Original article

Polyphenol intake and mortality: A nationwide cohort study in the adult population of Spain

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SUMMARY

Background and aims: Polyphenols are secondary metabolites present in small quantities in plant-based food and beverages, with antioxidant and anti-inflammatory properties. Main groups of polyphenols include flavonoids, phenolic acids, stilbenes, and lignans, but their association with mortality has barely been examined. We aimed to assess the association between the intake of 23 polyphenol subgroups and all-cause, cardiovascular, and cancer mortality in a representative sample of the Spanish adult population.

Methods: Population-based cohort study conducted with 12,161 individuals aged 18+ recruited in 2008 −2010 and followed-up during a mean of 12.5 years. At baseline, food consumption was obtained with a validated dietary history, and the Phenol-Explorer database was used to estimate polyphenol intake. Associations were examined using Cox regression adjusted for main confounders.

Results: During follow-up, 967 all-cause deaths occurred, 219 were cardiovascular, and 277 cancer. Comparing extreme categories of consumption, hazard ratios (95% CI) of total mortality for subgroups were: dihydroflavonols 0.85 (0.72−1.00; p-trend:0.046); flavonols 0.79 (0.63−0.97; p-trend:0.04); methoxyphenols 0.75 (0.59−0.94; p-trend:0.021); tyrosols 0.80 (0.65−0.98; p-trend:0.044); alkylmethoxyphenols 0.74 (0.59−0.93; p-trend:0.007); hydroxycinnamic acids 0.79 (0.64−0.98; p-trend:0.014); and hydroxyphenilacetic acids 0.82 (0.67−0.99; p-trend:0.064). For cardiovascular mortality, hazard ratios were: methoxyphenols 0.58 (0.38−0.89; p-trend:0.010); alkylmethoxyphenols 0.59 (0.39−0.90; p-trend:0.011); hydroxycinnamic acids 0.63 (0.42−0.94; p-trend:0.020); and hydroxyphenilacetic acids 0.69 (0.48−0.99; p-trend:0.044), when comparing extreme tertiles of consumption. No statistically significant associations were observed for cancer. The main food sources for these polyphenol subgroups were red wine, leafy green vegetables, olive oil, green olives, and coffee (the latter being the major contributor of methoxyphenols, alkylmethoxyphenols, and hydroxycinnamic acids).

Conclusions: In the Spanish adult population, intake of specific polyphenol subgroups was prospectively associated with a 20% lower all-cause mortality risk. This decrease was mainly due to a 40% lower cardiovascular mortality risk over time.

1. Introduction

Polyphenols are secondary metabolites and natural functional compounds present in food and beverages of plant origin [1]. Some of them contribute to their specific color [1] and sensory

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characteristics [2]. Polyphenols are also one of the most abundant dietary bioactive compounds [3] of plants, and in contrast to vitamins and minerals, a low intake of them is not linked to any deficiency diseases, however, an adequate consumption has beneficial effects on health [4]. Based on their chemical structure, polyphenols are classified into four main groups: flavonoids, phenolic acids, stilbenes, and lignans [5].

Polyphenols have been suggested to have health benefits because of their antioxidant [6] and anti-inflammatory effects [7], also including anti-hypertensive [8], and antidiabetic [9] properties. As a result, polyphenols have been associated with a lower risk of chronic diseases, such as cardiovascular disease (CVD) [4,10,11], diabetes [4,12], and some types of cancer, including colorectal [13], and breast cancer [14].

Some studies have also shown that polyphenol intake is associated with a lower mortality risk. In this line, some studies have already been performed in Spain, a Mediterranean country with a traditional plant-based diet, and with one of the highest life expectancies in the world. For example, the PREDIMED study showed that the intake of total polyphenols, lignans, as well as stilbenes, were associated with a reduced risk of all-cause mortality [15]. This study was conducted with participants that were at high risk for CVD. Also, the EPIC-Spain cohort study (whose participants were mainly volunteers) showed that the intake of flavonols and flavanones was associated with a lower all-cause mortality risk, as well as the intake of total flavonoids and flavanols was associated with a lower CVD mortality risk [16].

Similar results have also been obtained in other countries when studying polyphenol intake and mortality risk [17] [−] [22]. However, most of the studies focused on the intake of the group of flavonoids, but other polyphenol subgroups that are also present in the diet have hardly been studied [23]. Therefore, the study of a wide variety of polyphenols and their relationship with mortality is of interest in order to enhance the identification of their benefits and to improve nutritional advice at a population level.

The aim of this study was to evaluate the association between the consumption of 23 different subclasses of polyphenols, according to the first comprehensive database on polyphenol content in foods, the Phenol Explorer dataset, and all-cause mortality, as well as mortality for specific causes such as CVD and cancer. The study sample for these analyses is a representative sample of the non-institutionalized adults from the general Spanish population, allowing us to provide results at a country-level.

2. Material and methods

2.1. Study design and population

Participants come from the Study on Nutrition and Cardiovascular Risk (ENRICA), a population-based cohort. Details of the study design were reported elsewhere [24]. Briefly, ENRICA is a representative sample of the non-institutionalized Spanish population aged 18 and older. Data collection was carried out from June 2008 to October 2010. Participants were selected using random stratified cluster sampling. First, the sample was stratified by province and size of the municipality. Second, clusters were selected randomly based on municipalities and census sections. Finally, within each section, households were selected by random telephone dialing. Within each household, participants were selected proportionally according to the sex and age distribution of the Spanish population. Data collection included a health questionnaire, blood and urine samples, a physical examination, as well as a dietary history.

Of the 13,105 total participants, 60 were excluded because of missing information on diet, and 884 with total energy intake outside a plausible range (800–5000 kcal/d in men, or

500–4000 kcal/d in women). Therefore, the analyses were conducted with 12,161 individuals (5760 men and 6401 women).

Written informed consent was obtained from all participants. The study was approved by the Clinical Research Ethics Committees of La Paz University Hospital in Madrid and the Hospital Clinic in Barcelona.

2.2. Diet and polyphenol intake assessment

A validated computer-based dietary history (DH-ENRICA) conducted by trained and certified interviewers was used to ascertain habitual diet during the preceding year [25]. The DH-ENRICA is a face-to-face dietary questionnaire that includes computerized information on 880 foods as well as 184 recipes of the most common dishes eaten in the different regions of Spain. Food habitually consumed was considered when eaten at least once every two weeks, and food consumption was expressed in g/d.

