of individuals according to their longitudinal IC trajectories. We hypothesized that older adults with higher levels of inflammation-related biomarkers would have lower IC at baseline and faster IC decline over time.

Methods

Data source

This is a secondary analysis of the Multidomain Alzheimer Preventive Trial (MAPT). MAPT Study is a multicentre, randomized controlled trial investigating the preventive effects of omega-3 polyunsaturated fatty acid (PUFA) supplementation and multidomain lifestyle interventions on cognitive decline in community-dwelling older adults.⁵¹⁴ Participants were randomized into four groups: receiving both omega-3 PUFA supplementation and multidomain intervention (including exercise advice, cognitive training and nutritional counselling), receiving omega-3 PUFA supplementation only, receiving placebo and multidomain intervention and a placebo control group. After the 3-year intervention, no beneficial effects of the omega-3 supplementation and multidomain interventions, either combined or alone, on cognitive function⁵¹⁵ and IC⁵¹⁶ were observed. An additional 2-year observation without any intervention was conducted on the MAPT participants after the intervention was completed. The MAPT Study [no. NCT00672685] was approved by the French Ethical Committee located in Toulouse (CPP SOOM II) and authorized by the French Health Authority. All participants signed informed consent.

Study population

The MAPT Study recruited 1679 adults aged 70 years and over with the following inclusion criteria: spontaneous memory complaint, limitations in one instrumental activity of daily living or gait speed ≤ 0.8 m/s. Patients were excluded if presenting with a Mini-Mental State Examination (MMSE)⁵¹⁷ score < 24 , diagnosis of dementia, limitation in any basic activities of daily living and taking omega-3 supplements within the past 6 months before study enrolment. The current study included 1238 subjects with data for plasma biomarkers and IC from the 12- to 60-month visits. Among them, 535 participants in the MAPT multidomain intervention groups (either combined omega-3 supplementation or not) underwent vision and hearing assessments at the 12-month and 24-month visits and were included to estimate the five-domain IC as an exploratory outcome.

Measurement of plasma biomarkers

Plasma biomarkers were measured during the 12-month visit in the MAPT Study. CRP was measured (mg/L) by immunoturbidity according to standard protocols. Plasma levels of IL-6, TNFR-1, MCP-1 and GDF-15 were assessed using the fully automated immunoassay platform, Ella (ProteinSimple/Bio-Techne, San Jose, CA, USA). Proteins were

quantified using a single disposable microfluidic SimplePlex™ cartridge. The plasma samples were thawed on ice, diluted 1:4 in sample diluent (SD 13) and loaded into cartridges with high and low control concentrates. Each plasma sample was divided into four unique microfluidic parallel channels within the cartridge, which were specific for each of the four proteins being analysed. Each protein channel contains three analyte-specific glass nanoreactors (GNRs), allowing each plasma sample to be run in triplicates for each of the four protein samples. Cartridges included a built-in lot-specific standard curve for each defined protein. All steps in the procedure were conducted automatically by the instrument without user activity. The obtained protein concentrations were calculated by the internal instrument software and displayed in pg/mL.

Measurement of IC

The primary outcome was the four-domain IC composed of cognition, locomotion, psychological and vitality. Cognition was assessed by the 30-item MMSE (a higher score indicates better cognitive function).^{S17} Locomotion was evaluated by the Short Physical Performance Battery (SPPB; ranging from 0 to 12; higher means better performance).^{S18} The psychological domain was measured by the 15-item Geriatric Depression Scale (GDS), with scores varying from 0 to 15 (higher is worse).^{S19} We used the handgrip strength of the dominant hand, measured with a hydraulic dynamometer (Jamar, Bolingbrook, IL), for vitality. Participants were asked to hold the dynamometer in a standing position with the arm straight down and squeeze it as hard as possible. The maximum value of three attempts was recorded [in kilograms (kg)]. All four domains were annually evaluated for the entire study population from the 12-month visit (defined as the baseline in this study) to the 60-month visit (the average length of follow-up: 3.1 ± 1.3 years). To obtain the global IC score, we first rescaled the measurements of each domain into the 100-scale system (higher indicates better function); the original scores of GDS were weighted as -1 before rescaling. We further calculated the global IC score by the arithmetic mean of these four domains.

