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Association between physical activity, growth differentiation factor 15 and bodyweight in older adults: A longitudinal mediation analysis

Jérémy Raffin^{1*} , Yves Rolland^{1,2}, Angelo Parini^{3,4}, Alexandre Lucas^{3,4}, Sophie Guyonnet^{1,2}, Bruno Vellas^{1,2}, Philippe de Souto Barreto^{1,2} & For the MAPT/DSA Group

¹Gérontopôle de Toulouse, Institut du Vieillissement, Centre Hospitalo-Universitaire de Toulouse, Toulouse, France; ²CERPOP UMR 1295, University of Toulouse III, Inserm, UPS, Toulouse, France; ³Institute of Metabolic and Cardiovascular Diseases, UMR1048, Toulouse Cedex 4, France; ⁴Paul Sabatier University, Toulouse Cedex 9, France

Abstract

Background Late-life aging is often associated with appetite reduction and weight loss. Physical activity (PA) may prevent these processes, but the molecular mechanisms involved remain elusive. The present study investigated the putative mediating aspect of growth differentiation factor 15 (GDF-15), a stress signalling protein involved in aging, exercise and appetite control, on the association between PA and late-life-associated weight loss.

Methods One thousand eighty-three healthy adults (63.8% women) aged 70 years and over who participated in the Multidomain Alzheimer Preventive Trial were included. Bodyweight (kg) and PA levels (square root of metabolic equivalent of task-min/week) were assessed repeatedly from baseline to the 3-year visit, whereas plasma GDF-15 (pg/mL) was measured at the 1-year visit. Multiple linear regressions were performed to test the association between first-year mean PA level, 1-year visit GDF-15 concentration and subsequent bodyweight changes. Mediation analyses were used to investigate whether GDF-15 mediated the association between first-year mean PA levels and consecutive bodyweight changes.

Results Multiple regression analyses demonstrated that higher first-year mean PA levels significantly predicted lower GDF-15 and bodyweight at 1 year ($B = -2.22$; $SE = 0.79$; $P = 0.005$). In addition, higher 1-year visit GDF-15 levels were associated with faster subsequent bodyweight loss (Time \times GDF-15 interaction $B = -0.0004$; $SE = 0.0001$; $P = 0.003$). Mediation analyses confirmed that GDF-15 mediated the association between first-year mean PA levels and subsequent bodyweight changes (mediated effect $ab = 0.0018$; bootstrap $SE = 0.001$; $P < 0.05$) and revealed that mean PA had no direct effect on subsequent bodyweight changes ($c' = 0.006$; $SE = 0.008$; $P > 0.05$).

Conclusions This study suggests that GDF-15 may be one of the molecules mediating the link between PA and late-life weight loss, but mechanistic studies are necessary to further support the present findings.

Keywords aging; GDF-15, physical activity, weight loss; older adults

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*Correspondence to: Jérémy Raffin, PhD, Gérontopôle de Toulouse, Institut du Vieillissement, Centre Hospitalo-Universitaire de Toulouse, Bâtiment B, 37 Allées Jules Guesde, 31000 Toulouse, France. Email: jeremy.raffin@live.fr

Introduction

The last decades of life are characterized by a loss of bodyweight¹ that is partially caused by a reduction of appetite,² changes in body composition³ and metabolic alterations.⁴ Physical activity (PA) is a well-known lifestyle factor that contributes to the control of bodyweight,⁵ but the molecular mechanisms through which it prevents weight loss in late life remain complex and not fully understood. Several breakthroughs have been made over the last decades since it was discovered that a myriad of proteins, collectively called exerkines, are released during and after physical exercise.⁶ These molecules play an important role in controlling energy metabolism^{5,1} and coordinate the cross-talks between the different organs and tissues, including the skeletal muscles, the adipose tissue, the heart and the brain.^{6, 52}

One of these proteins is the growth differentiation factor 15 (GDF-15), a stress signalling cytokine involved in a myriad of age-related physiological processes⁷ that has been the focus of intense research since the discovery that it plays a major role in appetite regulation through binding on the GFRAL receptors located in the brainstem.⁸ Although the role of GDF-15 in the late-life-associated weight loss has yet to be investigated,⁹ animal studies indicated that GDF-15 overexpression associates with anorexia and cachexia,¹⁰ and the pharmacological administration of GDF-15 reduced appetite in mice.¹¹ In human, increases in GDF-15 concentrations have been reported in cancer-related cachexia¹² and have been suggested to mediate the effects of metformin on weight loss in type-2 diabetic patients.^{13,14} Besides its role on weight regulation, elevated circulating levels in GDF-15 have also been associated with higher chronological and biological age,¹⁵ higher inflammation¹⁶ and mitochondrial dysfunction.¹⁷

Data on PA demonstrated that an acute bout of exercise,¹⁸ as well as short-period exercise training,¹⁹ induced increases in circulating GDF-15, whereas observational data indicated that higher long-term PA volumes²⁰ and better cardiorespiratory fitness²¹ associate with lower resting GDF-15 levels. Conversely, it has been shown that pharmacologically induced but not exercise-induced increases in circulating GDF-15 suppress food intake,¹⁸ indicating the need for further research on this topic. Although the current literature is still sparse, and that other proteins, such as fibroblast growth factor 21 (FGF21), also represent important modulators of energy balance in the context of PA and aging,^{22,23, 53} it can be hypothesized that GDF-15 may be one of the molecules mediating the benefits of PA on late-life bodyweight loss, but no study addressed this question so far.

