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Coffee Drinking and Mortality in 10 European Countries

A Multinational Cohort Study

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Background: The relationship between coffee consumption and mortality in diverse European populations with variable coffee preparation methods is unclear.

Objective: To examine whether coffee consumption is associated with all-cause and cause-specific mortality.

Design: Prospective cohort study.

Setting: 10 European countries.

Participants: 521 330 persons enrolled in EPIC (European Prospective Investigation into Cancer and Nutrition).

Measurements: Hazard ratios (HRs) and 95% CIs estimated using multivariable Cox proportional hazards models. The association of coffee consumption with serum biomarkers of liver function, inflammation, and metabolic health was evaluated in the EPIC Biomarkers subcohort (n = 14 800).

Results: During a mean follow-up of 16.4 years, 41 693 deaths occurred. Compared with nonconsumers, participants in the highest quartile of coffee consumption had statistically significantly lower all-cause mortality (men: HR, 0.88 [95% CI, 0.82 to 0.95]; P for trend < 0.001; women: HR, 0.93 [CI, 0.87 to 0.98]; P for trend = 0.009). Inverse associations were also observed for digestive disease mortality for men (HR, 0.41 [CI, 0.32 to 0.54]; P for trend < 0.001) and women (HR, 0.60 [CI, 0.46 to 0.78]; P for trend < 0.001). Among women, there was a statistically significant inverse association of coffee drinking with circulatory disease mortality (HR, 0.78 [CI, 0.68 to 0.90]; P for trend < 0.001) and cerebrovascular disease mortality (HR, 0.70 [CI, 0.55 to 0.90]; P for trend = 0.002) and a positive association with ovarian cancer mortality (HR, 1.31 [CI, 1.07 to 1.61]; P for trend = 0.015). In the EPIC Biomarkers subcohort, higher coffee consumption was associated with lower serum alkaline phosphatase; alanine aminotransferase; aspartate aminotransferase; γ-glutamyltransferase; and, in women, C-reactive protein, lipoprotein(a), and glycated hemoglobin levels.

Limitations: Reverse causality may have biased the findings; however, results did not differ after exclusion of participants who died within 8 years of baseline. Coffee-drinking habits were assessed only once.

Conclusion: Coffee drinking was associated with reduced risk for death from various causes. This relationship did not vary by country.

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Coffee is among the most commonly consumed beverages, with an estimated 2.25 billion cups drunk worldwide per day. Coffee drinking provides exposure to a range of biologically active compounds (1), and higher consumption has been linked with lower levels of inflammation (2, 3), insulin resistance, and risk for diabetes (4–6). Initial studies investigating the relationship between coffee consumption and risk for all-cause death were of limited size and reported inconsistent results (7–9). However, recent U.S.-based analyses have reported that higher consumption was related to lower risk for all-cause death (10–12). To date, a large-scale European-based analysis of coffee consumption and mortality has not been done.

For cause-specific mortality, findings on coffee drinking and cardiovascular disease mortality have been mixed (13–16), although a U.S. study and a meta-analysis recently reported a lower risk for cardiovascular disease death for persons with high consumption compared with nonconsumers (10, 17). Coffee drinking has generally not been associated with cancer mortality (8, 10, 15, 17), and data are limited for mortality from other chronic diseases, such as digestive and respiratory disease.

We investigated the association of coffee consumption with all-cause and cause-specific mortality in EPIC (European Prospective Investigation into Cancer

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and Nutrition), a large multinational cohort that captured country-specific coffee preparation methods. In addition, to gain insight into potential biological mechanisms, we investigated the association of coffee drinking with selected serum biomarkers of liver function, inflammation, and metabolic health.

METHODS

Study Population

EPIC is a multicenter prospective cohort of 521 330 participants, mostly aged 35 years or older, who were recruited in 1992 to 2000, predominantly from the general population of 10 European countries (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom) (18, 19). Additional detail on the study population is provided in Appendix 1 (available at Annals.org). Written informed consent was provided by all study participants, and ethical approval for EPIC was provided by the International Agency for Research on Cancer and local participating centers. Participants who reported cancer (n = 22 537), heart disease (n = 12 619), stroke (n = 3683), or diabetes (n = 12 461); those in the highest and lowest 1% of the distribution for the ratio of energy intake to estimated energy requirement (n = 8828); and those missing information on coffee consumption and follow-up (n = 9459) were excluded from analyses. The final analytic data set included 451 743 participants (130 662 men and 321 081 women).

Diet, Lifestyle, and Anthropometric Information

Dietary intake was assessed by different instruments that had been developed and validated within the EPIC source populations to reflect each country's local context (18, 19). Self-administered questionnaires were used in all centers, except in Greece, Spain, and Ragusa (Italy), where data were collected at a personal interview. Information specifically on caffeinated and decaffeinated coffee drinking was collected from participants in Germany, Greece, Italy (excluding Naples and Ragusa), the Netherlands, and the United Kingdom. Participants recorded the number of cups of coffee consumed per month, week, or day. Coffee consumption (in milliliters per day) was calculated using the typical sizes of cups for each center. Lifestyle questionnaires were used to obtain information on education; smoking; alcohol consumption; physical activity; use of oral contraceptives and menopausal hormone therapy; menopausal status; and, in 5 centers, nonsteroidal anti-inflammatory drug use.

Liver Function, Circulatory Disease, and Metabolic Biomarker Measurement

Baseline data on serum levels of albumin, alkaline phosphatase (ALP), alanine aminotransferase (ALT), aspartate aminotransferase (AST), γ-glutamyltransferase (GGT), high-sensitivity C-reactive protein (CRP), glycated hemoglobin (HbA_{1c}), high-density lipoprotein cholesterol (HDL-C), and lipoprotein(a) were available for the EPIC Biomarkers subcohort of 16 775 randomly selected participants (see Appendix Table 1, available at Annals.org, for details on measurement methods). After the same exclusion criteria used in the main coffee–mortality analyses were applied, 14 800 participants remained.

Assessment of Mortality

Data on vital status and cause and date of death were collected at the EPIC study centers using record linkages with cancer registries, boards of health, and death indices in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom and through active follow-up (inquiries by mail or telephone, municipal registries, regional health departments, and physicians or hospitals) in Germany, Greece, and France. Data on causes of death were coded in accordance with the International Classification of Diseases, 10th Revision (ICD-10). The following causes of death were investigated: cancer (ICD-10 codes C00 to D48), circulatory diseases (codes I00 to I99), ischemic heart diseases (codes I20 to I25), cerebrovascular diseases (codes I60 to I69), respiratory diseases (codes J30 to J98), digestive diseases (codes K00 to K93), external causes (codes S00 to Y98), and suicide (codes X60 to X84).

Statistical Analysis

Hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models, with age as the primary time metric. Time of study entry was age at recruitment, and exit time was age at death or the last date at which follow-up was considered complete in each center. Models were also stratified by age at recruitment (in 1-year categories) and center to minimize departure from proportionality and to control for differences across centers, such as in follow-up procedures and questionnaire design.

To account for between-country variability in the volume and concentration of the type of coffee locally consumed, total, caffeinated, and decaffeinated coffee were modeled using country-specific quartiles among coffee drinkers compared with nondrinkers. Analyses based on daily number of cups of coffee consumed (0, <1, 1 to <2, 2 to <3, and ≥3 cups per day [1 cup = 237 mL]) were also done. Trend tests across exposure groups were done by entering the category variables into the Cox models as continuous terms. Continuous models (HR expressed per cup per day) were also used. The multivariable models were adjusted for a set of a priori–determined covariates that included body mass index (<22, 22 to 24.9, 25 to 29.9, 30 to 34.9, or ≥35 kg/m^2), physical activity (inactive, moderately inactive, moderately active, or active), smoking status and intensity (never, current [1 to 15, 16 to 25, or ≥26 cigarettes per day], or former [≤10, 11 to <20, or ≥20 years since quitting]; current pipe, cigar, or occasional smoking; current vs. former; missing; or unknown), smoking duration (<10, 10 to <20, 20 to <30, 30 to <40, or ≥40 years or unknown), education (none, primary school, technical or professional school, secondary school, higher education [including university], or not specified), menopausal status (premenopausal,

postmenopausal, perimenopausal, surgically postmenopausal, or unknown), ever-use of oral contraceptives or menopausal hormone therapy, alcohol consumption (0, <5, 5 to 14.9, 15 to 29.9, or ≥30 g of ethanol per day), total energy intake (in kilocalories per day), consumption of red and processed meats (in grams per day), and consumption of fruits and vegetables (in grams per day). Further adjustment for intake of fiber, calcium, fish, and soft drinks and use of nonsteroidal anti-inflammatory drugs resulted in virtually unchanged risk estimates, so these variables were excluded from the final multivariable models.

The association between coffee consumption and mortality was further assessed across subgroups based on smoking status, body mass index, physical activity, alcohol intake, red and processed meat consumption, and fruit and vegetable consumption. Interaction terms (multiplicative scale) between these variables and coffee intake were included in separate models; the statistical significance of the cross-product terms was evaluated using the likelihood ratio test. Similar analyses examined associations according to follow-up categories (<5, 5 to <10, and ≥10 years). Heterogeneity across countries was explored using a meta-analytic approach (20). To detect possible reverse causality, sensitivity analyses were conducted by excluding deaths within the first 5 and 8 years of follow-up and including only participants who reported being in "excellent" or "good" health at recruitment. To assess the possible effect of an unmeasured confounder on the results, we used a sensitivity analysis described by Ding and VanderWeele (21). In a supplementary analysis, flexible parametric survival models (22) were used to allow direct estimation of the conditional cumulative incidence and, thus, absolute risks for death by sex and coffee consumption categories, with adjustment for other covariates. Within these models, we used restricted cubic splines with 3 internal knots to model the baseline hazard, using attained age as the time scale. Model-based survival functions were obtained from fitted models by coffee consumption category and sex.

Table 1. Baseline Characteristics of Study Participants, by Category of Daily Coffee Consumption

Characteristic	Total Coffee Consumption*					
	Men			Women		
	Nonconsumers	Quartile 2	Quartile 4	Nonconsumers	Quartile 2	Quartile 4
Median total coffee consumption, *mL/d*	0	300	855	0	253	684
Participants, *n*	6477	29 809	28 535	25 384	66 279	62 773
All-cause deaths, *n*	1039	4440	3601	1817	5236	4162
Median age at recruitment (IQR), *y*	52.7 (45.3–59.6)	53.3 (47.3–59.9)	50.1 (42.7–56.2)	50.8 (45.4–57.2)	51.8 (45.2–58.9)	49.2 (44.1–54.6)
Median body mass index (IQR), kg/m^2	26.3 (24.1–28.7)	26.1 (24.0–28.4)	26.2 (24.1–28.5)	23.6 (21.3–26.8)	24.1 (21.9–27.1)	24.3 (22.0–27.3)
Higher education (including university), %	23.2	26.1	26.9	23.0	23.2	23.0
Current smoker, %	18.1	26.3	42.8	11.2	16.3	31.1
Physically active, %†	25.5	24.6	23.7	11.9	16.4	14.3
Median total energy intake (IQR), *kcal/d*	2300 (1893–2773)	2312 (1914–2756)	2469 (2049–2960)	1906 (1547–2312)	1867 (1551–2240)	1947 (1604–2356)
Median consumption (IQR), *g/d*						
Red and processed meat	82.4 (49.0–123.2)	86.9 (51.6–128.7)	95.1 (58.8–137.6)	59.7 (35.4–88.0)	59.5 (34.6–88.5)	65.3 (38.9–95.5)
Fruits and vegetables	380.8 (229.3–615.6)	325.9 (200.8–512.2)	315.5 (192.8–516.4)	461.2 (305.7–645.5)	416.3 (278.4–588.7)	419.4 (268.9–605.5)
Alcohol	7.4 (0.6–24.0)	12.9 (4.4–30.2)	12.5 (4.1–28.5)	1.2 (0–6.7)	4.0 (0.8–11.5)	3.7 (0.6–11.3)
Ever-use of contraceptive pill, %	–	–	–	52.0	55.9	61.4
Ever-use of menopausal hormone therapy, %	–	–	–	23.8	23.9	22.7
Postmenopausal, %	–	–	–	41.5	46.2	35.4

IQR = interquartile range.
* Quartiles are country-specific.
† Defined as those with a sedentary job with >1 h of recreational activity per day, a standing job with >0.5 h of recreational activity per day, a physical job with at least some recreational activity, or a heavy manual job.