Polyphenol intake was calculated in mg/d (expressed as aglycones) and derived from the Phenol-Explorer database version 3.6 [26]. This tool provides information on polyphenol content obtained by chromatography with and without hydrolysis. When polyphenol data obtained through chromatography without hydrolysis had missing values, this information was replaced with data on chromatography after hydrolysis. Information from the Phenol-Explorer dataset was insufficient to apply retention factors in the calculation of polyphenol intake.

Our study included 23 different polyphenol subgroups: anthocyanins, chalcones, dihydrochalcones, dihydroflavonols, flavanols, flavanones, flavones, flavonols, isoflavonoids, hydrobenzaldehydes, methoxyphenols, tyrosols, alkymethoxyphenols, alkylphenols, other polyphenols, furanocoumarins, hydroxybenzoketones, hydroxycoumarins, hydroxybenzoic acids, hydroxycinnamic acids, hydroxyphenilacetic acids, hydroxyphenilpropanoic acids, and stilbenes. For other polyphenols including curcuminoids, hydroxycinamaldehydes, hydroxyphenilpropenes, naphtoquinones, and phenolic terpenes, no consumption was observed in our sample, or it was obtained from only a few participants. For this reason, meaningful analyses were not possible with these subgroups.

2.3. Mortality ascertainment

Information on the vital status of all participants was obtained from the Spanish National Death Index. Data on all-cause mortality were available from baseline 2008–2010 to January 31, 2022. Specific causes of death were obtained for National Statistics Office, based on death certificates, with data available up to December 31, 2020; death causes were coded according to the International Classification of Diseases, Tenth Revision (ICD-10): CVD corresponded to codes I00–I099, and cancer to codes C00-D49. Follow-up was censored at the date of death or at the end of follow-up, whichever occurred first.

2.4. Covariates

Participants reported their age, sex, level of education (primary, secondary, or university), smoking status (never smoker, former or current), leisure time and household physical activity, and time watching TV (h/wk). Alcohol drinking status was defined as follows: never drinker if ethanol consumption was less than 1 g/d, former drinker if participants used to drink alcohol and stopped, and ethanol consumption was less than <1 g/d, and current drinker if ethanol consumption was more than 1 g/d. Leisure time and household physical activity were obtained with the questionnaire used in the EPIC-cohort of Spain and expressed in metabolic equivalents (METs-h/wk) [27]. Weight and height were measured

at home under standardized conditions, and body mass index (BMI) was calculated as weight in kg divided by height in m squared and classified as normal (<25.0 kg/m^2), overweight ($\geq$25−29.9 kg/m^2) or obese ($\geq$30 kg/m^2). Total energy intake (Kcal/d) and fiber intake (g/d) were derived from Spanish food composition tables [28]. A nurse checked the number of medications against drug packages. Self-reported chronic conditions diagnosed by a physician (chronic obstructive pulmonary disease, asthma, coronary heart disease, stroke, heart failure, osteoarthritis, cancer, depression, and diabetes) were also collected. Hypertriglyceridemia was defined as fasting triglycerides $\geq$150 mg/dL; hypercholesterolemia as fasting total cholesterol $\geq$200 mg/dL or taking lipid-lowering medications; low HDL-cholesterol was defined as <40 mg/dL in men and <50 mg/dL in women, and hypertension as blood pressure $\geq$140/90 mmHg or taking antihypertensive medications.

2.5. Statistical analysis

Participants were categorized into sex-specific quartiles when studying all-cause mortality, and into sex-specific tertiles when studying cause-specific mortality. Eight polyphenols were only consumed by a limited number of participants. In that case, participants were classified into two categories: no consumption and some consumption. Cox proportional hazards models were used to assess the association between polyphenol intake and mortality. The category with the lowest consumption was used as a reference (first quartile, first tertile, or no consumption). Analyses were weighted, and confidence intervals (CIs) were corrected, to account for the complex sampling design. P values for linear trend were calculated including quartiles or tertiles of polyphenol consumption as continuous variables in the models.

Cox models were built and hazard ratios (HR) were calculated with three successive levels of additional adjustments: model 1 adjusted for age and sex; model 2 further adjusted for level of education, smoking status, leisure time and household physical activity, time watching TV, former drinker status, BMI, energy intake, fiber intake, number of medications per day, and number of chronic diseases; and model 3 additionally adjusted for hypertriglyceridemia, hypercholesterolemia, low HDL-cholesterol, and hypertension. We used stochastic regressions for the imputation of missing values (<1%) in covariates, such as level of education, smoking status, BMI, hypertriglyceridemia, hypercholesterolemia, low HDL-cholesterol, and hypertension.

The food sources were computed for each polyphenol subgroup. When consumption was above 5%, the food was reported as a contributor source. Analyses were performed with STATA software version 17.0 for Windows, and statistical significance was set at P-value <0.05 (two-tailed).

3. Results

During a mean 12.5-year follow-up, 55, 320, 305 person-years were accrued, and 967 allcause deaths occurred. For cause-specific death, the mean follow-up was 11.5 years (50, 985, 544 person-years), 219 deaths were due to CVD, and 277 to cancer.

In order to simplify and better communicate the results, the description will be focused on the polyphenol subgroups that showed a statistically significant association with mortality. Out of the 23 studied subgroups, 7 were associated with mortality. The mean intake for these polyphenol subgroups were: 2.47 mg/d for dihydroflavonols, 22.89 mg/d for flavonols, 0.15 mg/d for methoxyphenols, 15.28 mg/d for tyrosols, 1.11 mg/d for alkylmethoxyphenols, 261.22 mg/d for hydroxycinnamic acids, and 0.28 mg/d for hydroxyphenilacetic acids (Supplemental Table 1, see Supporting Information). At baseline, participants in the highest

versus the lowest category of polyphenol subgroups intake were older, more educated, less frequently never smokers, more current drinkers, and had higher physical activity, BMI, and energy and fiber intake. They also reported lower use of medications and fewer chronic diseases and were more likely to present hypercholesterolemia and hypertension (Table 1).

3.1. Polyphenol intake and all-cause mortality

In fully adjusted analyses (model 3), the HR (95% CI) for all-cause mortality (some consumption vs. no consumption) was 0.85 (0.72−1.00), p-trend: 0.046, for dihydroflavonols (Table 2). The HRs when comparing the highest versus the lowest quartile of polyphenol intake were: 0.79 (0.63−0.97), p-trend: 0.04, for flavonols; 0.75 (0.59−0.94), p-trend: 0.021, for methoxyphenols; 0.80 (0.65−0.98), p-trend: 0.044, for tyrosols; 0.74 (0.59−0.93), p-trend: 0.007, for alkylmethoxyphenols; 0.79 (0.64−0.98), p-trend: 0.014, for hydroxycinnamic acids; and 0.82 (0.67−0.99), p-trend: 0.064, for hydroxyphenilacetic acids (Table 3). No statistical association was observed for other polyphenol subgroups (Tables 2 and 3). Additional analyses were performed adjusting the models for alcohol drinking status and the results remain similar.