In the present work, we examined the direct and mediating associations between PA, GDF-15 and bodyweight changes in older adults. We hypothesized that higher chronic levels of PA would be associated with less late-life body-

weight loss and that this association would be mediated by circulating levels of GDF-15.

Methods

The present study used data from the first 3 years (period in which PA data were available) of the Multidomain Alzheimer Preventive Trial (MAPT) (clinicaltrials.gov; NCT00672685). MAPT was a 3-year interventional placebo-controlled study followed by a 2-year observational follow-up that demonstrated no effect of omega-3 supplementation, multidomain intervention (composed of cognitive training as well as nutritional and PA counselling) or their combination on cognitive function in adults aged 70 and above.⁵⁴ The MAPT study was conducted in agreement with the Declaration of Helsinki's principles and its protocol was approved by the French Health Authority and was authorized by the advisory Committee for the Protection of Persons involved in Biomedical Research of the Toulouse University Hospital (CPP Sud-Ouest et Outre-Mer). All participants provided their informed consent before entering the study.

Study population

In accordance with the MAPT study inclusion criteria, the present investigation involved community-dwelling older adults aged 70 and over who met one or more of the following criteria: spontaneous memory complaints, slow gait speed (as defined by the inability to walk 4 m within 5 s or less) and limitation in one instrumental activity of daily living. Subjects were not included if they had omega-3 supplementation, struggles with daily living basic activities, diagnosed dementia or a score in the Mini Mental State Examination (MMSE) lower than 24. The study sample was restricted to the subjects who underwent GDF-15 measurement at 1 year ($n = 1096$) and also had full data for PA from baseline to 1 year and bodyweight information at 1 year, which led to a final sample of 1083 subjects.

Plasma growth differentiation factor 15 measurement

Blood testing was performed in 1096 subjects at the 1-year time point of MAPT. The fully automated immunoassay platform, Ella (ProteinSimple/Bio-technie, San Jose, CA, USA), was used to quantify GDF-15 plasma levels (pg/mL). Single disposable microfluidic SimplePlex™ cartridges that can hold up to 30 plasma samples per assay were used to quantify GDF-15. Plasma samples were thawed on ice and diluted 1:4 in a sample diluent (SD 13) before being loaded into cartridges with relevant high and low control concentrates.

Each plasma sample was run in triplicates using three analyte-specific glass nanoreactors (GNRs). Each cartridge included a built-in lot-specific standard curve for GDF-15. All steps in the procedure and the obtained data were automatically run and calculated by the instrument with no user intervention.

Physical activity assessment and operationalization

The short form of the Minnesota Leisure Time Activities questionnaire⁵⁵ was utilized for PA assessment at baseline, 6-month, 1-, 2- and 3-year visits in MAPT. Subjects documented the duration and frequency of the leisure time and household PAs they achieved over the past 2 weeks. Two independent raters estimated the intensity (in metabolic equivalent of task [MET]) of each declared PA based on the PAs' compendium,⁵⁶ and any divergence between assessors was resolved by discussion. The weekly total PA (TPA; in MET-min/week) volume was then calculated by multiplying intensity, duration and frequency of each PA and dividing by 2. Additional computations were performed while differentiating light PA (LPA; defined as <3 METs) from moderate to vigorous PA (MVPA; defined as ≥ 3 METs)⁵⁷ volumes such that an estimation of TPA, LPA and MVPA was obtained for each subject at each time point. For analyses purposes, the mean PA levels declared over the first year of MAPT (preceding thus the GDF-15 measurement) were computed using the baseline, 6-month and 1-year values, leading to the creation of 3 additional variables: mean TPA (mTPA), mean MVPA (mMVPA) and mean LPA (mLPA).