Considering the sensory function was only measured in half of the MAPT population at 12 and 24 months, we evaluated the five-domain IC as an exploratory outcome. This outcome consisted of the prior four domains plus the sensory according to the original IC construct.² The sensory domain included the near-vision acuity and the hearing impairment indicated by the Screening Version of Hearing Handicap Inventory for the Elderly (HHIE-S).^{S20,S21} The near-vision acuity was measured by a Monoyer chart with a score ranging from 0 to 10 (a higher score indicates better performance); the average performance of the left and right eyes was applied. The HHIE-S scale comprises 10 questions about the perception of

hearing difficulty in older adults' daily lives. Participants were scored as 0 if they perceived no difficulty, 2 if they reported sometimes and 4 if they reported difficulty. The overall HHIE-S score ranged from 0 to 40; a higher score indicates worse hearing performance.^{S20,S21} We rescaled the HHIE-S score and visual acuity following the abovementioned method; the original scores of HHIE-S were weighted as -1 before rescaling. The score of the sensory domain was calculated by averaging the rescaled values of the HHIE-S and visual acuity. The five-domain IC score was determined as the mean value of the five IC domains (cognition, locomotion, psychological, vitality and sensory).

Trajectories of IC

Participants were classified into three IC trajectory groups according to their IC rate of change over time (details described in the 'Statistical analysis' section): (1) 'Accelerated IC decline', if their IC slopes were < -1.78 points per year (the lowest 20%); (2) 'Slight IC decline', if their IC slopes were within -1.78 to -0.53 (middle 60%); and (3) 'Stable IC', if their IC slopes were > -0.53 (the highest 20%).

Covariates

The demographic covariates used for the analyses were age, sex, MAPT group allocation and educational level (no diploma, primary school certificate, secondary education, high school diploma, university level).

Statistical analysis

Descriptive data were presented as means and standard deviations (SD), medians and interquartile ranges (IQRs) or frequencies and percentages, as appropriate. We first used linear mixed-effects regressions to identify the longitudinal trajectories of IC in our study population. When examining the primary outcome (i.e. repeated four-domain IC measurements from 12 to 60 months), a random effect at participant level and a random slope on time were included in the mixed-effects models. For the exploratory outcome (i.e. repeated five-domain IC measurements at 12 and 24 months), only a random effect at participant level was considered (insignificant random effect on time). The linear mixed-effects models showed that IC trajectories were linear in our population; the time coefficient represented the slope of IC change over time.

To evaluate the associations of IC with each plasma biomarker, we introduced plasma biomarkers into the linear mixed-effects models (a separate model per biomarker). IC was evaluated as a global score and as separate IC domains. The biomarker coefficients in the models indicated

cross-sectional associations, and the coefficients for biomarker–time interaction indicated longitudinal associations. All models were adjusted for the covariates mentioned above. We kept all biomarker values in our main analysis because there are no established cut-offs for extreme values of plasma biomarkers in the literature. We further conducted a sensitivity analysis with biomarker outliers (defined as >4 SD from the mean) removed to test whether such values have altered the associations.

We estimated each participant's IC trajectory slope based on their longitudinal measurements of four-domain IC and demographic covariates using the linear mixed-effects model aforementioned (without plasma biomarkers). The differences in plasma biomarker concentrations between IC trajectory groups were compared using analysis of covariance (ANCOVA) with adjustment for age and sex, followed by the Tukey–Kramer post hoc test for pairwise comparisons. All analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC) and STATA version 17 (College Station, TX), with a significance level of 0.05.

