Coffee consumption and total mortality in a Mediterranean prospective cohort

Adela M Navarro,[1,2] Miguel Á Martinez-Gonzalez,[1,3,4,5] Alfredo Gea,[1,3,4] Giuseppe Grosso,[6,7] José M Martín-Moreno,[8] Esther Lopez-Garcia,[9,10,11] Nerea Martin-Calvo,[1,3,4] and Estefanía Toledo[1,3,4]

[1]Department of Preventive Medicine and Public Health, School of Medicine, University of Navarra, Pamplona, Spain; [2]Department of Cardiology, Complejo Hospitalario de Navarra, Servicio Navarro de Salud Osasunbidea, Pamplona, Spain; [3]IdiSNA, Navarra Institute for Health Research, Pamplona, Spain; [4]Centro de Investigación Biomédica en Red Área de Fisiopatología de la Obesidad y la Nutrición (CIBEROBN), Madrid, Spain; [5]Department of Nutrition, Harvard TH Chan School of Public Health, Boston, MA; [6]Integrated Cancer Registry of Catania-Messina-Siracusa-Enna, Azienda Ospedaliera Policlinico-Universitaria "Vittorio Emanuele," Catania, Italy; [7]The Need for Nutrition Education/Innovation Programme (NNEdPro), University of Cambridge, Cambridge, United Kingdom; [8]Department of Preventive Medicine and Public Health & INCLIVA, Universidad de Valencia, Valencia, Spain; [9]Department of Preventive Medicine and Public Health, School of Medicine, Universidad Autónoma de Madrid, Madrid, Spain; [10]IdiPAZ (Instituto de Investigación Sanitaria Hospital Universitario La Paz), Madrid, Spain; and [11]CIBERESP (CIBER of Epidemiology and Public Health), Madrid, Spain

ABSTRACT

Background: The relation of coffee consumption with total mortality is controversial, because the available evidence is still inconsistent.

Objective: This study aimed to assess this association in a highly educated, middle-aged Mediterranean cohort.

Design: We analyzed data from 201,055 person-years of follow-up arising from 19,888 participants. Coffee consumption was obtained at baseline with the use of a previously validated semi-quantitative food-frequency questionnaire. Information on mortality was ascertained by permanent contact with the "Seguimiento Universidad de Navarra" (SUN) participants and their families, postal authorities, and consultation of the National Death Index. We used Cox regression models to estimate HRs and 95% CIs for mortality according to baseline total coffee consumption adjusted for potential confounders. Sex, age, and baseline adherence to the Mediterranean diet were considered as potential effect modifiers.

Results: Among the 19,888 participants, 337 died. Overall, in the multivariable adjusted analysis, we found a 22% lower risk of all-cause mortality for each 2 additional cups of total coffee per day (HR: 0.78; 95% CI: 0.66, 0.93). This association was stronger for participants aged ≥55 y (HR: 0.67; 95% CI: 0.52, 0.86) than for younger participants, who showed no significant association (P-interaction = 0.002).

Conclusion: In a Mediterranean cohort, we found an inverse linear association between total coffee consumption and the risk of all-cause mortality that was strongest among participants older than 54 y. *Am J Clin Nutr* 2018;108:1113–1120.

Keywords: coffee, caffeine, total mortality, polyphenols, Mediterranean diet

INTRODUCTION

Coffee is one of the most commonly consumed beverages worldwide. Its consumption was claimed as potentially detrimental for human health because of the short-term blood pressure–raising effect of caffeine (1) and its reported association with increased LDL cholesterol concentrations (2, 3). However, coffee contains highly concentrated antioxidant substances with potentially beneficial properties, e.g., chlorogenic acid, flavonoids, melanoidins, and various lipid-soluble compounds such as furans, pyrroles, and maltol (4). These components may counteract the potentially harmful effects of caffeine. Also, the methods for coffee preparation may determine the concentrations of the different compounds (5).

Several observational studies have reported a weak inverse association between coffee consumption and overall mortality. The strongest risk reductions for all-cause mortality have been observed for ≤4 cups of coffee/d, whereas no further risk reduction has been observed for higher intakes according to available meta-analyses (6–10). In addition, given the important

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Address correspondence to ET (e-mail: etoledo@unav.es).

Abbreviations used: CVD, cardiovascular disease; FFQ, food-frequency questionnaire; MedDiet, Mediterranean diet; MET, activity metabolic equivalent; SUN Project, Seguimiento Universidad de Navarra—University of Navarra Follow-Up Project.