Bodyweight measurement and operationalization

Bodyweight (kg) was measured in the research unit with a standard medical scale all along the MAPT study, every 6 months from baseline onwards. For the mediation analyses, bodyweight changes from 1 to 3 years were calculated by subtracting the 1-year bodyweight to bodyweight measured at each subsequent time point such that positive and negative differences indicated weight gain and weight loss, respectively. For analyses purposes, we defined and operationalized a variable named bodyweight stability that was defined as any weight variation inferior to 2.5% within 6 months or to 5% within 1 year.⁵⁸

Statistical analyses

Participant characteristics were calculated at 1 year, using means and standard deviations (SDs) for continuous variables and absolute numbers with percentages for categorical variables. All PA variables were square-root transformed to reduce skewness and 9 outliers (defined as values distant of 4

SDs or more from the mean) for GDF-15 were removed. Three steps of analyses were then performed using separate models for TPA, MVPA or LPA. The normality of the residuals was systematically checked through visual inspection.

In the first step of analysis, mixed-model multiple linear regressions were run to examine the association of the 1-year GDF-15 levels (continuous predictor) and first-year mean PA levels (continuous predictor) with bodyweight (continuous outcome measure) over time (in year, continuous predictor) from 1 to 3 years. The terms included in the model were time, GDF-15, mean PA and their interaction with time. The model was adjusted for confounders and their interaction with time, including age, sex, height, education level,²⁴ MAPT multidomain group, diabetes mellitus status,²⁵ cancer,²⁶ risk of depression²⁷ defined as having geriatric depression scale (GDS) score of 5 or above, cognitive status determined by the clinical dementia rating (CDR) scale²⁸ and PA changes from the 1-year time point. For each analysis, the main effect of time was estimated while fixing PA, GDF-15 and confounders at their means. These analyses were conducted using a random intercept and a random time slope at the subject level.

In the second step of analysis, we examined whether the first-year mean PA levels (continuous predictor) were associated with GDF-15 levels (continuous outcome measure) obtained at 1 year. These analyses were controlled for age,¹⁵ sex,²⁹ body mass index (BMI),³⁰ MAPT group, inflammation assessed through C-reactive protein (CRP) and interleukin (IL)-6 blood levels measurement,³¹ hypertension,⁷ diabetes mellitus status,⁷ hypercholesterolaemia,⁷ cardiovascular disease (defined as having at least one of stroke, heart failure or ischaemic heart disease),⁷ creatinine levels,³² metformin medication,¹⁴ cancer,¹² asthma or chronic obstructive pulmonary disease (COPD),³³ and mitochondrial function assessed through the measurement of circulating ATPase inhibitory factor 1 (IF1).³⁴

In the third step of analysis, the mediation analysis was performed using first-year mean PA level as predictor, 1-year GDF-15 levels as mediator and bodyweight changes calculated from 1-year to the subsequent time points (2 and 3 years in separate models) as the outcome. Consistent with the previous steps, confounders assigned to the mediator GDF-15 were age, sex, BMI, MAPT group, IL-6, CRP, diabetes mellitus status, hypertension, hypercholesterolaemia, cardiovascular disease, creatinine levels, metformin, cancer, asthma or COPD, and IF1; and confounders assigned to the outcome bodyweight changes were age, sex, height changes from 1 year, education level, MAPT multidomain group, diabetes mellitus status, cancer, depressive (GDS) and cognitive (CDR score) status and their changes from the 1-year visit, as well as PA changes from the 1-year time point.

Supplementary analyses were performed. Using a similar approach to those described in the first and third steps of analysis, we replaced the continuous outcome of bodyweight

change by the dichotomous variable bodyweight stability. This analysis was performed because we hypothesized that PA would be associated with weight maintenance (not necessarily with weight changes). To do such, bodyweight stability

Table 1 Participants' characteristics at 1 year

	Total (n = 1083)	
Age (years)	76.8	4.4
Female	691	63.8%
Height (cm)	161.9	8.9
Bodyweight (kg)	68.9	12.9
BMI (kg/m ²)	26.2	4.0
Education	1083	100.0%
Missing	17	1.6%
No primary education	48	4.4%
Primary school certificate	178	16.4%
Secondary education diploma	348	32.1%
High school diploma	167	15.4%
University diploma	325	30.0%
Systolic blood pressure (mmHg) (n = 1076)	135.9	18.2
Diastolic blood pressure (mmHg) (n = 1076)	76.7	11.7
Heart rate (b.p.m.) (n = 1077)	69.7	11.1
Haemoglobin (g/dL) (n = 974)	13.9	1.1
MAPT group	1083	100.0%
Omega 3 + Multidomain intervention	270	24.9%
Omega 3	264	24.4%
Multidomain intervention + Placebo	271	25.0%
Placebo	278	25.7%
GDF-15 (pg/mL)	1104.7	448.3
IL-6 (pg/mL) (n = 1082)	3.9	12.3
CRP (mg/L) (n = 903)	3.0	4.9
Creatinine (μmol/L) (n = 969)	78.8	19.0
IF1 (ng/mL) (n = 1079)	574.7	276.9
mTPA (MET-min/week)	1812.4	1373.0
mMVPA (MET-min/week)	1539.5	1198.6
mLPA (MET-min/week)	272.8	552.5
Gait speed (m/s) (n = 1064)	1.1	0.2
Handgrip strength (kg) (n = 981)	26.7	9.7
MMSE score (n = 1077)	28.1	1.8
CDR score (n = 1081)	1081.0	100.0%
0	574	53.1%
0.5	501	46.3%
1	5	0.5%
2	1	0.1%
GDS score (n = 1072)	3.1	2.6
Depressive risk (GDS ≥ 5) (n = 1072)	247	23.0%
Diabetes	100	9.2%
Hypertension	534	49.3%
Hypercholesterolaemia	373	34.4%
Cardiovascular disease	97	9.0%
Stroke	23	2.1%
Ischaemic heart disease	65	6.0%
Heart failure	15	1.4%
Active cancer	37	3.4%
COPD or asthma	76	7.0%
Number of drugs	6.3	3.8
Metformin	42	3.9%