Results

Characteristics of the study population and IC trajectories

Of 1238 participants, the mean age was 76.2 (SD = 4.3) years, and 63.7% were female. The mean value of the baseline four-domain IC score was 78.9 (SD = 9.3) of 100 points possible (Table 1), and the annual IC decline rate was 1.2 points per year on average (adjusted β = -1.17 ; 95% CI: -1.30 to -1.05 ; $P < 0.001$; Table S1). Similar baseline IC score and annual IC decline rate were found using the five-domain measure (Tables 1 and S1).

Association between plasma biomarkers and global IC score

Table 2 displays the cross-sectional and longitudinal associations between plasma inflammation-related biomarkers and IC. Regarding the four-domain IC, higher CRP, IL-6, TNFR-1 and GDF-15 were associated with lower IC scores at baseline. In addition, participants with higher TNFR-1, MCP-1 and GDF-15 had faster IC declines over time. Significant associations of IL-6, TNFR-1 and GDF-15 with IC were observed with five-domain IC at the cross-sectional level, but none of these biomarkers was associated with IC change over time. Sensitivity analysis removing the extreme plasma biomarkers values provided similar results, except for plasma TNFR-1 (Table S2); plasma TNFR-1 was not associated with baseline

Table 1 Characteristics of study population at the 12-month visit of the MAPT Study

	N	Median (IQR) or n (%)
Age (year), mean (SD)	1238	76.2 (4.3)
Female	1238	789 (63.7%)
MAPT group		
Multidomain intervention + omega-3	1238	309 (25.0%)
Omega-3		303 (24.5%)
Multidomain intervention		317 (25.6%)
Placebo		309 (25.0%)
Education		
No diploma	1238	62 (5.0%)
Primary school certificate		210 (17.0%)
Secondary education		408 (33.0%)
High school diploma		185 (14.9%)
University level		373 (30.1%)
Measurement for IC domain ^a		
Cognitive: MMSE, 0–30	1238	29 (27, 29)
Locomotion: SPPB, 0–12	1217	11 (10, 12)
Psychological: GDS, 0–15	1233	3 (1, 4)
Vitality: Handgrip strength (kg)	1135	25 (20, 34)
Sensory		
Visual acuity—Monoyer scale, 0–10	510	7 (5.5, 9)
HHIE-S, 0–40	536	4 (0, 12)
Global IC score, 0–100 ^b , mean (SD)		
4 domains (without sensory)	1115	78.9 (9.3)
5 domains (with sensory)	462	78.9 (8.3)
Plasma biomarker		
CRP, mg/L	1060	1.8 (1, 3.7)
IL-6, pg/mL	1062	2.57 (1.81, 3.8)
TNFR-1, pg/mL	1063	1142 (957, 1386)
MCP-1, pg/mL	1063	204 (170, 252)
GDF-15, pg/mL	1062	1003.5 (804, 1309)

CRP, C-reactive protein; GDF-15, growth differentiation factor-15; GDS, Geriatric Depression Scale; HHIE-S, Hearing Handicap Inventory for the Elderly—the Screening Version; IC, intrinsic capacity; IL-6, interleukin-6; MAPT, Multidomain Alzheimer Preventive Trial; MCP-1, monocyte chemoattractant protein-1; MMSE, Mini-Mental State Examination; SPPB, Short Physical Performance Battery; TNFR-1, tumour necrosis factor receptor-1.

Value presented in median (IQR) for continuous variables or number (%) for categorical variables except where indicated other.

^aHigher value indicates better function except for GDS and HHIE-S.

^bHigher value indicates better IC.

five-domain IC score after removing one outlier (adjusted β = -3.20 ; 95% CI: -8.38 to 1.98 ; $P = 0.225$; Table S2).