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effect of high-quality dietary patterns in reducing all-cause mortality, it seems interesting to assess whether coffee consumption remains inversely associated with all-cause mortality even after controlling for adherence to a high-quality dietary pattern. In fact, among studies assessing the association between coffee consumption and the risk of death, only the Nurses' Health Studies I and II and the Health Professionals Follow-Up Study adjusted for the dietary pattern, and, more concretely, for the Alternate Healthy Eating Index (8). None of these studies have adjusted for adherence to the traditional Mediterranean diet (MedDiet), for which there is substantial evidence of benefits (11). In the present study, we analyzed the association of coffee consumption with all-cause mortality in a Mediterranean population of middle-aged university graduates.

METHODS

Study population

The methods and design of the SUN (Seguimiento Universidad de Navarra—University of Navarra Follow-Up) Project have been described elsewhere (12). Briefly, the SUN Project is a dynamic cohort assessing the relation between diet and chronic disease. It was developed inspired by the models of the Nurses' Health Studies and the Health Professionals Follow-Up Study. Recruitment started in December 1999 and is permanently open. After the initial questionnaire, follow-up questionnaires were mailed every other year to participants to update information on covariates and collect information on health outcomes which might have happened in the previous 2 y. Participants are middle-aged university graduates from different Spanish regions.

Among the available 22,320 participants recruited earlier than March 2014 (**Figure 1**), we excluded those with total energy intake outside of predefined limits (<1st or >99th percentile, $n = 404$) and those participants with no information during follow-up ($n = 2028$). Finally, our analyses comprised 19,888 participants.

Ethics

This study was conducted according to the guidelines laid down in the Declaration of Helsinki, and all procedures involving human subjects/patients were approved by the Institutional Review Board of the University of Navarra. Freely given informed consent, and voluntary completion of the baseline questionnaire were obtained from all participants according to the methods approved by our Institutional Review Board.

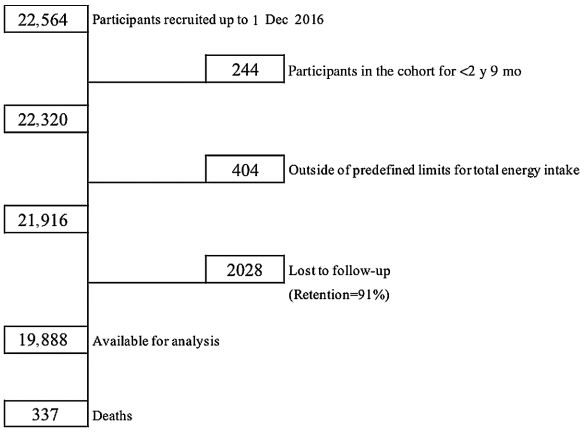

FIGURE 1 Flow chart of participants.

Coffee consumption assessment

Diet was assessed with the use of a previously validated Spanish semiquantitative food-frequency questionnaire (FFQ) (13–15). Participants were asked about their usual consumption of regular coffee and decaffeinated coffee (cup size, 50 cc) over the previous year. The FFQ included 9 possible categories for coffee consumption: "never/seldom," "1–3 servings/month," "1 serving/week," "2–4 servings/week," "5–6 servings/week," "1 serving/day," "2–3 servings/day," "4–6 servings/day," and "6+ servings/day."

Mortality assessment

Information on mortality and its cause was ascertained by permanent contact with the SUN participants and their families, by communication from postal authorities, and by periodic consultation of the National Death Index for those participants who were lost to follow-up.

Other covariates

BMI was calculated as the self-reported weight in kilograms over the square of height in meters (kg/m^2). Self-reported information about weight and height has been previously validated in this cohort (16). Information on leisure-time physical activity was collected with a validated questionnaire (17). To quantify leisure-time physical activity, an activity metabolic equivalent (MET) index was computed by assigning a multiple of resting metabolic rate (MET score) to each activity and calculating overall MET-hours per week. Adherence to the MedDiet was assessed by the a priori–defined Mediterranean Diet Score proposed by Trichopoulou et al. (18) (range from 0 to 9, with higher scores indicating greater adherence).

Statistical analysis

Coffee consumption was categorized into 4 categories (<1 serving/d; 1 serving/d; >1 to <4 servings/d; and ≥4 servings/d). Consumption of foods was adjusted for total energy intake via the residual method (19).