Abbreviations: BMI, body mass index; CDR, clinical dementia rating; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; GDF-15, growth differentiation factor 15; GDS, geriatric depression scale; IF1, ATPase inhibitory factor 1; IL-6, interleukin 6; MAPT, Multidomain Alzheimer Preventive Trial; MET, metabolic equivalent of task; mLPA, first-year mean light physical activity volume; MMSE, Mini Mental State Examination; mMVPA, first-year mean moderate to vigorous physical activity volume; mTPA, first-year mean total physical activity volume.

Note: Values are presented as mean and standard deviation (SD) unless indicated otherwise.

Table 2 Estimated effects of PA (square root of MET-min/week), GDF-15 (pg/mL) and time (years) on bodyweight (kg)

	Model 1: mTPA			Model 2: mMVPA			Model 3: mLPA		
	B	SE	P	B	SE	P	B	SE	P
PA*	-0.0871	0.0210	0.000	-0.0803	0.0215	0.000	-0.1225	0.0258	0.200
GDF-15	0.0008	0.0008	0.278	0.0009	0.0008	0.260	-0.0006	0.0008	0.152
Time	-0.3668	0.1572	0.020	-0.3682	0.1572	0.019	-0.6768	0.1570	0.021
Time × PA*	0.0031	0.0036	0.386	0.0020	0.0037	0.580	-0.0052	0.0045	0.305
Time × GDF-15	-0.0004	0.0001	0.002	-0.0004	0.0001	0.002	-0.0007	0.0001	0.002
				ULCI			ULCI		
				LLCI			LLCI		
				ULCI			ULCI		
				LLCI			LLCI		

Abbreviations: GDF-15, growth differentiation factor 15; LLCI, lower limit confidence interval; MET, metabolic equivalent of task; mLPA, first-year mean light physical activity volume; mMVPA, first-year mean moderate to vigorous physical activity volume; mTPA, first-year mean total physical activity volume; PA, physical activity; SE, standard error; ULCI, upper limit confidence interval.

*Indicates either mTPA (Model 1), mMVPA (Model 2) or mLPA (Model 3).

was defined using the cut-off values of 2.5% for 6-month changes or 5% for 1-year changes presented previously. For the mediation analyses, bodyweight was considered stable if it never went out of these cut-off values throughout each considered time point from 1 to 3 years.

All statistical analyses were undertaken using IBM SPSS Statistics Version 23 (Chicago, IL, USA). Mediation analyses were performed using the PROCESS macro Version 3.5.3 for SPSS developed by Andrew F. Hayes (<http://www.afhayes.com>). The level of significance was defined as P values < 0.05 , or 95% bootstrap confidence intervals not containing zero for indirect effects estimation in the mediation analyses, as recommended.⁵⁹

Results

Characteristics of the participants

At the 1-year visit, participants' mean age was 76.8 years and the sample was composed of 63.8% women. The whole sample characteristics are detailed in *Table 1*.

Associations between physical activity, growth differentiation factor 15 and bodyweight

The results for the mixed-model linear regressions are presented in *Table 2*. They indicate a significant bodyweight loss over time of ~ 0.37 kg/year and significant GDF-15 \times Time

interaction such that higher levels of GDF-15 at the 1-year visit predicted faster subsequent weight loss, as illustrated in *Figure 1*. Higher levels of mTPA and mMVPA were associated with lower bodyweight at 1 year, but PA was not associated with bodyweight longitudinal evolution (Non-significant PA \times Time interactions).

The associations between mean PA (from baseline to 1-year visit) and 1-year visit GDF-15 levels are displayed in *Table 3* and illustrated in *Figure 2*. They demonstrated that higher levels of first-year mTPA and mMVPA, but not mLPA, were associated with lower circulating GDF-15 at 1 year.