Table 2. Associations of Daily Coffee Consumption and All-Cause and Cause-Specific Mortality Among Men and Women

Variable	Coffee Consumption*					*P* Value for Trend	Per Cup Per Day
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)		
All-cause mortality							
Men							
Deaths, *n*	1039	4972	4440	4250	3601		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.89 (0.83–0.95)	0.89 (0.83–0.95)	0.90 (0.84–0.96)	1.07 (0.99–1.15)	<0.001	–
Basic model plus smoking variables†	1.00 (reference)	0.88 (0.82–0.94)	0.83 (0.77–0.89)	0.78 (0.73–0.84)	0.83 (0.77–0.89)	<0.001	–
Multivariable model‡	1.00 (reference)	0.94 (0.87–1.00)	0.88 (0.82–0.95)	0.84 (0.78–0.90)	0.88 (0.82–0.95)	<0.001	0.97 (0.96–0.98)
Women							
Deaths, *n*	1817	6882	5236	5294	4162		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.90 (0.85–0.95)	0.90 (0.85–0.95)	0.95 (0.90–1.01)	1.10 (1.04–1.16)	<0.001	–
Basic model plus smoking variables†	1.00 (reference)	0.91 (0.86–0.96)	0.87 (0.82–0.91)	0.87 (0.82–0.92)	0.90 (0.85–0.96)	0.004	–
Multivariable model‡	1.00 (reference)	0.94 (0.89–0.99)	0.90 (0.85–0.95)	0.90 (0.85–0.95)	0.93 (0.87–0.98)	0.009	0.99 (0.98–1.00)
Cancer (ICD-10 codes C00–D48)							
Men							
Deaths, *n*	386	1923	1861	1816	1628		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.90 (0.81–1.01)	1.01 (0.90–1.13)	1.04 (0.93–1.16)	1.27 (1.13–1.42)	<0.001	–
Multivariable model‡	1.00 (reference)	0.92 (0.82–1.03)	0.97 (0.86–1.08)	0.92 (0.82–1.03)	0.99 (0.88–1.11)	0.45	1.00 (0.99–1.02)
Women							
Deaths, *n*	645	2917	2305	2417	2105		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.98 (0.90–1.07)	1.07 (0.98–1.17)	1.12 (1.03–1.23)	1.33 (1.22–1.46)	<0.001	–
Multivariable model‡	1.00 (reference)	1.00 (0.92–1.10)	1.05 (0.96–1.15)	1.04 (0.95–1.14)	1.12 (1.02–1.23)	0.001	1.03 (1.01–1.04)
Circulatory diseases (ICD-10 codes I00–I99)							
Men							
Deaths, *n*	257	1352	1148	1091	922		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.96 (0.84–1.10)	0.91 (0.80–1.05)	0.92 (0.80–1.05)	1.12 (0.97–1.29)	0.033	–
Multivariable model‡	1.00 (reference)	1.02 (0.89–1.17)	0.93 (0.80–1.07)	0.87 (0.76–1.00)	0.93 (0.80–1.08)	0.004	0.97 (0.95–0.99)
Women							
Deaths, *n*	334	1399	968	959	676		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.85 (0.75–0.96)	0.75 (0.66–0.85)	0.82 (0.72–0.93)	0.94 (0.82–1.08)	0.95	–
Multivariable model‡	1.00 (reference)	0.89 (0.78–1.01)	0.74 (0.65–0.85)	0.77 (0.67–0.88)	0.78 (0.68–0.90)	<0.001	0.96 (0.94–0.99)
Cerebrovascular diseases (ICD-10 codes I60–I69)							
Men							
Deaths, *n*	58	284	231	195	150		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.89 (0.66–1.19)	0.80 (0.60–1.08)	0.77 (0.57–1.04)	0.92 (0.67–1.25)	0.42	–
Multivariable model‡	1.00 (reference)	0.94 (0.70–1.27)	0.83 (0.61–1.12)	0.76 (0.56–1.04)	0.83 (0.60–1.14)	0.043	0.94 (0.89–0.99)
Women							
Deaths, *n*	114	472	358	317	201		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.83 (0.67–1.03)	0.78 (0.63–0.98)	0.77 (0.62–0.97)	0.82 (0.64–1.04)	0.154	–
Multivariable model‡	1.00 (reference)	0.85 (0.68–1.05)	0.77 (0.62–0.96)	0.74 (0.59–0.92)	0.70 (0.55–0.90)	0.002	0.94 (0.90–0.99)
Ischemic heart diseases (ICD-10 codes I20–I25)							
Men							
Deaths, *n*	112	597	533	534	474		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.94 (0.77–1.15)	0.92 (0.75–1.13)	0.94 (0.77–1.15)	1.15 (0.94–1.42)	0.015	–
Multivariable model‡	1.00 (reference)	1.03 (0.84–1.26)	0.96 (0.78–1.18)	0.92 (0.75–1.13)	0.97 (0.79–1.20)	0.24	0.99 (0.96–1.02)
Women							
Deaths, *n*	83	415	296	266	216		–
HR (95% CI)							
Basic model†	1.00 (reference)	0.96 (0.75–1.23)	0.84 (0.65–1.09)	0.81 (0.63–1.05)	1.07 (0.83–1.40)	0.96	–
Multivariable model‡	1.00 (reference)	1.03 (0.80–1.32)	0.83 (0.64–1.08)	0.74 (0.57–0.96)	0.82 (0.62–1.07)	<0.001	0.94 (0.90–0.98)

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Table 2–Continued

Variable	Coffee Consumption*					*P* Value for Trend	Per Cup Per Day
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)		
Digestive diseases (ICD-10 codes K00-K93)§							
Men							
Deaths, *n*	274	144	105	82			–
HR (95% CI)							
Basic model†	1.00 (reference)	0.72 (0.59-0.89)	0.53 (0.42-0.67)	0.55 (0.42-0.70)		<0.001	–
Multivariable model‡	1.00 (reference)	0.69 (0.56-0.85)	0.46 (0.37-0.59)	0.41 (0.32-0.54)		<0.001	0.77 (0.72-0.81)
Women							
Deaths, *n*	273	134	122	79			–
HR (95% CI)							
Basic model†	1.00 (reference)	0.75 (0.60-0.92)	0.76 (0.61-0.94)	0.77 (0.60-1.00)		0.004	–
Multivariable model‡	1.00 (reference)	0.70 (0.56-0.86)	0.67 (0.54-0.84)	0.60 (0.46-0.78)		<0.001	0.86 (0.81-0.92)
Respiratory diseases (ICD-10 codes J30-J98)§							
Men							
Deaths, *n*	240	162	161	151			–
HR (95% CI)							
Basic model†	1.00 (reference)	0.89 (0.73-1.09)	1.03 (0.84-1.27)	1.55 (1.25-1.91)		0.004	–
Multivariable model‡	1.00 (reference)	0.81 (0.66-0.99)	0.84 (0.69-1.04)	1.05 (0.84-1.30)		0.62	1.01 (0.96-1.06)
Women							
Deaths, *n*	316	212	185	162			–
HR (95% CI)							
Basic model†	1.00 (reference)	1.08 (0.91-1.29)	1.16 (0.96-1.40)	1.74 (1.43-2.13)		<0.001	–
Multivariable model‡	1.00 (reference)	0.95 (0.79-1.14)	0.83 (0.69-1.01)	0.91 (0.74-1.12)		0.142	0.98 (0.94-1.03)
External causes (ICD-10 codes S00-Y98)§							
Men							
Deaths, *n*	285	181	187	183			–
HR (95% CI)							
Basic model†	1.00 (reference)	0.84 (0.70-1.02)	0.87 (0.72-1.05)	1.03 (0.85-1.25)		0.66	–
Multivariable model‡	1.00 (reference)	0.83 (0.68-1.00)	0.82 (0.68-1.00)	0.90 (0.74-1.10)		0.099	0.96 (0.91-1.01)
Women							
Deaths, *n*	284	157	157	137			–
HR (95% CI)							
Basic model†	1.00 (reference)	0.93 (0.76-1.13)	0.93 (0.76-1.14)	1.07 (0.86-1.32)		0.96	–
Multivariable model‡	1.00 (reference)	0.93 (0.76-1.13)	0.91 (0.74-1.11)	0.96 (0.77-1.20)		0.47	0.98 (0.93-1.04)
Suicide (ICD-10 codes X60-X84)§							
Men							
Deaths, *n*	91	51	47	53			–
HR (95% CI)							
Basic model†	1.00 (reference)	0.78 (0.55-1.10)	0.72 (0.50-1.03)	0.91 (0.64-1.30)		0.25	–
Multivariable model‡	1.00 (reference)	0.75 (0.52-1.06)	0.64 (0.44-0.92)	0.71 (0.50-1.02)		0.016	0.90 (0.83-0.98)
Women							
Deaths, *n*	67	40	31	38			–
HR (95% CI)							
Basic model†	1.00 (reference)	1.06 (0.71-1.58)	0.81 (0.52-1.25)	1.19 (0.78-1.81)		0.82	–
Multivariable model‡	1.00 (reference)	1.06 (0.71-1.59)	0.77 (0.50-1.20)	0.98 (0.63-1.51)		0.61	0.97 (0.87-1.09)

HR = hazard ratio; ICD-10 = International Classification of Diseases, 10th Revision.

* Based on country-specific quartiles of coffee consumption after exclusion of nonconsumers. Quartile cutoffs were 500, 900, and 1300 mL/d in Denmark; 150, 280, and 450 mL/d in France; 261, 395, and 580 mL/d in Germany; 70, 140, and 240 mL/d in Greece; 60, 92, and 138 mL/d in Italy; 375, 500, and 750 mL/d in the Netherlands; 300, 420, and 540 mL/d in Norway; 50, 105, and 196 mL/d in Spain; 300, 400, and 601 mL/d in Sweden; and 83, 380, and 488 mL/d in the United Kingdom.

† Cox regression with adjustment for total energy intake (in kilocalories per day) and stratification by age (1-y categories) and center.

‡ Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); education (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of contraceptive pill or menopausal hormone therapy (yes, no, or unknown); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

§ Reference category was merged with low consumption (quartile 1) due to low case numbers among nonconsumers.

Liver Function, Inflammation, and Metabolic Biomarker Measurements

In the EPIC Biomarkers subcohort, mean serum levels of liver function, inflammatory, and metabolic biomarkers were calculated for coffee consumption categories. For biomarker values that were nonnormally distributed, data were log-transformed and geometric means were calculated for each category (see the footnote to Table 3 for multivariable adjustments). Also in the subcohort, Cox proportional hazards models using the same criteria as the analyses of coffee consumption and mortality were used to assess the relationships of serum levels (sex-specific quartiles) of albumin, ALP, ALT, AST, GGT, CRP, HbA_{1c}, HDL-C, and lipoprotein(a) with all-cause mortality (see the legend of Appendix Figure 1, available at Annals.org, for multivariable adjustments).

All statistical tests were 2-sided, and a *P* value less than 0.05 was considered statistically significant.

Ethical Approval

All participants provided informed consent, and ethical approval for the entire EPIC cohort was obtained from the Institutional Review Board of the International Agency for Research on Cancer in Lyon, France, under protocol numbers SC/24/4 and SC/24/6, as well as from local ethics committees in the participating countries.

Role of the Funding Source

The funders of the EPIC study had no role in study design, conduct, or reporting of the results.

RESULTS

After a mean follow-up of 16.4 years, 18 302 and 23 391 deaths were recorded among men and women, respectively. Of the 41 693 total deaths, 18 003 were from cancer, 9106 were from circulatory diseases, 2380 were from cerebrovascular diseases, 3536 were from ischemic heart diseases, 1213 were from digestive diseases, 1589 were from respiratory diseases, 1571 were from external causes, and 418 were from suicide. Mortality rates, age-adjusted to European standard populations (23), were 118 and 78 deaths per 10 000 person-years in men and women, respectively. Daily volume of coffee consumed was highest in Denmark (median, 900 mL/d for men and women) and lowest in Italy (median, 91 mL/d for men and 93 mL/d for women) (Appendix Table 2, available at Annals.org). Compared with nonconsumers, participants with higher reported coffee intake were more likely to be younger and current smokers, reported higher intake of red and processed meats and alcohol, and reported lower consumption of fruits and vegetables (Table 1).

