



Original Article

Growth differentiation factor 15 and malnutrition in older adults

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ABSTRACT

Objectives: Growth differentiation factor 15 (GDF-15) levels increase due to systemic inflammation and chronic disease burden. Since these biological processes are pathogenic factors of malnutrition, we examined the prospective association between GDF-15 serum levels and subsequent malnutrition in older adults.

Methods: We used data from 723 women and 735 men aged ≥ 65 years [mean age (SD): 71.3 (4.18) years] participating in the Seniors-ENRICA-2 cohort, who were followed-up for 2.2 years. Malnutrition was assessed with the Mini Nutritional Assessment-Short form (MNA-SF), where a 12–14 score indicates normal nutritional status, an 8–11 score indicates at risk of malnutrition, and a 0–7 score malnutrition. Associations of GDF-15 and malnutrition were analyzed, separately in women and men, using linear and logistic regression and adjusted for the main potential confounders.

Results: The mean (SD) MNA-SF score at baseline was 13.2 (1.34) for women and 13.5 (1.13) for men. Incident malnutrition (combined endpoint “at risk of malnutrition or malnutrition”) over 2.2 years was identified in 55 (9.7%) of women and 38 (5.4%) of men. In women, GDF-15 was linearly associated with a decrease in the MNA-SF score; mean differences (95% confidence interval) in the MNA-SF score were -0.07 (-0.13 ; -0.01) points per 25% increase in GDF-15, and -0.49 (-0.83 ; -0.16) for the highest versus lowest quartile of GDF-15. Also in women, GDF-15 was linearly associated with a higher malnutrition incidence, with odds ratio (95% confidence interval) of 1.24 (1.06; 1.46) per 25% increment in GDF-15 and of 3.05 (1.21; 7.65) for the highest versus lowest quartile of GDF-15. Results were similar after excluding subjects with cardiovascular disease and diabetes. No association of GDF-15 with changes in MNA score or malnutrition incidence was found in men.

Conclusion: Higher serum GDF-15 concentrations are associated with worsening nutritional status in older women. Further studies should elucidate the reasons for the sex differences in this association and explore the therapeutic potential of modifying GDF-15 to prevent malnutrition.

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1. Introduction

Malnutrition is a global concern in older adults due to its high prevalence and the resulting substantial burden on health and social systems [1]. According to a meta-analysis of prevalence rates using the Mini Nutritional Assessment (MNA), which is the most used nutritional

assessment tool in older adults, the prevalence of malnutrition is 3.1%, 22.0%, and 28.7% in the community, hospital, and residential care settings, respectively [2]. Besides, among community-dwelling older adults, as much as 26.5% are at risk of malnutrition [2]. Malnutrition is associated with adverse health outcomes, such as frailty, delirium, osteoporosis, cognitive impairment, poor quality of life, and premature

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; CVD, cardiovascular disease; GDF-15, growth differentiation factor 15; GFRAL, glial cell-derived neurotrophic factor family receptor alpha-like; GM, geometric mean; GSD, geometric standard deviation; HDL-c, high-density lipoprotein cholesterol; IL-6, interleukin-6; LDL-c, low-density lipoprotein cholesterol; MEDAS, Mediterranean Diet Adherence Screener; MET, metabolic equivalent of task; MNA-SF, Mini Nutritional Assessment – short form; OR, odds ratio; SD, standard deviation; SPB, systolic blood pressure; β , β -coefficient.

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mortality [3–9]. Thus, preventing malnutrition in older adults could help palliate the rise in the burden of disease and its consequent health and social care impact due to the progressive aging of the population [10].

Although the causes of malnutrition (or undernutrition) in older adults are not completely known, a frequent one is a reduced nutrient intake or assimilation caused by acute or chronic disease accompanied or not by inflammation [11,12]. Therefore, it would be sensible to study the association of malnutrition with a biomarker of chronic disease burden and inflammation that could allow early detection of at-risk persons and the installation of effective preventive interventions. Growth differentiation factor 15 (GDF-15) is a member of the transforming growth factor- β (TGF- β) superfamily produced in response to oxidative, metabolic, and inflammatory stress, which has been recognized as a biomarker of chronic disease burden [13]. Thus, GDF-15 levels are increased in aging and as a result of obesity, metabolic syndrome, cardiovascular disease (CVD), chronic kidney disease, cancer, and type 2 diabetes mellitus [14–17]; GDF-15 also predicts all-cause and cardiovascular death [18,19]. Although some features of malnutrition, such as reduced appetite or weight loss, have been associated with higher levels of GDF-15 in animal models [20], to our knowledge, only one study in humans [21] has assessed the association between this biomarker and nutritional status, and found that GDF-15 plasma levels were related to key malnutrition criteria in older adults.

Therefore, in this study, we aimed to assess the prospective association between serum levels of GDF-15 and subsequent malnutrition in older adults.

2. Methods

2.1. Study population and design

We used data from participants in the Seniors-ENRICA-2 cohort [22,23]; in total, 3273 individuals were selected between 2015 and 2017 by stratified random sampling of all community-dwelling individuals aged ≥ 65 years holding a national healthcare card and living in the Madrid region (Spain). The information on sociodemographic data, lifestyle, and morbidity was collected through a computer-assisted telephone interview. Also, two home visits were conducted to collect blood samples, perform a physical examination, and obtain a diet history [23]. In 2019 participants were re-interviewed and a new physical exam was conducted to update information [24]. The study was approved by the Clinical Research Ethics Committee of “La Paz” University Hospital in Madrid, and all study participants gave their written informed consent.