Mediation analyses

Mediation analyses are presented in *Table 4* and illustrated in *Figure 3*. Consistent with the previous analyses, higher first-year mTPA and mMVPA volumes predicted lower circulating GDF-15 levels at 1 year, and higher GDF-15 concentra-

Table 3 Associations between first-year mean PA volumes (square root of MET-min/week) and GDF-15 levels (pg/mL)

	<i>n</i>	B	SE	<i>P</i>	LLCI	ULCI
Model 1: mTPA	886	-2.221	0.784	0.005	-3.760	-0.682
Model 2: mMVPA	886	-2.154	0.804	0.007	-3.732	-0.577
Model 3: mLPA	886	-0.969	0.966	0.317	-2.865	0.928

Abbreviations: GDF-15, growth differentiation factor 15; LLCI, lower limit confidence interval; MET, metabolic equivalent of task; mLPA, first-year mean light physical activity volume; mMVPA, first-year mean moderate to vigorous physical activity volume; mTPA, first-year mean total physical activity volume; PA, physical activity; SE, standard error; ULCI, upper limit confidence interval.

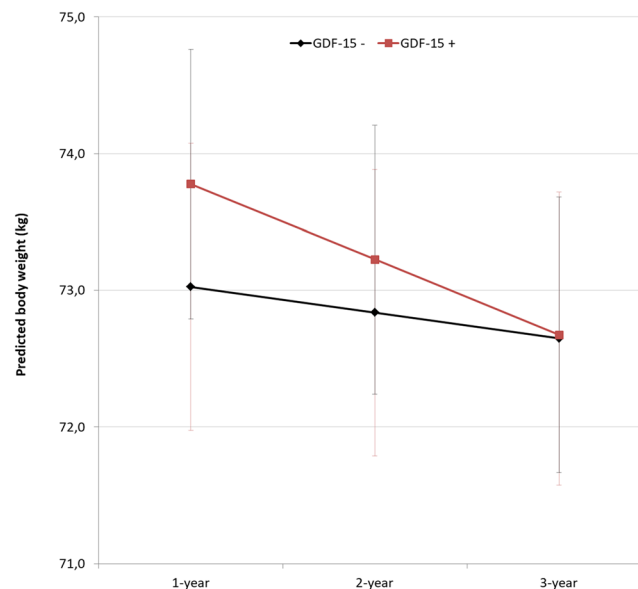


Figure 1 Estimated bodyweight loss according to growth differentiation factor 15 (GDF-15) levels. The graph indicates significant GDF-15 \times Time interaction such that higher GDF-15 concentrations (pg/mL) at 1 year were associated with faster subsequent weight loss (kg) over the next 2 years ($B = -0.0004$; $SE = 0.0001$; $P = 0.002$). Error bars represent standard errors.

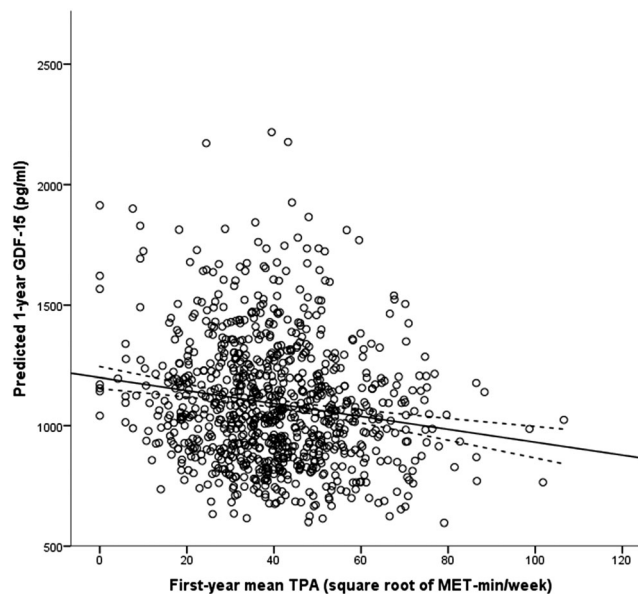


Figure 2 Associations between first-year mean PA volumes and GDF-15 levels. The graph indicates that higher mean PA volume (square root of MET-min/week) was associated with lower GDF-15 levels (pg/mL) at the 1-year visit ($B = -2.22$; $SE = 0.79$; $P = 0.005$). GDF-15, growth differentiation factor 15; MET, metabolic equivalent of task; PA, physical activity; TPA, total PA

tions predicted faster subsequent bodyweight reduction over the next 2 years. In addition, there was a significant indirect effect of PA such that higher GDF-15-mediated levels in mTPA and mMVPA were associated with smaller bodyweight loss from 1 to 3 years. No direct effect of mean PA levels was detected on bodyweight change.

Supplementary analyses

When using bodyweight stability as the outcome, none of the previous association remained significant, except the relationships between mean PA levels and GDF-15. The results of these analyses are provided in Supporting Information Tables S1 and S2.