3.2. Polyphenol intake and cause-specific mortality

In model 3, HRs for CVD mortality when comparing the highest versus the lowest tertile of polyphenol intake were: 0.58 (0.38−0.89), p-trend: 0.010, for methoxyphenols; 0.59 (0.39−0.90) p-trend: 0.011, for alkylmethoxyphenols; 0.63 (0.42−0.94), p-trend: 0.020 for hydroxycinnamic acids; 0.69 (0.48−0.99), p-trend: 0.044, for hydroxyphenilacetic acids (Table 4). No statistical association was observed for other polyphenol subgroups (Table 4 and Supplemental Table 2, see Supporting Information). For cancer mortality, no significant associations were observed (Supplemental Table 3 and Supplemental Table 4, see Supporting Information).

3.3. Main polyphenol sources

The main food sources of the following polyphenol subgroups were: red wine (99%) for dihydroflavonolds; lettuce (34%), cooked spinach (14%), and red wine (13%) for flavonols; coffee, including coffee made with an Italian coffee maker, filtered coffee, and decaffeinated expresso (93%) for methoxyphenols; olive oil (common and extra virgin) (57%), and green olives (18%) for tyrosols; coffee, including coffee made with an Italian coffee maker, filtered coffee, and decaffeinated expresso (87% and 71%) for alkylmethoxyphenols and hydroxycinnamic acids, respectively; and green olives (52%), red wine (25%), and lager (12%) for hydroxyphenyl acetic acids (Supplemental Table 1, see Supporting Information).

4. Discussion

In this large prospective cohort, a higher intake of dihydroflavonols, flavonols, methoxyphenols, tyrosols, alkylmethoxyphenols, hydroxycinnamic acids, and hydroxyphenilacetic acids was associated with lower all-cause mortality risk of around 20%, when studying extreme categories of consumption. In addition, the main protective associations were obtained for CVD mortality. A higher intake of methoxyphenols, alkylmethoxyphenols, hydroxycinnamic acids, and hydroxyphenilacetic acids was linked to an approximately 40% lower risk of CVD death. By contrast, no associations were found for cancer mortality.

The major food sources of polyphenols associated with a lower risk of all-cause or CVD mortality were red wine, cooked spinach, lettuce, olive oils (common and extra virgin), green olives, and

Table 1
Baseline characteristics according to quartiles of polyphenol intake in the ENRICA study (2008—10). N = 12,161.

	Dihydroflavonols		Flavonols		Methoxyphenols		Tyrosols		Alkylmethoxyphenols		Hydroxycinnamic acids		Hydroxyphenilacetic acids	
	No consumption	Some consumption	Q1	Q4 Highest	Q1	Q4 Highest	Q1	Q4 Highest	Q1	Q4 Highest	Q1	Q4 Highest	Q1	Q4 Highest
Age, mean (SD)	45.3 (17.3)	51.1 (15.0) †	43.5 (17.8)	51.1 (15.3) †	42.5 (18.8)	50.0 (13.9)†	45.5 (17.9)	49.9 (15.7) †	44.7 (19.4)	49.9 (13.9) †	43.5 (19.0)	49.4 (13.8)†	45.8 (18.4)	50.2 (15.5) †
Women, %	59.9	40.6	52.7	52.6	52.7	52.6	52.7	52.6	53.1	51.8	52.7	52.6	52.7	52.6
Level of education, %														
Primary	29.0	29.3 †	29.0	29.28 †	24.8	29.5 †	29.3	30.2 **	27.9	29.6 †	27.1	28.2 †	31.2	30.7 †
Secondary	43.9	38.9	46.7	38.19	47.3	38.8	44.1	39.4	44.8	39.4	45.5	40.2	43.4	38.6
University	27.1	31.8	24.3	32.5	28.0	30.7	26.5	30.4	27.3	31.1	27.4	31.6	25.4	30.8
Smoking status, %														
Never smoker	51.3	47.6 †	48.2	45.3 †	59.0	37.3 †	51.0	43.1 †	58.9	36.9 †	58.2	37.2 †	51.9	41.7 †
Former	21.2	32.3	19.8	31.3	20.0	28.0	20.8	29.6	21.6	28.2	20.4	27.8	20.4	29.3
Current	27.4	26.3	32.0	23.5	21.0	34.8	28.2	27.2	19.5	34.9	21.3	35.0	27.7	29.1
Leisure time and household physical activity, METs*hr/wk, mean (SD)	69.8 (42.1)	65.5 (39.8) †	65.9 (41.8)	69.9 (40.5) *	66.0 (40.9)	70.4 (42.5)†	66.8 (47.6)	68.7 (40.8)	66.0 (41.2)	70.1 (42.6) †	65.9 (40.2)	70.2 (42.4)†	66.0 (41.3)	68.2 (40.6) *
Time watching TV, h/wk, mean (SD)	1.9 (1.4)	2.0 (1.4)	2.0 (1.5)	1.9 (1.3) *	1.9 (1.4)	2.0 (1.5)	2.0 (1.5)	1.9 (1.3)	1.9 (1.4)	2.0 (1.4)	1.9 (1.4)	1.9 (1.4)	2.0 (1.5)	1.9 (1.4)
Drinking status, %														
Never drinker	63.1	11.1	59.0	32.3†	52.9	40.7†	60.5	30.9†	58.6	37.6†	55.1	38.9†	72.9	19.0†
Former drinker	8.1	1.3	6.3	5.1	6.4	5.0	7.5	4.4	7.4	4.6	6.1	4.7	9.3	2.9
Current drinker	28.9	87.6	34.8	62.6	40.7	54.3	32.0	64.7	34.0	57.8	38.9	56.4	17.8	78.1
BMI, %														
< 25 kg/m²	41.3	32.6 †	43.4	34.2 †	48.2	32.4 †	40.6	35.4 †	46.0	32.0 †	46.6	33.9 †	40.3	34.9 †
≥25−30 kg/m²	37.2	44.9	34.6	43.1	34.1	41.8	38.4	41.7	34.8	42.5	34.9	41.3	37.3	44.2
≥30 kg/m²	21.5	22.5	22.0	22.7	17.7	25.8	21.0	22.9	19.2	25.4	18.6	24.9	22.4	21.0
Total energy intake, kcal/d, mean (SD)	2131 (649)	2297 (601) †	2110 (669)	2275 (618) †	2182 (663)	2193 (636)	1948 (641)	2421 (609) †	2145 (449)	2209 (646) †	2073 (615)	2250 (638) †	2006 (658)	2334 (604) †
Total fiber intake, g/d, mean (SD)	22.9 (8.3)	24.3 (8.0) †	20.4 (8.0)	26.3 (8.6) †	23.2 (8.8)	23.4 (8.3)	20.3 (7.6)	26.1 (8.7) †	23.2 (8.9)	23.3 (8.1)	21.8 (8.4)	24.0 (8.5) †	21.4 (8.2)	24.2 (8.2) †
Number of medications per day, (%)														
0	66.7	61.8 †	70.0	59.3 †	68.1	62.8 †	67.5	60.4 †	64.8	63.3 *	67.2	64.5 **	65.3	61.7 †
1-3	25.9	30.9	24.2	32.5	25.1	29.7	25.1	32.04	26.7	29.3	24.8	28.8	26.6	30.9
>3	7.3	7.3	5.8	8.2	6.8	7.6	7.4	7.6	8.5	7.4	8.1	6.7	8.1	7.4
Number of chronic conditions, (%)														
0	66.7	67.6 †	69.1	63.5 †	71.5	63.8 †	66.6	65.03 *	68.2	64.4 **	69.6	65.6 **	64.3	65.9 †
1	23.4	24.7	22.2	26.7	19.9	26.9	24.1	25.6	21.95	26.2	20.98	25.6	24.8	25.2
≥2	9.9	7.8	8.7	9.8	8.6	9.4	9.3	9.3	9.8	9.4	9.4	8.8	10.7	8.9
Hypertriglyceridemia, %	16.9	20.4 †	19.0	18.4	15.0	21.0 †	17.7	17.9	15.5	21.6 †	16.0	20.6 †	18.3	19.3
Hypercholesterolemia, %	47.1	58.9 †	45.5	58.3 †	40.5	59.2 †	47.3	56.8 †	43.2	59.5 †	42.8	58.7 †	46.9	58.0 †
Low HDL-cholesterol, %	29.3	22.4 †	30.9	22.9 †	26.7	26.7	30.7	22.5 †	27.3	27.0	27.9	26.2	30.5	22.6 †
Hypertension, %	30.0	37.7 †	29.2	36.9 †	28.2	36.2 †	30.5	35.8 †	31.3	36.5 †	28.9	34.7 †	31.8	35.5 **