2.2. Study variables

2.2.1. GDF-15

Fasting blood samples were collected at the first home visit in serum tubes with a thrombin-based clot activator and polymer gel (Becton Dickinson) [25]. Within 1 h after collection, tubes were centrifuged at 2520 g and room temperature (20–23 °C) for 10 min, and serum was aliquoted, frozen at -80°C , and stored up to 3.6 years at the Department of Preventive Medicine and Public Health of the Universidad Autónoma de Madrid.

Serum GDF-15 was measured at the Department of Laboratory Medicine of “La Paz” University Hospital by an electrochemiluminescence Elecsys[®] immunoassay method using a cobas[®] 6000 analyzer (Roche Diagnostics). The inter-assay coefficient of variation was 5.4% for a mean concentration of 7343 pg/mL, and 7.7% for a mean concentration of 1428 pg/mL [25].

2.2.2. Assessment of malnutrition

The Mini Nutritional Assessment is a screening tool for malnutrition in older adults [26]. The full MNA is a validated test that takes 10–15 min to complete while the MNA-short form (MNA-SF) [27], which we used in our

study, is a reduced version of the MNA that maintains its accuracy and validity and is completed in less than 5 min. The MNA-SF consists of six items assessing food intake, recent involuntary weight loss, impaired mobility, psychological stress or acute illness, neuropsychological problems, and body mass index (BMI) [28] (or calf circumference if BMI is not available) [29]. A 12–14 score indicates normal nutritional status, a 8–11 score indicates at risk of malnutrition, and a 0–7 score malnutrition [28]. Since the number of malnourished individuals in our study was very low (8 at baseline), we combined the individuals at risk of malnutrition and the malnourished ones into a single endpoint of malnutrition. Then, we ascertained the number of incident cases of this endpoint over 2.2 years among those with normal nutritional status at baseline. Additionally, we calculated changes in the MNA-SF score from baseline to follow-up.

2.2.3. Potential confounders

We also obtained data on sociodemographic and lifestyle variables at baseline, including age, sex, educational level (primary or less, secondary, or university), living conditions (very easy/easy, somewhat easy/difficult, or difficult/very difficult to make ends meet), cohabitation (alone, with family, or other), smoking status (never, former, or current smoker), and alcohol consumption (never, former, moderate [≤ 10 g/day in women and ≤ 20 g/day in men], or heavy/binge drinker). Usual food consumption in the past year was obtained with a validated diet history developed from the one used in the EPIC cohort study in Spain [30]. Diet quality was estimated with the Mediterranean Diet Adherence Screener (MEDAS), ranging from 0 to 14, with higher scores indicating better adherence to the Mediterranean diet [31]. Protein (g/day) and energy intake (kcal/day) were estimated using standard composition tables [30]. Leisure-time physical activity (metabolic equivalents of task-h/week) and sedentary behavior (time spent watching television, h/day) were estimated with the Spanish-validated EPIC-cohort [32] and the Nurses’ Health Study [33] questionnaires, respectively. Systolic blood pressure (SBP) was obtained from three sequential blood pressure readings under standardized conditions using a validated device [34], and the average of the second and third measurements were used for analyses. Fasting serum glucose, creatinine, total cholesterol, high-density lipoprotein cholesterol (HDL-c), and triglycerides were measured with colorimetric enzymatic methods using Atellica[®] Solution-CH chemistry analyzer (Siemens Healthineers). LDL-cholesterol (LDL-c) measurement depended on triglycerides levels: if triglycerides < 250 mg/dL, LDL-c was calculated with the Friedewald formula ($\text{LDL-c} = \text{total cholesterol} - \text{triglycerides}/5 - \text{HDL-c}$) [35], and if triglycerides ≥ 250 mg/dL, LDL-c was determined on Atellica[®] Solution-CH chemistry analyzer (Siemens Healthineers) by a colorimetric enzymatic method. Serum interleukin-6 (IL-6) was measured by an electrochemiluminescence Elecsys[®] immunoassay method using a cobas[®] 6000 analyzer (Roche Diagnostics) [25]. Frailty was ascertained using the operational definition developed by Fried et al. in the Cardiovascular Health Study [36], which includes the following 5 criteria: 1) Exhaustion, evaluated as a response of at least “3 to 4 days a week” to any of the two following questions from the Center for Epidemiological Studies Depression Scale [37]: “I felt that anything I did was a big effort” and “I felt that I could not keep on doing things”; 2) Muscle weakness, defined as the lowest quintile in the maximum grip strength on the dominant hand measured with a Jamar dynamometer, adjusted for sex and BMI; 3) Low physical activity, defined as waking ≤ 2.5 h/week for men and ≤ 2 h/week for women; 4) Slow walking speed, defined as the lowest quintile in the 2.44-m walking speed test, performed as a part of the Short Physical Performance Battery [38], adjusted for sex and height; and 5) Unintentional weight loss, when ≥ 4.5 kg of body weight was lost in the preceding year. We defined frailty as having 3 or more of the above-mentioned criteria, prefrailty as having 1 or 2, and robustness as having none. Lastly, CVD was assessed by asking the study participants if they had ever been diagnosed with myocardial infarction, stroke, or congestive heart failure; and diabetes if they reported a medical

Table 1

GDF-15 concentrations at baseline according to characteristics of study participants, stratified by sex.

