


Alcohol consumption patterns and growth differentiation factor 15 among life-time drinkers aged 65+ years in Spain: a cross-sectional study

Rosario Ortola^{1,2}  | Esther García-Esquinas^{1,2} | Antonio Buño-Soto³ |
Adrián Carballo-Casla^{1,2} | Mercedes Sotos-Prieto^{1,2,4} | José R. Banegas^{1,2} |
Fernando Rodríguez-Artalejo^{1,2,5}

¹Department of Preventive Medicine and Public Health, Universidad Autónoma de Madrid and IdiPaz, Madrid, Spain

²CIBER of Epidemiology and Public Health (CIBERESP), Madrid, Spain

³Department of Laboratory Medicine, La Paz University Hospital-IdiPaz, Madrid, Spain

⁴Department of Environmental Health and Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA, USA

⁵IMDEA Food Institute. CEI UAM+CSIC, Madrid, Spain

Correspondence

Rosario Ortola MD, Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid, Calle del Arzobispo Morcillo 4, 28029 Madrid, Spain.
Email: ortolarosario@gmail.com

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Abstract

Aims: To examine the association of alcohol consumption patterns with growth differentiation factor 15 (GDF-15) in older drinkers, separately among individuals with cardiovascular disease (CVD)/diabetes and those without them, as GDF-15 is a strong biomarker of chronic disease burden.

Design: Cross-sectional study.

Setting: Population-based study in Madrid (Spain).

Participants: A total of 2051 life-time drinkers aged 65+ years included in the Seniors-ENRICA-2 study in 2015–17. Participants' mean age was 71.4 years and 55.4% were men.

Measurements: According to their average life-time alcohol intake, participants were classified as occasional (≤ 1.43 g/day), low-risk (men: > 1.43 –20 g/day; women: > 1.43 –10 g/day), moderate-risk (men: > 20 –40 g/day; women: > 10 –20 g/day) and high-risk drinkers (men: > 40 g/day; women: > 20 g/day; or binge drinkers). We also ascertained wine preference ($> 80\%$ of alcohol derived from wine), drinking with meals and adherence to a Mediterranean drinking pattern (MDP) defined as low-risk drinking, wine preference and one of the following: drinking only with meals; higher adherence to the Mediterranean diet; or any of these.

Findings: In participants without CVD/diabetes, GDF-15 increased by 0.27% [95% confidence interval (CI) = 0.06%, 0.48%] per 1 g/day increment in alcohol among high-risk drinkers, but there was no clear evidence of association in those with lower intakes or in the overall group, or across categories of alcohol consumption status. Conversely, among those with CVD/diabetes, GDF-15 rose by 0.19% (95% CI = 0.05%, 0.33%) per 1 g/day increment in the overall group and GDF-15 was 26.89% (95% CI = 12.93%, 42.58%) higher in high-risk versus low-risk drinkers. Drinking with meals did not appear to be related to GDF-15, but among those without CVD/diabetes, wine preference and adherence to the MDP were associated with lower GDF-15, especially when combined with high adherence to the Mediterranean diet.

Conclusions: Among older life-time drinkers in Madrid, Spain, high-risk drinking was positively associated with growth differentiation factor 15 (a biomarker of chronic disease burden). There was inconclusive evidence of a beneficial association for low-risk consumption.

KEYWORDS

Alcohol, GDF-15, life-time alcohol intake, Mediterranean drinking pattern, older adults, population-based study

INTRODUCTION

The relationship between intake of small quantities of alcohol and health is controversial. The quality of the evidence supporting the J-shaped association between alcohol and mortality, especially cardiovascular mortality, found in epidemiological studies [1–3] has been questioned due to several selection biases: (a) the ‘abstainer’ bias when abstainers are considered as reference; (b) the removal of former drinkers from the drinker categories when using current alcohol intake; and (c) the ‘healthy drinker/survivor’ bias due to overrepresentation of healthier drinkers who have survived the deleterious effects of alcohol [4]. A focus upon drinkers and categorizing alcohol use according to the average alcohol consumption during a person’s life-time may help to overcome these problems, and also allow for studying the effects of cumulative exposure to alcohol. In addition, reverse causation and residual confounding may also bias the results, but these could be mitigated by excluding participants in poorer health and adequately adjusting for potential confounders. Recent research aiming to overcome some of these methodological issues has found conflicting results for the relationship between light alcohol intake and all-cause mortality [5–7]; however, it also found some benefits for cardiovascular deaths [6], ischaemic heart disease [5,8] and diabetes [8], which were counterweighed by detrimental effects on other health outcomes, mainly cancer mortality [6] and cancer, injuries and communicable diseases [8]. Thus, a systematic analysis for the Global Burden of Disease Study 2016 in 195 locations [8] concluded that overall health risks rise with increasing alcohol intake and that the safest level of drinking is no drinking at all.

Given the complex relationship between alcohol and health, understanding the underlying mechanisms of action of alcohol is key to interpret the current literature. Previous research in this field has found beneficial effects of alcohol on several biomarkers of cardiometabolic risk [increased levels of high-density lipoprotein (HDL)-cholesterol and adiponectin, and lower levels of fibrinogen, leptin, glycated hemoglobin and insulin resistance] that could support a potential protective effect of low-to-moderate alcohol use on ischaemic heart disease [9,10]. However, given that alcohol use is a leading cause of disease, disability and death throughout the world [11], it would be sensible to study its association with a biomarker of chronic disease burden, especially in older adults, as alcohol may have cumulative health effects with long induction periods. In this regard, growth differentiation factor 15 (GDF-15) is a cytokine produced in response to oxidative, metabolic and inflammatory stress [12,13] that has been recognized as a

biomarker of chronic disease burden due to its reported association with mortality and many chronic diseases, such as cardiovascular disease (CVD), insulin resistance and Type 2 diabetes, neurodegenerative diseases, chronic renal disease and several cancers [13–15] as well as with the prognosis of heart failure, coronary artery disease and atrial fibrillation [13,16–18]. However, we are not aware of previous studies assessing the relationship between alcohol use and GDF-15.

