Association of Coffee Consumption With Total and Cause-Specific Mortality in 3 Large Prospective Cohorts

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Background—The association between consumption of caffeinated and decaffeinated coffee and risk of mortality remains inconclusive.

Methods and Results—We examined the associations of consumption of total, caffeinated, and decaffeinated coffee with risk of subsequent total and cause-specific mortality among 74 890 women in the Nurses' Health Study (NHS), 93 054 women in the Nurses' Health Study II, and 40 557 men in the Health Professionals Follow-up Study. Coffee consumption was assessed at baseline using a semiquantitative food frequency questionnaire. During 4 690 072 person-years of follow-up, 19 524 women and 12 432 men died. Consumption of total, caffeinated, and decaffeinated coffee were nonlinearly associated with mortality. Compared with nondrinkers, coffee consumption of 1 to 5 cups per day was associated with lower risk of mortality, whereas coffee consumption of more than 5 cups per day was not associated with risk of mortality. However, when restricting to never smokers compared with nondrinkers, the hazard ratios (and 95% confidence intervals) of mortality were 0.94 (0.89–0.99) for 1.0 or less cup per day, 0.92 (0.87–0.97) for 1.1 to 3.0 cups per day, 0.85 (0.79–0.92) for 3.1 to 5.0 cup per day, and 0.88 (0.78–0.99) for more than 5.0 cup per day (*P* value for nonlinearity = 0.32; *P* value for trend < 0.001). Significant inverse associations were observed for caffeinated (*P* value for trend < 0.001) and decaffeinated coffee (*P* value for trend = 0.022). Significant inverse associations were observed between coffee consumption and deaths attributed to cardiovascular disease, neurologic diseases, and suicide. No significant association between coffee consumption and total cancer mortality was found.

Conclusions—Higher consumption of total coffee, caffeinated coffee, and decaffeinated coffee was associated with lower risk of total mortality. (***Circulation***. 2015;132:2305-2315. DOI: 10.1161/CIRCULATIONAHA.115.017341.)

Key Words: coffee ■ mortality ■ smoking

Coffee is one of the most commonly consumed beverages worldwide. The associations between coffee consumption and risks of several disease outcomes have been investigated. Coffee consumption has been inversely associated with risks of type 2 diabetes mellitus,[1] liver cancer,[2] endometrial cancer,[3] lethal prostate cancer,[4] basal cell carcinoma of the skin,[5] and neurologic diseases,[6] as well as with risk of cardiovascular disease (CVD) when consumed in moderation.[7]

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The association between coffee consumption and risk of total mortality has also been investigated. Recent studies have shown an inverse association between moderate coffee consumption and risk of mortality and an inverse or null association between heavy coffee consumption and risk of mortality.[8–16] However, some earlier studies[17–19] and a recent study[20] found heavy coffee consumption to be associated with a higher risk of mortality. Summarizing individual studies, meta-analyses have concluded that coffee consumption is not associated with higher risk of mortality; however, there was significant between-study heterogeneity in the effect estimates.[21–23] The associations between coffee consumption and cause-specific mortality, especially CVD and cancer mortality, have been sporadically investigated together with total mortality,[8,10,11,23] with most studies finding an inverse

association with CVD mortality and no association with cancer mortality.

On the basis of the results of previous studies, 4 questions remain unanswered. First, does a nonlinear relationship exist between coffee consumption and risk of mortality, that is, is moderate coffee consumption associated with lower risk of mortality and heavy coffee drinking not associated with risk of mortality or even with an increased risk? Second, if a nonlinear association exists, is it truly a biological effect of coffee or is it an artifact because of the confounding of smoking? Third, what are the associations of coffee consumption with risks of cause-specific mortality? Fourth, do caffeinated and decaffeinated coffee have similar associations with risk of mortality?

We therefore examined the association of coffee consumption with total and cause-specific mortality in 3 large, ongoing, independent cohort studies of men and women. This analysis updated our earlier publication on coffee consumption and total mortality in the Nurses' Health Study (NHS) and Health Professionals Follow-up Study (HPFS) with 6888 total deaths and extended to a younger cohort of nurses (NHS II). These cohorts provide measures of caffeinated and decaffeinated coffee consumption, extensive data on known or suspected confounders, and ≤30 years of follow-up, during which more than 30 000 deaths have been recorded.