Coffee Consumption and All-Cause Mortality

Participants in the highest quartile of coffee consumption had lower risk for all-cause death than nonconsumers after adjustment for smoking and other covariates in the multivariable models (men: HR, 0.88 [95% CI, 0.82 to 0.95]; *P* for trend < 0.001; women: HR, 0.93 [CI, 0.87 to 0.98]; *P* for trend = 0.009) (Table 2). When categories of daily consumption (in cups) were used, similar inverse associations were observed for men (HR for ≥3 cups per day vs. nonconsumers, 0.82 [CI, 0.76 to 0.89]; *P* for trend < 0.001) and women (HR for ≥3 cups per day vs. nonconsumers, 0.92 [CI, 0.87 to 0.98]; *P* for trend < 0.001) (data not shown). We found no evidence of heterogeneity by country for the association between coffee drinking and all-cause mortality (*P* for heterogeneity = 0.71 for men and 0.37 for women). Overall, similar inverse associations and linear trends were observed for consumption of caffeinated and decaffeinated coffee, although the association with all-cause mortality was less pronounced for caffeinated than decaffeinated coffee in men, with a statistically significantly lower risk not observed in the highest quartile of consumption (Appendix Tables 3 and 4, available at Annals.org).

Adjusted cumulative incidence curves for all-cause mortality by coffee consumption categories are presented in Appendix Figure 2 (available at Annals.org). For men, the cumulative incidence of death until age 80 years was 3.1% (CI, 1.7% to 4.5%) and 2.2% (CI, 0.8% to 3.7%) lower among participants in the third and highest quartiles of consumption, respectively, compared with nonconsumers. For women, the cumulative incidence of death until age 80 years was 1.4% (CI, 0.6% to 2.3%) and 0.8% (CI, −0.1% to 1.7%) lower among those in the third and highest quartiles of consumption compared with nonconsumers.

Coffee Consumption and Cause-Specific Mortality

Strong inverse associations were observed between coffee consumption and risks for death from digestive disease for men (highest quartile vs. nonconsumers and first quartile: HR, 0.41 [CI, 0.32 to 0.54]; *P* for trend < 0.001) and women (highest quartile vs. nonconsumers and first quartile: HR, 0.60 [CI, 0.46 to 0.78]; *P* for trend < 0.001) (Table 2). Similar inverse associations were observed when categories of daily consumption (in cups) were used (data not shown). Slightly more than one third of digestive disease deaths were due to liver disease. There was a statistically significant inverse association between coffee drinking and liver disease death (highest quartile vs. nonconsumers [sexes combined]: HR, 0.20 [CI, 0.13 to 0.29]), whereas the results for nonliver digestive disease deaths were inconclusive (highest quartile vs. nonconsumers [sexes combined]: HR, 0.81 [CI, 0.56 to 1.16]). We found a strong inverse association between death from cirrhosis and coffee drinking (highest quartile vs. nonconsumers [sexes combined]: HR, 0.21 [CI, 0.13 to 0.34]). Similar inverse associations were observed for alcoholic and nonalcoholic cirrhosis (data not shown).

Coffee consumption was also inversely associated with circulatory disease; this relationship was more pronounced in women, and the associations were stronger for deaths from cerebrovascular disease (highest quartile vs. nonconsumers: HR, 0.70 [CI, 0.55 to 0.90]; *P* for trend = 0.002) (Table 2). In general, the associations

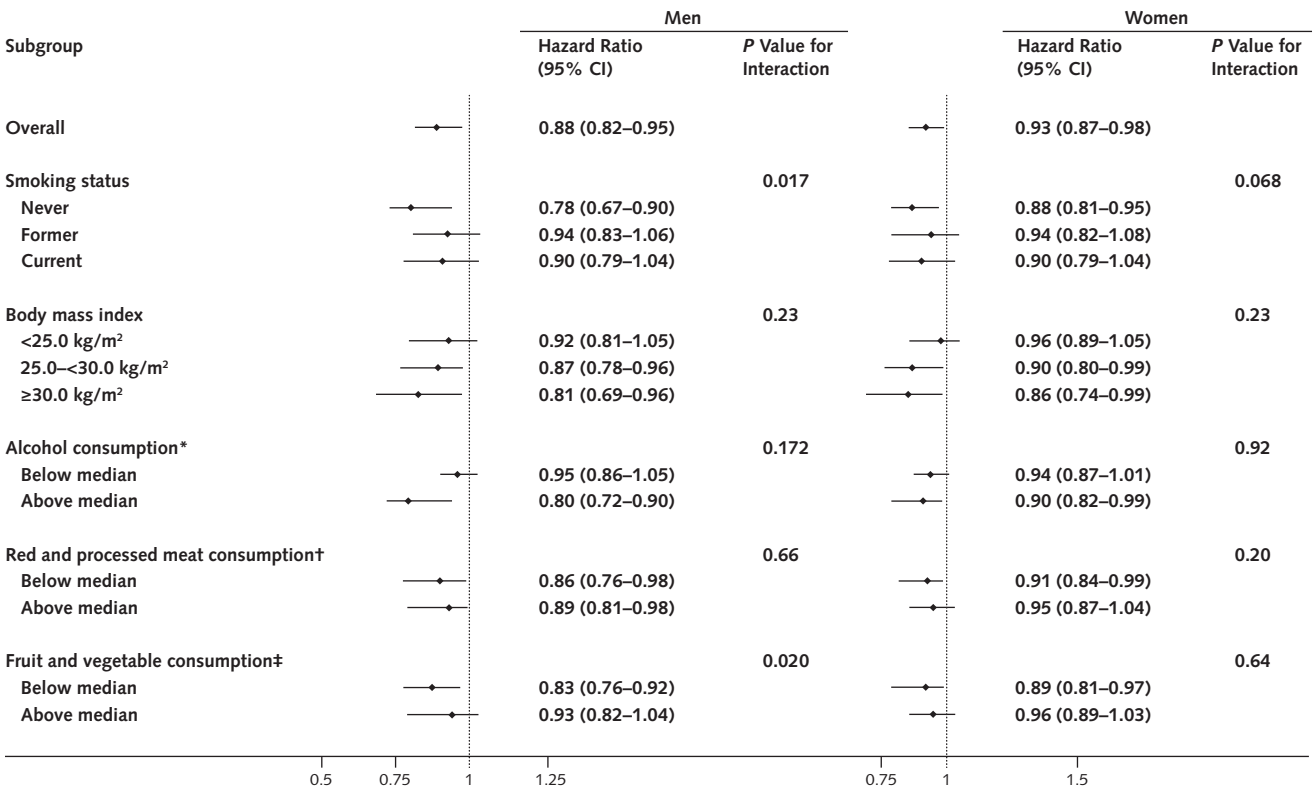
between coffee consumption and cause-specific mortality were weaker when caffeinated and decaffeinated coffee were analyzed separately, although associations were in the same direction for both types (Appendix Tables 3 and 4). The association of coffee drinking with cancer-related mortality was not statistically significant in men, whereas a positive association was found in women (highest quartile vs. nonconsumers: HR, 1.12 [CI, 1.02 to 1.23]; *P* for trend = 0.001). In further analyses by cancer type, we observed a statistically significant positive association between coffee consumption and ovarian cancer mortality (highest quartile vs. nonconsumers: HR, 1.31 [CI, 1.07 to 1.61]; *P* for trend = 0.015) in a multivariable model that included smoking and other risk factors (Appendix Table 5, available at Annals.org). In men, there were statistically significant inverse associations between medium-low coffee consumption and lung cancer mortality (Appendix Table 5). Coffee drinking was inversely associated with liver cancer mortality in both men and women. Respiratory disease mortality was not related to coffee consumption in the full models (Table 2). Coffee drinking was not associated with deaths from external causes; however, an inverse relationship was observed with suicide for men but not women (Table 2).

Subgroup and Sensitivity Analyses

Smoking was the most influential confounder for the analyses of all-cause mortality (Table 2). However, because smoking is positively associated with both coffee consumption and risk for death, confounding in this case would obscure a possible reduction in risk associated with coffee consumption. As expected, statistical adjustment for smoking strengthened the association between coffee drinking and reduced risk for death. Furthermore, coffee drinking was inversely associated with all-cause mortality among never-smokers and across subgroups of other mortality risk factors (Figure). Similarly, among never-smokers, coffee drinking was inversely associated with death from cancer and circulatory, digestive, and respiratory diseases (Appendix Table 6, available at Annals.org).

The associations of coffee consumption with all-cause mortality did not differ according to follow-up

Figure. Subgroup analysis of association between daily coffee consumption and all-cause mortality among men and women.



Hazard ratios are for the comparison of participants in the highest quartile of consumption vs. nonconsumers. The multivariable model used Cox regression with adjustment for the covariates listed in the Statistical Analysis section of the text and stratification by age (1-y categories) and center. Categories were based on country-specific quartiles of coffee consumption after exclusion of nonconsumers. Quartile cutoffs were 500, 900, and 1300 mL/d in Denmark; 150, 280, and 450 mL/d in France; 261, 395, and 580 mL/d in Germany; 70, 140, and 240 mL/d in Greece; 60, 92, and 138 mL/d in Italy; 375, 500, and 750 mL/d in the Netherlands; 300, 420, and 540 mL/d in Norway; 50, 105, and 196 mL/d in Spain; 300, 400, and 601 mL/d in Sweden; and 83, 380, and 488 mL/d in the United Kingdom.

* Median was 12.6 g/d in men and 3.4 g/d in women.

† Median was 90.2 g/d in men and 60.3 g/d in women.

‡ Median was 324 g/d in men and 413 g/d in women.

Table 3. Multivariable-Adjusted Mean Serum Levels of Liver Function, Circulatory Disease, and Metabolic Biomarkers Across Coffee Consumption Categories Among Men and Women (n = 14 800)*

Variable	Coffee Consumption†					*P* Value for Trend
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)	
Albumin level, *g/L*‡						
Men	46.70	46.18	46.49	46.61	46.93	0.005
Women	45.95	45.56	45.80	46.03	46.04	0.006
Alkaline phosphatase level, *μkat/L*§						
Men	1.15	1.10	1.10	1.07	1.09	<0.001
Women	1.08	1.07	1.04	1.04	1.01	<0.001
Alanine aminotransferase level, *U/L*§						
Men	25.37	24.49	24.60	24.23	23.77	<0.001
Women	17.32	17.53	17.30	17.09	16.81	0.028
Aspartate aminotransferase level, *U/L*						
Men	32.18	30.92	29.96	29.57	29.31	<0.001
Women	26.80	26.51	26.02	25.82	25.53	0.001
γ-Glutamyltransferase level, *μkat/L*§						
Men	0.53	0.56	0.56	0.53	0.51	<0.001
Women	0.29	0.33	0.31	0.32	0.29	<0.001
High-sensitivity C-reactive protein level, *nmol/L*§						
Men	10.93	11.05	11.26	11.50	12.76	0.068
Women	13.56	13.20	12.22	12.00	11.01	<0.001
Glycated hemoglobin level, %‡						
Men	5.50	5.50	5.50	5.50	5.50	0.028
Women	5.50	5.40	5.40	5.40	5.40	0.007
High-density lipoprotein cholesterol level‡						
Men						0.25
mmol/L	1.31	1.32	1.30	1.29	1.28	
mg/dL	50.65	50.81	50.37	49.81	49.50	
Women						0.001
mmol/L	1.60	1.62	1.62	1.61	1.62	
mg/dL	61.64	62.71	62.62	62.24	62.47	
Lipoprotein(a), *μmol/L*§						
Men	14.28	14.49	14.62	14.06	13.89	0.24
Women	12.93	12.39	12.06	12.25	11.14	0.002

* Multivariable means were adjusted for country, smoking status (never, former, current, or missing), age (continuous), body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2), alcohol consumption (in grams per day [continuous]), and total energy intake (in kilocalories per day [continuous]). Trend tests across exposure groups were calculated by entering the category variables into the models as continuous terms.
† Based on country-specific quartiles of coffee consumption after exclusion of nonconsumers. Quartile cutoffs were 500, 900, and 1300 mL/d in Denmark; 151, 277, and 437 mL/d in France; 262, 404, and 580 mL/d in Germany; 60, 90, and 130 mL/d in Italy; 447, 536, and 768 mL/d in the Netherlands; 50, 110, and 200 mL/d in Spain; 321, 455, and 611 mL/d in Sweden; and 192, 477, and 855 mL/d in the United Kingdom.
‡ Arithmetic mean.
§ Geometric mean.

categories (Appendix Table 7, available at Annals.org) and were virtually unchanged when deaths occurring during the first 5 and 8 years of follow-up were excluded (Appendix Tables 8 and 9, available at Annals.org). Similar associations were also observed when analyses were limited to participants who reported being in "excellent" or "good" health at baseline (Appendix Table 10, available at Annals.org) and to consumers of caffeinated or decaffeinated coffee only (data not shown). The sensitivity analysis on the possible effect of residual confounding found that an unmeasured confounder would need to be strongly associated with all-cause mortality (HR <0.75) and substantially imbalanced between non–coffee drinkers and persons with high consumption (>20% difference in prevalence) to attenuate the upper limit of the CI to greater than 1.00 (Appendix 2 and Appendix Table 11, available at Annals.org).