P for linear trend or χ^2: * <0.05; **p < 0.01; †p < 0.001.
Chronic conditions: sum of chronic obstructive pulmonary disease, asthma, coronary heart disease, stroke, heart failure, osteoarthritis, cancer, depression, and diabetes.

Table 2
Hazard Ratio (HR) for all-cause mortality by categories of polyphenol consumption in the ENRICA Study (2008–10 to 2022). N = 12,161.

	No consumption HR (95% CI)	Some consumption HR (95% CI)	P for linear trend
Chalcones			
n/events	9094/809	3067/158	
Model 1	1 (Ref)	0.98 (0.80–1.20)	0.83
Model 2	1 (Ref)	1.03 (0.84–1.27)	0.756
Model 3	1 (Ref)	1.03 (0.83–1.26)	0.81
Dihydrochalcones			
n/events	8041/591	4120/376	
Model 1	1 (Ref)	0.90 (0.78–1.04)	0.151
Model 2	1 (Ref)	0.92 (0.80–1.07)	0.281
Model 3	1 (Ref)	0.92 (0.80–1.07)	0.275
Dihydroflavonols			
n/events	7593/583	4568/384	
Model 1	1 (Ref)	0.79 (0.68–0.92) **	0.002
Model 2	1 (Ref)	0.83 (0.70–0.98) *	0.025
Model 3	1 (Ref)	0.85 (0.72–1.00) *	0.046
Isoflavonoids			
n/events	8713/797	3448/170	
Model 1	1 (Ref)	0.96 (0.80–1.16)	0.694
Model 2	1 (Ref)	1.02 (0.84–1.24)	0.827
Model 3	1 (Ref)	1.03 (0.85–1.24)	0.786
Furanocoumarins			
n/events	6130/442	6031/525	
Model 1	1 (Ref)	0.97 (0.84–1.13)	0.706
Model 2	1 (Ref)	0.93 (0.80–1.08)	0.354
Model 3	1 (Ref)	0.93 (0.81–1.08)	0.362
Hydroxybenzoketones			
n/events	9081/807	3080/160	
Model 1	1 (Ref)	0.98 (0.80–1.20)	0.846
Model 2	1 (Ref)	1.03 (0.84–1.27)	0.751
Model 3	1 (Ref)	1.03 (0.84–1.26)	0.805
Hydroxycoumarins			
n/events	7066/703	5095/264	
Model 1	1 (Ref)	0.98 (0.83–1.15)	0.793
Model 2	1 (Ref)	0.97 (0.83–1.15)	0.74
Model 3	1 (Ref)	0.98 (0.83–1.16)	0.837
Hydroxyphenylpropanoicacids			
n/events	7066/703	5095/264	
Model 1	1 (Ref)	0.98 (0.83–1.15)	0.793
Model 2	1 (Ref)	0.97 (0.83–1.15)	0.74
Model 3	1 (Ref)	0.98 (0.83–1.16)	0.837

P value: * <0.05; **p < 0.01; †p < 0.001.
Model 1: adjusted for age and sex.
Model 2: as in model 1 and additionally adjusted for level of education, smoking status, leisure time and household physical activity, time watching TV, former drinker, BMI, total energy intake, total fiber intake, number of medications per day, number of chronic conditions.
Model 3: as in model 2 and additionally adjusted for hypertriglyceridemia, hypercholesterolemia, low HDL-cholesterol, and hypertension.

coffee, which was the main contributor of methoxyphenols, alkyl-methoxyphenols, and hydroxycinnamic acids intake.

In Spain, two studies focused on polyphenol intake and mortality. In the PREDIMED study [15] (a randomized clinical trial on the effects of the Mediterranean diet) the authors found that higher total polyphenol intake was associated with a 37% lower risk of all-cause death. Only stilbenes and lignans showed a protective association with mortality [15]. Our results for total polyphenol intake and stilbenes were in line with these findings, but the associations did not achieve statistical significance. In addition, the EPIC-Spain study [16] found a protective association between flavanones and flavonols intake and all-cause mortality, and a protective association for flavanols, flavanones, as well as flavonols intake, and a lower risk of CVD mortality [16]. Our results are in line with those for flavonols intake and its association with total mortality, but without achieving statistical significance for CVD mortality.