Association between plasma biomarkers and individual IC domain

After adjusting for covariates, all plasma biomarkers showed associations with locomotion change. Furthermore, elevated MCP-1 and GDF-15 were associated with worsening function in the psychological domain. Increasing MCP-1 levels were also associated with worse vitality over time. None of the five plasma biomarkers predicted the change of cognitive domain (Figure 1 and Table S3).

Table 2 Associations between plasma inflammation-related biomarkers and IC

Plasma biomarker ^a	Four-domain IC score ^b				Five-domain IC score ^c				
	N	β	95% CI	P	N	β	95% CI	P	
Cross-sectional									
CRP	1060	-1.56	-2.64 -0.48	0.005	453	-1.13	-2.70 0.43	0.156	
IL-6	1062	-3.16	-4.82 -1.50	<0.001	460	-2.76	-5.19 -0.32	0.026	
TNFR-1	1063	-6.86	-10.25 -3.47	<0.001	461	-5.01	-9.99 -0.02	0.049	
MCP-1	1063	1.08	-1.99 4.16	0.490	461	0.01	-4.28 4.29	0.998	
GDF-15	1062	-7.07	-10.02 -4.12	<0.001	460	-5.20	-9.48 -0.92	0.017	
Longitudinal									
CRP	1060	-0.13	-0.45 0.19	0.429	453	0.40	-0.96 1.76	0.566	
IL-6	1062	-0.36	-0.85 0.13	0.150	460	1.59	-0.52 3.70	0.139	
TNFR-1	1063	-1.28	-2.29 -0.27	0.013	461	-2.03	-6.20 2.14	0.341	
MCP-1	1063	-1.33	-2.24 -0.42	0.004	461	0.25	-3.52 4.03	0.895	
GDF-15	1062	-1.42	-2.26 -0.58	0.001	460	-1.24	-4.66 2.19	0.479	

CRP, C-reactive protein; GDF-15, growth differentiation factor-15; IC, intrinsic capacity; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; TNFR-1, tumour necrosis factor receptor-1.

^aAll values of biomarkers were log-transformed.

^bComposed of cognitive, locomotive, psychological and vitality domains; evaluated by linear mixed-effects regression with adjustment for age, sex, Multidomain Alzheimer Preventive Trial (MAPT) group allocation and educational level.

^cComposed of cognitive, locomotive, psychological, vitality and sensory (vision + hearing) domains; evaluated by linear mixed-effects regression with adjustment for age, sex, MAPT group allocation and educational level.