Serum Levels of Liver, Inflammation, and Metabolic Biomarkers, by Coffee Consumption

Compared with non–coffee drinkers or persons with low consumption, those with higher consumption had statistically significantly lower mean serum levels of ALP, ALT, AST, and GGT and higher albumin levels (P for trend < 0.05 for all) (Table 3). For women only, higher coffee consumption was correlated with lower CRP, serum HbA_{1c}, and lipoprotein(a) levels and higher HDL-C levels. A total of 891 all-cause deaths were recorded in the EPIC Biomarkers subcohort. Serum levels

of ALP, AST, GGT, and CRP were associated with all-cause mortality when the highest and lowest quartiles were compared (Appendix Figure 1). Higher serum levels of albumin and ALT were associated with lower all-cause mortality.

DISCUSSION

In this analysis of a multinational European population, higher consumption of coffee was associated with lower risk for death, particularly that due to digestive and circulatory diseases. The inverse association with all-cause mortality was generally apparent for both caffeinated and decaffeinated coffee. Coffee drinking was also associated with variation in serum biomarkers of liver function, inflammation, insulin sensitivity, and blood lipids, adding biological plausibility to the potential protective effects of coffee on common health outcomes.

Consistent with the current investigation, prospective studies in Japan and the United States have found inverse associations between coffee consumption and all-cause mortality (10–12, 15, 16, 24). Previous European studies were much smaller and were done in individual countries, where coffee intake and preparation methods are relatively homogeneous. In contrast, our analysis of EPIC data from 10 European countries with almost 42 000 documented deaths better captured different coffee preparation methods and customs. Similar to the findings from the analysis of the National Institutes of Health-AARP cohort (10), our observed inverse association between coffee consumption and all-cause mortality was consistent across subgroups based on lifestyle, anthropometric, and dietary variables and was apparent for both caffeinated and decaffeinated coffee. The findings for both types of coffee should, however, be interpreted cautiously because not all EPIC centers collected data on decaffeinated coffee consumption. Furthermore, the analyses may have been contaminated by participants habitually consuming both types. Nevertheless, in sensitivity analyses where consumers of only caffeinated or decaffeinated coffee were analyzed, the associations were essentially unaltered.

Our results revealed a strong inverse association between coffee consumption and liver disease mortality. Previous studies have reported inverse associations between coffee drinking and both alcoholic and nonalcoholic cirrhosis (25–27). The results of our study, which had the largest number of liver disease cases to date, are consistent with these smaller studies. Serum levels of several indicators of altered hepatic function, including ALP, ALT, AST, and GGT, were lower among coffee drinkers than non–coffee drinkers and those with low consumption in the current analysis. This is consistent with prior data (25, 28) and suggests that coffee may have beneficial effects on hepatic function and health. Experimental evidence suggests that caffeine has antifibrogenic effects on hepatocytes and hepatic stellate cells by lowering proliferation, stimulating apoptosis, and inhibiting adhesion (29–31). Coffee has also been shown to impede progression of fatty liver disease by reducing fat accumulation, oxidative stress, and liver inflammation in murine models (32), and a possible beneficial role of coffee in liver disease progression in patients with hepatitis C has also been reported (33).

The observed inverse associations between coffee drinking and circulatory disease mortality are also consistent with the prior National Institutes of Health-AARP analysis (10). This relationship was stronger among women than men, with the difference between sexes driven by a strong inverse association with cerebrovascular mortality risk in women, a finding consistent with previous studies that reported lower incidence of stroke in women who drank coffee (34, 35). Of note, our analysis showed that levels of HDL-C, which has been inversely related to risk for stroke and other circulatory disease outcomes (36), were higher among coffee drinkers than nondrinkers in women but not men. Furthermore, among women only, levels of lipoprotein(a), CRP, and HbA_{1c}–which have been positively associated with cardiovascular disease outcomes (37–40)–were generally lower among coffee drinkers than nondrinkers. Given that the inverse relationship between coffee drinking and circulatory disease mortality was stronger in women, we hypothesize that this association might be driven by sex-specific beneficial effects of coffee on lipid, inflammatory, and metabolic profiles.

Of note, we observed a positive association between coffee drinking and overall cancer mortality among women in this population. This was driven primarily by a statistically significant positive association between coffee consumption and ovarian cancer mortality. To our knowledge, there is no prevailing hypothesis as to why coffee drinking should increase the risk for death specifically from ovarian cancer. Although this result may be spurious and requires follow-up in additional studies on ovarian cancer survival, we note that a positive association between coffee consumption and ovarian cancer incidence has previously been observed (41), although other prospective studies did not report similar relationships (42, 43).

We also found a statistically significant inverse relationship between coffee consumption and suicide for men but not women. Coffee consumption was previously reported to be associated with lower suicide risk in a pooled analysis of 2 U.S. cohorts (44), whereas a Finnish study reported higher suicide risk among persons with high consumption (45). Our analysis included only 418 suicides, and we lacked information on other factors related to suicide risk, such as antidepressant medication use and mental health status, which may have confounded the relationship between coffee drinking and suicide.

Our prospective study was the largest to date to investigate the relationship between coffee consumption and mortality, and we controlled for important potential confounding factors. However, we recognize that the associations may be biased due to residual confounding. In our analyses, smoking was the most influential confounder of the relationship between cof-

fee drinking and mortality. However, the large number of participants and recorded deaths allowed us to restrict our analyses to never-smokers. Although we cannot exclude residual confounding as a potential explanation of our findings, we found limited evidence that our findings resulted from confounding bias due to smoking or other established risk factors for death. Reverse causality, whereby participants experiencing early disease symptoms at baseline may have recorded lower coffee consumption, may also have been a source of bias in our analysis. However, we excluded participants who reported previous ill health. Furthermore, similar associations were observed when the analyses were limited to participants who reported being in "excellent" or "good" health at baseline and when participants who died during the first 5 and 8 years of follow-up were excluded. An additional limitation is that coffee consumption was assessed only at baseline, and changes in consumption may have occurred during follow-up. However, other studies in Western populations that measured diet repeatedly during follow-up found relatively stable coffee consumption patterns over time, indicating that a single assessment likely captures medium- to long-term drinking habits (11). Finally, because coffee drinking was self-reported, some measurement error is likely.

In summary, our results suggest that higher levels of coffee drinking are associated with lower risk for death from various causes, specifically digestive and circulatory diseases. The consistency of the results of this European study versus those from other cohort studies around the world, as well as biomarker data indicating that coffee drinkers have a more favorable liver function and inflammatory biomarker profile than non–coffee drinkers or those with low consumption, support the hypothesis that coffee may confer health benefits. Because coffee consumption is so widespread and intakes are modifiable, its potentially beneficial clinical implications should be carefully considered.

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Reproducible Research Statement: *Study protocol and statistical code:* Available from Dr. Gunter (e-mail, gunterm@iarc.fr). *Data set:* Requests for the data require formal approval by the EPIC principal investigators (e-mail, gunterm@iarc.fr).

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Appendix 1: Additional Details on Study Population

Participants were recruited from 23 study centers in 10 European countries: Denmark (Aarhus and Copenhagen), France, Germany (Heidelberg and Potsdam), Greece, Italy (Florence, Naples, Ragusa, Turin, and Varese), the Netherlands (Bilthoven and Utrecht), Norway (Tromsø), Spain (Asturias, Granada, Murcia, Navarra, and San Sebastián), Sweden (Malmö and Umeå), and the United Kingdom (Cambridge and Oxford). Participants were recruited from the general population of their respective countries, with the following exceptions: The French cohort comprised teacher health insurance program members; the Italian and Spanish cohorts included members of blood donor associations and the general population; the Utrecht (the Netherlands) and Florence (Italy) cohorts comprised participants from mammographic screening programs; the Oxford (United Kingdom) cohort included a large proportion of vegetarians, vegans, and persons with low consumption of meat; and the France, Norway, Naples (Italy), and Utrecht (the Netherlands) cohorts included only women. All study participants provided written informed consent.

Appendix 2: Sensitivity Analysis to Assess Possible Effect of an Unmeasured Confounder on Observed Relationship Between Coffee Consumption and All-Cause Mortality

Compared with nonconsumers, statistically significantly lower all-cause mortality was observed among participants in the highest quartile of coffee consumption (men: HR, 0.88 [CI, 0.82 to 0.95]; P for trend < 0.001; women: HR, 0.93 [CI, 0.87 to 0.98]; P for trend = 0.009). When both sexes were combined, an HR of 0.91 (CI, 0.87 to 0.95) was observed for the high-consumption group compared with nonconsumers. In this sensitivity analysis to assess the possible effect of unmeasured confounding, using the method described by Ding and VanderWeele (21), the association (HR) between the confounder and all-cause mortality varied from 0.50 to 2.50, and the prevalence of the confounder between non–coffee drinkers and those in the highest quartile of coffee consumption varied from −50% to 50% (**Appendix Table 11**).

How an unmeasured confounder would influence the relationship between coffee and all-cause mortality depends on whether it is a positive or negative confounder. A positive confounder is a variable that is either positively associated with both coffee consumption and all-cause mortality or negatively associated with coffee consumption and all-cause mortality. Statistical adjustment for such a positive confounder would result in a lower HR than a crude unadjusted HR. A negative confounder is a variable that is either negatively associated with coffee consumption and positively associated with all-cause mortality or positively associated with coffee consumption and negatively associated with risk for all-cause death. Such an unmeasured confounder has the potential to attenuate the observed relationship between coffee consumption and all-cause mortality. As an example, an unmeasured negative confounder would need to have a greater than 20% difference in prevalence between nonconsumers and those in the highest quartile of coffee consumption and an HR for all-cause mortality less than 0.75 to attenuate the upper CI limit for the association between coffee and mortality to above 1.00.

For example, physical activity has been consistently related to lower risk for all-cause death. In the current EPIC study, compared with being physically inactive, being physically active was related to a 20% (HR, 0.80 [CI, 0.76 to 0.82]) lower risk for all-cause death in the model with sexes combined. The prevalence of being physically active was 19.2% in the highest quartile of coffee consumption and 5.7% among nonconsumers (a difference of 13.5 percentage points).

Appendix Table 1. Analytic Methods Used to Measure Liver Function, Circulatory Disease, and Metabolic Biomarkers*

Biomarker	Serum/Plasma	Assay Name	Assay Type	Analyzer
Liver function				
Albumin	Serum, except Umeå (plasma)	Cobas	Enzymatic colorimetric	Roche Hitachi Modular P
Alkaline phosphatase	Serum, except Umeå (plasma)	Cobas	Enzymatic colorimetric	Roche Hitachi Modular P
Alanine aminotransferase	Serum, except Umeå (plasma)	Cobas	Enzymatic UV test	Roche Hitachi Modular P
Aspartate aminotransferase	Serum, except Umeå (plasma)	Cobas	Enzymatic UV test	Roche Hitachi Modular P
γ-Glutamyltransferase	Serum, except Umeå (plasma)	Cobas	Enzymatic colorimetric	Roche Hitachi Modular P
Circulatory disease and metabolic				
Glycated hemoglobin	Erythrocyte fraction	Tosoh (HLC-723G8)	Ion exchange high-performance liquid chromatography	Tosoh G8
High-density lipoprotein cholesterol	Serum, except Umeå (plasma)	Cobas	Homogeneous enzymatic colorimetric test	Roche Hitachi Modular P
Lipoprotein(a)	Serum, except Umeå (plasma)	Cobas	Immunoturbidimetric assay	Roche Hitachi Modular P
High-sensitivity C-reactive protein	Serum, except Umeå (plasma)	Cobas	Particle-enhanced immunoturbidimetric assay	Roche Hitachi Modular P

* Samples were taken over approximately 1 y. Batch size varied depending on the given capacity, and Westgard rules were applied.