Other studies conducted in different countries also assessed the association between polyphenol intake and mortality [17] [–] [22]. However, only flavonoids have been considerably investigated. A meta-analysis reported that total flavonoid intake was associated with a significant 26% lower risk of all-cause mortality. For CVD mortality, a non-significant 17% lower risk was observed [29]. Most

recently, another meta-analysis found that total flavonoid intake was associated with a significant 13% lower risk of all-cause mortality when comparing high versus low intake, and for CVD mortality, a significant 15% decrease was observed [30]. In our study, we only found that dihydroflavonols and flavonols were associated, respectively, with a 15% and 21% lower all-cause mortality risk.

Differences in the results could be due to methodological issues, such as the characteristics of the participants, the instruments for dietary assessment, differences in nutritional and culinary habits across countries, the use of different food composition tables, and the number of flavonoid subgroups that were considered [29,30].

Our results for cancer are in line with a recent meta-analysis [30], in which a non-significant association between flavonoid intake and cancer mortality was observed; of note, this meta-analysis only included four studies. By contrast, a recent study from Iran showed that some flavonoid subgroups, such as iso-flavonoids and dihydrochalcones, were associated with a 16–18% lower risk of cancer mortality [18]. More evidence is clearly needed to fully understand this relationship.

Several mechanisms could explain the health benefits associated with polyphenols intake, such as their anti-inflammatory, anti-microbial, and antioxidant effects [31]. Among them, their

Table 3
Hazard Ratio (HR) for all-cause mortality according to quartiles of polyphenol consumption in the ENRICA Study (2008–10 to 2022). N = 12,161.

	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	P for linear trend
Anthocyanins					
n/events	3041/248	3040/202	3040/217	3040/300	
Model 1	1 (Ref)	0.84 (0.68–1.03)	0.84 (0.68–1.03)	0.81 (0.66–0.98)	0.05
Model 2	1 (Ref)	0.84 (0.68–1.04)	0.87 (0.71–1.07)	0.84 (0.69–1.04)	0.158
Model 3	1 (Ref)	0.83 (0.67–1.03)	0.86 (0.70–1.06)	0.86 (0.70–1.05)	0.198
Flavanols					
n/events	3041/232	3040/259	3040/222	3040/254	
Model 1	1 (Ref)	1.07 (0.88–1.31)	0.95 (0.77–1.17)	0.89 (0.72–1.09)	0.134
Model 2	1 (Ref)	1.11 (0.91–1.36)	1.00 (0.81–1.23)	0.98 (0.79–1.20)	0.608
Model 3	1 (Ref)	1.13 (0.92–1.38)	1.01 (0.82–1.25)	1.00 (0.81–1.23)	0.767
Flavanones					
n/events	3041/252	3040/167	3040/248	3040/300	
Model 1	1 (Ref)	0.73 (0.58–0.91)	0.82 (0.67–1.01)	0.85 (0.70–1.03)	0.228
Model 2	1 (Ref)	0.75 (0.60–0.93)	0.88 (0.72–1.08)	0.88 (0.73–1.08)	0.486
Model 3	1 (Ref)	0.74 (0.59–0.93)	0.89 (0.72–1.09)	0.89 (0.73–1.08)	0.524
Flavones					
n/events	3042/283	3039/248	3040/229	3040/207	
Model 1	1 (Ref)	1.16 (0.95–1.41)	1.19 (0.97–1.45)	1.07 (0.87–1.32)	0.315
Model 2	1 (Ref)	1.13 (0.92–1.40)	1.26 (1.02–1.55) *	1.15 (0.90–1.47)	0.127
Model 3	1 (Ref)	1.11 (0.89–1.37)	1.23 (1.00–1.52) *	1.13 (0.88–1.45)	0.168
Flavonols					
n/events	3041/237	3040/222	3040/255	3040/253	
Model 1	1 (Ref)	0.78 (0.63–0.96) *	0.76 (0.62–0.93) **	0.75 (0.61–0.92) **	0.008
Model 2	1 (Ref)	0.79 (0.64–0.98) *	0.78 (0.64–0.96) *	0.77 (0.62–0.95) *	0.023
Model 3	1 (Ref)	0.79 (0.64–0.98) *	0.79 (0.65–0.96) *	0.79 (0.63–0.97) *	0.04
Total flavonoids					
n/events	3041/238	3040/232	3040/213	3040/284	
Model 1	1 (Ref)	1.01 (0.83–1.23)	0.86 (0.70–1.06)	0.85 (0.70–1.04)	0.05
Model 2	1 (Ref)	1.02 (0.83–1.24)	0.91 (0.73–1.13)	0.90 (0.74–1.11)	0.218
Model 3	1 (Ref)	1.03 (0.84–1.27)	0.90 (0.72–1.13)	0.92 (0.75–1.13)	0.257
Hydroxybenzaldehydes					
n/events	3041/359	3040/176	3040/150	3040/282	
Model 1	1 (Ref)	0.81 (0.65–1.00) *	0.78 (0.63–0.96) *	0.81 (0.67–0.97) *	0.024
Model 2	1 (Ref)	0.80 (0.65–0.99) *	0.80 (0.64–1.00) *	0.87 (0.71–1.05)	0.144
Model 3	1 (Ref)	0.80 (0.65–0.99) *	0.80 (0.64–1.00)	0.88 (0.73–1.07)	0.194
Methoxyphenols					
n/events	3041/235	3040/283	3041/222	3039/227	
Model 1	1 (Ref)	0.79 (0.64–0.96) *	0.78 (0.63–0.97) *	0.81 (0.65–1.01)	0.078
Model 2	1 (Ref)	0.76 (0.62–0.94) *	0.77 (0.61–0.97) *	0.74 (0.59–0.93) *	0.018
Model 3	1 (Ref)	0.76 (0.61–0.94 *	0.77 (0.61–0.96) *	0.75 (0.59–0.94) *	0.021
Tyrosols					
n/events	3041/275	3040/215	3040/238	3040/239	
Model 1	1 (Ref)	0.79 (0.65–0.96) *	0.80 (0.66–0.97) *	0.77 (0.64–0.92) **	0.009
Model 2	1 (Ref)	0.82 (0.67–1.00) *	0.83 (0.68–1.01)	0.79 (0.65–0.96) *	0.031
Model 3	1 (Ref)	0.83 (0.68–1.00)	0.83 (0.68–1.01)	0.80 (0.65–0.98) *	0.044
Alkylmethoxyphenols					
n/events	3070/289	3131/257	3047/219	2913/202	
Model 1	1 (Ref)	0.82 (0.67–1.00)	0.80 (0.65–0.98) *	0.78 (0.63–0.97) *	0.022
Model 2	1 (Ref)	0.84 (0.69–1.03)	0.79 (0.63–0.98) *	0.74 (0.60–0.93) **	0.007
Model 3	1 (Ref)	0.84 (0.69–1.02)	0.78 (0.63–0.97)	0.74 (0.59–0.93) *	0.007
Alkyphenols					
n/events	3041/352	3040/238	3040/167	3040/210	
Model 1	1 (Ref)	0.98 (0.81–1.18)	0.88 (0.71–1.07)	0.91 (0.75–1.11)	0.232
Model 2	1 (Ref)	0.97 (0.80–1.19)	0.86 (0.69–1.08)	0.96 (0.78–1.19)	0.509
Model 3	1 (Ref)	0.94 (0.77–1.15)	0.85 (0.68–1.06)	0.95 (0.77–1.17)	0.434
Ohter polyphenols					
n/events	3041/286	3040/267	3040/205	3040/209	
Model 1	1 (Ref)	0.91 (0.74–1.11)	0.84 (0.69–1.03)	0.92 (0.75–1.14)	0.295
Model 2	1 (Ref)	0.88 (0.73–1.07)	0.82 (0.66–1.01)	0.90 (0.74–1.11)	0.207
Model 3	1 (Ref)	0.89 (0.73–1.08)	0.83 (0.67–1.02)	0.91 (0.741.11)	0.232
Total other polyphenols					
n/events	3041/269	3040/238	3040/224	3040/236	
Model 1	1 (Ref)	1.01 (0.82–1.24)	0.86 (0.71–1.04)	0.90 (0.74–1.10)	0.14
Model 2	1 (Ref)	1.04 (0.85–1.28)	0.88 (0.71–1.08)	0.97 (0.79–1.20)	0.483
Model 3	1 (Ref)	1.05 (0.86–1.29)	0.89 (0.72–1.10)	0.98 (0.79–1.22)	0.524
Hydroxybenzoic acids					
n/events	3041/267	3040/213	3040/201	3040/286	
Model 1	1 (Ref)	0.98 (0.79–1.21)	0.83 (0.67–1.02)	0.83 (0.69–1.01)	0.027
Model 2	1 (Ref)	1.05 (0.85–1.29)	0.87 (0.70–1.07)	0.90 (0.74–1.10)	0.141
Model 3	1 (Ref)	1.04 (0.85–1.28)	0.88 (0.71–1.08)	0.92 (0.75–1.12)	0.218
Hydroxycinnamic acids					
n/events	3041/258	3040/276	3040/230	3040/203	
Model 1	1 (Ref)	0.84 (0.69–1.02)	0.78 (0.63–0.97) *	0.82 (0.66–1.01)	0.043
Model 2	1 (Ref)	0.88 (0.72–1.06)	0.78 (0.63–0.97) *	0.78 (0.63–0.96) *	0.010

