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Circulating Levels of Apelin, GDF-15 and Sarcopenia: Lack of Association in the MAPT Study

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Abstract

OBJECTIVES: Apelin and GDF-15 have been proposed as biomarkers of age-related sarcopenia but evidence in human models is scarce. This study aimed to explore the associations between blood apelin and GDF-15 with sarcopenia incidence and the evolution of sarcopenia components over two years in older adults >70 years.

DESIGN: Secondary longitudinal analysis of the Multidomain Alzheimer Preventive Trial.

PARTICIPANTS: Older adults (>70 years) attending primary care centers in France and Monaco. Setting. Community.

MEASUREMENTS: Serum Apelin (pg/mL) and plasma GDF-15 (pg/mL) were measured. Outcomes included sarcopenia defined by the European Working Group on Sarcopenia in Older People (EWGSOP) and its determinants (appendicular lean mass [ALM] evaluated through a Dual-energy X-ray Absorptiometry (DXA) scan, handgrip strength (HGS) and the 4-meter gait speed) measured over 2 years. Linear mixed models and logistic regression were used to explore the longitudinal associations.

RESULTS: We included 168 subjects from MAPT (median age=76y, IQR=73-79; 78% women). Serum apelin was not significantly associated with sarcopenia incidence (OR=1.001;95%CI=1.000,1.001;p-value>0.05 in full-adjusted models) nor with ALM ($\beta=-5.8E-05$;95%CI=-1.0E-04,2.12E-04;p>0.05), HGS ($\beta=-1.1E-04$;95%CI=-5.0E-04,2.8E-04;p>0.05), and GS ($\beta=-5.1E-06$;95%CI=-1.0E-05,2.0E-05;p>0.05) in fully adjusted models. Similarly, plasma GDF-15 was not associated with both the incidence of sarcopenia (OR=1.001,95%CI=1.000,1.002,p>0.05) and the evolution of its determinants ([ALM, $\beta=2.1E-05$;95%CI=-2.6E-04,3.03E-04;p>0.05], HGS [$\beta=-5.9E-04$;95%CI=-1.26E-03,8.1E-05;p>0.05] nor GS [$\beta=-2.6E-06$;95%CI=-3.0E-05, 2.3E-05;p>0.05]) in fully adjusted models.

CONCLUSIONS: Blood apelin and GDF-15 were not associated with sarcopenia incidence or with the evolution of sarcopenia components over a 2-year follow-up in community-dwelling older adults. Well-powered longitudinal studies are needed to confirm or refute our findings.

Key words: Biomarkers, muscle mass, gait speed, handgrip strength.

Introduction

Sarcopenia is characterized by age-related loss of muscle mass and function; it plays a crucial role in the development of late-life disability (1) and negatively impacts the skeletal muscle homeostatic functions (immune, metabolic and endocrine roles), contributing to the development of age-related diseases such as type 2 diabetes, cardiovascular disease and osteoporosis (2). Sarcopenia is an important public health issue due to its association with adverse events in older populations (3). Despite its recent recognition as a disease (ICD code M62.84), aspects related to its prevalence, pathophysiology, associated factors and prevention/treatment options remain to be elucidated. Especially appealing is the need for strategies for sarcopenia prevention, diagnosis, monitoring and treatment (4). This requires the identification of putative molecular therapeutic targets that are involved in the physiological processes underlying sarcopenia. To date, several blood-based analytes associated with different pathways involved in muscle tissue metabolism have been proposed as sarcopenia markers but so far, none of them has shown any acceptable predictive ability alone (5).

Recently, apelin and growth differentiating factor 15 (GDF-15) have arisen as potential blood-based sarcopenia biomarkers and therapeutic targets (6, 7) because of their connections with age-associated musculoskeletal health declines (8). Apelin, the ligand of the APJ G-protein coupled receptor, is a pleiotropic endogenous peptide that has been shown to modulate several processes involved in cardiovascular regeneration, neuroprotection, immunity and glucose metabolism (5). Recent research has pointed that age-related apelin declines might negatively impact mitochondrial amount and function, as well as local skeletal muscle regeneration, which further contribute to age-related muscle mass and function losses (9). Nevertheless, in human studies, the association between blood apelin and prevalence of sarcopenia remains disputable (10, 11). GDF-15, also known as macrophage inhibitory cytokine 1 (MIC-1), belongs to the transforming growth factor β superfamily (12). It is involved in inflammatory and apoptotic pathways and is associated with all-cause mortality