Appendix Table 2. Descriptive Information on EPIC Participant Countries

Country	Participants, *n*		Person-Years		All-Cause Deaths, *n*		Median Coffee Intake (5th–95th Percentile), *mL/d**	
	Men	Women	Men	Women	Men	Women	Men	Women
Denmark	23 864	27 329	380 989	451 251	4566	3435	900 (86–1600)	900 (86–1600)
France	–	65 566	–	1 260 077	–	4141	–	280 (32–821)
Germany	19 203	26 229	266 471	360 631	1709	998	427 (30–1050)	392 (39–939)
Greece	9361	13 653	100 715	155 158	916	761	175 (16–550)	140 (14–480)
Italy	13 427	29 518	212 546	453 989	895	1302	91 (30–214)	93 (30–230)
Norway	–	33 341	–	462 605	–	1086	–	420 (60–960)
Spain	13 962	23 359	255 654	435 509	1705	1212	100 (2–300)	118 (2–400)
Sweden	20 891	25 606	373 548	470 767	4171	3363	438 (100–1013)	400 (100–986)
The Netherlands	9262	25 807	155 184	432 359	731	2347	625 (107–1250)	500 (125–1000)
United Kingdom	20 692	50 673	340 564	855 520	3609	4746	475 (4–1140)	380 (4–1140)
All	130 662	321 081	2 085 672	5 337 865	18 302	23 391	380 (16–1300)	300 (11–1000)

EPIC = European Prospective Investigation into Cancer and Nutrition.
* Among coffee drinkers only.

Appendix Table 3. Multivariable Associations of Daily Caffeinated Coffee Consumption and All-Cause and Cause-Specific Mortality*

Variable	Caffeinated Coffee Consumption†					*P* Value for Trend
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)	
All-cause mortality						
Men	1.00 (reference)	0.99 (0.92–1.06)	0.97 (0.91–1.04)	0.93 (0.86–0.99)	0.96 (0.88–1.03)	0.04
Women	1.00 (reference)	0.93 (0.87–0.99)	0.88 (0.83–0.94)	0.89 (0.83–0.95)	0.90 (0.84–0.97)	0.002
Cancer (ICD-10 codes C00–D48)						
Men	1.00 (reference)	0.93 (0.83–1.05)	1.05 (0.94–1.18)	0.97 (0.87–1.10)	1.05 (0.93–1.19)	0.17
Women	1.00 (reference)	0.98 (0.89–1.09)	0.99 (0.90–1.11)	1.03 (0.93–1.14)	1.07 (0.96–1.19)	0.06
Circulatory diseases (ICD-10 codes I00–I99)						
Men	1.00 (reference)	1.04 (0.91–1.20)	0.95 (0.83–1.08)	0.89 (0.78–1.03)	0.93 (0.80–1.09)	0.02
Women	1.00 (reference)	0.92 (0.80–1.06)	0.77 (0.67–0.88)	0.77 (0.67–0.89)	0.85 (0.72–0.99)	0.001
Cerebrovascular diseases (ICD-10 codes I60–I69)						
Men	1.00 (reference)	0.91 (0.67–1.24)	0.83 (0.62–1.12)	0.82 (0.60–1.12)	0.67 (0.46–0.96)	0.02
Women	1.00 (reference)	0.84 (0.67–1.06)	0.78 (0.63–0.98)	0.72 (0.57–0.92)	0.78 (0.59–1.03)	0.02
Ischemic heart diseases (ICD-10 codes I20–I25)						
Men	1.00 (reference)	1.16 (0.95–1.42)	1.00 (0.82–1.22)	0.99 (0.82–1.22)	1.10 (0.89–1.36)	0.75
Women	1.00 (reference)	1.02 (0.80–1.31)	0.82 (0.64–1.05)	0.72 (0.56–0.93)	0.85 (0.64–1.12)	0.002
Digestive diseases (ICD-10 codes K00–K93)‡						
Men	1.00 (reference)		1.06 (0.81–1.37)	0.46 (0.33–0.64)	0.49 (0.35–0.70)	<0.001
Women	1.00 (reference)		0.90 (0.70–1.16)	0.71 (0.53–0.94)	0.52 (0.34–0.77)	0.001
Respiratory diseases (ICD-10 codes J30–J98)‡						
Men	1.00 (reference)		0.69 (0.51–0.93)	0.85 (0.65–1.13)	0.99 (0.73–1.36)	0.48
Women	1.00 (reference)		0.91 (0.72–1.16)	0.80 (0.62–1.03)	0.89 (0.66–1.18)	0.15
External causes (ICD-10 codes S00–Y98)‡						
Men	1.00 (reference)		1.11 (0.87–1.43)	0.92 (0.71–1.19)	1.05 (0.80–1.38)	0.99
Women	1.00 (reference)		0.86 (0.66–1.12)	0.98 (0.75–1.29)	0.91 (0.65–1.28)	0.59
Suicide (ICD-10 codes X60–X84)‡						
Men	1.00 (reference)		1.23 (0.75–1.99)	0.70 (0.41–1.20)	0.67 (0.39–1.17)	0.11
Women	1.00 (reference)		1.31 (0.78–2.21)	0.84 (0.47–1.53)	1.22 (0.66–2.25)	0.78

ICD-10 = International Classification of Diseases, 10th Revision.

* Multivariable models used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

† Values are hazard ratios (95% CIs). Categories were based on country-specific quartiles of caffeinated coffee consumption after exclusion of nonconsumers. Quartile cutoffs were 261, 320, and 573 mL/d in Germany; 11, 170, and 340 mL/d in Greece; 51, 85, and 120 mL/d in Italy; 225, 450, and 675 mL/d in the Netherlands; 300, 420, and 540 mL/d in Norway; 2, 4, and 50 mL/d in Spain; 300, 450, and 685 mL/d in Sweden; and 14, 190, and 475 mL/d in the United Kingdom.

‡ Reference category merged with low consumption (quartile 1) due to low case numbers among nonconsumers.

Appendix Table 4. Multivariable Associations of Daily Decaffeinated Coffee Consumption and All-Cause and Cause-Specific Mortality*

Variable	Decaffeinated Coffee Consumption†					*P* Value for Trend
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)	
All-cause mortality						
Men	1.00 (reference)	0.90 (0.82–1.00)	0.85 (0.74–0.98)	0.88 (0.80–0.97)	0.91 (0.84–0.99)	0.01
Women	1.00 (reference)	0.99 (0.92–1.08)	0.96 (0.87–1.07)	1.01 (0.92–1.10)	0.93 (0.86–0.99)	0.04
Cancer (ICD-10 codes C00–D48)						
Men	1.00 (reference)	0.92 (0.78–1.08)	0.88 (0.72–1.08)	0.97 (0.83–1.13)	0.90 (0.79–1.04)	0.25
Women	1.00 (reference)	0.95 (0.84–1.07)	0.96 (0.82–1.11)	1.04 (0.91–1.18)	0.92 (0.82–1.04)	0.57
Circulatory diseases (ICD-10 codes I00–I99)						
Men	1.00 (reference)	0.84 (0.69–1.03)	0.69 (0.52–0.93)	0.78 (0.63–0.96)	0.89 (0.75–1.05)	0.09
Women	1.00 (reference)	0.97 (0.82–1.15)	1.02 (0.81–1.29)	1.02 (0.85–1.22)	0.95 (0.81–1.11)	0.66
Cerebrovascular diseases (ICD-10 codes I60–I69)						
Men	1.00 (reference)	0.96 (0.60–1.53)	1.39 (0.72–2.69)	0.82 (0.49–1.36)	0.98 (0.66–1.46)	0.77
Women	1.00 (reference)	0.95 (0.72–1.26)	1.16 (0.78–1.74)	1.34 (1.00–1.78)	1.13 (0.88–1.45)	0.04
Ischemic heart diseases (ICD-10 codes I20–I25)						
Men	1.00 (reference)	0.73 (0.55–0.97)	0.71 (0.48–1.07)	0.75 (0.56–1.01)	0.86 (0.68–1.08)	0.24
Women	1.00 (reference)	1.11 (0.81–1.52)	1.11 (0.72–1.70)	0.88 (0.62–1.26)	0.85 (0.64–1.14)	0.06
Digestive diseases (ICD-10 codes K00–K93)‡						
Men	1.00 (reference)		1.17 (0.61–2.23)	1.04 (0.66–1.65)	0.44 (0.25–0.76)	0.02
Women	1.00 (reference)		0.69 (0.39–1.24)	1.07 (0.72–1.59)	0.99 (0.73–1.35)	0.99
Respiratory diseases (ICD-10 codes J30–J98)‡						
Men	1.00 (reference)		1.20 (0.57–2.52)	0.83 (0.48–1.44)	0.93 (0.62–1.41)	0.61
Women	1.00 (reference)		1.00 (0.64–1.57)	0.87 (0.58–1.31)	0.77 (0.56–1.06)	0.11
External causes (ICD-10 codes S00–Y98)‡						
Men	1.00 (reference)		0.90 (0.50–1.61)	0.73 (0.47–1.15)	1.32 (0.95–1.85)	0.52
Women	1.00 (reference)		0.82 (0.47–1.41)	0.99 (0.66–1.49)	0.83 (0.58–1.17)	0.34
Suicide (ICD-10 codes X60–X84)‡						
Men	1.00 (reference)		0.80 (0.24–2.66)	1.48 (0.75–2.89)	1.64 (0.88–3.08)	0.10
Women	1.00 (reference)		0.67 (0.23–1.96)	1.58 (0.79–3.15)	1.47 (0.79–2.74)	0.15

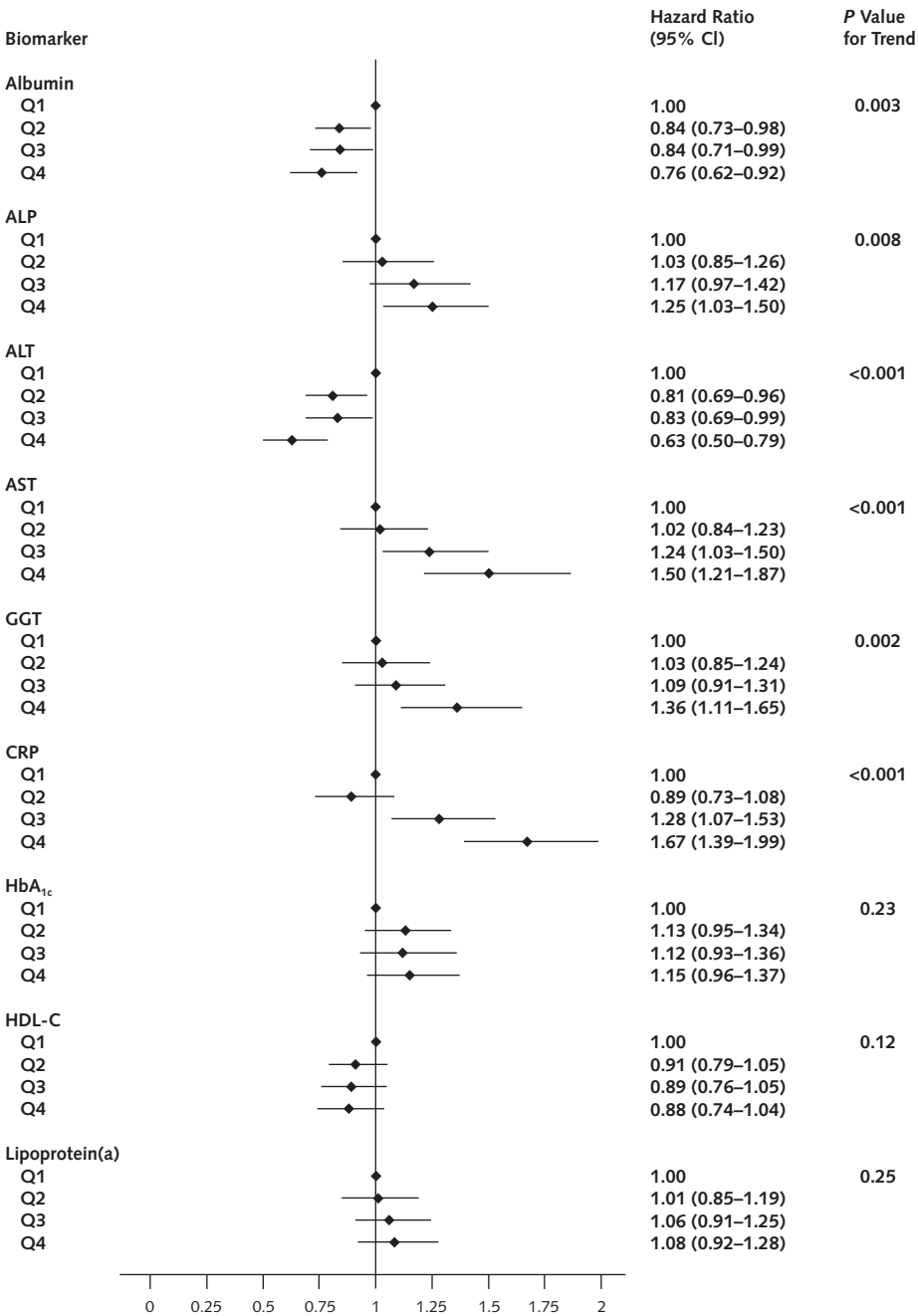
ICD-10 = International Classification of Diseases, 10th Revision.