Therefore, the purpose of our study is to add to the debated relationship between alcohol and health in older adults from a Mediterranean country including whether, as well as average alcohol intake, the type of alcoholic beverage or the context of drinking might also influence health, which is unclear. To do that, we examined: (1) the association of average life-time alcohol consumption with GDF-15 in older drinkers; and (2) the association of several patterns of alcohol consumption typical of the Mediterranean basin, such as wine preference, drinking only with meals, adherence to the Mediterranean diet and a combination of both, with GDF-15, separately among individuals with CVD or diabetes and those without them, as GDF-15 is a strong biomarker of chronic disease burden. We hypothesized that a higher average alcohol intake and a lower adherence to the Mediterranean drinking patterns would be related to higher levels of GDF-15.

METHODS

Study design and participants

We used data from the baseline wave of the Seniors-ENRICA-2 cohort [19,20]. Participants were selected between 2015 and 2017 by sex- and district-stratified random sampling of all community-dwelling individuals aged 65 years and older holding a national health-care card and living in two districts of the city of Madrid (Spain) and four surrounding large towns. An initial telephone call was made to the selected participants to explain the study, invite them to participate and obtain initial consent, and was followed by a mailed letter of invitation with detailed written information regarding the study. In a second telephone call a few days later, verbal consent to participate was confirmed and information on socio-demographic data, life-styles, self-rated health, health-related quality of life, use of health-care services and morbidity was obtained through a computer-assisted telephone interview by lay trained personnel. Then, two home visits were conducted: in the first visit, nurses obtained an informed written consent from each participant and collected biological samples; in the

second visit, lay trained personnel performed a physical examination, including anthropometry and blood pressure measurements, checked reported medications against drug packages kept at home and obtained a diet history. The Clinical Research Ethics Committee of 'La Paz' University Hospital in Madrid approved the study.

From the initial sample of 3273 participants in the Seniors-ENRICA-2 study, we excluded 473 individuals with no information on life-time alcohol consumption, 234 without GDF-15 measures and 61 with missing data on potential confounders of the association between alcohol consumption and GDF-15. Additionally, we excluded 454 life-time abstainers, so the sample for the main analyses comprised 2051 individuals who were or had been alcohol drinkers at any point in their lives (Supporting information, Fig. S1). Compared with participants included in the main analyses, life-time abstainers and those excluded due to missing data were older, more frequently women and never smokers, had lower educational level, were more physically active and less sedentary and had a higher body mass index (BMI) (Supporting information, Table S1).

Study variables

Alcohol consumption patterns

Life-time alcohol consumption was estimated using the self-reported amount and frequency of the main types of alcoholic beverages consumed by the participants during each decade of their lives (10–19, 20–29, 30–39, 40–49, 50–59, 60–69 and ≥ 70 years). Alcohol content of each beverage was estimated using standard composition tables [21,22]. This information was complemented with that obtained through a validated diet history developed from the version used in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort study in Spain [23], which collected habitual food and beverage consumption in the previous year by occasion of intake, and was used to estimate current consumption. Also, binge drinking was ascertained by asking the participants if they had drunk ≥ 8 standard units for men or ≥ 6 for women during any drinking session in the preceding 30 days [21]. In Spain, the estimated alcohol standard unit is 10 g of pure alcohol [24]. We then derived the following variables:

1. Average life-time alcohol intake: participants were classified into: (a) occasional drinkers: ≤ 1.43 g/day (equivalent to ≤ 1 standard unit/week); (b) low-risk drinkers: > 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women; (c) moderate-risk drinkers: > 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women; and (d) high-risk drinkers: > 40 g/day for men and > 20 g/day for women, or binge drinkers [7]. Former drinkers were included in the drinking categories according to their alcohol consumption in the past.
2. Life-time beverage preference: a preference for a specific type of alcoholic beverage (wine or other) was considered when more than 80% of life-time alcohol intake was derived from such drink [21]. Participants were classified as: (a) those with preference for wine; and (b) those with preference for other drinks or with no

preference whatsoever; the latter were combined in a single category because of the low sample size of the groups with preference for beer or other drinks.

3. Current drinking with meals: participants were classified as: (a) those who drank only with meals (lunch and dinner); and (b) those who drank either only outside meals or at any time.
4. Current adherence to the Mediterranean diet: this was assessed with the Mediterranean Diet Adherence Screener (MEDAS) excluding the wine component, thus ranging from 0 (lowest) to 13 (highest adherence) [25]. Participants were classified as: (a) those with lower adherence to the Mediterranean diet (MEDAS score excluding wine \leq the median; that is, 7); and (b) those with higher adherence (MEDAS score excluding wine > 7).

Using these variables, we classified the participants into those who adhered to a Mediterranean drinking pattern (MDP), defined as low-risk drinking with preference for wine and one of the following: (a) drinking only with meals; or (b) higher adherence to the Mediterranean diet; or (c) drinking only with meals or higher adherence to the Mediterranean diet [26]; and those who did not fit this definition, who were considered as non-adherers to the MDP. Drinking both during meals and accompanied by a Mediterranean diet are typical habits of the Mediterranean area.

GDF-15

Fasting blood samples were collected from each participant at the first home visit in rapid serum tubes with thrombin-based clot activator and polymer gel (Becton Dickinson, Franklin Lakes, NJ, USA), which were centrifuged at 2520 g for 10 minutes. Serum was aliquoted and frozen at -80°C and stored up to 3.6 years in the Department of Preventive Medicine and Public Health at the Universidad Autónoma de Madrid. GDF-15 was measured in the frozen samples at the Department of Laboratory Medicine of 'La Paz' University Hospital by an electrochemiluminescence Elecsys[®] immunoassay method using a cobas[®] 6000 analyzer (Roche Diagnostics, Basel, Switzerland). The interassay 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.