We used Cox regression models to assess the association between coffee consumption and mortality. Age was used as the underlying time-variable in all the analyses. Age at study inception was used as entry time and age at death or age at last available follow-up as exit time. After stratifying for age and recruitment period, we fitted a model adjusted for sex. In addition, we adjusted for other risk factors such as alcohol consumption (linear and quadratic term), years of attained university education, marital status, smoking (ever, current, former, or missing), BMI (linear and quadratic term), total energy intake, adherence to the MedDiet, between-meal snacking and following special diets, leisure-time physical activity (MET-hours per week),

hours of television watching, hypertension, diabetes, baseline high blood cholesterol, previous history of cancer, previous history of cardiovascular disease (CVD), and previous history of depression.

The category-specific median of coffee consumption across these 4 categories was treated as quantitative for calculating linear trend tests.

In order to assess the linear trend for the association between drinking 2 additional cups of coffee per day and mortality, we assigned each participant the midpoint of the consumption frequency that they had reported in the FFQ, divided the obtained amount by 2, and treated the resulting variable as quantitative.

We used Nelson-Aalen plots to show the mortality rates during follow-up according to baseline total coffee consumption, with the inverse probability weighting method to adjust for smoking status and the other aforementioned potential confounders.

To assess effect modification, we calculated the *P* value for interaction between coffee consumption (for each additional 2 cups of coffee/d) and 4 prespecified variables: smoking, sex, age, and baseline chronic conditions, through the use of the likelihood-ratio test. We also stratified our analyses according to baseline adherence to the MedDiet (0–3 points/4–9 points), and assessed the interaction between adherence to the MedDiet and coffee consumption.

As sensitivity analyses, we ran our analyses again separately for caffeinated and decaffeinated coffee consumption (in addition adjusting these analyses for the other type of coffee consumption), we repeated our analyses for regular coffee consumption excluding participants who also reported decaffeinated coffee consumption, and ran separate analyses for mortality attributable to CVD, cancer, or other causes. Finally, based on the question "Do you add sugar to some beverages?" we separated coffee consumption of those participants who added sugar from those who did not. To explicitly address the possibility of reverse causality bias due to avoidance of coffee because of a previous chronic disease, the models were adjusted for prevalent chronic diseases at baseline (CVD, hypertension, dyslipidemia, diabetes, or cancer). We also conducted the following ancillary analyses: *1)* ascertained different assumptions on the induction period and reran the models after restricting the follow-up to 4, 8, or 12 y; *2)* excluded from the analyses deaths occurring early during follow-up, and *3)* reran our models after removing participants with prevalent or incident chronic diseases.

We used restricted cubic splines to assess nonlinear relations in the association between coffee and mortality.

All *P* values were 2-tailed. Statistical significance was set at the conventional 0.05 level.

We assumed an expected cumulative incidence of mortality of 0.025 in the lower coffee-consumption group, an expected cumulative incidence of mortality of 0.018 in the high coffee-consumption group, and a 2-sided α error of 0.05. Accordingly, with 7000 participants in the extreme groups of coffee consumption we would attain a statistical power of 80%.

RESULTS

Among 19,888 participants from the SUN cohort (Figure 1), we identified 337 deaths during 201,055 persons-years of follow-up (median follow-up time: 10 y). The mean ± SD age at enrollment was 38 ± 10 y. The mean ± SD age at death among deceased participants was 65 ± 16 y.

Table 1 shows baseline characteristics of participants according to coffee consumption. Participants who consumed ≥4 cups/d reported higher total energy intake and higher intake of alcohol, and were more likely to be current smokers and to present other cardiovascular risk factors (hypertension, abnormal lipids, or diabetes). Consequently, they showed higher prevalences of CVD and cancer at baseline.

Table 2 shows HRs and 95% CIs for all-cause mortality, according to total coffee consumption. No significant association was found in the age- and sex-adjusted analysis. The fully adjusted models showed a significant inverse association between total coffee consumption and all-cause mortality. The linear trend test was also statistically significant. The HR for death was 0.37 (95% CI: 0.19, 0.71) for ≥4 cups/d compared with <1 cup/d (*P*-trend = 0.013).

In analyses with coffee consumption as a continuous variable, we found for each additional 2 cups/d an HR for death of 0.78 (95% CI: 0.66, 0.93) after adjusting for smoking and the other covariates. Similar results were found when we adjusted coffee consumption for total energy intake with the residual method (Table 2).

Rates of mortality according to baseline total coffee consumption are shown in **Figure 2**, after applying inverse probability weighting to adjust for smoking status and the other potential confounders.

We found a significant interaction between regular coffee consumption and age (continuous) ($P = 0.002$). The association was stronger among participants aged ≥55 y (HR: 0.67; 95% CI: 0.52, 0.86) than among participants aged <55 y (HR: 0.94; 95% CI: 0.74, 1.20) (**Figure 3**). However, all our analyses included both older and younger participants.