* Multivariable models used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

† Values are hazard ratios (95% CIs). Categories were based on country-specific quartiles of decaffeinated coffee consumption after exclusion of nonconsumers. Quartile cutoffs were 11, 52, and 269 mL/d in Germany; 1, 11, and 79 mL/d in Greece; 5, 10, and 32 mL/d in Italy; 50, 75, and 125 mL/d in the Netherlands; and 2, 13, and 82 mL/d in the United Kingdom.

‡ Reference category merged with low consumption (quartile 1) due to low case numbers among nonconsumers.

Appendix Figure 1. Multivariable associations of serum liver function, circulatory disease, and metabolic biomarkers and all-cause mortality (*n* = 1597 deaths) among men and women, using sex-specific quartiles.



The multivariable model used Cox regression, with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2), physical activity (inactive, moderately inactive, moderately active, or active), education (none, primary school, technical or professional school, secondary school, higher education [including university], or not specified), alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d), smoking status (never, former, current, or missing/unknown), ever-use of contraceptive pill (yes, no, or unknown), menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown), and ever-use of menopausal hormone therapy (yes, no, or unknown) and stratification by sex, age (1-y categories), and center. The albumin multivariable model was also adjusted for serum levels of ALT, ALP, AST, and GGT (all continuous and log-transformed). The ALP multivariable model was also adjusted for serum levels of ALT, AST, GGT, CRP, HDL-C, and total cholesterol (all continuous and some log-transformed). The ALT multivariable model was also adjusted for serum levels of ALP, AST, GGT, CRP, HDL-C, and total cholesterol (all continuous and some log-transformed). The AST multivariable model was also adjusted for serum levels of ALT, ALP, GGT, CRP, HDL-C, and total cholesterol (all continuous and some log-transformed). The GGT multivariable model was also adjusted for serum levels of ALT, ALP, AST, CRP, HDL-C, and total cholesterol (all continuous and some log-transformed). The CRP multivariable model was also adjusted for serum levels of HDL-C and total cholesterol (both continuous and log-transformed). First and fourth quartile cut points were <45 to ≥50 g/L for men and <44 to ≥49 g/L for women for albumin, <0.94 to ≥1.31 μkat/L for men and <0.87 to ≥1.29 μkat/L for women for ALP, <19 to ≥33 U/L for men and <14 to ≥23 U/L for women for ALT, <26 to ≥35 U/L for men and <23 to ≥31 U/L for women for AST, <0.35 to ≥0.75 μkat/L for men and <0.23 to

(Continued on following page)

≥0.42 μkat/L for women for GGT, <5.14 to ≥20.57 nmol/L for men and <5.05 to ≥22.57 nmol/L for women for CRP, <5.2% to ≥5.7% for men and <5.3% to ≥5.7% for women for HbA_{1c}, <1.2 to ≥1.6 mmol/L for men and <1.4 to ≥2.0 mmol/L for women for HDL-C, and <8.35 to ≥25.49 μmol/L for men and <6.57 to ≥23.03 μmol/L for women for lipoprotein(a). Trend tests across exposure groups were done by entering the category variables into the models as continuous terms. ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CRP = high-sensitivity C-reactive protein; GGT = γ-glutamyltransferase; HbA_{1c} = glycated hemoglobin; HDL-C = high-density lipoprotein cholesterol; Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile.

Appendix Table 5. Associations of Daily Coffee Consumption and Overall and Individual Cancer Mortality*

Variable	Deaths, *n*	Coffee Consumption†					*P* Value for Trend
		Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)	
Cancer (ICD-10 codes C00–D48)							
Both sexes	18 003	1.00 (reference)	0.97 (0.91–1.04)	1.02 (0.95–1.09)	0.99 (0.92–1.07)	1.07 (0.99–1.15)	0.002
Men	7614	1.00 (reference)	0.92 (0.82–1.03)	0.97 (0.86–1.08)	0.92 (0.82–1.03)	0.99 (0.88–1.11)	0.45
Women	10 389	1.00 (reference)	1.00 (0.92–1.10)	1.05 (0.96–1.15)	1.04 (0.95–1.14)	1.12 (1.02–1.23)	0.001
Stomach cancer (ICD-10 code C16)‡							
Both sexes	622	1.00 (reference)		1.07 (0.87–1.33)	0.74 (0.59–0.94)	1.06 (0.84–1.34)	0.50
Men	345	1.00 (reference)		1.10 (0.83–1.45)	0.72 (0.52–0.99)	1.15 (0.85–1.57)	0.90
Women	277	1.00 (reference)		1.06 (0.77–1.45)	0.78 (0.55–1.10)	0.93 (0.65–1.34)	0.40
Colorectal cancer (ICD-10 codes C18–C20)							
Both sexes	2095	1.00 (reference)	0.92 (0.75–1.13)	1.07 (0.87–1.32)	1.01 (0.82–1.25)	1.14 (0.92–1.42)	0.01
Men	917	1.00 (reference)	0.82 (0.60–1.11)	0.93 (0.68–1.26)	0.84 (0.61–1.14)	1.00 (0.73–1.37)	0.36
Women	1178	1.00 (reference)	1.00 (0.76–1.32)	1.21 (0.91–1.60)	1.19 (0.89–1.57)	1.28 (0.96–1.71)	0.006
Upper aerodigestive tract cancer‡							
Both sexes	629	1.00 (reference)		1.04 (0.84–1.30)	0.92 (0.73–1.14)	0.95 (0.76–1.20)	0.54
Men	408	1.00 (reference)		0.94 (0.72–1.23)	0.73 (0.56–0.97)	0.80 (0.60–1.07)	0.04
Women	221	1.00 (reference)		1.27 (0.86–1.85)	1.34 (0.92–1.95)	1.27 (0.85–1.91)	0.14
Liver cancer (ICD-10 code C22)‡							
Both sexes	421	1.00 (reference)		0.62 (0.48–0.82)	0.72 (0.55–0.93)	0.56 (0.41–0.77)	<0.001
Men	224	1.00 (reference)		0.64 (0.45–0.92)	0.71 (0.50–1.01)	0.54 (0.36–0.81)	0.002
Women	197	1.00 (reference)		0.60 (0.41–0.89)	0.73 (0.50–1.07)	0.61 (0.38–0.97)	0.01
Pancreatic cancer (ICD-10 code C25)‡							
Both sexes	1375	1.00 (reference)		1.05 (0.91–1.21)	1.00 (0.87–1.16)	1.01 (0.86–1.18)	0.92
Men	567	1.00 (reference)		1.01 (0.81–1.27)	0.97 (0.77–1.22)	0.98 (0.76–1.26)	0.82
Women	808	1.00 (reference)		1.07 (0.89–1.30)	1.02 (0.85–1.24)	1.02 (0.82–1.26)	0.78
Lung cancer (ICD-10 code C34)							
Both sexes	3304	1.00 (reference)	0.83 (0.69–0.99)	0.87 (0.72–1.05)	0.92 (0.77–1.10)	1.09 (0.91–1.30)	<0.001
Men	1688	1.00 (reference)	0.67 (0.52–0.86)	0.75 (0.59–0.96)	0.80 (0.63–1.02)	0.95 (0.74–1.21)	0.001
Women	1616	1.00 (reference)	1.03 (0.79–1.35)	1.03 (0.78–1.35)	1.06 (0.81–1.39)	1.26 (0.96–1.65)	0.01
Breast cancer (ICD-10 code C50)							
Women	1402	1.00 (reference)	0.89 (0.71–1.12)	0.91 (0.72–1.16)	0.94 (0.74–1.19)	0.80 (0.62–1.02)	0.22
Endometrial cancer (ICD-10 code C54)‡							
Women	160	1.00 (reference)		0.93 (0.61–1.41)	0.95 (0.63–1.45)	0.69 (0.40–1.16)	0.28
Ovarian cancer (ICD-10 code C56)‡							
Women	848	1.00 (reference)		1.21 (1.00–1.46)	1.11 (0.92–1.35)	1.31 (1.07–1.61)	0.02
Prostate cancer (ICD-10 code C61)‡							
Men	907	1.00 (reference)		1.04 (0.87–1.24)	1.01 (0.84–1.21)	1.03 (0.84–1.27)	0.80
Kidney cancer (ICD-10 code C64)‡							
Both sexes	360	1.00 (reference)		0.89 (0.66–1.21)	1.18 (0.89–1.56)	1.23 (0.91–1.68)	0.15
Men	199	1.00 (reference)		0.94 (0.62–1.41)	1.14 (0.78–1.68)	1.21 (0.81–1.83)	0.33
Women	161	1.00 (reference)		0.82 (0.52–1.31)	1.21 (0.80–1.82)	1.23 (0.77–1.96)	0.32
Bladder cancer (ICD-10 code C67)‡							
Both sexes	396	1.00 (reference)		1.19 (0.91–1.56)	1.08 (0.82–1.42)	0.96 (0.70–1.31)	0.94
Men	268	1.00 (reference)		1.52 (1.09–2.14)	1.27 (0.90–1.79)	1.15 (0.78–1.68)	0.30
Women	128	1.00 (reference)		0.75 (0.46–1.20)	0.82 (0.51–1.31)	0.69 (0.39–1.21)	0.16

ICD-10 = International Classification of Diseases, 10th Revision.

* Multivariable model used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education status (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

† Values are hazard ratios (95% CIs).

‡ Reference category merged with low consumption (quartile 1) due to low case numbers among nonconsumers.

Appendix Table 6. Associations of Daily Coffee Consumption and Cause-Specific Mortality, by Smoking Status*

Stratification Variable	Men		Women	
	Hazard Ratio (95% CI) Per Cup Per Day	*P* Value for Interaction	Hazard Ratio (95% CI) Per Cup Per Day	*P* Value for Interaction
Cancer				
Full model	1.00 (0.99–1.02)		1.03 (1.01–1.04)	
Smoking status		0.06		0.03
Never	0.95 (0.91–0.99)		1.01 (0.99–1.04)	
Former	1.00 (0.97–1.03)		1.01 (0.98–1.05)	
Current	1.01 (0.99–1.03)		1.03 (1.00–1.05)	
Circulatory diseases				
Full model	0.97 (0.95–0.99)		0.96 (0.94–0.99)	
Smoking status		0.01		0.01
Never	0.96 (0.91–1.02)		0.93 (0.89–0.98)	
Former	0.94 (0.91–0.98)		0.95 (0.90–0.99)	
Current	0.98 (0.95–1.01)		0.98 (0.94–1.02)	
Cerebrovascular diseases				
Full model	0.94 (0.89–0.99)		0.94 (0.90–0.99)	
Smoking status		0.46		0.13
Never	0.97 (0.87–1.08)		0.95 (0.88–1.02)	
Former	0.93 (0.85–1.02)		0.86 (0.78–0.95)	
Current	0.93 (0.86–1.01)		0.97 (0.90–1.04)	
Ischemic heart diseases				
Full model	0.99 (0.96–1.02)		0.94 (0.90–0.98)	
Smoking status		0.51		0.003
Never	0.98 (0.91–1.06)		0.83 (0.76–0.91)	
Former	0.97 (0.91–1.02)		0.97 (0.88–1.07)	
Current	0.99 (0.95–1.04)		0.98 (0.92–1.05)	
Digestive diseases				
Full model	0.77 (0.72–0.81)		0.86 (0.81–0.92)	
Smoking status		0.19		0.29
Never	0.71 (0.60–0.84)		0.90 (0.80–1.01)	
Former	0.77 (0.68–0.86)		0.79 (0.68–0.92)	
Current	0.76 (0.71–0.83)		0.83 (0.76–0.92)	
Respiratory diseases				
Full model	1.01 (0.96–1.06)		0.98 (0.94–1.03)	
Smoking status		<0.001		0.01
Never	0.74 (0.60–0.95)		0.86 (0.75–0.99)	
Former	0.95 (0.87–1.04)		0.95 (0.85–1.06)	
Current	1.05 (0.98–1.12)		0.99 (0.95–1.05)	
External causes				
Full model	0.96 (0.91–1.01)		0.98 (0.93–1.04)	
Smoking status		0.57		0.46
Never	0.98 (0.88–1.09)		0.98 (0.89–1.08)	
Former	0.96 (0.88–1.05)		1.00 (0.88–1.13)	
Current	0.92 (0.86–1.00)		0.96 (0.87–1.06)	
Suicide				
Full model	0.90 (0.83–0.98)		0.97 (0.87–1.09)	
Smoking status		0.19		0.18
Never	0.81 (0.66–1.00)		0.89 (0.70–1.11)	
Former	0.86 (0.72–1.02)		1.06 (0.84–1.34)	
Current	0.94 (0.84–1.06)		0.93 (0.79–1.10)	