Methods

Study Population

The NHS began in 1976, when 121 700 female registered nurses aged 30 to 55 years residing in 11 states were recruited to complete a baseline questionnaire about their lifestyle and medical history. The NHS II was established in 1989 and consisted of 116 671 younger female registered nurses, aged 25 to 42 years at baseline. These nurses responded to a baseline questionnaire similar to the NHS. The HPFS was initiated in 1986 and was composed of 51 529 male dentists, pharmacists, veterinarians, optometrists, osteopathic physicians, and podiatrists aged 40 to 75 years at baseline. The male participants returned a baseline questionnaire about detailed medical history, lifestyle, and usual diet. In all 3 of the cohorts, questionnaires were collected at baseline and biennially thereafter to update information on lifestyle factors and the occurrence of chronic diseases. All of the 3 cohorts are composed of ≈95% white participants.

For the current analysis, we excluded participants who reported CVD or cancer at baseline (1984 for the NHS, 1991 for the NHS II, and 1986 for the HPFS). We additionally excluded participants with missing caffeinated or decaffeinated coffee consumption at baseline, those who left more than 70 food items blank, or had daily energy intakes <600 or >3500 kcal for women and <800 or >4200 kcal for men. The study protocol was approved by the institutional review boards of Brigham and Women's Hospital and Harvard School of Public Health.

Assessment of Coffee Consumption

In 1984, a 116-item food frequency questionnaire (FFQ) was administered to the NHS participants to obtain information on usual intake of food and beverages. Starting in 1986, an expanded 131-item FFQ was administered every 4 years to update diet. Using a similar FFQ, dietary data were collected every 4 years from the NHS II participants starting in 1991 and from the HPFS participants starting in 1986. In all of the FFQs, participants were asked how often (from "never or less than once per month" to "6 or more times per day") on average they consumed a standard portion size of each food item during the previous year. The questionnaire items for coffee included "caffeinated coffee" and "decaffeinated coffee." Consumption of total coffee was calculated as the sum of intakes of caffeinated and decaffeinated coffee. The validity and reproducibility of the FFQ have been described in detail

elsewhere.[24–27] In brief, the validation study found a correlation coefficient of 0.78 between coffee intake assessed on the baseline FFQ and coffee intake assessed on four 1-week dietary records collected over a 1-year period.[26] Because mean coffee consumption did not change in NHS II and decreased slightly in NHS and HPFS over time (Figure I in the online-only Data Supplement), we used baseline coffee consumption as primary exposure and further conducted several sensitivity analyses using updated dietary information.

Assessment of Covariates

In the biennial follow-up questionnaires, updated information was collected on age, weight, smoking status, physical activity, medication use, family history of diabetes mellitus, and self-reported diagnosis of diseases, including hypertension, hypercholesterolemia, CVD, and cancer. For NHS and NHS II participants, we also ascertained data on menopausal status and postmenopausal hormone use. We calculated the Alternate Healthy Eating Index as an overall measure of diet quality using FFQ data.[28]

Assessment of Deaths

Our primary end point was death from any cause. We performed systematic searches of the vital records of states and of the National Death Index. This search was supplemented by reports from family members and postal authorities. Using these methods, we were able to ascertain >98% of the deaths in each cohort.[29] A physician who was blinded to data on coffee consumption and other risk factors reviewed death certificates and medical charts to classify the cause of death according to the eighth and ninth revisions of the *International Classification of Diseases*. Deaths were grouped into 9 major categories (Table I in the online-only Data Supplement).

Statistical Analysis

We calculated each individual's person-time from the date of the return of the baseline questionnaire to the date of death or the end of follow-up (December 31, 2012, for all 3 studies), whichever came first. We used Cox proportional hazards regression models to examine the association between coffee consumption (5 categories) and risk of mortality. The regression models included calendar time in 2-year intervals as the time scale and were stratified by age in years. In the multivariable analysis, we further adjusted for body mass index, physical activity, overall dietary pattern (Alternate Healthy Eating Index), total energy intake, smoking status, sugar-sweetened beverage consumption, and alcohol consumption, all of which were updated from follow-up questionnaires. We additionally adjusted for baseline hypertension, hypercholesterolemia, and diabetes mellitus status in both men and women, as well as menopausal status and postmenopausal hormone use among women.

We also used restricted cubic splines with 3 knots to flexibly model the association between coffee consumption and risk of mortality. To test for a potential nonlinear association between coffee consumption and risk of mortality, a likelihood ratio test was used comparing the model with only the linear term of coffee consumption with the model with both the linear and the cubic spline terms, with $P<0.05$ denoting significant nonlinearity. All of the analyses were performed separately in each cohort and then pooled to obtain the overall hazard ratio using a fixed-effects model.