The test for interaction between coffee consumption and adherence to the MedDiet was not statistically significant ($P = 0.81$).

When we separately considered the consumption of regular and decaffeinated coffee in the multivariable models, we found that for every 2 additional cups of regular coffee per day, the HR for total mortality was 0.77 (95% CI: 0.64, 0.92) adjusted for decaffeinated coffee consumption. For each additional 2 cups of decaffeinated coffee/d, the HR for total mortality was 0.83 (95% CI: 0.62, 1.12) adjusted for regular coffee consumption.

In progressive adjustments for smoking, we found an HR of 0.83 (95% CI: 0.70, 0.97) for each additional 2 cups/d when we did not adjust for smoking, an HR of 0.81 (95% CI: 0.68, 0.95) when we grossly adjusted for smoking status (ever/never), an HR of 0.80 (95% CI: 0.67, 0.94) when we adjusted for smoking in 3 categories (current/former/never), and an HR of 0.78 (95% CI: 0.66, 0.93) when we adjusted for both the category of smoking status and the number of pack-years as a continuous variable. Among participants who never smoked (for whom no residual confounding can be assumed, and this restriction may represent the strongest degree of control for confounding by smoking) the HR was 0.59 (95% CI: 0.38, 0.93).

In order to avoid unaccounted-for confounding, we performed sensitivity analyses (Figure 3). The inverse association between coffee consumption and all-cause mortality persisted after assuming different induction periods (4, 8, and 12 y of follow-up, i.e., excluding the early deaths), and with the use of structural

TABLE 1
Distribution of baseline characteristics according to total coffee consumption, for the SUN Project 1999–2016[1]

	Total coffee consumption, cups/d			
	<1	1	>1 to <4	≥4
Cups/d[2]	0	1	2.5	5
Regular coffee consumption, cups/d	0	1	2.5	5
Decaffeinated coffee consumption, cups/d	0	0	0.07	0
n	7118	3598	8297	875
Age, y	35.9 ± 13.1	38.8 ± 12.6	38.3 ± 11.4	40.8 ± 11.6
Male, %	40.7	39.4	37	44.6
Period of inclusion	2004 ± 3	2004 ± 3	2003 ± 3	2003 ± 3
Years of attained university education	4.9 ± 1.5	5.1 ± 1.5	5.1 ± 1.5	5.1 ± 1.6
Physical activity, MET-h/wk	28.7 ± 26.2	26.6 ± 23.1	25.9 ± 21.6	26.6 ± 24.8
TV watching, h/d	1.6 ± 1.2	1.6 ± 1.2	1.6 ± 1.2	1.6 ± 1.3
Smoking				
Current smokers, %	19.5	22.3	29.8	41.1
Former smokers, %	20	27.8	27.6	28.3
Missing smoking, %	3.01	2.42	2.17	3.54
Marital status				
Single, %	53.1	41.3	41.9	35.8
Married, %	42.9	54.4	54.0	59.3
Others, %	3.98	4.22	4.06	4.91
BMI, kg/m^2	23.3 ± 3.5	23.5 ± 3.4	23.6 ± 3.5	24.3 ± 3.8
Alcohol intake, g/d	5.3 ± 8.7	7.5 ± 11.2	7.6 ± 11.1	8.7 ± 15.2
Total energy intake, kcal/d	2435 ± 786	2467 ± 742	2558 ± 770	2718 ± 884
MedDiet adherence, 0–9	4.0 ± 1.8	4.3 ± 1.8	4.3 ± 1.8	4.3 ± 1.7
Hypertension at baseline, %	11.4	11.3	10.3	13.7
High blood cholesterol, %	15.1	17.5	18.0	23.0
Diabetes at baseline, %	1.9	1.8	1.8	3.1
History of cancer, %	3.0	3.3	3.9	4.6
History of depression, %	11.4	11.1	11.6	15.4
History of cardiovascular disease, %	9.6	10.3	10.0	12.6
Between-meal snacking, %	36.8	30.1	33.5	38.7
Following special diets, %	7.5	7.7	8.3	11.7

[1]Means ± SDs are shown, unless otherwise stated. MedDiet, Mediterranean diet; MET-h, metabolic equivalent task hours; SUN Project, Seguimeiento Universidad de Navarra—University of Navarra Follow-Up Project.
[2]Values are medians.

equations with inverse probability weighting. The magnitude of the observed association remained stable for the exclusive use of regular coffee and among the subgroups defined by the cause of death (CVD, cancer, and others) (Figure 3) and by the use of sugar in the coffee. Also, results hardly changed when we excluded deaths occurring at the beginning of follow-up. The lack of statistically significant results in some subgroup analyses may be explained by a loss of statistical power due to the limited number of events in some subgroups.