The reference values and clinically meaningful differences for GDF-15 are not well established. Doerstling *et al.* [27] estimated GDF-15 age-dependent centile values in a sample of 268 apparently healthy older adults, and found median values (5th–95th percentiles) of 838 (478–1470), 1066 (608–1868) and 1354 (772–2375) pg/ml at the ages of 60, 70 and 80 years, respectively.

Potential confounders

We also collected current information on socio-demographic and life-style characteristics including sex (self-reported), age (calculated using the date of birth), educational level (primary or less, secondary or university), tobacco smoking (never, former or current), leisure-time

physical activity (metabolic equivalents of task-hour/week) [19] and sedentary behaviour (time spent watching TV in hours/day) [19]. Energy intake (kcal/day) was obtained from the diet history, and the BMI was calculated as the weight (in kg) divided by the squared height (in m), both measured by standardized procedures [28]. Fasting serum glucose (mg/dl), creatinine (mg/dl), triglycerides (mg/dl), total cholesterol (mg/dl), high-density lipoprotein (HDL)-cholesterol (mg/dl) and low-density lipoprotein (LDL)-cholesterol (mg/dl) (for triglycerides ≥ 250 mg/dl) were measured with colorimetric enzymatic methods using Atellica[®] solution (Siemens Healthineers, Erlangen, Germany), and LDL-cholesterol was calculated with the Friedewald formula ($\text{LDL} = \text{total cholesterol} - \text{triglycerides}/5 - \text{HDL}$) for triglycerides < 250 mg/dl. Serum interleukin (IL)-6 (pg/ml), N-terminal pro-B-type natriuretic peptide (NT-proBNP) (pg/ml) and high-sensitivity cardiac troponin T (cTnT-hs) (pg/ml) were measured by an electrochemiluminescence Elecsys[®] immunoassay method using a cobas[®] 6000 analyzer (Roche Diagnostics). Blood pressure (mmHg) was measured three times at 1–2-minute intervals under standardized conditions using validated devices (Omron model M6), and the average of the second and third measurements was used for analyses. Lastly, CVD was ascertained by asking the study participants if they had been previously diagnosed with myocardial infarction, stroke or heart failure, and diabetes if they had a fasting blood glucose ≥ 126 mg/dl, or reported having been diagnosed with diabetes or had been prescribed anti-diabetic medication.

Statistical analysis

Differences in the participants' characteristics among categories of life-time alcohol consumption status were analyzed with χ^2 tests, one-way analysis of variance or Kruskal–Wallis tests, as appropriate.

The association between the average amount of alcohol consumed by drinkers during their life-time and GDF-15 concentrations was summarized with mean percentage differences per 1 g/day increment in alcohol intake and their 95% confidence intervals (CIs) overall, and by categories of life-time alcohol consumption status (occasional, low-, moderate- and high-risk drinkers) using interaction terms defined as the product of average life-time alcohol consumption by categories of life-time alcohol consumption status.

Analyses were conducted using linear regression models with log-transformed GDF-15 as the dependent variable; thus, mean percentage differences were calculated by subtracting 1 from the exponentiated β coefficients, and multiplying the result by 100. We built five models with incremental adjustment for potential confounders: model 0 was unadjusted; model 1 adjusted for sex, age and educational level; model 2 further adjusted for tobacco smoking, energy intake, MEDAS score excluding the wine component, leisure-time physical activity and time watching TV; and model 3 further adjusted for BMI, glucose, LDL-cholesterol, systolic blood pressure (SBP) and log-transformed serum creatinine.

Additionally, associations of life-time alcohol consumption status, life-time beverage preference, current drinking with meals, current

adherence to the Mediterranean diet and the three definitions of the MDP with GDF-15 levels were also summarized with mean percentage differences in GDF-15 among categories of these variables obtained using the same statistical methods.

Given that GDF-15 is a strong biomarker of chronic disease burden, the statistical models used interaction terms defined as the product of average life-time alcohol consumption and alcohol consumption patterns by presence of CVD and diabetes, and results are presented separately for individuals with CVD or diabetes and those without them.

We also conducted a number of additional analyses: (1) further adjusting for biomarkers of inflammation (IL-6) or myocardial stress/damage (NT-proBNP, cTnT-hs); (2) including those individuals who were never drinkers; (3) including former drinkers in a separate category; (4) without stratification by presence of CVD and diabetes; (5) imputing missing values using multiple imputation by chained equations; and (6) using current alcohol intake estimated with the validated diet history instead of life-time alcohol intake. The associations of covariates (including biomarkers of CVD) with GDF-15 levels were also examined. Finally, we assessed whether socio-demographic and life-style variables modified the study associations by testing interaction terms defined as the product of average life-time alcohol consumption by categories of such variables.

Statistical significance was set at two-sided P -value < 0.05 . Analyses were performed with Stata[®], version 15 (StataCorp LLC, College Station, TX, USA). Code details are presented in the Supporting information, Methodological Appendix. GDF-15, creatinine, IL-6, NT-proBNP and cTnT-hs were log-transformed to reduce the skewness of their distributions. As our sample was not representative of the population living in the Madrid region, our analyses did not account for the sampling design. Finally, as the analysis plan was not pre-registered, the results should be considered exploratory.