in humans (13). GDF-15 has been shown to be upregulated in contexts of neural injury (14), stress (15), and mitochondrial dysfunction (16), all of which are key players in sarcopenia pathogenesis (17). Serum and muscle GDF-15 increase with age and are associated with reduced skeletal muscle mass and function in murine models (18). Recent cross-sectional studies have explored potential links between plasma GDF-15 and sarcopenia determinants, such as muscle mass and function (strength and power output) in different clinical populations of older adults, yielding mixed results (19–23), whereas it is not clear whether GDF-15 can predict sarcopenia onset (24). Despite the promising role of apelin and GDF-15 as sarcopenia biomarkers, so far, there is a lack of studies investigating their longitudinal associations in samples of older adults.

The aim of the present study was to explore whether blood apelin and GDF-15 would be associated with the 2-year incidence of sarcopenia and the evolution of sarcopenia components (ie, muscle mass, strength and physical performance) in an older adult population. Our hypothesis was that higher levels of apelin and lower levels of GDF-15 would be associated with both a reduced probability of developing sarcopenia and a better evolution of musculoskeletal health parameters.

Methods

Study design

This is a secondary longitudinal analysis of the Multidomain Alzheimer Preventive Trial (MAPT, ClinicalTrials.gov [NCT00672685]) study. In brief, MAPT was a clinical trial that aimed to explore the effectiveness of a multidomain intervention (physical activity, nutrition advices and cognitive stimulation) and omega-3 polyunsaturated fatty acid (PUFA) supplementation jointly or in isolation for the prevention of cognitive decline over a 3-year follow-up in older adults (25). After the intervention, subjects were followed-up for two additional observational years. Participants were recruited in 13 different primary care centers in France and Monaco between May 2008 and February 2011. The last follow-up visit took place in April 2016. Further details of the design of the study were published elsewhere (25). In the present analysis, baseline data corresponded to the 12-month follow-up in MAPT study, when serum apelin and plasma GDF15 were measured.

The present study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. The ethics committee in Toulouse (CPP SOOM II) approved MAPT protocol, that followed the Declaration of Helsinki. Participants provided written consent forms prior to participation.

Participants

MAPT study included non-demented community-dwelling older adults (>70 years) with difficulty in at least one instrumental activity of daily living, spontaneous memory complaints and/or low gait speed (GS, <0.8 m/s). Subjects with

a Mini-Mental State Examination (MMSE) score lower than 24, dependency for basic activities of daily living, contraindications for practicing physical activity or who had been supplemented with omega-3 PUFA in the previous six months were excluded from the analysis. From the 1679 participants of MAPT, 168 had available data on sarcopenia components and at least one of the biomarkers of interest (apelin and GDF-15) at baseline; and thus constituted the population of the present study.

Apelin and GDF-15 measurements

Blood-borne analytes were determined at the first-year visit in MAPT. Venous full blood was centrifuged at 14,000 rpm, and then serum was collected and frozen at -80 °C. We measured serum apelin using a nonselective apelin-12 EIA kit that recognizes the C-terminal sequence of 12 amino acids shared among all the apelin isoforms (Phoenix Pharmaceuticals; Belmont, CA, USA). Samples were supplemented with aprotinin (0.6 TIU/ml of total fluid) and purified by a 10-kDa cutoff column before snap freezing (Amicon Ultra, 10,000 molecular weight cut-off, Millipore, Temecula, CA). We quantified plasma GDF-15 using the fully automated immunoassay platform Ella (ProteinSimple/Bio-technique, San Jose, CA, USA). The plasma samples were thawed on ice and diluted 1:4 in sample diluent (SD 13) and loaded into cartridges with relevant high and low control concentrates. Within the cartridge, each plasma sample was further divided into four unique microfluidic parallel channels that are specific for up to four proteins simultaneously being analyzed. Each protein channel contained three analyte-specific glass nanoreactors (GNRs), which allowed for each plasma samples 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. The instrument run automatically all the steps of the procedure with no user activity. The internal instrument software automatically calculated values, displayed as pg/mL.