We found no deviation from linearity for the inverse coffee-mortality association in the restricted cubic spline analyses (P for nonlinearity = 0.67) (**Figure 4**).

DISCUSSION

We found an inverse linear association between coffee consumption and all-cause mortality among highly educated, middle-aged Spanish adults. Every additional 2 cups of coffee/d were associated with a significant 22% lower risk of all-cause mortality.

Although previous prospective studies in Europe, the United States, and Asia have reported associations between coffee and lower mortality (7, 8, 20–25), our study assessed a cohort from a Mediterranean country, and addressed the potential confounding effect of the Mediterranean dietary pattern. Although a substantial number of participants living in Mediterranean countries was included in the European Prospective Investigation into Cancer and Nutrition (EPIC) study (22), no country-specific estimates were provided, and the EPIC study reported no assessment of confounding by or interaction with the dietary pattern.

Several meta-analyses (7–10) reported inverse associations between coffee and mortality, supporting the contention that coffee may be part of a healthy diet. However, no further risk reduction was reported for levels of consumption >4 cups/d (9, 10).

In agreement with recent studies [including also smaller proportions of smokers (22, 23, 25)], we found an inverse linear association. Progressive adjustments for smoking rendered stronger inverse associations between coffee and mortality. Residual confounding by smoking might spuriously attenuate or even hide this inverse association. A recent meta-analysis (8),

TABLE 2
HRs (95% CIs) for total mortality according to baseline total coffee consumption[1]

	Coffee consumption, cups/d					For each additional 2 cups/d	
	<1	1	>1 to <4	≥4	*P*-trend	HR (95% CI)	*P*
Cups/d[2]	0	1	2.5	5		—	
All participants							
n	7118	3598	8297	875		—	
Cases	129	64	133	11		—	
Persons-years	69,967	35,724	86,002	9354		—	
Model 1	1 (ref.)	0.94 (0.70, 1.27)	1.03 (0.80, 1.32)	0.59 (0.32, 1.09)	0.373	—	
Model 2	1 (ref.)	0.90 (0.66, 1.23)	0.90 (0.70, 1.16)	0.37 (0.19, 0.71)	0.013	0.78 (0.66, 0.93)	0.004
Model 2 (resid.)[3]	1 (ref.)	0.92 (0.33, 2.55)	0.87 (0.69, 1.09)	0.36 (0.19, 0.70)	0.004	0.78 (0.66, 0.92)	0.004
Participants aged <55 y							
n	6366	3159	7573	761		—	
Model 2	1 (ref.)	1.04 (0.61, 1.77)	1.22 (0.80, 1.85)	0.59 (0.24, 1.45)	0.822	0.94 (0.74, 1.20)	0.627
Participants aged ≥55 y							
n	752	439	724	114		—	
Model 2	1 (ref.)	0.80 (0.54, 1.18)	0.73 (0.52, 1.03)	0.24 (0.09, 0.67)	0.003	0.67 (0.52, 0.86)	0.001

[1]Results from Cox regression models. Model 1: adjusted for sex and stratified by categories of age and recruitment period. Model 2: adjusted for sex, alcohol consumption (linear + quadratic), years of attained university education, marital status, smoking (4 categories), pack-years of smoking, BMI (linear + quadratic), total energy intake, adherence to the Mediterranean diet, between-meal snacking and following special diets, leisure-time physical activity (MET-h/wk), television watching (hours), baseline hypertension, diabetes, and high blood cholesterol, and previous history of cancer, cardiovascular disease, and depression; stratified by categories of age and recruitment period. MET-h, metabolic equivalent task-hours; ref., reference; resid., residual method.

[2]Values are medians.

[3]Coffee intake was also adjusted for total energy intake via the residual method.

with stratification by smoking status, reported an inverse linear relation only among never-smokers.