	Men			Women		
	n (%)	Geometric mean (GSD)	P ^a	n (%)	Geometric mean (GSD)	P ^a
Overall	735 (100)	1261 (1.59)		723 (100)	1150 (1.59)	
Age (years)			<0.001			<0.001
65 to 70	371 (50.5)	1139 (1.59)		325 (44.9)	1032 (1.51)	
> 70	364 (49.5)	1399 (1.55)		398 (55.0)	1257 (1.62)	
Education			0.006			0.319
Primary or less	381 (51.8)	1320 (1.59)		487 (67.4)	1169 (1.56)	
Secondary	149 (20.2)	1148 (1.52)		122 (17.0)	1135 (1.74)	
University	205 (28.0)	1241 (1.62)		114 (16.0)	1090 (1.50)	
Living conditions (making ends meet)			0.062			<0.001
Very easy/easy	14(2.0)	1590 (1.50)		31(4.3)	1603 (1.89)	
Somewhat easy/difficult	185 (25.1)	1308 (1.60)		257 (35.5)	1226 (1.61)	
Difficult/very difficult	536 (73.0)	1238 (1.58)		435 (60.1)	1082 (1.52)	
Cohabitation			0.472			0.471
Alone	90 (12.2)	1369 (1.73)		234 (32.3)	1172 (1.61)	
With family	635 (86.4)	1248 (1.56)		475 (65.7)	1144 (1.57)	
Other	10 (1.3)	1145 (1.84)		14 (1.9)	1014 (1.68)	
Smoking status			0.042			0.208
Never smoker	236 (32.1)	1201 (1.54)		512 (70.8)	1148 (1.57)	
Former smoker	415 (56.5)	1272 (1.61)		157 (21.7)	1118 (1.66)	
Current smoker	84 (11.4)	1385 (1.60)		54 (7.5)	1271 (1.49)	
Alcohol consumption			0.037			<0.001
Never drinker	44 (6.0)	1375 (1.70)		203 (28.0)	1206 (1.62)	
Moderate drinker ^b	415 (56.5)	1267 (1.55)		370 (51.1)	1144 (1.58)	
Heavy/binge drinker ^b	232 (31.5)	1198 (1.62)		110 (15.2)	1007 (1.48)	
Former drinker	44 (6.0)	1450 (1.63)		40 (5.5)	1368 (1.62)	
MEDAS score^c			0.158			0.446
< 7	258 (35.1)	1318 (1.61)		253 (35.0)	1173 (1.64)	
7 to 8	299 (40.7)	1235 (1.58)		333 (46.0)	1164 (1.59)	
> 8	178 (24.2)	1225 (1.57)		137 (19.0)	1079 (1.45)	
Protein intake (g/day)^d			0.349			0.114
T1	245 (33.3)	1280 (1.63)		241 (33.3)	1208 (1.58)	
T2	245 (33.3)	1236 (1.61)		241 (33.3)	1112 (1.54)	
T3	245 (33.3)	1267 (1.52)		241 (33.3)	1133 (1.63)	
Energy intake (kcal/day)^e			0.246			0.703
T1	245 (33.3)	1303 (1.61)		241 (33.3)	1163 (1.58)	
T2	245 (33.3)	1216 (1.62)		241 (33.3)	1161 (1.58)	
T3	245 (33.3)	1265 (1.53)		241 (33.3)	1127 (1.60)	
Leisure-time physical activity (METs-h/week)^f			<0.001			0.029
T1	245 (33.3)	1395 (1.59)		247 (34.1)	1200 (1.63)	
T2	245 (33.3)	1220 (1.57)		236 (32.6)	1079 (1.53)	
T3	245 (33.3)	1179 (1.58)		240 (33.2)	1173 (1.59)	
Time watching TV (hours/day)			0.798			0.062
< 3	294 (40.0)	1263 (1.61)		249 (34.4)	1098 (1.48)	
3 to < 4	214 (29.1)	1241 (1.54)		203(28.0)	1110 (1.57)	
≥ 4	227(30.8)	1278 (1.60)		271(37.5)	1232 (1.67)	
Systolic blood pressure (mmHg)			0.587			0.334
<130	288 (39.1)	1276 (1.61)		339 (46.9)	1130 (1.59)	
≥130	447 (60.8)	1252 (1.57)		384 (53.1)	1168 (1.58)	
Glucose (mg/dL)			<0.001			<0.001
<100	435 (59.1)	1148 (1.51)		510 (70.5)	1059 (1.49)	
≥100	300 (40.8)	1445 (1.64)		213 (29.5)	1403 (1.71)	
LDL-c (mg/dL)			<0.001			<0.001
<130	568 (77.2)	1318 (1.62)		464 (64.1)	1206 (1.62)	
≥130	167 (22.7)	1086 (1.40)		259 (35.8)	1057 (1.51)	
Creatinine (mg/dL)			<0.001			<0.001
≤ 1.2	693 (94.3)	1229 (1.57)		714 (98.8)	1137 (1.57)	
>1.2	42 (5.7)	1925 (1.53)		9 (1.2)	2799 (1.40)	
Cardiovascular disease^g			0.051			0.124
No	716 (97.4)	1254 (1.59)		697 (96.4)	1144 (1.58)	
Yes	19 (2.6)	1546 (1.56)		26 (3.6)	1318 (1.74)	
Diabetes Mellitus			<0.001			<0.001
No	581 (79.0)	1158 (1.51)		612 (84.6)	1069 (1.48)	
Yes	154 (20.9)	1741 (1.66)		111 (15.3)	1721 (1.81)	

GSD: Geometric Standard Deviation; **LDL-c:** Low-Density Lipoprotein Cholesterol; **MEDAS:** Mediterranean Diet Adherence Screener; **MET:** Metabolic Equivalent of Task; **T:** Tertile.

^a P-value for differences among groups, analyzed with t-tests, one-way analysis of variance, or Kruskal-Wallis tests, as appropriate.

^b Moderate drinker: ≤10 g/day in women and ≤20 g/day in men; heavy drinker: >10 g/day in women and >20 g/day in men; binge drinker: ≥6 standard units in women or ≥8 in men during any drinking session in the preceding 30 days.