Stratified analyses were conducted according to body mass index (≤25 kg/m^2 or >25 kg/m^2), age (≤70 years or >70 years), Alternate Healthy Eating Index (median score or less or more than median score), physical activity (median score or less or more than median score), smoking status (never smokers or ever smokers), sex (male or female), and individual cohort. We tested for potential effect modification by these stratification variables by including interaction terms between the exposure and potential effect modifier in the multivariate adjusted model and conducting a likelihood ratio test comparing the models with and without interaction terms.

The proportional hazard assumption of the Cox model was tested by adding interaction terms between exposure and the dichotomized indicator of time intervals to the multivariate adjusted model within

each cohort and conducting a likelihood ratio test comparing the models with and without interaction terms. All of the statistical tests were 2-sided and performed using SAS version 9.2 for UNIX (SAS Institute Inc, Cary, NC).

Results

Coffee Consumption and Dietary and Lifestyle Factors

The percentages of never coffee drinkers were 12% in NHS, 30% in NHS II, and 17% in HPFS. The percentages of those who drank more than 5 cups per day were 8% in NHS, 3% in NHS II, and 5% in HPFS. There was a strong correlation between frequent coffee consumption and smoking status (Table 1). The proportions of never smokers among those who did not drink coffee were 63%, 80%, and 71% in NHS, NHS II, and HPFS, respectively, whereas the proportions of never smokers among those who drank more than 5 cups per day were 24%, 35%, and 25% in NHS, NHS II, and HPFS. Those who drank coffee more frequently were also more likely to consume alcohol and consumed less sugar-sweetened beverages and fruits but more red meats.

Coffee Consumption and All-Cause Mortality

During 28 years of follow-up (1 894 292 person-years) among women in the NHS, we documented 17 468 deaths; during 21

years of follow-up (1 882 464 person-years) among women in the NHS II, we documented 2056 deaths; during 26 years of follow-up (913 316 person-years) among men in the HPFS, we documented 12 432 deaths. In total, 31 956 deaths were recorded during 4 690 072 person-years of follow-up across all 3 of the cohorts.

Age-adjusted analysis showed that the highest categories of consumption of total and caffeinated coffee were associated with a higher risk of all-cause mortality across the 3 cohorts. The association between consumption of total, caffeinated, and decaffeinated coffee and all-cause mortality attenuated significantly after further adjusting for smoking. Multivariate-adjusted analysis showed a nonlinear association between consumption of total, caffeinated, and decaffeinated coffee and all-cause mortality (P values for nonlinearity using likelihood ratio test < 0.001; P values for nonlinear trend < 0.001; Table 2). Relative to no consumption of coffee, the pooled hazard ratio for death was 0.95 (95% confidence interval [CI], 0.91–0.99) for 1.0 or less cup of total coffee per day, 0.91 (95% CI, 0.88–0.95) for 1.1 to 3.0 cups per day, 0.93 (95% CI, 0.89–0.97) for 3.1 to 5.0 cups per day, and 1.02 (95% CI, 0.96–1.07) for more than 5.0 cups per day. Similar results were found when caffeinated and decaffeinated coffees were examined separately. Examining the 3 cohorts individually, the

Table 1. Age-Adjusted Baseline Characteristics of Participants by Frequency of Total Coffee Consumption (Including Caffeinated and Decaffeinated Coffee) in NHS, NHS II, and HPFS