RESULTS

Study participants had a mean age of 71.4 years; 55.4% were men. As expected, GDF-15 concentrations were higher among participants with CVD or diabetes than among those without [geometric means of 1787 (95% CI = 1696, 1881) and 1116 (95% CI = 1097, 1139) pg/ml, respectively]. Participants with CVD or diabetes were also older, more frequently men, less frequently never smokers, performed less physical activity, had higher average life-time alcohol intake, BMI, glycaemia, SBP and creatinine, but had lower LDL-cholesterol than those without CVD and diabetes, although participants with CVD had lower alcohol intake and SBP (Supporting information, Table S2). High-risk drinkers were younger, more frequently men and less frequently never smokers, and occasional drinkers had lower energy intake and levels of serum creatinine. Among participants without CVD and diabetes, high-risk drinkers were also more physically active and had a higher glycaemia, whereas occasional drinkers had a lower educational level. Among those with CVD or diabetes, high-risk drinkers had higher BMI (Table 1).

TABLE 1 Characteristics of older life-time drinkers by categories of life-time alcohol consumption status, stratified by presence of cardiovascular disease and diabetes

	Participants without CVD and diabetes				P-value ^a	Participants with CVD or diabetes				P-value ^a
	Occasional drinkers n = 271	Low-risk drinkers n = 919	Moderate-risk drinkers n = 274	High-risk drinkers n = 135		Occasional drinkers n = 85	Low-risk drinkers n = 231	Moderate-risk drinkers n = 78	High-risk drinkers n = 58	
Sex: men, no. (%)	51 (18.8)	511 (55.6)	176 (64.2)	116 (85.9)	< 0.001	16 (18.8)	155 (67.1)	54 (69.2)	56 (96.6)	< 0.001
Age (years)	71.7 (4.5)	71.3 (4.2)	71.5 (4.1)	70.2 (3.8)	0.02	72.1 (4.3)	71.9 (4.4)	72.1 (5.0)	70.1 (4.3)	0.03
Educational level: primary or less, no. (%)	185 (68.3)	525 (57.1)	177 (64.6)	81 (60.0)	0.006	58 (68.2)	144 (62.3)	52 (66.7)	40 (69.0)	0.39
Tobacco smoking: never smoker, no. (%)	162 (67.2)	443 (48.2)	120 (43.8)	29 (21.5)	< 0.001	58 (68.2)	95 (41.1)	23 (29.5)	10 (17.2)	< 0.001
Leisure-time physical activity (MET-hours/week)	25.6 (16.6)	30.4 (20.0)	30.9 (18.8)	33.4 (21.2)	< 0.001	22.0 (15.5)	27.0 (18.9)	27.3 (19.4)	27.5 (22.3)	0.20
Time watching TV (hours/day)	3.1 (1.7)	3.1 (1.5)	3.3 (1.5)	3.3 (1.6)	0.18	3.4 (1.6)	3.3 (1.5)	3.2 (1.6)	3.3 (1.9)	0.94
Energy intake (kcal/day)	1802 (265)	1962 (308)	2095 (372)	2288 (426)	< 0.001	1764 (261)	1960 (309)	2073 (380)	2287 (476)	< 0.001
Average life-time alcohol intake (g/day)	0.7 (0.4)	7.2 (4.7)	22.4 (8.3)	62.3 (32.6)	< 0.001	0.7 (0.4)	7.4 (5.7)	22.6 (8.4)	76.5 (38.9)	< 0.001
MEDAS score excluding the wine component	6.9 (1.6)	6.9 (1.7)	6.8 (1.7)	6.8 (1.6)	0.44	7.0 (1.6)	6.9 (1.7)	7.2 (2.0)	6.8 (1.8)	0.24
Body mass index (kg/m ²)	27.4 (4.5)	27.2 (3.9)	27.6 (4.0)	27.8 (3.7)	0.21	29.1 (5.8)	28.2 (4.3)	29.5 (5.9)	30.3 (4.6)	0.005
Serum fasting glucose (mg/dl)	93 (10.9)	92 (11.5)	94 (10.4)	95 (12.5)	0.003	126 (36.4)	125 (35.1)	128 (32.7)	133 (35.7)	0.68
Serum LDL-cholesterol (mg/dl)	120 (26.5)	118 (27.3)	119 (28.2)	117 (29.0)	0.68	101 (27.9)	96 (25.9)	101 (30.4)	91 (24.2)	0.07
Systolic blood pressure (mmHg)	133 (18.4)	134 (17.7)	136 (18.1)	136 (15.4)	0.16	138 (19.8)	135 (17.5)	136 (19.7)	139 (18.2)	0.27
Serum creatinine (mg/dl)	0.74 (0.18)	0.82 (0.29)	0.83 (0.18)	0.86 (0.15)	< 0.001	0.75 (0.18)	0.88 (0.23)	0.90 (0.25)	0.89 (0.18)	< 0.001
GDF-15 (pg/ml), geometric mean (GSD)	1115 (1.51)	1106 (1.52)	1142 (1.54)	1132 (1.42)	0.70	1800 (1.72)	1710 (1.79)	1786 (1.66)	2101 (1.75)	0.10

Values are means (standard deviations) unless indicated.

CVD = cardiovascular disease; GDF-15 = growth differentiation factor 15; GSD = geometric standard deviation factor; LDL = low-density lipoprotein; MEDAS = Mediterranean Diet Adherence Screener score; MET = metabolic equivalent of task.

Occasional drinkers ≤ 1.43 g/day; low-risk drinkers > 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women; moderate-risk drinkers > 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women; high-risk drinkers > 40 g/day for men and > 20 g/day for women, or binge drinkers.

^aP-value across categories of life-time alcohol consumption status analyzed with χ^2 tests, one-way analysis of variance or Kruskal–Wallis tests, as appropriate.