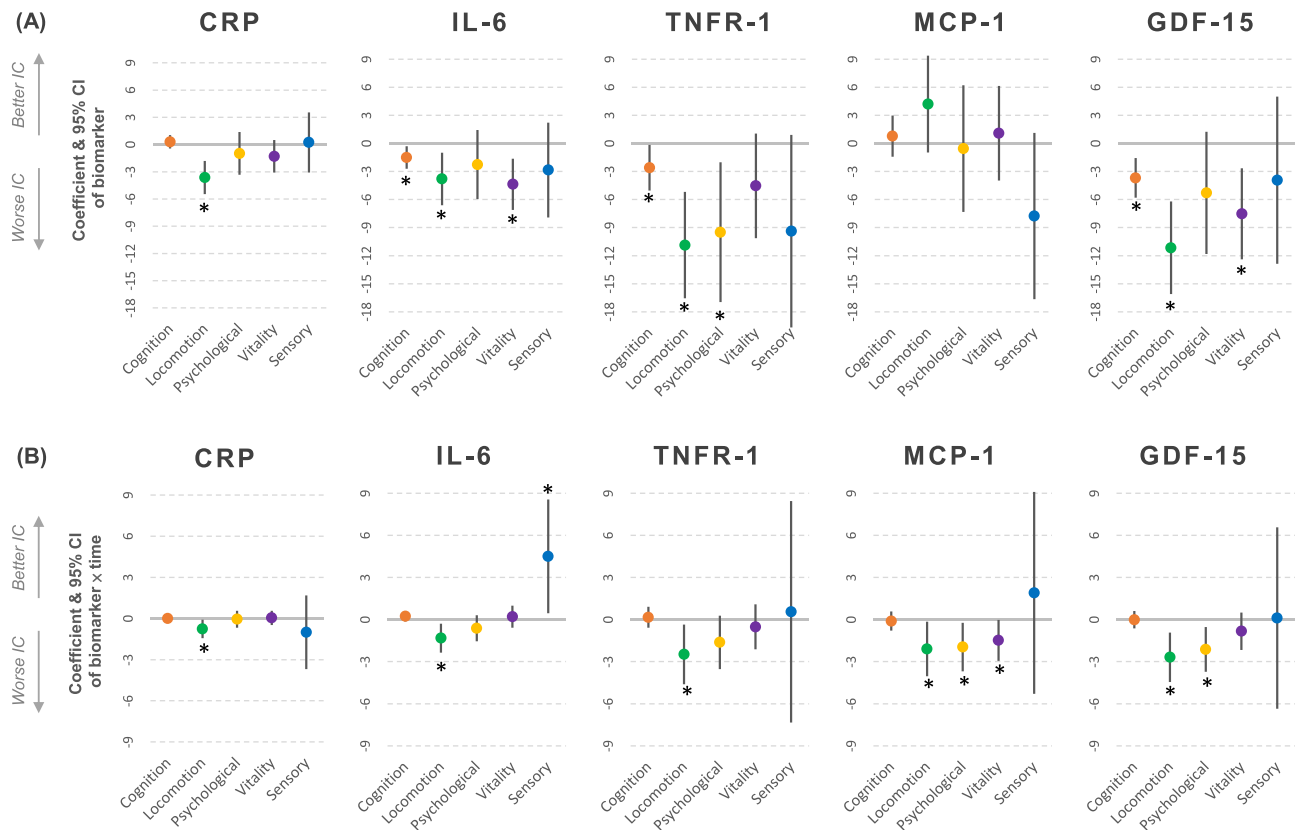


Figure 1 (A) Cross-sectional; (B) longitudinal associations between plasma inflammation-related biomarkers and intrinsic capacity (IC) domains examining by linear mixed-effects regression. The sensory domain is composed of vision and hearing capacities. **P* < 0.05.

Descriptive inflammatory profile according to different IC trajectory groups

Plasma levels of TNFR-1, MCP-1 and GDF-15 presented significant differences between participants with different IC trajectories (adjusted *P* value for difference <0.05; Table 3). A gradient in the levels of all biomarkers was observed, with the highest levels obtained in the IC accelerated group and the lowest in the IC stable group. Compared with participants with stable or slight declined IC, those with accelerated IC decline were more likely to have higher plasma TNFR-1, MCP-1 and GDF-15 at baseline (post hoc *P* value < 0.05 for all pairwise comparisons; Table 3), indicating that these three plasma biomarkers had potential to identify older adults with worse IC trajectories.

Discussion

This study investigated the associations of five circulating inflammation-related markers with IC in older adults. We demonstrated that higher TNFR-1 and GDF-15 were consistently associated with four-domain IC, consisting of cognition, locomotion, psychological and vitality capacities, at both cross-sectional and longitudinal levels. Domain-specific analysis revealed that all inflammatory biomarker concentrations predicted the locomotion change over time; higher plasma GDF-15 levels were associated with faster psychological declines, and higher plasma MCP-1 levels were related to the impairment of psychological and vitality domains. Furthermore, plasma levels of TNFR-1, MCP-1 and GDF-15 showed a gradient in reference to the IC longitudinal trajectories,

with the highest levels observed in the accelerated group and the lowest in the IC stable group. Taken together, these findings supported our hypothesis that higher levels of inflammation-related biomarkers were associated with lower initial IC levels and faster IC declining rates in older adults.