Outcome measures: Sarcopenia incidence and its components

The assessment team registered data on the outcome measures at 12-, 24- and 36-month time-points (we did not include outcome assessments performed before apelin and GDF-15 measures). Body lean mass was measured using dual-energy X-ray absorptiometry (DXA) scan (Hologic QDR-4500W). All DXA scan tests were analyzed using the software Physician's Viewer, APEX System Software Version 3.1.2. (Hologic QDR-4500W, Bedford, MA). Whole-body scans were made in a supine position, in which the participants were scanned wearing light clothing with no metal and no shoes or jewelry. We used Appendicular skeletal mass (ALM) as the marker of muscle mass to define sarcopenia status. Low muscle strength in kilograms was assessed through the handgrip strength (HGS) measurement using a JAMAR hydraulic hand dynamometer (J. A. Preston Corporation, Clifton, NJ, USA); we performed three attempts in the dominant hand with the elbow extended while standing. Subjects squeezed with their best effort, and the best record was registered. Low physical performance was defined as a low GS, computed by measuring the time (in seconds) needed to cover a 4-m path at a usual

Table 1. Baseline (MAPT Study Year 1 visit) characteristics of the sample

Parameters	n	Value*
Age, y	168	76 (73 – 79)
Women, No. (%)	168	129 (77)
MAPT group allocation, No. (%)		
Omega 3 + MDI group	168	40 (24)
Omega 3 group	168	40 (24)
MDI group	168	45 (27)
Control group	168	43 (26)
Body Mass Index	168	26.3 (22.6 – 28.8)
Moderate and vigorous physical activity (MET-min/week)	168	804 (315 – 1492)
Grip strength (kg)	168	25.0 (21.0 – 31.0)
Appendicular lean mass (kg)	168	17.4 (15.2 – 20.8)
Gait speed (m/s)	154	1.08 (0.93 – 1.18)
Apelin (pg/ml)	126	1617.0 (987.9 – 2413.4)
GDF15 (pg/ml)	148	983.5 (761.0 – 1279.5)
IL6 (pg/ml)	148	2.38 (1.65 – 3.82)

*Median (interquartile range) for continuous variables; count (percentage) for categorical variables; Abbreviations: GDF-15= Growth Differentiating Factor-15; IL-6= interleukin 6; MAPT=Multidomain Alzheimer Preventive Trial; MDI= Multi-Domain Intervention.

pace. The best of two measurements was recorded. In this study, we used the definition of the European Working Group on Sarcopenia in Older People (EWGSOP) (26). According to this algorithm, sarcopenia is defined by clinically relevant low ALM (<20kg for men and <15 kg for women) and meeting one of the following criteria: weakness (low HGS [<27 kg for men and <16 kg for women) or GS <0.8 m.s⁻¹ (see Supplementary Table 1).

Potential Confounders

Potential confounders consisted of age, sex, body mass index (BMI; kg/m²), MAPT group allocation, vascular risk (participants with any of type 2 diabetes, hypertension and hypercholesterolemia were regarded as having vascular risk), moderate and vigorous physical activity (evaluated through the Minnesota Leisure Time Activities questionnaire) and plasma interleukin-6 (IL-6 pg/ml; measured using the same assay than GDF-15 as described above) levels. All confounders were measured at the 1-year MAPT visit, ie, the same time-point as measurements of apelin and GDF-15.

Statistical Analysis

Descriptive statistics (median \pm interquartile range or frequencies and percentages, as appropriate) were used for the characterization of the study population.

To determine the associations of baseline apelin and GDF-15 levels with the evolution of ALM, HGS and GS we used linear mixed-effects (LME) regression analyses (with random intercept and random slope for each participant). The LME models included the fixed effects of baseline plasma apelin/GDF-15, time, their interaction and potential confounders.

Logistic regression was performed to evaluate the associations of apelin and GDF-15 values with sarcopenia incidence during the 2-year follow-up in people without sarcopenia at baseline (ie, 12-month visit of the MAPT study).

Both logistic and linear mixed-effects regression models were adjusted for: model 1: age and sex; model 2: age, sex, BMI, MAPT group, vascular risk, moderate and vigorous physical activity and IL-6. All analyses were performed using SAS 9.4 software. Statistical significance was set at an alpha value of 0.05.

Results

Characterization of the sample

Table 1 shows the characteristics of the 168 participants included in the present analyses. Supplementary Table 2 shows the differences at baseline (ie, the MAPT 1-year visit in which plasma apelin and GDF-15 were measured) between MAPT participants included in the present study and those not included. Median apelin and GDF-15 levels were 1617.0 pg/ml (interquartile range [IQR]= 987.9 – 2413.4) and 983.5 pg/ml (IQR=761.0 – 1279.5), respectively. At baseline, only 1 subject had sarcopenia according to EWGSOP, while 22 subjects had missing data on sarcopenia at follow-up, yielding a final sample of 145 in the sarcopenia incidence analyses.