Table 3 (*continued*)

	Q1 HR (95% CI)	Q2 HR (95% CI)	Q3 HR (95% CI)	Q4 HR (95% CI)	P for linear trend
Model 3	1 (Ref)	0.88 (0.72–1.06)	0.78 (0.62–0.97) *	0.79 (0.64–0.98) *	0.014
Hydroxyphenilacetic acids					
n/events	3042/309	3039/209	3040/206	3040/243	
Model 1	1 (Ref)	0.75 (0.62–0.91) **	0.70 (0.58–0.85) *	0.78 (0.64–0.94) *	0.005
Model 2	1 (Ref)	0.76 (0.62–0.92) **	0.79 (0.64–0.97) *	0.81 (0.66–0.98) *	0.042
Model 3	1 (Ref)	0.76 (0.62–0.92) **	0.79 (0.64–0.97) *	0.82 (0.67–0.99) *	0.064
Total phenolic acids					
n/events	3041/246	3040/283	3040/236	3040/202	
Model 1	1 (Ref)	0.92 (0.76–1.11)	0.83 (0.67–1.02)	0.81 (0.66–1.01)	0.034
Model 2	1 (Ref)	0.95 (0.78–1.15)	0.82 (0.66–1.02)	0.78 (0.63–0.96) *	0.01
Model 3	1 (Ref)	0.96 (0.79–1.16)	0.82 (0.66–1.02)	0.79 (0.64–0.99) *	0.016
Stilbenes					
n/events	3050/280	3031/173	3040/218	3040/296	
Model 1	1 (Ref)	0.90 (0.73–1.10)	0.83 (0.68–1.01)	0.82 (0.68–1.00) *	0.039
Model 2	1 (Ref)	0.86 (0.70–1.06)	0.83 (0.68–1.01)	0.87 (0.71–1.07)	0.171
Model 3	1 (Ref)	0.87 (0.70–1.07)	0.84 (0.69–1.03)	0.90 (0.73–1.10)	0.257
Total polyphenols					
n/events	3041/263	3040/231	3040/229	3040/244	
Model 1	1 (Ref)	0.77 (0.63–0.93) **	0.74 (0.61–0.91) **	0.81 (0.67–0.98) *	0.024
Model 2	1 (Ref)	0.79 (0.65–0.97) *	0.73 (0.60–0.90) **	0.82 (0.67–1.01)	0.032
Model 3	1 (Ref)	0.79 (0.65–0.97) *	0.74 (0.60–0.91) **	0.84 (0.68–1.03)	0.050

P value: * <0.05; **p < 0.01; †p < 0.001.
Model 1: adjusted for age and sex.
Model 2: as in model 1 and additionally adjusted for level of education, smoking status, leisure time and household physical activity, time watching TV, former drinker, BMI, total energy intake, total fiber intake, number of medications per day, number of chronic conditions.
Model 3: as in model 2 and additionally adjusted for hypertriglyceridemia, hypercholesterolemia, low HDL-cholesterol, and hypertension.

anti-inflammatory effects stand out [32], including cellular signaling pathways and modulation of the synthesis of tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), and other inflammatory mediators [4]. Polyphenols are also able to inhibit certain enzymes involved in the production of reactive oxygen species as well as eicosanoid production. Specific cardiometabolic properties of these compounds have also been described, including beneficial effects on glucose metabolism [4], cholesterol levels [4], platelet function [4], and antithrombotic [31] as well as vasodilator effects [4,31].