Despite the slight differences in the measurement for each IC domain, our study population presented similar baseline IC levels (78.9 ± 9.3 points) to the PEP cohort from the USA (77 ± 11 points; mean age 78.4 years)³ and was relatively higher compared with the Mexican population in the SAGE study (range from 36.9 to 61.2 points in a cohort aged ≥50 years).⁵ We demonstrated that IC decreased 1.2 points per year in older adults. Furthermore, a 10-fold increase in plasma levels of TNFR-1, MCP-1 and GDF-15 was associated with an additional 1.3–1.4 points of IC decline per year. Although there is no established cut-off for clinically meaningful IC decline, Stolz et al.³ found that a 1-point decrease in IC was associated with a 7% increased risk of ADL disability and a 5% increased risk of mortality in older adults. Taken together, the inflammation-related IC decline in older individuals may indicate a doubling or even higher risk of adverse health outcomes in the future.

Age-related inflammation can be derived from extrinsic causes—diet, smoking, chronic infections, etc.²⁰—and intrinsic mechanisms, including cellular senescence and associated secretory phenotype (SASP)^{20–22} and increased oxidative stress due to mitochondrial dysfunction.²² IL-6,²³ TNFR-1,²⁴ MCP-1²⁵ and GDF-15^{26,27} have been identified as the SASP components in different senescence cells. Elevated GDF-15 levels were also observed in response to impaired mitochondria, despite the unknown function remaining.²⁷ The persistent stimulation from the inflammation sources and age-associated immune dysregulation may lead to chronically

Table 3 Descriptive inflammatory profile according to categories of IC trajectory

Mean (SD)	Whole study population	IC slopes (point per year) ^a			<i>P</i> value for difference ^b	Post hoc analysis ^c
		Accelerated IC decline (lowest 20%, <−1.78)	Slight IC decline (middle 60%, −1.78 to −0.53)	Stable IC (highest 20%, > −0.53)		
IC at baseline, 0–100	78.9 (9.3)	78.2 (8.9)	79.3 (9.4)	78.5 (9.4)	0.512	
IC slopes (change per year)	−1.17 (0.86)	−2.46 (0.68)	−1.10 (0.32)	−0.10 (0.36)	<0.001	* * * * *
Inflammation-related biomarkers						
CRP, mg/L	3.3 (5.2)	3.4 (5.4)	3.4 (5.4)	2.9 (4.6)	0.419	
IL-6, pg/mL	3.9 (12.4)	4.0 (9.6)	4.1 (14.9)	3.2 (3.0)	0.324	
TNFR-1, pg/mL	1223.7 (441.2)	1282.3 (455.6)	1239.8 (459.3)	1119.1 (346.5)	0.001	* * * * *
MCP-1, pg/mL	221.7 (86.2)	231.7 (80.1)	222.5 (88.9)	209.7 (82.6)	0.035	* * * * *
GDF-15, pg/mL	1125.7 (504.9)	1201.7 (550.2)	1145.9 (524.1)	991.8 (356.2)	0.002	* * * * *

CRP, C-reactive protein; GDF-15, growth differentiation factor-15; IC, intrinsic capacity; IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; TNFR-1, tumour necrosis factor receptor-1.

Values are presented as mean (SD); raw biomarker levels are provided in the table and log-transformed values were used in the parametric analysis.

^aIC was composed of cognitive, locomotive, psychological and vitality domains (four-domain measure).

^b*P* value was calculated by one-way analysis of covariance (ANCOVA) with adjustment for age and sex.