^c Range:0–14.

^d Protein intake tertiles, Men: T1: ≤ 88; T2: > 88 to ≤ 101; T3: >101 g/day, Women: T1: ≤ 78; T2: > 78 to ≤ 91; T3: > 91 g/day.

^e Energy intake tertiles, Men: T1: ≤ 1948; T2: > 1948 to ≤ 2226; T3: > 2226 kcal/day, Women: T1: ≤ 1680; T2: > 1680 to ≤ 1893; T3: > 1893 kcal/day.

^f Physical activity tertiles, Men: T1: ≤ 42; T2: > 42 to ≤ 68; T3: > 68 METs-h/week, Women: T1: ≤ 58; T2: > 58 to ≤ 84; T3: > 84 METs-h/week.

^g Including acute myocardial infarction, stroke, and congestive heart failure.

diagnosis of diabetes, had been under antidiabetic medication, or had a fasting blood glucose ≥ 126 mg/dL.

2.3. Statistical analyses

From the initial sample of 3273 participants, we excluded 46 who had died at follow-up and 1333 who were lost to follow-up. From the remaining 1894, we also excluded 137 with missing data on GDF-15 at baseline, 255 without information on the MNA-SF score at baseline or follow-up, and 44 without data on potential confounders. Thus, 1458 participants were included in the analyses. Women had a slightly lower retention rate than men (Fig. S1).

The prospective association of serum GDF-15 concentrations with malnutrition was assessed with both linear and logistic regression; given the non-normal distribution of GDF-15, log transformation was performed and log-transformed serum GDF-15 levels were modeled: a) per 25% increment; b) as quartiles, using the lowest one as the reference; and c) as restricted cubic splines with knots at the 10th, 50th, and 90th percentiles, to assess potential nonlinear relationships.

In the linear regression models, the association of baseline serum GDF-15 with mean changes from baseline to follow-up in the MNA-SF score as a continuous variable was summarized with β -coefficients and their 95% confidence interval (CI), whereas in the logistic regression models, the association of baseline serum GDF-15 levels with the incidence of malnutrition over the follow-up was assessed with odds ratios (OR) and their 95% CI. Three hierarchical models were fitted in both linear and logistic regression analyses: Model 1 adjusted for sociodemographic characteristics: age, education, living conditions, and cohabitation; Model 2 further adjusted for lifestyle and clinical variables: smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, SBP, serum glucose, serum LDL-c, serum creatinine, CVD and diabetes; and Model 3 further adjusted for energy and protein intake.

Since there is overlap in the definition and treatment of malnutrition and frailty because they have similar characteristics, including loss of body mass and functional impairment [39], we examined the overlap of these two conditions in our study, and conducted an additional analysis with further adjustment for frailty status at baseline. Moreover, we conducted another analysis with further adjustment for IL-6, a biomarker of inflammation, to assess its impact on the study association. Also, as GDF-15 is a strong biomarker of chronic disease burden, we replicated the main analyses excluding participants with CVD and diabetes. Lastly, we examined if sociodemographic, lifestyle, and clinical variables modified the study associations by testing interaction terms defined as the product of GDF-15 by categories of such variables. Since statistically significant interactions were found by sex, indicating that the study associations were different in women and men, the analyses were conducted separately in women and men, and the main results are presented stratified by sex.

Statistical significance was set at a two-sided p -value < 0.05 . Analyses were performed with Stata[®], version 17.0 MP (College Station, TX: StataCorp LLC).

3. Results

GDF-15 levels increased with age and were higher in former drinkers and participants with lower physical activity, higher levels of glucose and creatinine, lower LDL-c, and diabetes, as well as in men with lower education and current smokers and women with better living conditions (Table 1). Men had somewhat higher serum levels of GDF-15 than women, with geometric means (geometric standard deviations) of 1261 pg/mL (1.59) and 1150 pg/mL (1.59), respectively. This difference may have been driven by their worse habits (less frequently never smokers and never drinkers, and less physically active) and clinical parameters, although they had more favorable sociodemographic characteristics than women (younger, more educated, more affluent and lived alone less frequently) (Table S1).

The mean (SD) MNA-SF score at baseline was 13.2 (1.34) for women and 13.5 (1.13) for men. A total of 55 (9.7%) out of 565 women and 38 (5.4%) out of 699 men without malnutrition at baseline developed malnutrition over 2.2 years.

In women, serum GDF-15 concentrations were linearly associated with a decrease in the MNA-SF score over 2.2 years (Fig. 1). The mean difference (95% CI) in MNA-SF score was -0.07 (-0.13 ; -0.01) points per 25% increment in GDF-15, and -0.49 (-0.83 ; -0.16) for the highest versus the lowest quartile of GDF-15 in the fully adjusted model (Table 2). Also in women, GDF-15 was linearly associated with a higher incidence of malnutrition over 2.2 years (Fig. 2), with OR (95% CI) of 1.24 (1.06; 1.46) per 25% increment in GDF-15 and of 3.05 (1.21; 7.65) for the highest versus the lowest quartile of GDF-15 in the fully adjusted model (Table 2). No association of GDF-15 with changes in the MNA-SF score or malnutrition incidence over 2.2 years was found in men (Figs. 1 and 2, Table 2).