Regarding foods providing polyphenols, the main source of dihydroflavonols (a flavonoid associated with a 15% lower risk of all-cause mortality and a non-significant 12% lower risk of CVD mortality in our analyses) was red wine. Moderate red wine consumption has been associated with health benefits, mainly due to its cardiovascular benefits [10]. In the Nurses' Health Study II, red wine showed a 40% lower risk of all-cause mortality, when comparing frequent consumers versus non-consumers [22]. Many health benefits associated with red wine consumption have been attributed to its composition of flavonoids [33,34].

The major food sources of flavonols were leafy green vegetables such as lettuce and cooked spinach. In our study, flavonols intake was associated with a 21% lower all-cause mortality risk and a non-significant 10% lower risk of CVD mortality. In line with this, a dose–response meta-analysis showed a 22% lower risk of all-cause mortality per each 100 g/d increment in the consumption of leafy green vegetables [35]. Other studies have also shown the beneficial cardiovascular properties of flavonol intake [36].

In our results, tyrosol, which mainly comes from olive oils (common and extra virgin), showed a protective association with a lower all-cause mortality risk of 20%, and a non-significant lower CVD mortality risk of 29%. In addition, in a meta-analysis on olive oil consumption, a higher intake was associated with a 23% lower risk of all-cause mortality [37]. Olive oil polyphenols are known for their antioxidant, anti-inflammatory, and cardio-protective properties [38].

The major food contributor to hydrophenylacetic acids intake was green table olives. In our results, the hydroxyphenylacetic acids showed a lower all-cause mortality risk of 18% and a 31% lower risk

of CVD mortality. Olives are rich in other polyphenols [39,40] and are well known for their antioxidant and anti-inflammatory properties [41]. However, the consumption of table olives has scarcely been studied taking into consideration that they are consumed in small quantities as snacks in Spain, which are high in salt, and the difficulty of information collection as they do not appear as a single item in most food frequency questionnaires.

The intake of methoxyphenols, alkylmethoxyphenols, and hydroxycinnamic acids showed the lowest risk of all-cause and CVD mortality in our analyses, all of them coming from coffee. In a meta-analysis on coffee intake, drinking 3.5 cups/d of coffee was associated with a 15% lower risk of all-cause mortality, and 2.5 cups/d with a 17% lower risk of CVD mortality, when compared to no consumption [42]. Also, in an umbrella meta-analysis, a non-linear association was observed, where 3–4 cups/d versus no consumption showed the lowest risk of mortality with a 17% lower risk of all-cause mortality and a 19% lower risk of CVD mortality [43].

The main strengths of this study are its prospective design, and the use of a representative sample of the Spanish adult population. In addition, detailed food consumption was collected with a validated dietary history, which allowed the identification of a varied range of food sources. Also, a comprehensive data set (the Phenol-Explorer) was used to derive polyphenol consumption. To our knowledge, this is the first observational study that analyzed a wide variety of polyphenol subgroups.

Our study also has some limitations. First, we did not consider changes in diet consumption during follow-up, which could derive from a certain degree of non-differential misclassification. Second, cooking methods were only considered for a limited number of foods, however, we did consider oils that were added during cooking or frying. Third, despite adjusting for many confounding factors, residual confounding could not be ruled out. Finally, although several comparisons were performed, all the hypotheses were considered "a priori" based on specific and previously planned research questions.

In conclusion, our results show that higher consumption of specific polyphenol subgroups is associated with a substantially lower risk of all-cause mortality, which is mainly due to a lower CVD death risk. Among the polyphenol subgroups, the stronger

Table 4
Hazard Ratio (HR) for cardiovascular disease mortality according to tertiles of polyphenol consumption in the ENRICA Study (2008–10 to 2022). N = 12,161.