Discussion

The present study investigated whether GDF-15 could mediate the association between PA and bodyweight in older adults. PA was not directly associated with bodyweight changes, whereas GDF-15 was associated to bodyweight loss over time. Mediation analysis demonstrated that higher chronic levels of PA estimated over 1 year were associated with lower circulating levels in GDF-15 by the end of the year, which, in turn, predicted reduced weight loss over the next 2 years. In other words, this study showed for the first time an indirect association of PA with bodyweight change through the mediation of GDF-15 levels in older adults.

Previous longitudinal investigations indicated that bodyweight increases until the age of 60, after which it stabilizes for a few years before declining until the end of life.¹ This late-life-related bodyweight reduction has multifactorial causes, including appetite loss,³⁵ changes in body composition,³⁶ PA reduction⁵¹⁰ and metabolic homeostasis disruption.⁴ Our finding that higher GDF-15 levels predict faster bodyweight loss is consistent with the known anorectic effect of GDF-15.⁸ Indeed, animal experimentations demonstrated that high-fat diet promotes obesity in GDF-15-deficient mice,³⁷ and clinical trials suggested that, in type-2 diabetic patients, metformin causes appetite and bodyweight reduction through the elevation of GDF-15 concentrations.^{13,14} Interestingly, increased GDF-15 levels have been reported following high-fat diet-induced obesity in mice,³⁸ as well as in humans with obesity.³⁰ It has been proposed that this elevation might be a counteracting feedback mechanism to prevent further body fat accumulation, as leptin does.³⁹ Such observations are consistent with our finding that 1-year bodyweight was higher in subjects with high GDF-15 levels compared with those with lower concentrations and that the former group experienced faster subsequent weight loss (Figure 1). Further, experimentations conducted in obese older adults demonstrated that exercise training-induced increases in GDF-15 levels were correlated with fat mass reduction,¹⁹ supporting the hypothesis of a protective role of GDF-15 against excessive fat accumulation.

In accordance with observational data derived from the literature, we found that higher chronic levels in PA were associated with lower GDF-15 concentrations. These results are consistent with studies demonstrating that resting levels in

Table 4 Mediation analyses on the associations between first-year mean PA volume (square root of MET-min/week), 1-year GDF-15 concentrations (pg/ml) and subsequent bodyweight changes (kg)

	n	Direct effects			Mediated effects			
		PA → Bodyweight changes			PA → GDF-15			
		c'	SE	ULCI	a	SE	ULCI	
Model 1: mTPA	758	0.00092	0.00623	-0.01131	-2.06219	0.82842	-3.68853	-0.43584
Model 2: mMVPA	758	0.00278	0.00639	-0.00976	-1.92284	0.84906	-3.58969	-0.25599
Model 3: mLPA	758	-0.00447	0.00788	-0.01994	-1.02633	1.01561	-3.02016	0.96750
				1- to 2-year bodyweight changes				
Model 1: mTPA	755	0.00594	0.00801	-0.00978	-1.85749	0.81105	-3.44974	-0.26524
Model 2: mMVPA	755	0.00432	0.00819	-0.01177	-1.83323	0.83279	-3.46817	-0.19830
Model 3: mLPA	755	0.00693	0.01019	-0.01307	-0.81488	0.99973	-2.77755	1.14778

Abbreviations: BootLLCI, bootstrap lower limit confidence interval; BootULCI, bootstrap upper limit confidence interval; GDF-15, growth differentiation factor 15; LLCI, lower limit confidence interval; MET, metabolic equivalent of task; mLPA, first-year mean light physical activity volume; mMVPA, first-year mean moderate to vigorous physical activity volume; mTPA, first-year mean total physical activity volume; PA, physical activity; SE, standard error; ULCI, upper limit confidence interval.

Table 4 (continued)

	b	GDF-15 → Bodyweight changes			Mediated effects		
		PA → GDF-15 → Bodyweight changes			PA → GDF-15 → Bodyweight changes		
		SE	LLCI	ULCI	ab	BootSE	BootLLCI
Model 1: mTPA	-0.00057	0.00024	-0.00105	0.00118	0.00074	0.00003	0.00290
Model 2: mMVPA	-0.00057	0.00024	-0.00104	0.00109	0.00073	-0.00001	0.00278
Model 3: mLPA	-0.00058	0.00024	-0.00106	0.00060	0.00072	-0.00068	0.00219
				1- to 3-year bodyweight changes			
Model 1: mTPA	-0.00099	0.00032	-0.00161	0.00184	0.00118	0.00003	0.00461
Model 2: mMVPA	-0.00100	0.00032	-0.00162	0.00183	0.00120	0.00001	0.00467
Model 3: mLPA	-0.00099	0.00032	-0.00162	0.00081	0.00116	-0.00000	0.00339

Abbreviations: BootLLCI, bootstrap lower limit confidence interval; BootULCI, bootstrap upper limit confidence interval; GDF-15, growth differentiation factor 15; LLCI, lower limit confidence interval; MET, metabolic equivalent of task; mLPA, first-year mean light physical activity volume; mMVPA, first-year mean moderate to vigorous physical activity volume; mTPA, first-year mean total physical activity volume; PA, physical activity; SE, standard error; ULCI, upper limit confidence interval.