* Multivariable model used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education status (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

Appendix Table 7. Associations of Daily Coffee Consumption and All-Cause Mortality, by Follow-up Time Categories*

All-Cause Mortality	Coffee Consumption*					*P* Value for Trend	*P* Value for Heterogeneity
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)		
Men							
Full model†	1.00 (reference)	0.94 (0.87–1.00)	0.88 (0.82–0.95)	0.84 (0.78–0.90)	0.88 (0.82–0.95)	<0.001	
Follow-up†‡							0.61
<5 y (*n* = 2651 deaths)	1.00 (reference)	1.03 (0.86–1.23)	0.89 (0.74–1.07)	0.82 (0.68–0.98)	0.90 (0.74–1.09)	0.002	
5–<10 y (*n* = 4604 deaths)	1.00 (reference)	0.87 (0.76–0.99)	0.84 (0.73–0.96)	0.77 (0.67–0.89)	0.83 (0.72–0.95)	0.004	
≥10 y (*n* = 11 047 deaths)	1.00 (reference)	0.94 (0.86–1.03)	0.90 (0.82–0.99)	0.87 (0.79–0.95)	0.90 (0.82–0.99)	0.004	
Women							
Full model†	1.00 (reference)	0.94 (0.89–0.99)	0.90 (0.85–0.95)	0.90 (0.85–0.95)	0.93 (0.87–0.98)	0.01	
Follow-up†‡							0.23
<5 y (*n* = 2596 deaths)	1.00 (reference)	0.93 (0.79–1.10)	0.91 (0.77–1.07)	0.88 (0.75–1.05)	0.97 (0.82–1.16)	0.82	
5–<10 y (*n* = 5464 deaths)	1.00 (reference)	0.87 (0.78–0.97)	0.81 (0.72–0.90)	0.81 (0.72–0.90)	0.85 (0.75–0.95)	0.012	
≥10 y (*n* = 15 331 deaths)	1.00 (reference)	0.97 (0.91–1.04)	0.93 (0.87–0.99)	0.94 (0.87–1.00)	0.95 (0.88–1.02)	0.11	

* Values are hazard ratios (95% CIs). Categories were based on country-specific quartiles of coffee consumption after exclusion of nonconsumers. Quartile cutoffs were 500, 900, and 1300 mL/d in Denmark; 150, 280, and 450 mL/d in France; 261, 395, and 580 mL/d in Germany; 70, 140, and 240 mL/d in Greece; 60, 92, and 138 mL/d in Italy; 375, 500, and 750 mL/d in the Netherlands; 300, 420, and 540 mL/d in Norway; 50, 105, and 196 mL/d in Spain; 300, 400, and 601 mL/d in Sweden; and 83, 380, and 488 mL/d in the United Kingdom.

† Multivariable model used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education status (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

‡ Follow-up <5 y indicates that follow-up for all participants was censored after 5 y (i.e., only deaths occurring during the first 5 y were considered). Follow-up of 5–<10 y indicates that only person-time and incident events that occurred during this period were included. Follow-up ≥10 y indicates that person-time and incident events from the first 10 y of follow-up were excluded (i.e., only deaths that occurred after >10 y of follow-up were included).

Appendix Table 8. Multivariable Associations of Daily Coffee Consumption and All-Cause and Cause-Specific Mortality Among Men and Women After Exclusion of Deaths Occurring During the First 5 Years of Follow-up (n = 5247)*

Variable	Coffee Consumption†					*P* Value for Trend	Per Cup Per Day†
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)		
All-cause mortality							
Men	1.00 (reference)	0.91 (0.85–0.99)	0.88 (0.82–0.95)	0.82 (0.76–0.89)	0.87 (0.80–0.94)	<0.001	0.98 (0.97–0.99)
Women	1.00 (reference)	0.94 (0.89–0.99)	0.90 (0.85–0.95)	0.90 (0.85–0.96)	0.92 (0.87–0.98)	0.009	0.99 (0.98–1.00)
Cancer (ICD-10 codes C00–D48)							
Men	1.00 (reference)	0.91 (0.80–1.03)	0.96 (0.85–1.08)	0.93 (0.82–1.05)	0.97 (0.85–1.10)	0.40	1.00 (0.99–1.02)
Women	1.00 (reference)	0.99 (0.90–1.09)	1.02 (0.93–1.13)	1.02 (0.93–1.13)	1.09 (0.99–1.21)	0.005	1.02 (1.01–1.04)
Circulatory diseases (ICD-10 codes I00–I99)							
Men	1.00 (reference)	0.99 (0.85–1.15)	0.91 (0.78–1.06)	0.83 (0.70–0.97)	0.92 (0.78–1.08)	0.01	0.97 (0.95–0.99)
Women	1.00 (reference)	0.87 (0.76–1.00)	0.73 (0.64–0.84)	0.77 (0.66–0.89)	0.78 (0.67–0.90)	<0.001	0.96 (0.94–0.99)
Cerebrovascular diseases (ICD-10 codes I60–I69)							
Men	1.00 (reference)	0.97 (0.71–1.34)	0.86 (0.63–1.18)	0.81 (0.57–1.13)	0.85 (0.60–1.20)	0.09	0.93 (0.88–0.98)
Women	1.00 (reference)	0.89 (0.70–1.12)	0.78 (0.61–0.99)	0.79 (0.61–1.02)	0.74 (0.58–0.97)	0.01	0.95 (0.90–0.99)
Ischemic heart diseases (ICD-10 codes I20–I25)							
Men	1.00 (reference)	1.03 (0.81–1.30)	0.99 (0.78–1.25)	0.88 (0.69–1.13)	1.00 (0.79–1.28)	0.40	0.99 (0.96–1.03)
Women	1.00 (reference)	0.97 (0.74–1.26)	0.78 (0.59–1.02)	0.68 (0.51–0.90)	0.77 (0.58–1.03)	<0.001	0.93 (0.89–0.98)
Digestive diseases (ICD-10 codes K00–K93)‡							
Men	1.00 (reference)		0.70 (0.56–0.88)	0.51 (0.39–0.66)	0.45 (0.34–0.60)	<0.001	0.79 (0.73–0.84)
Women	1.00 (reference)		0.81 (0.65–1.00)	0.65 (0.50–0.83)	0.55 (0.41–0.74)	<0.001	0.86 (0.80–0.92)
Respiratory diseases (ICD-10 codes J30–J98)‡							
Men	1.00 (reference)		0.86 (0.70–1.07)	0.91 (0.72–1.14)	1.09 (0.87–1.38)	0.89	1.02 (0.97–1.07)
Women	1.00 (reference)		0.89 (0.74–1.07)	0.88 (0.72–1.07)	0.95 (0.77–1.17)	0.31	0.99 (0.94–1.03)
External causes (ICD-10 codes S00–Y98)‡							
Men	1.00 (reference)		0.88 (0.71–1.10)	0.85 (0.67–1.07)	0.93 (0.74–1.18)	0.30	0.96 (0.91–1.02)
Women	1.00 (reference)		0.93 (0.74–1.16)	0.82 (0.64–1.03)	0.93 (0.73–1.20)	0.24	0.97 (0.91–1.04)

ICD-10 = International Classification of Diseases, 10th Revision.

* Multivariable models used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education status (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

† Values are hazard ratios (95% CIs).

‡ Reference category merged with low consumption (quartile 1) due to low case numbers among nonconsumers.

Appendix Table 9. Multivariable Associations of Daily Coffee Consumption and All-Cause and Cause-Specific Mortality Among Men and Women After Exclusion of Deaths Occurring During the First 8 Years of Follow-up (n = 10 790)*

Variable	Coffee Consumption†					*P* Value for Trend	Per Cup Per Day†
	Nonconsumers	Quartile 1 (Low)	Quartile 2 (Medium-Low)	Quartile 3 (Medium-High)	Quartile 4 (High)		
All-cause mortality							
Men	1.00 (reference)	0.92 (0.85–1.00)	0.90 (0.82–0.97)	0.85 (0.78–0.92)	0.88 (0.81–0.96)	0.001	0.98 (0.97–0.99)
Women	1.00 (reference)	0.96 (0.90–1.02)	0.91 (0.86–0.97)	0.93 (0.87–0.99)	0.94 (0.88–1.01)	0.08	0.99 (0.99–1.01)
Cancer (ICD-10 codes C00–D48)							
Men	1.00 (reference)	0.95 (0.83–1.09)	0.99 (0.86–1.13)	0.97 (0.84–1.11)	1.02 (0.88–1.18)	0.28	1.00 (0.98–1.02)
Women	1.00 (reference)	1.00 (0.90–1.12)	1.01 (0.90–1.12)	1.04 (0.93–1.16)	1.09 (0.97–1.21)	0.03	1.02 (1.01–1.04)
Circulatory diseases (ICD-10 codes I00–I99)							
Men	1.00 (reference)	1.00 (0.84–1.19)	0.93 (0.78–1.10)	0.88 (0.73–1.05)	0.91 (0.76–1.10)	0.03	0.97 (0.95–0.99)
Women	1.00 (reference)	0.92 (0.79–1.07)	0.79 (0.68–0.92)	0.81 (0.69–0.96)	0.85 (0.72–1.01)	0.013	0.98 (0.95–1.01)
Cerebrovascular diseases (ICD-10 codes I60–I69)							
Men	1.00 (reference)	0.92 (0.65–1.31)	0.88 (0.62–1.25)	0.81 (0.56–1.17)	0.78 (0.53–1.14)	0.09	0.94 (0.88–0.99)
Women	1.00 (reference)	0.89 (0.68–1.15)	0.80 (0.62–1.04)	0.79 (0.60–1.05)	0.77 (0.57–1.03)	0.04	0.97 (0.92–1.02)
Ischemic heart diseases (ICD-10 codes I20–I25)							
Men	1.00 (reference)	1.13 (0.86–1.49)	1.06 (0.81–1.39)	0.99 (0.75–1.32)	1.08 (0.75–1.32)	0.59	0.99 (0.95–1.03)
Women	1.00 (reference)	1.06 (0.79–1.43)	0.87 (0.64–1.18)	0.73 (0.53–1.01)	0.86 (0.62–1.19)	0.004	0.95 (0.90–0.99)
Digestive diseases (ICD-10 codes K00–K93)‡							
Men	1.00 (reference)		0.67 (0.52–0.87)	0.52 (0.39–0.69)	0.44 (0.32–0.61)	<0.001	0.80 (0.74–0.86)
Women	1.00 (reference)		0.92 (0.73–1.16)	0.72 (0.55–0.95)	0.66 (0.48–0.89)	0.002	0.90 (0.84–0.97)
Respiratory diseases (ICD-10 codes J30–J98)‡							
Men	1.00 (reference)		0.85 (0.67–1.07)	0.97 (0.76–1.25)	1.09 (0.85–1.41)	0.74	1.01 (0.96–1.07)
Women	1.00 (reference)		0.93 (0.76–1.14)	0.87 (0.70–1.08)	0.98 (0.78–1.22)	0.47	0.99 (0.94–1.04)
External causes (ICD-10 codes S00–Y98)‡							
Men	1.00 (reference)		1.02 (0.79–1.31)	0.92 (0.70–1.20)	1.11 (0.85–1.44)	0.74	1.01 (0.95–1.08)
Women	1.00 (reference)		1.00 (0.78–1.29)	0.89 (0.68–1.17)	1.05 (0.80–1.39)	0.92	1.01 (0.93–1.08)

ICD-10 = International Classification of Diseases, 10th Revision.

* Multivariable models used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education status (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center.

† Values are hazard ratios (95% CIs).