	T1 HR (95% CI)	T2 HR (95% CI)	T3 HR (95% CI)	P for linear trend
Anthocyanins				
n/events	4054/75	4054/63	4053/81	
Model 1	1 (Ref)	0.93 (0.64–1.36)	0.81 (0.56–1.19)	0.285
Model 2	1 (Ref)	0.86 (0.59–1.26)	0.82 (0.56–1.19)	0.302
Model 3	1 (Ref)	0.87 (0.59–1.28)	0.81 (0.56–1.19)	0.286
Flavanols				
n/events	4054/75	4054/69	4053/75	
Model 1	1 (Ref)	0.76 (0.52–1.12)	0.91 (0.61–1.36)	0.658
Model 2	1 (Ref)	0.82 (0.55–1.22)	1.04 (0.69–1.56)	0.882
Model 3	1 (Ref)	0.82 (0.55–1.22)	1.03 (0.69–1.55)	0.14
Flavanones				
n/events	4054/65	4054/56	4053/98	
Model 1	1 (Ref)	0.73 (0.48–1.11)	1.11 (0.78–1.57)	0.483
Model 2	1 (Ref)	0.78 (0.52–1.18)	1.18 (0.82–1.68)	0.316
Model 3	1 (Ref)	0.77 (0.51–1.18)	1.18 (0.82–1.69)	0.309
Flavones				
n/events	4054/88	4054/68	4053/63	
Model 1	1 (Ref)	1.02 (0.72–1.46)	1.04 (0.73–1.49)	0.832
Model 2	1 (Ref)	0.98 (0.67–1.42)	1.00 (0.65–1.52)	0.977
Model 3	1 (Ref)	1.02 (0.69–1.49)	1.02 (0.67–1.55)	0.09
Flavonols				
n/events	4054/73	4054/72	4053/74	
Model 1	1 (Ref)	0.91 (0.62–1.32)	0.89 (0.59–1.35)	0.586
Model 2	1 (Ref)	0.97 (0.66–1.44)	0.91 (0.60–1.38)	0.660
Model 3	1 (Ref)	0.69 (0.65–1.42)	0.90 (0.60–1.37)	0.630
Total flavonoids				
n/events	4054/61	4054/77	4053/81	
Model 1	1 (Ref)	1.03 (0.70–1.51)	0.97 (0.65–1.44)	0.871
Model 2	1 (Ref)	1.14 (0.75–1.73)	1.05 (0.69–1.58)	0.853
Model 3	1 (Ref)	1.15 (0.76–1.75)	1.06 (0.70–1.59)	0.820
Hydroxybenzaldehydes				
n/events	4054/108	4054/44	4053/67	
Model 1	1 (Ref)	0.94 (0.64–1.40)	0.79 (0.54–1.15)	0.220
Model 2	1 (Ref)	0.90 (0.61–1.31)	0.83 (0.56–1.23)	0.351
Model 3	1 (Ref)	0.89 (0.60–1.30)	0.82 (0.56–1.22)	0.324
Methoxyphenols				
n/events	4062/99	4051/63	4048/57	
Model 1	1 (Ref)	0.66 (0.46–0.93) *	0.61 (0.41–0.92) *	0.013
Model 2	1 (Ref)	0.68 (0.47–0.97) *	0.57 (0.37–0.88) *	0.009
Model 3	1 (Ref)	0.69 (0.48–0.99) *	0.58 (0.38–0.89) *	0.010
Tyrosols				
n/events	4054/90	4054/64	4053/65	
Model 1	1 (Ref)	0.72 (0.51–1.03)	0.73 (0.51–1.05)	0.086
Model 2	1 (Ref)	0.71 (0.49–1.03)	0.73 (0.50–1.07)	0.105
Model 3	1 (Ref)	0.69 (0.47–1.00)	0.71 (0.49–1.04)	0.081
Alkylmethoxyphenols				
n/events	4054/102	4054/62	4053/55	
Model 1	1 (Ref)	0.66 (0.46–0.94) *	0.62 (0.41–0.92) *	0.014
Model 2	1 (Ref)	0.67 (0.47–0.96) *	0.58 (0.38–0.89) *	0.010
Model 3	1 (Ref)	0.68 (0.47–0.98) *	0.59 (0.39–0.90) *	0.011
Alkylphenols				
n/events	4054/100	4054/52	4053/67	
Model 1	1 (Ref)	0.86 (0.59–1.27)	1.07 (0.76–1.49)	0.818
Model 2	1 (Ref)	0.79 (0.52–1.21)	1.10 (0.75–1.61)	0.725
Model 3	1 (Ref)	0.82 (0.53–1.25)	1.11 (0.76–1.62)	0.692
Other polyphenols				
n/events	4054/86	4054/74	4053/59	
Model 1	1 (Ref)	0.96 (0.67–1.39)	0.98 (0.67–1.44)	0.912
Model 2	1 (Ref)	0.94 (0.65–1.37)	1.02 (0.68–1.51)	0.970
Model 3	1 (Ref)	0.94 (0.65–1.36)	1.02 (0.69–1.52)	0.963
Total other polyphenols				
n/events	4054/91	4054/62	4053/66	
Model 1	1 (Ref)	0.82 (0.56–1.19)	0.80 (0.56–1.14)	0.216
Model 2	1 (Ref)	0.82 (0.56–1.20)	0.82 (0.57–1.19)	0.284
Model 3	1 (Ref)	0.82 (0.56–1.20)	0.81 (0.56–1.18)	0.270
Hydroxybenzoic acids				
n/events	4054/80	4054/50	4053/89	
Model 1	1 (Ref)	0.70 (0.46–1.07)	0.96 (0.68–1.38)	0.887
Model 2	1 (Ref)	0.75 (0.49–1.14)	1.09 (0.76–1.58)	0.608
Model 3	1 (Ref)	0.75 (0.49–1.14)	1.08 (0.75–1.55)	0.669
Hydroxycinnamic acids				
n/events	4054/92	4054/71	4053/56	
Model 1	1 (Ref)	0.70 (0.49–1.01)	0.67 (0.45–1.00)	**0.040**
Model 2	1 (Ref)	0.70 (0.48–1.02)	**0.62 (0.41–0.93) ***	**0.018**

(continued on next page)

Table 4 (*continued*)

	T1 HR (95% CI)	T2 HR (95% CI)	T3 HR (95% CI)	P for linear trend
Model 3	1 (Ref)	0.71 (0.48–1.03)	0.63 (0.42–0.94) *	0.020
Hydroxyphenylacetic acids				
n/events	4056/104	4052/51	4053/64	
Model 1	1 (Ref)	0.76 (0.52–1.09)	0.69 (0.47–1.00)	0.048
Model 2	1 (Ref)	0.84 (0.58–1.21)	0.71 (0.49–1.02)	0.62
Model 3	1 (Ref)	0.83 (0.57–1.21)	0.69 (0.48–0.99) *	0.044
Total phenolic acids				
n/events	4054/94	4054/67	4053/58	
Model 1	1 (Ref)	0.67 (0.46–0.97) *	0.66 (0.45–0.98) *	0.031
Model 2	1 (Ref)	0.68 (0.46–1.00)	0.62 (0.41–0.93) *	0.017
Model 3	1 (Ref)	0.69 (0.47–1.01)	0.62 (0.41–0.93) *	0.019
Stilbenes				
n/events	4054/89	4054/53	4053/77	
Model 1	1 (Ref)	0.73 (0.51–1.06)	0.69 (0.47–1.00)	0.054
Model 2	1 (Ref)	0.71 (0.49–1.03)	0.71 (0.48–1.05)	0.083
Model 3	1 (Ref)	0.70 (0.48–1.01)	0.70 (0.47–1.04)	0.071
Total polyphenols				
n/events	4054/81	4054/74	4053/64	
Model 1	1 (Ref)	0.94 (0.66–1.33)	0.88 (0.60–1.31)	0.529
Model 2	1 (Ref)	0.98 (0.67–1.42)	0.91 (0.60–1.38)	0.668
Model 3	1 (Ref)	1.00 (0.68–1.45)	0.92 (0.61–1.39)	0.687

P value: * <0.05; **p < 0.01; †p < 0.001.
Model 1: adjusted for age and sex.
Model 2: as in model 1 and additionally adjusted for level of education, smoking status, leisure time and household physical activity, time watching TV, former drinker, BMI, total energy intake, total fiber intake, number of medications per day, number of chronic conditions.
Model 3: as in model 2 and additionally adjusted for hypertriglyceridemia, hypercholesterolemia, low HDL-cholesterol, and hypertension.

beneficial associations were observed with those coming from coffee (methoxyphenols, alkylmethoxyphenols, and hydroxycinnamic acids). Red wine, leafy green vegetables, olive oil, and green table olives are also other main sources of the polyphenol subgroups associated with lower mortality risk.

Author contributions

Diana María Mérida: Formal analysis, Writing-original draft. **Facundo Vitelli-Storelli:** Formal analysis, Software. **Belén Moreno-Franco:** Writing-review&editing. **Montserrat Rodríguez-Ayala:** Writing-review&editing. **Esther López-García:** Writing-review&editing. **José R. Banegas:** Resources, Writing-review&editing. **Fernando Rodríguez-Artalejo:** Resources, Writing-review&editing. **Pilar Guallar-Castillón:** Conceptualization, Resources, Supervision.

Conflicts of interest

The authors have no conflict of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.05.020.

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