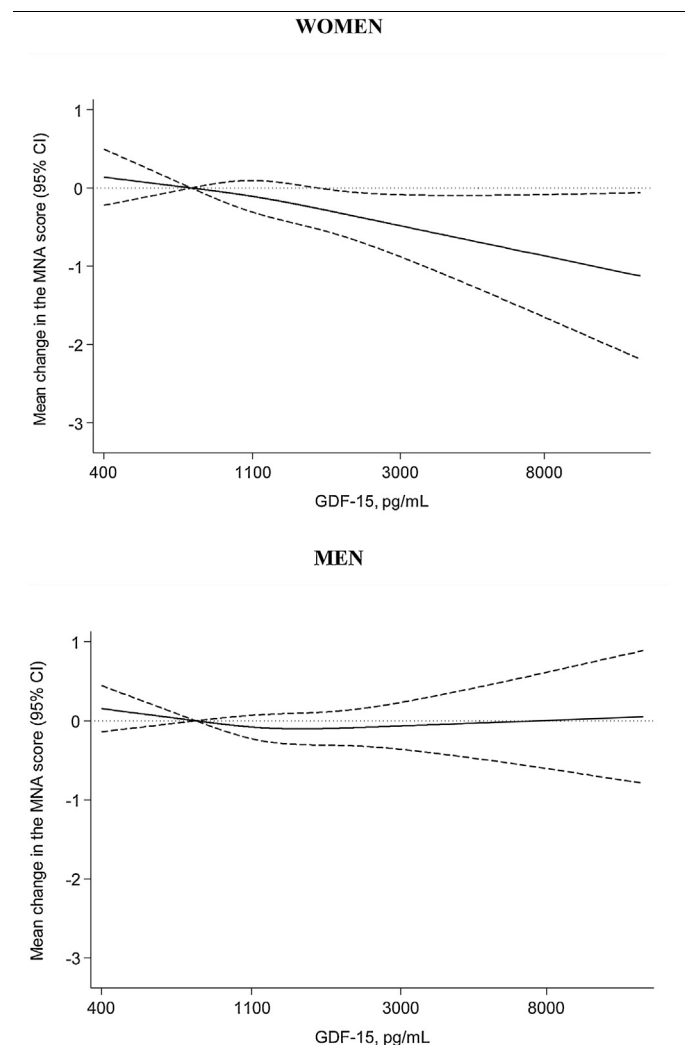


Fig. 1. Dose-response association of baseline GDF-15 with changes in the Mini Nutritional Assessment-Short Form (MNA-SF) score over 2.2 years, stratified by sex.

CI: confidence interval; **GDF-15:** Growth differentiation factor 15.

Restricted cubic splines (knots at the 10th, 50th and 90th percentile of GDF-15 concentration; reference at the median GDF-15 concentration for the first quartile) from a linear regression model adjusted for age, education, living conditions, cohabitation, smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, diabetes, and energy and protein intake.

Table 2

Association of baseline GDF-15 with changes in the Mini Nutritional Assessment-Short Form (MNA-SF) score and incidence of malnutrition over 2.2 years, stratified by sex.

WOMEN	GDF-15 (pg/mL)				P-trend	per 25% increase
	Q1 (≤834)	Q2 (>834 to ≤1085)	Q3 (>1085 to ≤1455)	Q4 (>1455)		
Change in the MNA-SF score^a						
N	181	181	182	179		723
Model 1, β (95% CI)	Ref.	−0.11 (−0.40; 0.19)	−0.02 (−0.32; 0.27)	−0.52 (−0.83; −0.21) **	0.004	−0.08 (−0.13; −0.02) **
Model 2, β (95% CI)	Ref.	−0.11 (−0.40; 0.18)	−0.00 (−0.30; 0.29)	−0.50 (−0.83; −0.17) **	0.019	−0.07 (−0.14; −0.01) *
Model 3, β (95% CI)	Ref.	−0.10 (−0.39; 0.19)	0.00 (−0.29; 0.30)	−0.49 (−0.83; −0.16) **	0.021	−0.07 (−0.13; −0.01) *
Malnutrition^b incidence						
No. Cases/N	10/169	10/163	8/170	27/154		55/565
Model 1B, OR (95% CI)	Ref.	0.94(0.38; 2.36)	0.73 (0.28; 1.93)	3.20 (1.42; 7.22) **	0.004	1.24 (1.09; 1.41) **
Model 2B, OR (95% CI)	Ref.	0.97(0.38; 2.48)	0.73 (0.27; 1.99)	3.12 (1.25; 7.82) *	0.022	1.24 (1.06; 1.46) **
Model 3B, OR (95% CI)	Ref.	0.94(0.37; 2.41)	0.72 (0.27; 1.97)	3.05 (1.21; 7.65) *	0.025	1.24 (1.06; 1.46) **
MEN	GDF-15 (pg/mL)				P-trend	per 25% increase
	Q1 (≤923)	Q2 (>923 to ≤1188)	Q3 (>1188 to ≤1681)	Q4 (>1681)		
Change in the MNA-SF score^a						
N	184	184	184	184		735
Model 1, β (95% CI)	Ref.	−0.12 (−0.35; 0.11)	0.11 (−0.13; 0.34)	−0.08 (−0.32; 0.16)	0.957	−0.00 (−0.04; 0.04)
Model 2, β (95% CI)	Ref.	−0.16 (−0.39; 0.08)	0.09 (−0.15; 0.33)	−0.14 (−0.40; 0.13)	0.744	−0.01 (−0.06; 0.03)
Model 3, β (95% CI)	Ref.	−0.16 (−0.39; 0.08)	0.09 (−0.15; 0.33)	−0.14 (−0.40; 0.13)	0.732	−0.01 (−0.06; 0.03)
Malnutrition^b incidence						
No. Cases/N	9/179	11/181	6/171	12/168		38/699
Model 1B, OR (95% CI)	Ref.	1.12 (0.45; 2.80)	0.56 (0.19; 1.69)	1.14 (0.44; 2.94)	0.963	1.01 (0.86; 1.19)
Model 2B, OR (95% CI)	Ref.	1.24 (0.47; 3.26)	0.57 (0.18; 1.80)	1.22 (0.41; 3.66)	0.976	1.05 (0.86; 1.28)
Model 3B, OR (95% CI)	Ref.	1.07 (0.40; 2.86)	0.57 (0.18; 1.82)	1.18 (0.39; 3.51)	0.994	1.05 (0.85; 1.28)

CI: confidence interval; **GDF-15**: Growth differentiation factor 15; **OR**: odds ratio.