The mean percentage differences (95% CI) in GDF-15 per 1 g/day increment in the average life-time alcohol intake among all drinkers and each category of life-time alcohol consumption status, stratifying by presence of cardiovascular disease and diabetes are presented in Table 2. Among participants without CVD and diabetes, the average life-time amount of alcohol consumed was not associated with GDF-15 concentrations when all drinkers were taken together, with mean percentage differences in GDF-15 per 1 g/day increment in alcohol intake of 0.09% (95% CI = -0.02%, 0.20%). However, when analyses were stratified by categories of life-time alcohol consumption status, although no evidence of an association was found for occasional, low-risk or moderate-risk drinkers, GDF-15 levels increased by 0.27% (95% CI = 0.06%, 0.48%) per 1 g/day increment in alcohol among high-risk drinkers. On the contrary, among participants with CVD or diabetes, the average life-time amount of alcohol consumed was associated with higher GDF-15 concentrations when all drinkers were taken together, with mean percentage differences in GDF-15 per 1 g/day increment in alcohol of 0.19% (95% CI = 0.05%, 0.33%). In this group, no associations were found when stratifying by categories of life-time alcohol consumption status, possibly because of the small number of subjects in each category.

With regard to alcohol consumption patterns, Table 3 shows the mean percentage differences (95% CI) in GDF-15 across categories of

each pattern, stratifying by presence of cardiovascular disease and diabetes. Life-time alcohol consumption status was not associated with GDF-15 among the healthier group, whereas among the group with CVD or diabetes, GDF-15 was 26.89% (95% CI = 12.93%, 42.58%) higher in high-risk drinkers and 12.75% (95% CI = 1.92%, 24.72%) higher in occasional drinkers compared with low-risk drinkers. Participants with a preference for wine had a tendency to have lower GDF-15 levels in both groups that only reached statistical significance in the fully adjusted model among the healthier participants, where GDF-15 was 5.15% (95% CI = 0.31%, 9.76%) lower than in those with no wine preference. Drinking with meals was not related to GDF-15 in any of the groups, but among participants without CVD and diabetes, adherence to the MDP was associated with lower GDF-15, strongly when adherence to the Mediterranean diet was included in the definition: 8.07% (95% CI = 0.06%, 15.44%) lower levels for low-risk drinkers with preference for wine and who drank only with meals, 11.46% (95% CI = 2.95%, 19.23%) lower levels for low-risk drinkers with preference for wine and MEDAS score excluding wine > 7, and 7.39% (95% CI = 0.90%, 13.45%) lower levels for low-risk drinkers with preference for wine and who drank only with meals or had a MEDAS score excluding wine > 7 (Table 3).

Additional analyses further adjusting for biomarkers of inflammation and myocardial stress/damage did not substantially modify the

TABLE 2 Association of the average life-time amount of alcohol consumed by older life-time drinkers with GDF-15 by categories of life-time alcohol consumption status, stratified by presence of cardiovascular disease and diabetes

		Mean percentage differences ^a (%) in GDF-15 per 1 g/day increment in alcohol (95% CI)			
	<i>n</i>	Model 0	Model 1	Model 2	Model 3
Participants without CVD and diabetes					
All drinkers	1599	0.11 (0.00, 0.23)*	0.07 (−0.05, 0.19)	0.07 (−0.04, 0.19)	0.09 (−0.02, 0.20)
Occasional drinkers	271	−2.41 (−14.90, 11.93)	−1.82 (−13.90, 11.95)	−2.83 (−14.62, 10.60)	−0.06 (−11.53, 12.90)
Low-risk drinkers	919	0.66 (0.04, 1.28)*	0.03 (−0.62, 0.67)	−0.04 (−0.67, 0.60)	−0.10 (−0.70, 0.50)
Moderate-risk drinkers	274	0.13 (−0.51, 0.77)	−0.10 (−0.75, 0.55)	−0.12 (−0.76, 0.53)	−0.11 (−0.71, 0.50)
High-risk drinkers	135	0.23 (−0.00, 0.46)	0.22 (−0.00, 0.45)	0.26 (0.04, 0.48)*	0.27 (0.06, 0.48)*
Participants with CVD or diabetes					
All drinkers	452	0.16 (0.01, 0.31)*	0.18 (0.04, 0.33)*	0.18 (0.03, 0.33)*	0.19 (0.05, 0.33)**
Occasional drinkers	85	−5.84 (−26.80, 21.10)	−3.61 (−24.20, 22.59)	−6.43 (−26.18, 18.62)	−9.46 (−27.59, 13.20)
Low-risk drinkers	231	−0.48 (−1.70, 0.77)	−0.50 (−1.69, 0.71)	−0.67 (−1.85, 0.51)	−0.51 (−1.62, 0.61)
Moderate-risk drinkers	78	1.18 (−0.02, 2.41)	0.77 (−0.40, 1.95)	0.83 (−0.33, 1.99)	0.89 (−0.20, 2.00)
High-risk drinkers	58	−0.13 (−0.43, 0.17)	−0.07 (−0.36, 0.21)	−0.09 (−0.38, 0.19)	−0.10 (−0.37, 0.17)

CI = confidence interval; CVD = cardiovascular disease; GDF-15 = growth differentiation factor 15; LDL = low-density lipoprotein; MET = metabolic equivalent of task.

Occasional drinkers: ≤ 1.43 g/day; low-risk drinkers: > 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women; moderate-risk drinkers: > 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women; high-risk drinkers: > 40 g/day for men and > 20 g/day for women or binge drinkers.

Model 0: unadjusted linear regression model with interaction terms defined as the product of average life-time alcohol consumption by the presence of CVD and diabetes and by categories of life-time alcohol consumption status.

Model 1: as model 0 and adjusted for sex, age and educational level (primary or less, secondary or university).

Model 2: as model 1 and further adjusted for smoking status (never, former or current), energy intake (kcal/day), Mediterranean Diet Adherence Screener score excluding the wine component, leisure-time physical activity (METs-hours/week) and TV-watching time (hours/day).