Associations between plasma apelin and GDF-15 levels with sarcopenia determinants

At the cross-sectional level, apelin was not associated with ALM, HGS or GS in our sample, independently of the

Table 2. Associations between apelin and evolution in sarcopenia determinants

	Model	Sample size	Apelin Coefficient	p-value	95% CI	Time Coefficient	p-value	95% CI	Apelin x Time Coefficient	p-value	95% CI
ALM	Model 1*	118	-4.9E-04	0.0686	-1.01E-03, 3.7E-05	0.1666	0.2786	-0.1357, 0.4689	3.4E-05	0.6692	-1.2E-04, 1.88E-04
	Model 2†	118	-3.7E-04	0.1387	-8.6E-04, 1.21E-04	0.1334	0.3825	-0.1670, 0.4337	5.8E-05	0.4570	-1.0E-04, 2.12E-04
Grip Strength	Model 1	118	-5.8E-04	0.3023	-1.67E-03, 5.21E-04	-3.5504	<0.0001	-4.3206, -2.7802	-1.2E-04	0.5597	-5.1E-04, 2.77E-04
	Model 2	118	-5.3E-04	0.3507	-1.65E-03, 5.86E-04	-3.5837	<0.0001	-4.3513, -2.8161	-1.1E-04	0.5754	-5.0E-04, 2.8E-04
Gait Speed	Model 1	118	3.1E-05	0.1414	-1.0E-05, 7.3E-05	-0.01324	0.3749	-0.04270, 0.01622	6.4E-06	0.3986	-8.62E-06, 2.2E-05
	Model 2	118	2.5E-05	0.2450	-2.0E-05, 6.7E-05	-0.00927	0.5408	-0.03924, 0.02070	5.1E-06	0.5122	-1.0E-05, 2.0E-05

Abbreviations: ALM= Appendicular Lean Mass, CI= confidence interval; *Adjusted by age and sex; †Adjusted by age, sex, body mass index, MAPT group, vascular risk, physical activity levels and interleukin-6 levels.

Table 3. Associations between GDF-15 and evolution in sarcopenia determinants

	Model	Sample size	GDF-15 Coefficient	p-value	95% CI	Time Coefficient	p-value	95% CI	GDF-15 x Time Coefficient	p-value	95% CI
ALM	Model 1*	139	6.61E-04	0.2198	-4.0E-04, 1.72E-03	0.1649	0.3352	-0.1715, 0.5013	2.2E-06	0.9881	-2.8E-04, 2.85E-04
	Model 2†	139	1.77E-04	0.7279	-8.2E-04, 1.18E-03	0.1508	0.3762	-0.1842, 0.4858	2.1E-05	0.8824	-2.6E-04, 3.03E-04
Grip Strength	Model 1	139	6.0E-04	0.5512	-1.39E-03, 2.61E-03	-3.2567	<0.0001	-4.0778, -2.4357	-5.8E-04	0.0883	-1.25E-03, 8.8E-05
	Model 2	139	3.58E-04	0.7311	-1.69E-03, 2.41E-03	-3.2796	<0.0001	-4.0991, -2.4600	-5.9E-04	0.0845	-1.26E-03, 8.1E-05
Gait Speed	Model 1	139	-4.0E-05	0.2922	1.2E-04, 3.5E-05	-0.0033	0.8334	-0.03424, 0.02765	1.3E-07	0.9921	-3.0E-05, 2.5E-05
	Model 2	139	-7.8E-06	0.8407	-8.0E-05, 6.8E-05	0.001797	0.9101	-0.02963, 0.03323	-2.6E-06	0.8393	-3.0E-05, 2.3E-05

Abbreviations: ALM= Appendicular Lean Mass, CI= confidence interval; GDF-15= Growth Differentiating Factor-15; *Adjusted by age and sex; †Adjusted by age, sex, body mass index, MAPT group, vascular risk, moderate-to-vigorous physical activity levels and plasma interleukin-6 levels.