Model 1: Linear regression model adjusted for age, education, living conditions, and cohabitation.

Model 2: As model 1 and further adjusted for smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, and diabetes.

Model 3: As model 2 and further adjusted for energy and protein intake.

Model 1B: Logistic regression model adjusted for age, education, living conditions, and cohabitation.

Model 2B: As model 1B and further adjusted for smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, and diabetes.

Model 3B: As model 2B and further adjusted for energy and protein intake.

* $p < 0.05$.

** $p < 0.01$.

^a Higher scores in the MNA-SF indicate a better nutritional status.

^b Including individuals at risk of malnutrition (MNA-SF score of 8–11) or malnourished (MNA-SF score <8).

There was some overlap of malnutrition and frailty: 38.9% of frail participants presented malnutrition at baseline, and from those who did not, 27.3% developed malnutrition over 2.2 years, whereas prevalent or incident malnutrition was much lower (<8%) in robust and prefrail individuals (Table S2). However, in additional analyses with adjustment for frailty status, the association between GDF-15 and changes in the MNA-SF score or incidence of malnutrition remained in women, with only slight changes in the effect estimates. No association was seen in men (Table 3). The study associations did not materially change either when we further adjusted for IL-6 (Table 3).

Results in women and men were similar in analyses excluding subjects with CVD and diabetes. In women, the MNA-SF score decreased linearly over follow-up according to baseline GDF-15 (Fig. S2), with mean differences (95% CI) of −0.11 (−0.18; −0.04) points in the MNA-SF score per 25% increment in GDF-15, and of −0.54 (−0.89; −0.19) for the highest compared with the lowest quartile of GDF-15 in Model 3 (Table S3). Also in women, GDF-15 was linearly associated with a higher incidence of malnutrition (Figure S3), with OR (95% CI) of 1.32 (1.08; 1.63) per 25% increment in GDF-15 and 3.45 (1.23; 9.67) for the highest versus the lowest quartile of GDF-15 (Table S3). Again, no association was found between GDF-15 and malnutrition in men (Figs. S2 and S3, Table S3).

Lastly, analyses in the overall sample showed that serum GDF-15 levels were associated with a decrease in the MNA-SF score and a higher incidence of malnutrition over 2.2 years (Table S4).

4. Discussion

In this study, older women with higher serum GDF-15 levels showed a worsened nutritional status and increased incidence of malnutrition over 2.2 years of follow-up, independently of the main potential confounders. This association remained after excluding individuals with CVD or diabetes. By contrast, GDF-15 and malnutrition did not appear to be associated in older men.

To our knowledge, this is the first study assessing the association between serum GDF-15 levels and malnutrition in community-dwelling older adults. However, previous clinic-based investigations have found a cross-sectional association between GDF-15 concentration and malnutrition in hemodialysis patients [40] and heart failure patients [41]. Specifically, among 158 hemodialysis patients, GDF-15 was significantly higher in those with higher (worse) malnutrition/inflammation scores (MIS). Also, GDF-15 levels significantly differentiated malnutrition/inflammation based on the area under a receiver operating characteristic curve (0.60; 95% CI: 0.51–0.69; $p = 0.031$) [40]. Among 73 heart failure

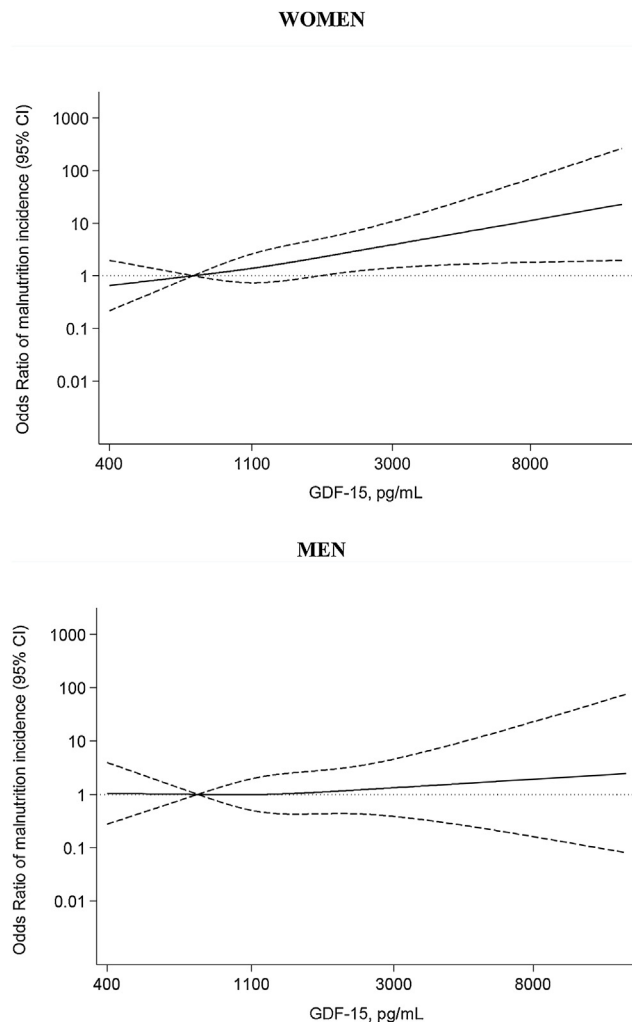


Fig. 2. Dose-response association of baseline GDF-15 with malnutrition incidence over 2.2 years, stratified by sex.