Model 3: as model 2 and further adjusted for body mass index (kg/m²), serum fasting glucose (mg/dl), serum LDL-cholesterol (mg/dl), systolic blood pressure (mmHg) and log-transformed serum creatinine (mg/dl).

*P < 0.05; **P < 0.01.

^a(Exponentiated differences in log-transformed values of GDF-15 - 1) × 100.

TABLE 3 Association of alcohol consumption patterns with GDF-15 in older life-time drinkers, stratified by presence of cardiovascular disease and diabetes

		Mean percentage differences ^a (%) in GDF-15 (95% CI)			
	<i>n</i>	Model 0	Model 1	Model 2	Model 3
Participants without CVD and diabetes					
Life-time alcohol consumption ^b					
Occasional drinkers	271	0.82 (−5.14, 7.15)	3.95 (−2.10, 10.37)	3.98 (−2.01, 10.33)	3.57 (−2.07, 9.52)
Low-risk drinkers	919	Ref.	Ref.	Ref.	Ref.
Moderate-risk drinkers	274	3.23 (−2.84, 9.69)	1.55 (−4.18, 7.62)	1.43 (−4.25, 7.45)	2.07 (−3.33, 7.77)
High-risk drinkers	135	2.31 (−5.67, 10.97)	1.66 (−6.02, 9.96)	0.72 (−6.94, 9.01)	2.05 (−5.29, 9.95)
Life-time beverage preference					
Other	1280	Ref.	Ref.	Ref.	Ref.
Wine	319	−1.37 (−6.66, 4.23)	−5.63 (−10.53, −0.46)*	−4.68 (−9.58, 0.49)	−5.15 (−9.76, −0.31)*
Current drinking with meals					
Other	955	Ref.	Ref.	Ref.	Ref.
Drinking only with meals	414	2.29 (−2.81, 7.66)	0.89 (−3.99, 6.03)	0.28 (−4.52, 5.32)	−0.44 (−4.98, 4.32)
MDP (drinking only with meals) ^c					
No MDP	1480	Ref.	Ref.	Ref.	Ref.
MDP	95	−2.31 (−11.05, 7.28)	−7.55 (−15.47, 1.12)	−6.80 (−14.70, 1.82)	−8.07 (−15.44, −0.06)*
MDP (MEDAS excluding wine >7) ^c					
No MDP	1522	Ref.	Ref.	Ref.	Ref.
MDP	77	−11.00 (−19.71, −1.34)*	−12.85 (−21.01, −3.84)**	−12.05 (−20.20, −3.06)**	−11.46 (−19.23, −2.95)*
MDP (drinking only with meals or MEDAS excluding wine > 7) ^c					
No MDP	1449	Ref.	Ref.	Ref.	Ref.
MDP	150	−3.31 (−10.35, 4.30)	−7.34 (−13.82, −0.36)*	−6.87 (−13.33, 0.06)	−7.39 (−13.45, −0.90)*
		Mean percentage differences ^a (%) in GDF-15 (95% CI)			
	<i>n</i>	Model 0	Model 1	Model 2	Model 3
Participants with CVD or diabetes					
Life-time alcohol consumption					
Occasional drinkers	85	5.26 (−5.87, 17.71)	10.94 (−0.44, 23.63)	11.39 (0.10, 23.96)*	12.75 (1.92, 24.72)*
Low-risk drinkers	231	Ref.	Ref.	Ref.	Ref.
Moderate-risk drinkers	78	4.42 (−6.96, 17.19)	3.95 (−6.89, 16.04)	4.12 (−6.61, 16.09)	4.50 (−5.69, 15.81)
High-risk drinkers	58	22.86 (7.94, 39.84)***	25.30 (10.66, 41.86)***	25.34 (10.79, 41.80)***	26.89 (12.93, 42.58)***
Life-time beverage preference					
Other	356	Ref.	Ref.	Ref.	Ref.
Wine	96	−10.16 (−18.82, −0.57)*	−12.85 (−20.91, −3.96)**	−12.33 (−20.35, −3.52)**	−8.65 (−16.60, 0.05)
Current drinking with meals					
Other	269	Ref.	Ref.	Ref.	Ref.
Drinking only with meals	107	6.77 (−3.33, 17.93)	2.80 (−6.61, 13.17)	2.42 (−6.90, 12.67)	5.11 (−4.04, 15.15)
MDP (drinking only with meals) ^c					
No MDP	414	Ref.	Ref.	Ref.	Ref.
MDP	27	11.09 (−6.81, 32.43)	8.01 (−8.67, 27.74)	7.24 (−9.16, 26.59)	7.29 (−8.25, 25.47)
MDP (MEDAS excluding wine > 7) ^c					
No MDP	432	Ref.	Ref.	Ref.	Ref.
MDP	20	−5.65 (−22.88, 15.43)	−5.02 (−21.63, 15.12)	−3.77 (−20.41, 16.33)	−1.35 (−17.59, 18.10)

(Continues)

TABLE 3 (Continued)

	n	Mean percentage differences ^a (%) in GDF-15 (95% CI)			
		Model 0	Model 1	Model 2	Model 3
MDP (drinking only with meals or MEDAS excluding wine > 7) ^c					
No MDP	406	Ref.	Ref.	Ref.	Ref.
MDP	46	4.91 (-8.55, 20.35)	0.75 (-11.64, 14.88)	2.15 (-10.28, 16.29)	1.89 (-9.88, 15.19)

CI = confidence interval; CVD = cardiovascular disease; GDF-15 = growth differentiation factor 15; MDP = Mediterranean drinking pattern; LDL = low-density lipoprotein; MEDAS = Mediterranean Diet Adherence Screener; MET = metabolic equivalent of task.

Model 0: Unadjusted linear regression model with interaction terms defined as the product of the corresponding pattern by the presence of CVD and diabetes.