^c*P* value was determined by the Tukey–Kramer post hoc test for pairwise comparisons; **P* < 0.05 between groups with slight IC decline and with accelerated IC decline; ***P* < 0.05 between groups with stable IC and with accelerated IC decline; ****P* < 0.05 between groups with stable IC and slight IC decline.

activated inflammation,²¹ which promotes an overall catabolic state in tissues and organs²¹ that eventually declines functional capacities. For example, the up-regulated cytokines can interfere with muscle^{6,7} and bone anabolism,²⁸ further inducing decreased physical performance.^{8,29} Moreover, neuroinflammation in the brain with activated microglia and astrocytes and over-producing pro-inflammatory cytokines may reduce neurogenesis and impair synaptic plasticity, resulting in cognitive decline.³⁰

Circulating CRP, IL-6 and TNFR-1 have been commonly regarded as markers of systemic inflammatory response in literature.¹¹ In the current study, only plasma TNFR-1 was associated with longitudinal IC change, suggesting that TNFR-1 may be a more reliable marker of inflammation-related functional decline than CRP and IL-6. Indeed, TNFR-1 levels are relatively stable in circulation.^{16,31} Similar results were observed in the prior study, which found significant associations of cognitive decline with TNFR-1 but not with IL-6.³² Given that IL-6 had been strongly associated with mortality^{33,34} and disability³⁵ in older people, it is also probable that plasma TNFR-1 is more sensitive to early functional decline, whereas IL-6 may be more related to long-term adverse outcomes. More mechanistic studies on testing this hypothesis, however, are acquired.

In the present study, higher plasma GDF-15 levels showed both cross-sectional and longitudinal associations with IC. GDF-15 had shown a protective effect against tissue inflammation.^{12,36} Increased GDF-15 levels facilitated survival during acute infections by promoting tolerance to cardiac tissue damage in mice models.³⁶ In addition, GDF-15 depletion in old mice presented increased inflammatory responses in liver and adipose tissues.¹² On the other hand, elevated GDF-15 levels were associated with age-related inflammatory diseases,³⁷ and long-term adverse outcomes included mortality.^{13,38} The exact biological function of GDF-15 during chronic inflammation is still unclear; however, our results contribute to the current body of evidence by showing higher GDF-15 levels were detrimental to IC evolution and suggesting plasma GDF-15 as a promising measure of biological age in older adults.

Despite lack of association with baseline IC, higher plasma MCP-1 levels were associated with longitudinal IC declines, particularly in the locomotion, psychological and vitality domains. MCP-1 has been known to enhance neuroinflammation and leads to cognitive impairment³⁹; however, studies on plasma MCP-1 with other functional outcomes are poorly investigated. To the best of our knowledge, this is the first study that found that higher MCP-1 was prospectively associated with physical function and handgrip strength (as vitality). MCP-1 had been recognized as a marker of ageing through cellular senescence.⁴⁰ However, compared with other inflammation-related biomarkers in this study, the evidence on MCP-1, cellular senescence and age-related outcomes is scarce and remains to be clarified by more updated research.

Concerning the domain-specific analysis, all inflammation-related biomarkers were associated with locomotion decline, suggesting an early effect of inflammation on physical performance. This finding was in line with previous works investigating the associations between physical function and individual inflammatory biomarkers.^{8,9,17} On the other hand, none of the plasma biomarker levels predicted cognitive capacity changes. This result was compatible with available research, which showed associations between IL-6 and cognitive declines in the studies with longer follow-up (7–9 years)^{14,41} but not in the one with short observation (median 2.7-year follow-up).¹⁵ It is worth noting that we observed the marginal association between increasing IL-6 levels and improved sensory capacity; however, we did not find individual associations of IL-6 levels with vision (adjusted $\beta = 4.38$; 95% CI: -1.69 to 10.45 ; $P = 0.158$) and hearing (adjusted $\beta = 3.54$; 95% CI: -1.32 to 8.41 ; $P = 0.153$).