CI: confidence interval; GDF-15: Growth differentiation factor 15.

Restricted cubic splines (knots at the 10th, 50th and 90th percentile of GDF-15 concentration; reference at the median GDF-15 concentration for the first quartile) from a logistic regression model adjusted for age, education, living conditions, cohabitation, smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, diabetes, and energy and protein intake.

patients with or without diabetes mellitus, GDF-15 was significantly higher in malnourished than well-nourished individuals, based on the Geriatric Nutritional Risk Index; also, after adjusting for sex and age, there was a 5.8-fold increased frequency of malnutrition per log increment in the GDF-15 level [41].

One potential contributor to our findings might be the increased levels of proinflammatory cytokines (e.g., TNF α , CRP, IL-1b, and IL-6) associated with GDF-15, which could negatively affect appetite by inhibiting gastric emptying, impairing the performance of appetite-controlling hormones and inducing skeletal muscle catabolism [42,43]. Indeed, GDF-15 correlates positively with biomarkers of inflammation (e.g., IL-6, IL1Ra, IL-2, IL-4, IL-9, IL-10, IP-10, INF γ , IP-10, MCP-1, MIP-1 α , MIP-1 β , TNF α , VEGFA, and activin A) in cancer patients; also, GDF-15, IL-6, IL-8, and IL-1ra levels significantly correlate with 6-month weight loss [44]. In addition, GDF-15 was correlated with a higher concentration of C-reactive protein (CRP) and with markers of poor nutrition, such as low serum albumin and potassium [40] in hemodialysis

patients. Also, GDF-15 has been found to positively correlate with CRP in patients with acute coronary syndrome [45], and in a population without CVD [46]. However, in an ancillary analysis further adjusted for IL-6, the association of higher levels of GDF-15 and subsequent changes in MNA-SF or malnutrition incidence remained in women. Therefore, it seems that factors other than IL-6, of inflammatory nature or not, should mediate the observed association.

Another mechanism that could explain the association between GDF-15 and malnutrition is anorexia. In fact, in cancer patients, GDF-15 has been implicated in the pathogenesis of anorexia [47], and in rodents, GDF-15 caused anorexia by a direct effect on the hypothalamus [48]. GDF-15 has also been found to activate a receptor composed of a glial cell-derived neurotrophic factor family receptor alpha-like (GFRAL) and receptor tyrosine kinase (RET) dimer, causing anorexia, vomiting, and nausea in mice and nonhuman primates [49]. Moreover, in older humans, GDF15–GFRAL receptor could also suppress food intake [50], GDF-15 has been associated with a higher risk of anorexia of aging [51], and in cancer patients, GDF-15 is elevated especially in those with anorexia compared to those with normal appetite [52]. However, in our study, it is unlikely that the association of GDF-15 and malnutrition is due to anorexia and reduced food intake because after adjustment of the regression models for the MEDAS score, and energy and protein intake, the association remained.

Notably, we found clear differences in the study association between women and men. However, although we observed sex differences in baseline GDF-15 concentrations, malnutrition incidence and sociodemographic, lifestyle and clinical characteristics, it is uncertain whether they could entirely explain the different associations found in women and men in our study. Similar sex differences have been found for the association of GDF-15 with other outcomes. For instance, one study reported that high GDF-15 levels predicted secondary CVD in women but not in men [53]. This might be related to atherosclerotic plaque morphology, since women are more likely to suffer plaque erosions than men [54]. Also, GDF-15 is expressed by macrophages activation, which contributes to atheromatosis and has a role in other chronic inflammatory diseases like rheumatoid arthritis; and it is known that many autoimmune diseases are more prevalent in women than in men [55].

In addition, there is some evidence that inflammatory responses differ between men and women [56], partly due to hormonal mediators such as testosterone in men and estrogens in women [57]. Estrogens seem to have a dose-dependent effect on the inflammatory system, so that low estrogen levels increase IL-6, IL-1 β and TNF- α and high estrogen levels can abolish inflammatory effects [58,56]. In line with this evidence, an acute laboratory stress resulted in a significant increase in expression of IL-6 and TNF- α , but not IL-1 β following lipopolysaccharide stimulation. Importantly, when stratified by sex, the inflammatory response was stronger in women [59]; of note also is that when women were further stratified by menopausal status, postmenopausal women presented higher levels of IL-6 and TNF- α in response to stress than men. Furthermore, in a recent study of 57 healthy midlife adults, stress-related increases in the secretion of IL-6 after an acute laboratory stressor in women were significantly higher than in men [60]. This result is compatible with several prior studies [61,62]. Finally, among menopausal women, those using oral conjugated equine estrogen or transdermal 17 β -estradiol for 36 months had lower levels of GDF-15, tumor necrosis factor receptor1, and FAS protein than those not taking such treatments [63]. Also, in men with coronary artery disease, levels of GDF-15 were increased, and testosterone and the testosterone/estradiol (T/E) ratio decreased, compared with men without the disease. As a consequence, GDF-15 levels had a negative correlation with testosterone levels and the T/E ratio [64]; similar results were obtained in men with major depressive disorder [65].