Model 1: as model 0 and adjusted for sex, age, and educational level (primary or less, secondary or university).

Model 2: as model 1 and further adjusted for smoking status (never, former or current), energy intake (kcal/day), Mediterranean Diet Adherence Screener score excluding the wine component, leisure-time physical activity (METs-hours/week), and TV-watching time (hours/day).

Model 3: as model 2 and further adjusted for body mass index (kg/m²), serum fasting glucose (mg/dl), serum LDL-cholesterol (mg/dl), systolic blood pressure (mmHg) and log-transformed serum creatinine (mg/dl).

None of the models adjusts for the other alcohol consumption patterns.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

^a(Exponentiated differences in log-transformed values of GDF-15 - 1) \times 100.

^bOccasional drinkers: ≤ 1.43 g/day; low-risk drinkers: > 1.43 to ≤ 20 g/day for men and > 1.43 to ≤ 10 g/day for women; moderate-risk drinkers: > 20 to ≤ 40 g/day for men and > 10 to ≤ 20 g/day for women; high-risk drinkers: > 40 g/day for men and > 20 g/day for women or binge drinkers.

^cLow-risk drinker with preference for wine and one of the following: (a) drinking only with meals; (b) MEDAS excluding wine > 7 ; or (c) drinking only with meals or MEDAS excluding wine > 7 .

results (Supporting information, Tables S3 and S4), despite the positive association in our study between the life-time alcohol intake and the levels of cardiac biomarkers among individuals with CVD or diabetes [mean percentage differences per 1 g/day increment in alcohol intake of 0.18% (95% CI = 0.05%, 0.50%) for cTnT-hs and 0.39% (95% CI = 0.12%, 0.66%) for NT-proBNP]. Among participants without CVD and diabetes, compared with low-risk drinkers, GDF-15 levels were 9% higher both in never drinkers when they were included in the analyses (Supporting information, Table S5) and in former drinkers when they were included in a separate category (Supporting information, Table S6). Analyses without stratification by the presence of CVD and diabetes showed a positive association between the average life-time amount of alcohol consumed and GDF-15, which was stronger in high-risk drinkers, although was not statistically significant (Supporting information, Table S7). Also in the total sample, GDF-15 was higher in high-risk drinkers and occasional drinkers compared with low-risk drinkers and lower in participants with wine preference, and with adherence to the MDP when adherence to the Mediterranean diet was included in the MDP definition (Supporting information, Table S8); never drinkers and former drinkers had higher GDF-15 levels than low-risk drinkers (Supporting information, Table S9). Analyses imputing missing data showed consistent results, although associations attenuated in the group with CVD or diabetes (Supporting information, Tables S10 and S11). Analyses using current alcohol intake also showed consistent results, except that among participants with CVD or diabetes, high-risk drinkers did not have statistically significant higher levels of GDF-15 than low-risk drinkers, and a positive association between the average current alcohol intake and GDF-15 levels was found for low- and moderate-risk drinkers (Supporting information, Tables S12 and S13).

Among the covariates used in the analyses, female sex, age, tobacco smoking, serum creatinine, cTnT-hs and IL-6 were strongly associated with higher levels of GDF-15 (Supporting information, Table S14). Finally, the association between the average life-time amount of alcohol and GDF-15 seemed somewhat stronger among men, younger individuals and former or current smokers in the group without CVD and diabetes, and among men, never or former smokers and more sedentary individuals in the group with CVD or diabetes; of note, however, is that a statistically significant interaction was found only for tobacco smoking among those without CVD and diabetes (Supporting information, Fig. S2).

DISCUSSION

In this study of older life-time alcohol drinkers in Spain, the relationship between the average amount of alcohol consumed during their life-time and GDF-15 varied with their health status. Among those free of CVD and diabetes, higher alcohol intakes were associated with higher levels of GDF-15 in high-risk drinkers, but no association was evident in those with lower intakes. On the contrary, among individuals with CVD or diabetes, GDF-15 rose with increasing life-time alcohol intake in the overall group, although a J-shaped relationship between life-time alcohol and GDF-15 was suggested by the fact that GDF-15 levels of low-risk drinkers were much lower than those of high-risk drinkers and also lower than those of occasional drinkers. With regard to patterns of alcohol consumption, participants free of CVD and diabetes with a life-time preference for wine or with a high adherence to the Mediterranean diet had lower GDF-15 levels, which led to an inverse relationship between the MDP and GDF-15, especially when the Mediterranean diet was part of the MDP definition.

Most of the found associations are modest, and might be of limited clinical relevance for individual patients. However, as each 25% increment in GDF-15 has been previously associated with hazard ratios for all-cause mortality over 8 years of 1.80 (95% CI = 1.48, 2.20) in unadjusted models and 1.38 (95% CI = 1.12, 1.71) when adjusting for age, sex, smoking status, NT-proBNP and cystatin C, a 1.5% increment in GDF-15 would be related to a 2% increase in total mortality, which is of public health relevance due to the high mortality rate of older adults.