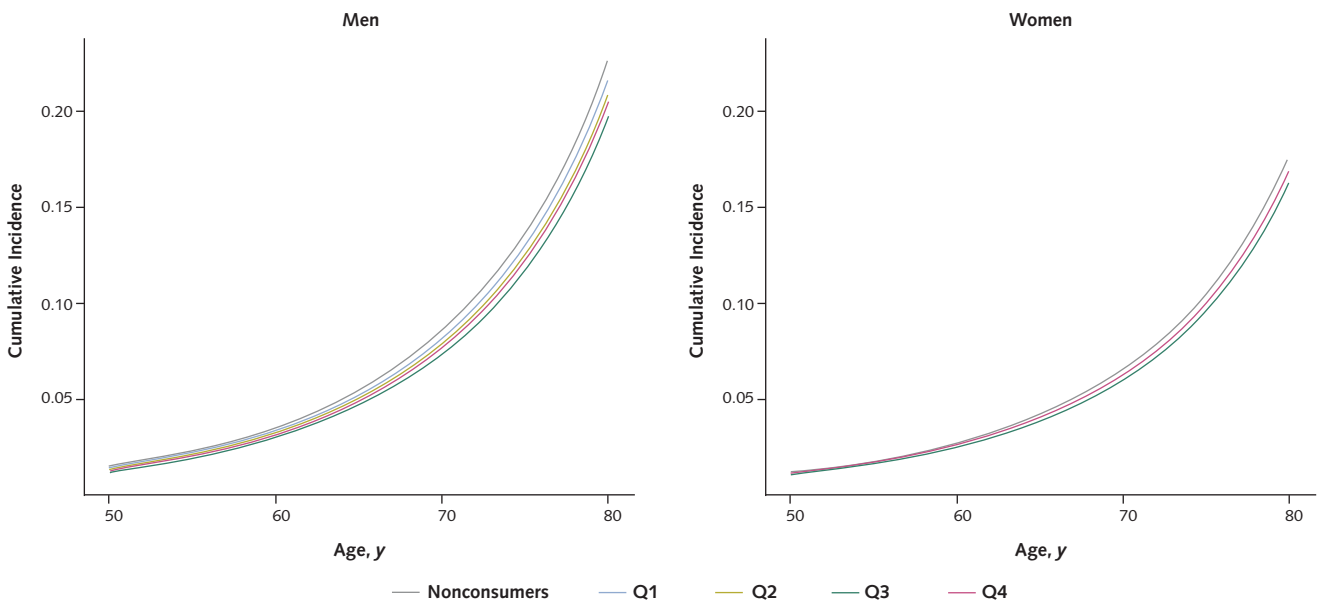
‡ Reference category merged with low consumption (quartile 1) due to low case numbers among nonconsumers.

Appendix Table 10. Associations of Daily Coffee Consumption and All-Cause and Cause-Specific Mortality Among Participants Who Self-Reported Being in "Excellent" or "Good" Health at Baseline (n = 119 609)*

Variable for Both Sexes	Deaths, *n*	Coffee Consumption†				*P* Value for Trend
		Nonconsumers	Tertile 1	Tertile 2	Tertile 3	
All-cause mortality	8643	1.00 (reference)	0.94 (0.86–1.02)	0.89 (0.81–0.97)	0.90 (0.82–0.99)	0.01
Cancer (ICD-10 codes C00–D48)	3717	1.00 (reference)	0.96 (0.83–1.11)	0.94 (0.81–1.09)	1.02 (0.88–1.19)	0.33
Circulatory diseases (ICD-10 codes I00–I99)	1839	1.00 (reference)	0.99 (0.82–1.20)	0.94 (0.77–1.14)	0.91 (0.75–1.12)	0.17
Respiratory diseases (ICD-10 codes J30–J98)‡	194	1.00 (reference)		0.79 (0.55–1.12)	0.82 (0.56–1.20)	0.18
Digestive diseases (ICD-10 codes K00–K93)‡	213	1.00 (reference)		0.50 (0.35–0.71)	0.50 (0.35–0.72)	<0.001
External causes (ICD-10 codes S00–Y98)‡	301	1.00 (reference)		0.98 (0.74–1.28)	0.79 (0.59–1.07)	0.19

ICD-10 = International Classification of Diseases, 10th Revision.
* Multivariable model used Cox regression with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education status (none, primary school, technical/professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], former [≤10, 11–<20, or ≥20 y since quitting], current pipe/cigar/occasional smoking, current vs. former, missing, or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 y or unknown); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories), sex, and center.
† Values are hazard ratios (95% CIs). Categories were based on country-specific tertiles of coffee consumption after exclusion of nonconsumers. Data on self-reported health were available from participants from 5 countries: Germany, the Netherlands, Norway, Sweden, and the United Kingdom. Participants in these countries were asked at recruitment to classify their health as excellent, good, moderate, or poor.
‡ Reference category merged with low consumption (tertile 1) due to low case numbers among nonconsumers.

Appendix Figure 2. Adjusted cumulative incidence of all-cause mortality, by coffee consumption categories among men and women.



Flexible parametric survival models were used to allow direct estimation of the conditional cumulative incidence and thus absolute risk for death by sex and coffee consumption categories, with adjustment for body mass index (<22, 22–24.9, 25–29.9, 30–34.9, or ≥35 kg/m^2); physical activity (inactive, moderately inactive, moderately active, or active); education (none, primary school, technical or professional school, secondary school, higher education [including university], or not specified); alcohol consumption (0, <5, 5–14.9, 15–29.9, or ≥30 g/d); smoking status and intensity (never, current [1–15, 16–25, or ≥26 cigarettes per day], or former [≤10, 11–<20, or ≥20 years since quitting]; current pipe, cigar, or occasional smoking; current vs. former; missing; or unknown); smoking duration (<10, 10–<20, 20–<30, 30–<40, or ≥40 years or unknown); ever-use of contraceptive pill (yes, no, or unknown); menopausal status (premenopausal, postmenopausal, perimenopausal, surgically postmenopausal, or unknown); ever-use of menopausal hormone therapy (yes, no, or unknown); and intake of total energy (in kilocalories per day), red and processed meat (in grams per day), and fruits and vegetables (in grams per day) (all continuous), with stratification by age (1-y categories) and center. Within these models, we used restricted cubic splines with 3 internal knots to model the baseline hazard, using attained age as the time scale. Model-based survival functions and their CIs were obtained from fitted models by coffee consumption category and sex, with other categorical covariates set to the most common category and continuous variables set to their sex-specific means. Categories were based on country-specific quartiles of coffee consumption after exclusion of nonconsumers. Quartile cutoffs were 500, 900, and 1300 mL/d in Denmark; 150, 280, and 450 mL/d in France; 261, 395, and 580 mL/d in Germany; 70, 140, and 240 mL/d in Greece; 60, 92, and 138 mL/d in Italy; 375, 500, and 750 mL/d in the Netherlands; 300, 420, and 540 mL/d in Norway; 50, 105, and 196 mL/d in Spain; 300, 400, and 601 mL/d in Sweden; and 83, 380, and 488 mL/d in the United Kingdom. Q1 = first quartile; Q2 = second quartile; Q3 = third quartile; Q4 = fourth quartile.

Appendix Table 11. Sensitivity Analysis to Assess the Possible Effect of an Unmeasured Confounder on the Observed Relationship Between Coffee Consumption and All-Cause Mortality*

Difference in Prevalence of the Unmeasured Confounder Between Nonconsumers and Persons With High Coffee Consumption	Hazard Ratio for Unmeasured Confounder and All-Cause Mortality													
	0.50	0.60	0.70	0.75	0.80	0.90	1.00	1.10	1.20	1.30	1.40	1.50	2.00	2.50
−50%	0.30 (0.29–0.32)	0.30 (0.29–0.32)	0.52 (0.50–0.54)	0.61 (0.58–0.63)	0.68 (0.65–0.71)	0.81 (0.77–0.84)	0.91 (0.87–0.95)	0.99 (0.95–1.04)	1.06 (1.02–1.11)	1.12 (1.07–1.17)	1.17 (1.12–1.22)	1.21 (1.16–1.27)	1.37 (1.31–1.43)	1.46 (1.39–1.52)
−40%	0.30 (0.29–0.32)	0.51 (0.48–0.53)	0.65 (0.62–0.68)	0.71 (0.68–0.74)	0.76 (0.73–0.79)	0.84 (0.81–0.88)	0.91 (0.87–0.95)	0.97 (0.92–1.01)	1.01 (0.97–1.06)	1.05 (1.00–1.10)	1.08 (1.04–1.13)	1.11 (1.06–1.16)	1.21 (1.16–1.27)	1.27 (1.22–1.33)
−30%	0.52 (0.50–0.54)	0.65 (0.62–0.68)	0.74 (0.71–0.78)	0.78 (0.75–0.81)	0.81 (0.78–0.85)	0.87 (0.83–0.90)	0.91(0.87–0.95)	0.95 (0.90–0.99)	0.98 (0.93–1.02)	1.00 (0.96–1.04)	1.02 (0.98–1.07)	1.04 (0.99–1.09)	1.11 (1.06–1.15)	1.14 (1.09–1.19)
−20%	0.68 (0.65–0.71)	0.76 (0.73–0.79)	0.81 (0.78–0.85)	0.83 (0.80–0.87)	0.85 (0.82–0.89)	0.88 (0.85–0.92)	0.91 (0.87–0.95)	0.93 (0.89–0.97)	0.95 (0.91–0.99)	0.96 (0.92–1.00)	0.98 (0.93–1.02)	0.99 (0.94–1.03)	1.02 (0.98–1.07)	1.05 (1.00–1.09)
−10%	0.81 (0.77–0.84)	0.84 (0.81–0.88)	0.87 (0.83–0.90)	0.88 (0.84–0.91)	0.88 (0.85–0.92)	0.90 (0.86–0.94)	0.91 (0.87–0.95)	0.92 (0.88–0.96)	0.93 (0.89–0.97)	0.93 (0.89–0.97)	0.94 (0.90–0.98)	0.94 (0.90–0.99)	0.96 (0.92–1.00)	0.97 (0.93–1.01)
0%	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.87–0.95)
10%	0.99 (0.95–1.04)	0.97 (0.92–1.01)	0.95 (0.90–0.99)	0.94 (0.90–0.98)	0.93 (0.89–0.97)	0.92 (0.88–0.96)	0.91 (0.87–0.95)	0.90 (0.86–0.94)	0.90 (0.86–0.94)	0.89 (0.85–0.93)	0.89 (0.85–0.93)	0.88 (0.84–0.92)	0.87 (0.83–0.91)	0.86 (0.82–0.90)
20%	1.06 (1.02–1.11)	1.01 (0.97–1.06)	0.98 (0.93–1.02)	0.96 (0.92–1.00)	0.95 (0.91–0.99)	0.93 (0.89–0.97)	0.91 (0.87–0.95)	0.90 (0.86–0.94)	0.88 (0.85–0.92)	0.88 (0.84–0.91)	0.87 (0.83–0.90)	0.86 (0.82–0.90)	0.83 (0.80–0.87)	0.82 (0.78–0.86)
30%	1.12 (1.07–1.17)	1.05 (1.00–1.10)	1.00 (0.96–1.04)	0.98 (0.94–1.02)	0.96 (0.92–1.00)	0.93 (0.89–0.97)	0.91 (0.87–0.95)	0.89 (0.85–0.93)	0.88 (0.84–0.91)	0.86 (0.82–0.90)	0.85 (0.81–0.89)	0.84 (0.80–0.88)	0.81 (0.77–0.84)	0.78 (0.75–0.82)
40%	1.17 (1.12–1.22)	1.08 (1.04–1.13)	1.02 (0.98–1.07)	1.00 (0.95–1.04)	0.98 (0.93–1.02)	0.94 (0.90–0.98)	0.91 (0.87–0.95)	0.89 (0.85–0.93)	0.87 (0.83–0.90)	0.85 (0.81–0.89)	0.84 (0.80–0.87)	0.82 (0.79–0.86)	0.78 (0.75–0.81)	0.75 (0.72–0.79)
50%	1.21 (1.16–1.27)	1.11 (1.06–1.16)	1.04 (0.99–1.09)	1.01 (0.97–1.06)	0.99 (0.94–1.03)	0.94 (0.90–0.99)	0.91 (0.87–0.95)	0.88 (0.84–0.92)	0.86 (0.82–0.90)	0.84 (0.80–0.88)	0.82 (0.79–0.86)	0.81 (0.77–0.84)	0.76 (0.73–0.79)	0.73 (0.70–0.76)

* Values are hazard ratios (95% CIs).