Coffee intake could eventually lead to an increased CVD risk due to the caffeine and diterpene alcohols present in coffee and associated with short-term elevations in arterial pressure (26), insulin resistance (27), and LDL rise (2). Nevertheless, this mechanistic hypothesis has not been corroborated in prospective cohort studies (with fewer biases) (28). Moreover, experimental

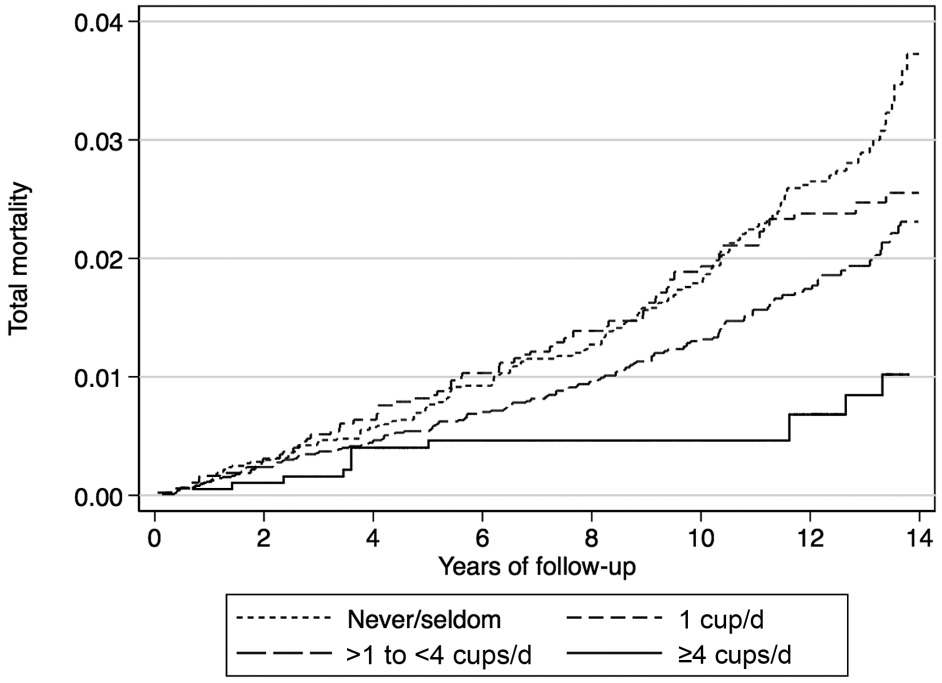

FIGURE 2 Nelson-Aalen plot for rates of mortality during follow-up according to baseline total coffee consumption. The estimates were adjusted for sex, age, alcohol consumption (linear + quadratic), years of attained university education, marital status, smoking (4 categories), pack-years of smoking, BMI (linear + quadratic), total energy intake, adherence to the Mediterranean diet, between-meal snacking and following special diets, leisure-time physical activity (MET-h/wk), television watching (hours), baseline hypertension, diabetes, and high blood cholesterol, and previous history of cancer, cardiovascular disease, and depression, with the use of inverse probability weighting. There were 7118 participants in the <1 coffee/d category, 3598 participants in the 1 coffee/d category, 8297 in the >1 to <4 coffees/d category, and 875 participants in the ≥4 coffees/d category. MET-h, metabolic equivalent task hours.