These analyses have been carefully designed to account for the main methodological issues inherent in the observational research on the relationship between alcohol and health. First, to measure alcohol intake, we used life-time consumption which, despite being more prone to recall error than current intake, provides an estimate of cumulative exposure to alcohol [3]. Also, this approach does not remove former drinkers from the drinking categories, but includes them in their corresponding categories according to their life-time alcohol intake, thus preventing the 'abstainer' bias. Secondly, analyses were restricted to life-time drinkers to avoid potential confounding due the reported life-style and health differences between life-time abstainers and drinkers [29]. This strategy also mitigates the potential 'healthy drinker/survivor' bias that may arise in cohorts of older adults, where only healthier drinkers who survived the deleterious effects of alcohol are able to participate [4]. Thirdly, analyses were adjusted for many socio-demographic, life-style and clinical variables to palliate residual confounding. Fourthly, although the study was cross-sectional, as the time-points of alcohol consumption assessments preceded GDF-15 measurements, we assumed that alcohol intake would have an effect on GDF-15 and not the other way around; this allowed us to examine the potential for reverse causation by performing analyses separately by chronic disease status. This last approach led to different results in each group, which may be partly explained by differences in the degree of reverse causation. There is evidence that, in older adults, alcohol consumption is an indicator of good health [30] and that health deterioration may lead to a subsequent reduction, and even cessation, of alcohol consumption [31]. Therefore, although it is unlikely that health status could have much influenced alcohol intake in those individuals with better health, it might have indeed played an important role in those who had developed CVD or diabetes. In fact, individuals in this latter group had a much greater mean reduction in alcohol intake from when they were in their 40s to their 60s than those in the healthier group [8.3 g/day (95% CI = 6.0, 10.7) versus 3.6 (95% CI = 2.8, 4.5)], so it is likely that health decline may have contributed to it. Any conclusions drawn from participants free of CVD and diabetes might, therefore, be more reliable. In any case, our study did not find any evidence of potential benefits of low amounts of alcohol on GDF-15 concentration, but a detrimental association of heavy consumption. Although GDF-15 is only a biomarker and no extension to clinical outcomes can be made, in our sample of drinkers a doubling increase in GDF-15 was associated with a 54% higher risk of incident CVD over 2.4 years. Therefore, the detrimental association of heavy consumption with GDF-15 is in line with much of the recent research on the relationship between

alcohol and health [6,8,9,32,33]. Because of the relatively low levels of GDF-15 in the group without CVD and diabetes, any effects of alcohol would be difficult to reveal; hence the lack of observed differences across categories of alcohol consumption status, although higher GDF-15 levels were present in never and former drinkers versus low-risk drinkers, and in high-risk drinkers with increasing life-time alcohol intake. However, among individuals with CVD or diabetes, on one hand, the observed higher GDF-15 levels in high-risk versus low-risk drinkers may be explained by a greater susceptibility of less healthy individuals to the detrimental effects of alcohol, a notion that would be supported by the higher GDF-15 levels present in low- and moderate-risk drinkers with increasing current alcohol intake in this group. On the other hand, the fact that in our study, occasional drinkers' characteristics are more similar to those of never drinkers, for whom worse health and health-related habits than regular drinkers have been previously reported [29], than to those of the remaining categories of drinkers (Supporting information, Table S15), might explain the higher GDF-15 levels observed in occasional drinkers versus low-risk drinkers. However, this finding warrants further investigation.

Regarding alcohol consumption patterns, the lower GDF-15 levels found among wine drinkers in our study concurs with previous research that has linked wine consumption to lower risk of mortality [34], cardiovascular morbimortality [35] and diabetes [36], attributing the beneficial effects of wine to its high content in polyphenols [37]. In this sense, wine might contribute to the beneficial health effects of the Mediterranean diet when taken in moderation. Unlike other studies reporting a lower risk of all-cause, non-cardiovascular and cancer deaths [38] or frailty [39] in drinkers of alcohol preferentially with meals, we did not find any association with GDF-15. Lastly, in line with previous research where a MDP was associated with reduced mortality in younger individuals [34] and with a lower risk of frailty and falls in older adults [20,40], healthier participants who adhered to the MDP in our study had lower levels of GDF-15, especially when accompanied by a high adherence to the Mediterranean diet.

Even though this study aimed to overcome most of the potential methodological limitations of epidemiological research on alcohol and health, it still has some. First, its cross-sectional design does not allow us to draw definitive causal inferences. Secondly, alcohol intake was self-reported, and therefore prone to some degree of misclassification. Thirdly, GDF-15 was measured in frozen-stored samples and the possibility of variable concentration decay during long-term storage cannot be excluded, so some measurement error may have occurred. Fourthly, the unequal size of the participants' groups and in the categories of alcohol consumption has led to varying precision of the estimates of the main study association across groups/categories. Also, this issue entails a substantial challenge for appropriate confounder control; nevertheless, we have carefully considered the variables that may influence the association between alcohol consumption patterns and GDF-15 and accounted for them using four hierarchically adjusted regression models, obtaining fairly consistent results across models. In any case, as in most observational studies, we cannot rule out some residual confounding. Fifthly, this study was

conducted in older adults of a Mediterranean country, with distinct life-styles and drinking patterns [41], so our results may not be generalizable to other populations.

In conclusion, this study among older life-time drinkers from a Mediterranean country found a detrimental association of high-risk drinking with GDF-15, a biomarker of chronic disease burden, and no evidence of a beneficial association for low-risk alcohol consumption. Also, wine drinkers had lower levels of GDF-15, drinking with meals did not appear to have any bearing and the benefits of the MDP were stronger when accompanied by a high adherence to the Mediterranean diet. These results may have important practical implications, because they suggest that older adults cannot gain any health benefits from low alcohol intake, but their associated chronic conditions might be aggravated by heavy drinking.

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DECLARATION OF INTERESTS

None.

AUTHOR CONTRIBUTIONS

Rosario Ortolá: Conceptualization; data curation; formal analysis. **Esther García-Esquinas:** Data curation. **Antonio Buño-Soto:** Writing - review & editing-Supporting. **Adrián Carballo-Casla:** Writing - review & editing-Supporting. **Mercedes Sotos-Prieto:** Writing - review & editing-Supporting. **José Ramón Banegas:** Writing - review & editing-Supporting. **Fernando Rodríguez-Artalejo:** Conceptualization; funding acquisition.

ORCID

Rosario Ortolá  <https://orcid.org/0000-0001-6952-9533>

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SUPPORTING INFORMATION

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