Our exploratory study observed no significant associations between inflammatory biomarkers and IC evolution when the sensory capacity was considered, suggesting that the sensory domain might be at a more 'distal' link with biological ageing than the other 'core' four domains. Further studies exploring the hierarchy of the IC domains are needed. The lack of association could be explained by the short follow-up period because the substantial change in functional performance may take several years.¹⁵ Moreover, the hearing capacity assessed by the handicap questionnaire (i.e. HHIE-S) may not be equivalent to the actual hearing ability of older individuals, and it can become less varied once they adapt to daily-life disabilities. Finally, it is not excluded that MAPT interventions may have affected this finding because all participants investigated for five-domain IC had received multidomain intervention during the follow-up period.

This is one of the first works to investigate the associations between plasma inflammation-related markers and IC using a longitudinal approach and multiple biomarkers. However, some limitations should be raised. First, there is no standard IC measurement yet in the current field. It is worth highlighting that five IC domains are interrelated, with changes in one that may affect others. Our current approach, which used the mean score of the domains to represent the global IC level, could not consider the within-domain interactions. Further research investigating the IC measurement that includes the dynamic interactions within domains can shed light on this issue. Second, our study is a secondary analysis of a randomized controlled trial, in which the sample size calculation was performed considering the primary analysis of the MAPT Study. Third, the MAPT Study enrolled subjects at risk of cognitive decline, which might affect the generalizability of our results to other populations. Fourth, we measured plasma biomarkers in a subset of MAPT participants 1 year after the study enrolment. Because three out of four subjects in the current study had received interventions, it is not excluded that their biomarker levels may be affected by MAPT

intervention. Although our analyses added MAPT group allocation as a covariate to minimize this bias, the intervention effects cannot be omitted, particularly in the analyses for five-domain IC and sensory domains. In other words, the lack of association in our study may be related to the potential beneficial effect from interventions and require cautious interpretation. Finally, the full-domain IC including sensory was only explored in half of our population for 1-year follow-up. Future longitudinal studies operationalizing the complete IC domains with several years of follow-up and a large sample are required.

Conclusion

In conclusion, our study supported that inflammation, measured via plasma TNFR-1, MCP-1 and GDF-15, may be involved in the faster IC decline of older individuals, indicating a doubling or even higher risk of adverse health outcomes in the future. Further mechanistic studies to understand the importance of the different markers for the decline in functions are encouraged.

Acknowledgements

The present work was performed in the context of the Inspire Programme, a research platform supported by grants from the Region Occitanie/Pyrénées-Méditerranée (Reference Number: 1901175) and the European Regional Development Fund (ERDF) (Project Number: MP0022856). This study received funds from Alzheimer Prevention in Occitania and Catalonia (APOC Chair of Excellence—Inspire Programme).

This work has been partially supported through the grant EUR CARE (ANR-18-EURE-0003) in the framework of the Programme des Investissements d'Avenir. JW supported by the Johns Hopkins Older Americans Independence Center, National Institute on Aging award P30 AGO21334.

The MAPT study was supported by grants from the Gérontopôle of Toulouse, the French Ministry of Health (PHRC 2008, 2009), Pierre Fabre Research Institute (manufacturer of the omega-3 supplement), ExonHit Therapeutics SA and Avid Radiopharmaceuticals Inc. 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 INSERM-University of Toulouse III UMR 1295 Unit.

WHL designed and conceptualized the research, performed the analyses, interpreted the data and drafted the manuscript. SG and JW interpreted the data and revised the draft critically for important intellectual content. AL and AP

managed data of plasma IL-6, TNFR-1, MCP-1 and GDF-15, interpreted the data and revised the draft critically for important intellectual content. BV conceived the MAPT study, interpreted the data and revised the draft critically for important intellectual content. EG and PSB designed and conceptualized the research, interpreted the data and revised the draft critically for important intellectual content. All authors have read and agreed with the final version to be submitted.

The authors certify that they comply with the ethical guidelines for authorship and publishing of the *Journal of Cachexia, Sarcopenia and Muscle*.⁴¹

Conflict of interest

The authors have no conflicts of interest.

MAPT/DSA Group

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Online supplementary material

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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