Table 4. Associations between baseline apelin and GDF-15 and sarcopenia incidence

Sarcopenia definition	Biomarker	Model	No. Sarcopenia incidence	n	Odds Ratio	95% Confidence Interval	p-value
EWGSOP	Apelin	Model 1*	10	110	1.000	1.000, 1.001	0.2041
		Model 2†	10	110	1.001	1.000, 1.001	0.1397
	GDF-15	Model 1	14	130	1.000	0.999, 1.001	0.7523
		Model 2	14	130	1.001	1.000, 1.002	0.1702

Abbreviations: ALM= Appendicular Lean Mass; EWGSOP=European Working Group on Sarcopenia in Older People; GDF-15= Growth Differentiation Factor-15; * Adjusted by age and sex; †Adjusted by age, sex, body mass index, MAPT group, vascular risk, physical activity levels and interleukin-6 levels.

adjustment model (Table 2). The absence of associations between apelin levels and sarcopenia determinants persisted in longitudinal analyses (apelin × time effects) (ALM [β=-5.8E-05; 95%CI=-1.0E-04, 2.12E-04; p>0.05], HGS [β=-1.1E-04; 95%CI=-5.0E-04, 2.8E-04; p>0.05], GS [β=-5.1E-06; 95%CI=-1.0E-05, 2.0E-05; p>0.05]).

In the case of GDF-15, no associations between its plasma levels at baseline with ALM, HGS or GS were observed in our analyses (Table 3). Linear mixed-effects regression failed at showing a significant GDF-15 × time interaction on any sarcopenia determinant, indicating the lack of associations between plasma GDF-15 and sarcopenia determinants in our sample (Table 3) (ALM, β=2.1E-05; 95%CI=-2.6E-04, 3.03E-04; p>0.05), HGS (β=-5.9E-04; 95%CI=-1.26E-03, 8.1E-05; p>0.05) nor GS (β=-2.6E-06; 95%CI=-3.0E-05, 2.3E-05; p>0.05).

Associations between blood apelin and GDF-15 levels with sarcopenia incidence

10 out of 110 (9.1%) subjects with data on apelin and sarcopenia determinants at baseline and the year 3 visit in MAPT developed sarcopenia according to EWGSOP, along the follow-up. Apelin levels at baseline did not associate

with sarcopenia onset (defined by EWGSOP) in our study (OR=1.001; 95% CI=1.000, 1.001; p-value>0.05 in full-adjusted models) (Table 4).

Fourteen out of 130 (10.7%) MAPT participants with data on GDF-15 and sarcopenia determinants progressed into a sarcopenia status during the same timeframe. Discrete time logistic regression analyses showed no association between baseline GDF-15 and sarcopenia incidence (defined by EWGSOP) in our sample (OR=1.001, 95% CI=1.000, 1.002, p>0.05) (Table 4).

Discussion

The present study investigated the associations of blood apelin and GDF-15 with sarcopenia incidence and the evolution of its determinants (muscle mass, HGS and GS) over a 2-year follow-up in a sample of community-dwelling older adults. Our analyses showed a lack of association of apelin and GDF-15 with the outcomes.

Previous studies have shown that both apelin and GDF-15 could act as markers of late-life musculoskeletal health. In a groundbreaking publication summarizing results of a series of experiments, Vinel et al. (9) linked apelin to age-associated declines in muscle mass and function. Briefly, they

showed a reduction of apelin production as a function of age in both humans and rodents; an accelerated sarcopenia onset in apelin-deficient mouse; the ability of apelin to promote beneficial metabolic, trophic and regenerative adaptations *in vitro* in muscle cells from aged donors through the upregulation of canonical skeletal muscle adaptative pathways; and the suppression of muscle-degradation pathways at old age (9). Altogether, their experiments support the role of apelin deficiency as a determinant of sarcopenia (9). Nevertheless, the utility of apelin as a predictor of sarcopenia in humans has been scarcely investigated and available studies show contradictory results (10, 11). In line with our findings, Jang et al. (38) showed a lack of cross-sectional associations between circulating apelin and sarcopenia determinants (muscle mass-measured by electrical bioimpedance-, grip strength and GS) in a small sample of Korean older adults ($n = 80$), whereas Chen et al. found reduced odds of having sarcopenia (defined by the Asian Working Group for Sarcopenia) with increasing serum apelin levels in a sample of Taiwanese older adults ($n = 436$, aged >65) (10).