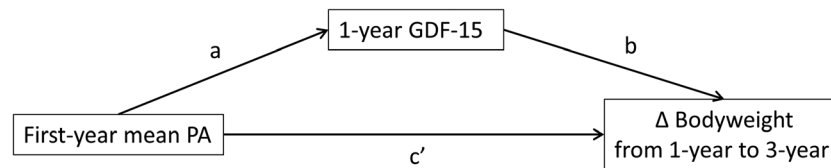


Figure 3 Mediation effect of growth differentiation factor 15 (GDF-15) on the association between physical activity (PA) and subsequent bodyweight changes. The diagram indicates that GDF-15 significantly mediated the associations between first-year mean PA (square root of metabolic equivalent of task-min/week) and subsequent bodyweight changes (kg) observed from 1 to 3 years ($a = -1.86$; $SE = 0.81$; $P < 0.05$; $b = -0.001$; $SE = 0.0003$; $P < 0.05$; $ab = 0.0018$; Bootstrap $SE = 0.001$; $P < 0.05$), whereas first-year mean PA had no direct effect on bodyweight changes ($c' = 0.006$; $SE = 0.008$; $P > 0.05$).

GDF-15 are inversely related with both long-term PA²⁰ and cardiorespiratory fitness.²¹ These findings also support the role of PA in preventing biological aging, because GDF-15 has been associated with several hallmarks of aging that can be modulated through PA.⁴⁰ These include telomere attrition,¹⁵ the senescence-associated secretory phenotype (SASP) and mitochondrial dysfunction. In contrast, it has been reported that acute physical exercise¹⁸ and short-term exercise training¹⁹ induce a raise in GDF-15 concentrations, suggesting that PA may exert distinct short-term and long-term effects on GDF-15, as it does on other exerkines such as IL-6, for instance.⁴¹

The results of the mediation analyses supported the hypothesis that PA could prevent late-life weight loss through the mediation of GDF-15. However, the question of whether this weight loss prevention occurs through a chronic modulation of GDF-15–GFRAL signalling or through other mechanisms such as those mentioned above is unknown and has yet to be resolved. The available evidence indicates that exercise-induced GDF-15 release does not affect food intake,¹⁸ but it is possible that other molecules secreted during exercise interact with GDF-15 to inhibit its effect on GFRAL. Furthermore, given that mean PA levels were associated with lower bodyweight at 1 year, it is possible that, besides preventing weight loss through directly decreasing GDF-15 concentrations, PA may also have limited fat mass accumulation preceding the 1-year measurements, which would have led to lower GDF-15 concentrations at 1 year and, consequently, smaller subsequent weight loss. Studies measuring body composition and fat distribution are thus required to further understand their role on the link between PA and GDF-15. Importantly also, it should be mentioned that other molecules secreted during exercise and implicated in the regulation of energy homeostasis such as FGF21 may also be involved in the relationship presented herein, which further indicates the need for mechanistic experimentations.

The fact that no mediated effects of PA were found when using bodyweight stability as the outcome may be explained by the inability of GDF-15 to predict bodyweight stability. Indeed, although PA may promote bodyweight stability by favouring lean mass conservation or increase on one hand and fat mass loss on the other hand, the effects of PA solely

mediated by GDF-15 measured at one unique time point may exclusively be unidirectional given that GDF-15 is a weight loss promoter. Although of scientific interest, the bodyweight stability hypothesis may be more appropriately addressed by future research using longitudinal measurements of GDF-15, with the underlying assumption that PA would stabilize GDF-15 levels over time.

The main strength of this study is that it is the first that investigated the mediating effects of GDF-15 on the association between PA and bodyweight changes in older adults, providing novel insights on the hypothetic mechanisms underlying the benefits of PA on late-life bodyweight maintenance. Other strengths are the longitudinal approach of the study, the large number of people with GDF-15 measurement and the adjustments for many confounders including inflammatory biomarkers. The limitations of this work rely to the use of data from a clinical trial that may have affected the investigated associations, the utilization of self-reported rather than objectively measured PA and the fact that GDF-15 levels were measured at one time point only. In addition, we could not include any measure of appetite, which would have been of relevance given its relationship with GDF-15. Lastly, the measure of body composition in addition to bodyweight would have further highlighted the present findings because bodyweight changes may occur through both fat mass and lean mass variations. Such analyses could not be performed due to the small number of subjects that had data for both GDF-15 and longitudinal assessment of body composition with dual-energy X-ray absorptiometry (DEXA) in MAPT ($n = 127$).