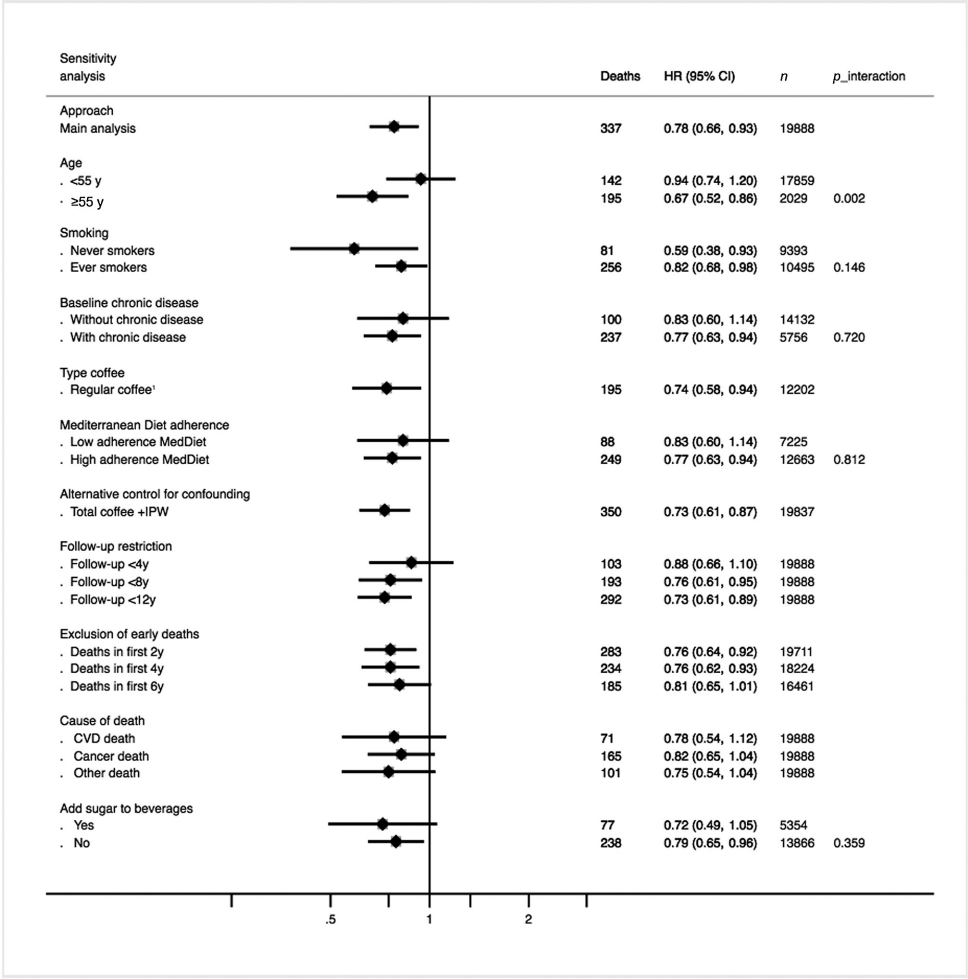

FIGURE 3 Sensitivity analysis. HRs for all-cause death associated with 2 additional cups of coffee per day, under diverse scenarios. Results from Cox regression models. All models adjusted for sex, alcohol consumption (adding a quadratic term), years of university education, marital status, year of recruitment, smoking, BMI (adding a quadratic term), total energy intake, adherence to the MedDiet, between-meal snacking and following special diets, leisure-time physical activity (MET-h/wk), hours of television watching, hypertension at baseline, diabetes at baseline, high blood cholesterol, previous history of cancer, previous history of CVD, and previous history of depression and stratified by categories of age and recruitment period. [1]Excluding participants who report regular consumption of decaffeinated coffee. CVD, cardiovascular disease; IPW, inverse probability weighting that used all potential confounders (as shown in Table 2); MedDiet, Mediterranean diet; MET-h, metabolic equivalent task hours.

studies on humans with long follow-ups showed that long-term caffeine intake was not related to hypertension, because it induces tolerance to its acute pressor effect (29). Bioactive substances in coffee other than caffeine could potentially counteract caffeine's adverse effects on blood pressure (30). Regarding diterpene alcohols, they have been suggested to be related to a higher endogenous antioxidant production and to enhanced detoxification processes on one hand (3), but on the other hand, they have shown adverse associations with lipid profiles after boiled coffee consumption (4). Diterpene alcohols are abundant in boiled coffee but they are eliminated when coffee is filtered (4). Inverse causality bias is not likely in our results because participants with chronic disease at baseline reported *higher* coffee consumption.

Coffee is usually the main dietary source of bioactive polyphenols with beneficial properties in countries with available cohort studies investigating the relation between coffee and mortality. Also, it is a major contributor of specific polyphenols such as chlorogenic acid in the diet. Contrary to studies conducted in other settings, in our cohort (as in other Spanish cohorts), the main source of total polyphenol intake as well as the main source of total polyphenol variability was not coffee but fruits (data not shown) (31).

The interaction found between age and coffee consumption may be explained by different underlying causes of death among younger and older subjects.

Limitations of our observational study include possible residual confounding. However, our results were robust after adjustments and sensitivity analyses and they had biological plausibility. Coffee consumption was assessed only at baseline, but this may not represent a strong limitation given that coffee consumption tends to remain stable over the years (11). Also, we had no information on the method of coffee preparation. The type of coffee consumed or the preparation method might be important. Previous studies conducted in Spain reported that nonfiltered coffee is the main type of coffee consumed in