This study had several strengths. Among them are the prospective design, the use of a validated tool (MNA-SF) to assess malnutrition in older adults, adjustment for a good number of potential confounders, and replication of the analyses excluding individuals with CVD or diabetes to minimize reverse causation. However, it also had some limitations. First,

Table 3

Association of baseline GDF-15 with changes in the Mini Nutritional Assessment-Short Form (MNA-SF) score and incidence of malnutrition over 2.2 years, stratified by sex and further adjusted for frailty status or interleukin-6.

	GDF-15 (pg/mL)					
WOMEN	Q1 (≤834)	Q2 (>834 to ≤1085)	Q3 (>1085 to ≤1455)	Q4 (>1455)	P-trend	per 25% increase
Change in the MNA-SF score^a						
N	181	181	182	179		723
Model 4, β (95% CI)	Ref.	−0.14 (−0.43; 0.15)	−0.05 (−0.35; 0.24)	−0.52 (−0.85; −0.18) **	0.012	−0.07 (−0.13; −0.01) *
Model 5, β (95% CI)	Ref.	−0.09 (−0.38; 0.20)	0.01 (−0.28; 0.30)	−0.48 (−0.82; −0.14) **	0.025	−0.07 (−0.13; −0.01) *
Malnutrition^b incidence						
No. Cases/N	10/169	10/163	8/170	27/154		55/565
Model 4B, OR (95% CI)	Ref.	0.97 (0.37; 2.51)	0.74 (0.27; 2.03)	3.22 (1.27; 8.19) *	0.020	1.24 (1.06; 1.46) **
Model 5B, OR (95% CI)	Ref.	0.94(0.36; 2.43)	0.72 (0.26; 1.99)	3.07 (1.21; 7.77) *	0.023	1.25 (1.06; 1.47) **
	GDF-15 (pg/mL)					
MEN	Q1 (≤923)	Q2 (>923 to ≤1188)	Q3 (>1188 to ≤1681)	Q4 (>1681)	P-trend	per 25% increase
Change in the MNA-SF score^a						
N	184	184	184	184		735
Model 4, β (95% CI)	Ref.	−0.13 (−0.37; 0.10)	0.10 (−0.14; 0.34)	−0.10 (−0.36; 0.17)	0.932	−0.01 (−0.05; 0.04)
Model 5, β (95% CI)	Ref.	−0.15 (−0.38; 0.08)	0.09 (−0.14; 0.33)	−0.12 (−0.38; 0.14)	0.816	−0.01 (−0.06; 0.04)
Malnutrition^b incidence						
No. Cases/N	9/179	11/181	6/171	12/168		38/699
Model 4B, OR (95% CI)	Ref.	1.06 (0.39; 2.85)	0.58 (0.18; 1.85)	1.19 (0.39; 3.56)	0.974	1.05 (0.86; 1.29)
Model 5B, OR (95% CI)	Ref.	1.04 (0.38; 2.78)	0.52 (0.16; 1.67)	1.05 (0.35; 3.15)	0.855	1.03 (0.84; 1.26)

CI: confidence interval; GDF-15: Growth differentiation factor 15; OR: odds ratio.

Model 4: Linear regression model adjusted for age, education, living conditions, cohabitation, smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, diabetes, energy and protein intake, and frailty status according to the Fried criteria (robust, prefrail or frail).

Model 5: Linear regression model adjusted for age, education, living conditions, cohabitation, smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, diabetes, energy and protein intake, and serum interleukin-6.

Model 4B: Logistic regression model adjusted for age, education, living conditions, cohabitation, smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, diabetes, energy and protein intake, and frailty status according to the Fried criteria (robust, prefrail or frail).

Model 5B: Logistic regression model adjusted for age, education, living conditions, cohabitation, smoking status, alcohol consumption, MEDAS score, physical activity, time watching TV, systolic blood pressure, serum glucose, serum LDL-cholesterol, serum creatinine, cardiovascular disease, diabetes, energy and protein intake, and serum interleukin-6.

* $p < 0.05$.

** $p < 0.01$.

^a Higher scores in the MNA-SF indicate a better nutritional status.

^b Including individuals at risk (MNA-SF score of 8–11) or malnourished (MNA-SF score <8).

data on some variables such as physical activity, diet, and chronic diseases were self-reported; thus, due to recall or social desirability biases, it could result in measurement errors that likely underestimate the actual association between GDF-15 and malnutrition. Second, using a single measure of GDF-15 may have introduced certain degree of measurement error, although likely non-differential. Third, we did not assess important inflammatory and chronic disease markers, such as IL-2, IL-4, IL-9, MCP-1, MIP-1α or TNFα, which may demonstrate a stronger impact on malnutrition or might explain the association between GDF-15 and malnutrition. Finally, as in any observational study, some residual confounding cannot be completely ruled out.

5. Conclusion

In our study, a higher level of GDF-15 was prospectively associated with worsening nutritional status in older women but not men. Future research should confirm these results, identify their biological mechanisms, and explore the therapeutic potential of modifying GDF-15 to prevent malnutrition.

Conflicts of interest

The authors declare that they have no conflict of interest.

Author contributions

F.R.-A. and R.O. conceived the study. N.R., B.F.E. and R.O. performed the statistical analyses. N.R., F.R.-A. and R.O. drafted the manuscript. B.F.E., A.B.S. and J.R.B. contributed to results interpretation. All authors reviewed the manuscript for important intellectual content, read, and approved the final manuscript.

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agencies had no role in study design, data collection and analysis, interpretation of results, manuscript preparation, or the decision to submit this manuscript for publication.

Ethical approval

The study was approved by the Clinical Research Ethics Committee of “La Paz” University Hospital in Madrid, and all study participants gave their written informed consent.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.jnha.2024.100230>.

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