In conclusion, this study demonstrated that GDF-15-mediated PA levels predict slower late-life weight loss in adults aged 70 and over. The observational nature of this study precludes any causal inference regarding the role of GDF-15 in the relationships depicted in this work. Long-term interventional investigations with continuous sampling of GDF-15 or genome-wide association studies are required to confirm the potential mechanistic pathways suggested in the present work. More specifically, it would be of relevance to investigate the mediating effect of GDF-15 on body composition and fat distribution in addition to bodyweight, as it may regulate metabolic health rather than bodyweight per se. Finally,

there is a need for further studies to elucidate whether and how long-term PA could affect GDF-15–GFRAL signalling.

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Conflict of interest

The authors declare that they have no conflict of interest.

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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Appendix A: MAPT/DSA Group

A.1 MAPT Study Group

Principal investigator: Bruno Vellas (Toulouse); Coordination: Sophie Guyonnet; Project leader: Isabelle Carrié; CRA: Lauréane Brigitte; Investigators: Catherine Faisant, Françoise Lala, Julien Delrieu, Hélène Villars; Psychologists: Emeline Combrouze, Carole Badufle, Audrey Zueras; Methodology, statistical analysis and data management: Sandrine Andrieu, Christelle Cantet, Christophe Morin; Multidomain group: Gabor Abellan Van Kan, Charlotte Dupuy, Yves Rolland (physical and nutritional components), Céline Caillaud, Pierre-Jean Ousset (cognitive component), Françoise Lala (preventive consultation) (Toulouse). The cognitive component was designed in collaboration with Sherry Willis from the University of Seattle, and Sylvie Belleville, Brigitte Gilbert and Francine Fontaine from the University of Montreal.

Co-Investigators in associated centres: Jean-François Dartigues, Isabelle Marcet, Fleur Delva, Alexandra Foubert, Sandrine Cerda (Bordeaux); Marie-Noëlle-Cuffi, Corinne Costes (Castres); Olivier Rouaud, Patrick Manckoundia, Valérie Quipourt, Sophie Marilier, Evelyne Franon (Dijon); Lawrence Bories, Marie-Laure Pader, Marie-France Basset, Bruno Lapoujade, Valérie Faure, Michael Li Yung Tong, Christine Malick-Loiseau, Evelyne Cazaban-Campistron (Foix); Françoise Desclaux, Colette Blatge (Lavaur); Thierry Dantoine, Cécile Laubarie-Mouret, Isabelle Saulnier, Jean-Pierre Clément, Marie-Agnès Picat, Laurence Bernard-Bourzeix, Stéphanie Willebois, Iléana Désormais, Noëlle Cardinaud (Li-

moges); Marc Bonnefoy, Pierre Livet, Pascale Rebaudet, Claire Gédéon, Catherine Burdet, Flavien Terracol (Lyon); Alain Pesce, Stéphanie Roth, Sylvie Chaillou, Sandrine Louchart (Monaco); Kristel Sudres, Nicolas Lebrun, Nadège Barro-Belaygues (Montauban); Jacques Touchon, Karim Bennys, Audrey Gabelle, Aurélie Romano, Lynda Touati, Cécilia Marelli, Cécile Pays (Montpellier); Philippe Robert, Franck Le Duff, Claire Gervais, Sébastien Gonfrier (Nice); Yannick Gasnier, Serge Bordes, Danièle Begorre, Christian Carpuat, Khaled Khaless, Jean-François Lefebvre, Samira Misbah El Idrissi, Pierre Skolil, Jean-Pierre Salles (Tarbes).

MRI group: Carole Dufouil (Bordeaux), Stéphane Lehericy, Marie Chupin, Jean-François Mangin, Ali Bouhayia (Paris); Michèle Allard (Bordeaux); Frédéric Ricolfi (Dijon); Dominique Dubois (Foix); Marie Paule Bonceour Martel (Limoges); François Cotton (Lyon); Alain Bonafé (Montpellier); Stéphane Chanalet (Nice); Françoise Hugon (Tarbes); Fabrice Bonneville, Christophe Cognard, François Chollet (Toulouse).

PET scans group: Pierre Payoux, Thierry Voisin, Julien Delrieu, Sophie Peiffer, Anne Hitzel, (Toulouse); Michèle Allard (Bordeaux); Michel Zanca (Montpellier); Jacques Monteil (Limoges); Jacques Darcourt (Nice).

Medico-economics group: Laurent Molinier, Hélène Derumeaux, Nadège Costa (Toulouse).

Biological sample collection: Bertrand Perret, Claire Vinel, Sylvie Caspar-Bauguil (Toulouse).

Safety management: Pascale Olivier-Abbal.

DSA Group: Sandrine Andrieu, Christelle Cantet, Nicola Coley.