Multiple reasons can contribute to the discrepancy between murine-based studies and our current results. Jang et al. (11) highlighted that the (1) physiological differences between murine and human models, and (2) the fact that differences in physiological apelin levels observed in human studies might be insufficient to promote the downstream effects achieved by total ablation of apelinergic activity or apelin infusion in mice, could underly these divergent observations between murine-based mechanistic and human-based observational research. Importantly, the immune essays used to determine blood apelin levels in available studies (including ours) do not differentiate between different apelin isoforms. Apelin is synthesized as the 77-aminoacid preproapelin and later cleaved into 13-36-residue active isoforms (27), which might act distinctly as biomarkers of different processes. For example, it has been suggested that despite all the isoforms interact with the APJ receptor in the context of ischemic-reperfusion injury, apelin-13 seems to be the most biologically active isoform (28), whereas apelin-36 presents the highest ligand-receptor affinity and therefore, even low apelin-36 levels may be sufficient to maintain APJ activation (29). In any case, given the lack of well-powered longitudinal studies, further research is needed to investigate the potential of different apelin isoforms as biomarkers and potential intervention targets in the scope of sarcopenia.

With regards to GDF-15, our finding showing an absence of association with incident sarcopenia is in line with the only study published to date prospectively exploring this link in older adults (24). Some previous research has shown inverse cross-sectional associations between GDF-15 and measures of muscle function (GS (30), lower limb function (30), HGS (18, 30) and muscle power (21)) in samples of community-dwelling older adults. Additionally, circulating levels of GDF-15 were previously found to be associated with functional measure, such as a worse longitudinal evolution in the Short Physical Performance Battery score (using data [$n=1096$] from the MAPT study) and the onset of mobility disability (inability to complete a 400-m walk) (31).

Altogether, the evidence generated so far suggest that GDF-

15 might be more related to functional (muscle function) rather than morphological (muscle mass) properties of ageing skeletal muscle (18, 30). In fact, the studies linking GDF-15 and muscle mass decreases have been performed in samples of hospitalized older adults (32) or in samples with severe clinical conditions (cancer, pulmonary arterial hypertension, chronic obstructive pulmonary disease) (33, 34) and therefore, these observations might reflect the effects of GDF-15 in the context of illness-induced extreme systemic stress and inflammation states leading to muscle wasting (e.g. cachexia) (35), rather than steady, long-lasting and progressive age-related muscle mass losses defining sarcopenia (1). This might explain the absence of associations with sarcopenic clinical definitions including muscle mass measures, such as the one used in our study, in non-hospitalized or otherwise healthy older adults (19, 30). Notably, given that muscle function is more tightly related to functional decline than muscle mass alone (36, 37), GDF-15, serving as a marker of the former, might be useful in identifying subjects at risk of functional decline, a core clinical outcome in older adults care (38). Nevertheless, well-powered longitudinal research is needed before GDF-15 is adopted as a biomarker of skeletal muscle aging, given the contradictory findings in the limited number of studies.

Our study presents strengths such as its novelty, given that it is the first study in exploring longitudinal plasma apelin-sarcopenia associations and one of the first in doing so with GDF-15 in humans. Furthermore, this study included relatively healthy older adults, which allowed us to investigate the physiological effects of both analytes in “normal ageing”. In addition, we measured muscle mass by using DXA, that has shown to overperform other devices such as bioimpedance in terms of accuracy and reliability (39). Nevertheless, our study should be interpreted considering several limitations. The main weakness of our study is the small sample size due to limited data on muscle mass measure in the MAPT study, which might have reduced the statistical power to some extent. In addition, the limited sample size also reduced the possibility of including more confounders in adjusted models. This study was carried out in a group of relatively healthy and highly educated older adults that together with the relatively short follow-up, might have reduced the number of sarcopenia cases in our sample. In fact, the use of other existing sarcopenia definitions was not possible in our study due to low number of cases (7 and 2 according to the Foundations of the National Institutes of Health and the EWGSOP2 definitions, respectively) at follow-up in our sample. Altogether, these limitations might have led to an underestimation of the true associations between the analytes and sarcopenia. Finally, our study is a secondary analysis of a randomized clinical trial; therefore, our results may differ in observational studies with demographically diverse populations and the generalization of results should be made with caution despite that the MAPT interventions did not have significant effects on sarcopenia-related parameters (25).

In conclusion, our study shows a lack of association between apelin and GDF-15 with sarcopenia and its determinants in relatively healthy French older adults. Considering its weaknesses, this study might serve as a proof of concept on a novel topic. Together with the limited accumulated evidence, it

supports the necessity of longitudinal population-based studies exploring the utility of accurately determined blood apelin and GDF-15 in predicting sarcopenia onset and progression. The investigation of how dynamic changes in plasma apelin and GDF-15 (by means of having more than a single point measurement of these biomarkers) might determine sarcopenia could be of special interest.

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