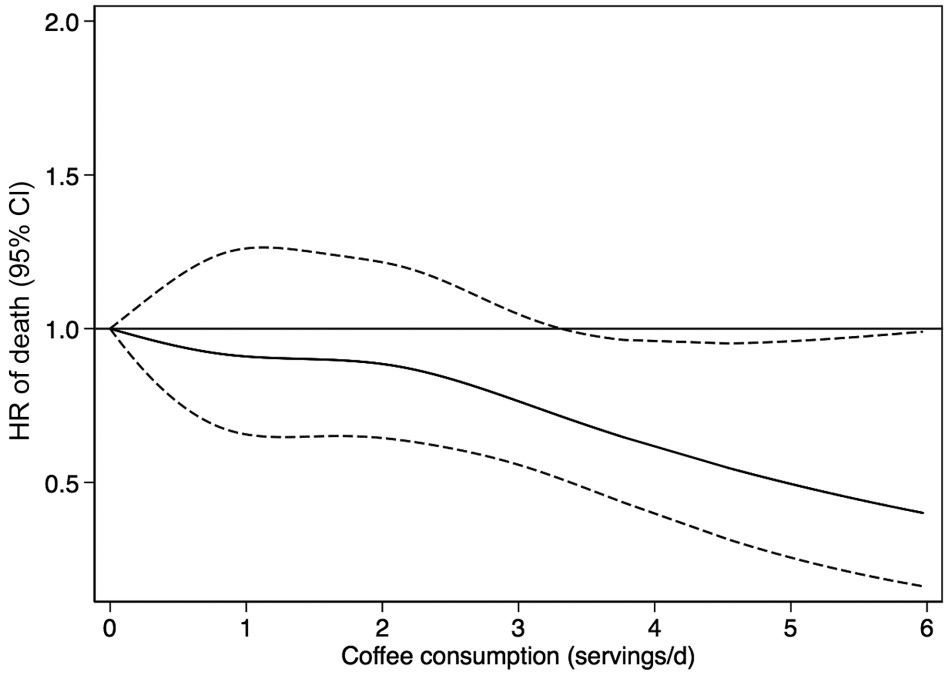

FIGURE 4 HRs (95% CIs) for the association between total coffee consumption and mortality, for the SUN Project 1999–2016 ($n = 19,888$ participants). P value for nonlinearity = 0.219. Results from Cox regression models. Adjusted for alcohol consumption (adding a quadratic term), years of university education, marital status, year of recruitment, smoking, BMI (adding a quadratic term), total energy intake, adherence to the Mediterranean diet, between-meal snacking and following special diets, leisure-time physical activity (MET-h/wk), hours of television watching, hypertension at baseline, diabetes at baseline, high blood cholesterol, previous history of cancer, previous history of cardiovascular disease, and previous history of depression and stratified by age, sex, and recruitment period. MET-h, metabolic equivalent task hours; SUN Project, Seguimiento Universidad de Navarra—University of Navarra Follow-Up Project.

Spain. This latter variety includes coffee prepared with the use of pressure (espresso coffee), a percolator (a type of pot that brews coffee by passing boiling water over the grounds), and also instant coffee (32). A recent study on adults aged >60 y reported that most coffee in Spain was consumed as unfiltered coffee (mean ± SD: 1.24 ± 1.30 cups unfiltered coffee/d, 0.16 ± 0.59 cups filtered coffee/d) (33). In addition, polyphenol content of coffee varies with coffee species, roasting degree, and brewing procedure. Total isoflavones were found to be similar in 30 mL espresso and in 120 mL filtered coffee (34). But the concentration of 3-O-caffeoyl quinic acid and 5-O-caffeoyl quinic acid according to 9 common coffee extraction methods was higher for espressi than for filtered extraction methods. Given the different quantities per cup of coffee (30 mL espresso, 120 mL lungo), the lungo contained more chlorogenic acids per cup of coffee than the espresso (35). Another methodologic limitation is that the question on added sugars to beverages was not exclusive to coffee. Our restriction to university graduates aims to control for confounding by socioeconomic status and educational level and could improve the validity of findings by also increasing the accuracy of self-reports. The apparent lack of specificity across strata might be considered to suggest a confounded association. However, we adjusted for a wide variety of confounders and, importantly, there are many exceptions to the intuitive idea that the more broadly an exposure is associated with a variety of outcomes (i.e., the lower its specificity), the less likely it is to be causally associated with any one of them. The principle of "specificity" is perhaps the weakest of the traditional 9 causality criteria. It is currently well-known that many true causal factors (e.g., smoking) are highly unspecific because they are causally related to many different outcomes. More importantly, the anti-inflammatory properties of polyphenols together with the inflammatory origins of a wide array of chronic diseases strengthen the biological plausibility of our findings. Nevertheless, we acknowledge the aforementioned limitations in our assessment and admit that further longitudinal studies and trials are needed to confirm our findings.

In conclusion, we found an inverse linear association between coffee consumption and all-cause mortality. The association became stronger among participants aged ≥55 y. These findings are consistent with previous studies and support the idea that coffee could be part of a healthful diet.

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NM-C: provided insight into the interpretation of results; and all authors: have revised the manuscript critically for important intellectual content, read the manuscript, and given final approval of the version to be published. None of the authors reported a conflict of interest related to the study.

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