Variable	NHS (1984)					NHS II (1991)					HPFS (1986)				
Cups per day	0	≤1.0	1.1–3.0	3.1–5.0	>5.0	0	≤1.0	1.1–3.0	3.1–5.0	>5.0	0	≤1.0	1.1–3.0	3.1–5.0	>5.0
N	9233	14 740	30 420	14 760	5737	27 888	22 837	29 239	10 049	3041	6863	11 402	14 264	5861	2167
Age, y	48.4	50.5	50.7	50.5	50.0	35.2	35.5	37.6	38.0	38	50.9	54.0	53.7	52.9	52.0
Caffeinated coffee, cups per day	0	0.4	1.7	3.2	4.7	0	0.4	1.9	3.4	5.15	0	0.4	1.6	3.0	4.3
Decaffeinated coffee, cups per day	0	0.3	0.6	1.2	1.6	0	0.2	0.4	0.9	1.1	0	0.3	0.7	1.3	2.0
Physical activity, MET-h/wk	14.1	14.1	14.4	13.8	13.3	23.1	24.8	25.5	24.2	25.6	21.7	22.2	21.1	20.3	18.2
aHEI*	46.9	48.0	47.8	47.8	47.3	46.0	49.0	50.2	49.7	48.5	51.9	53.7	52.7	51.7	50.2
Total energy intake, kcal/d	1720	1684	1748	1786	1815	1779	1768	1790	1836	1883	1934	1887	1973	2026	2086
Sugar-sweetened beverages, servings per day	1.30	1.2	1.1	1.0	0.9	1.4	1.2	1.1	0.9	0.9	1.4	1.3	1.1	1.0	0.9
Alcohol, g/d	3.7	5.8	7.8	7.7	7.1	1.6	2.7	4.3	4.4	4.2	5.7	10.0	13.1	14.1	14.8
Dairy, servings per day	1.9	1.9	2.0	2.07	2.1	2.1	2.2	2.4	2.4	2.6	2.2	2.1	2.2	2.4	2.5
Fruits, servings per day	2.2	2.3	2.2	2.1	1.9	1.8	2.0	1.9	1.8	1.6	2.6	2.4	2.2	2.1	2.0
Vegetables, servings per day	3.0	3.0	3.1	3.1	3.1	3.2	3.5	3.6	3.7	3.8	3.0	3.0	3.0	3.0	3.0
Meats, servings per day	1.4	1.4	1.5	1.5	1.6	1.4	1.4	1.4	1.4	1.5	1.4	1.4	1.6	1.6	1.8
Fish, servings per day	0.2	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.3	0.3	0.3	0.3	0.3
BMI, kg/m²	24.4	24.2	23.8	23.6	23.4	25.4	24.7	24.2	24.4	24.8	24.7	24.7	25.0	25.2	25.
Never smokers, %	63	53	42	34	24	80	70	57	47	35	71	54	42	33	25
Hypertension,%	9	10	8	7	6	4	4	3	3	3	18	21	20	19	17
Hypercholesterolemia, %	4	4	4	3	3	10	10	9	9	11	10	11	11	10	11
Postmenopausal women, %	48	48	48	49	49	3	3	3	3	4	NA	NA	NA	NA	NA
Current postmenopausal hormone use, % among total women	15	14	14	13	12	3	3	3	3	3	NA	NA	NA	NA	NA

aHEI indicates alternative healthy eating index; BMI, body mass index; HPFS, Health Professionals Follow-up Study; MET, metabolic equivalent; NA, not applicable; and NHS, Nurses' Health Study.

*aHEI ranges from 0 to 100, with a higher score indicating a healthier diet.

Table 2. HRs (95% CI) for the Association Between Consumption of Total Coffee, Caffeinated Coffee, and Decaffeinated Coffee and Risk of Mortality

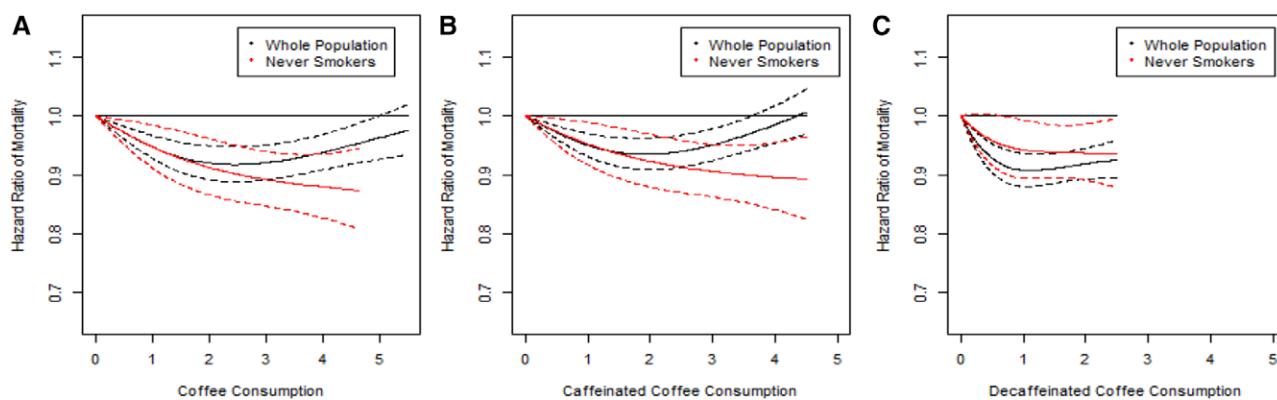| Variable	0 Cups per Day	1.0 or Less Cups per Day	1.1–3.0 Cups per Day	3.1–5.0 Cups per Day	More Than 5.0 Cups per Day	Per Cup Increase	P for Nonlinearity*	P for Linear Trend
Total coffee								
Cases/person-time	4166/958 267	7826/1 086 683	12 198/1 681 922	5456/709 646	2310/253 554			
NHS								
Age-adjusted	1.00	0.98 (0.93–1.04)	0.91 (0.87–0.96)	0.96 (0.91–1.02)	1.24 (1.16–1.33)	1.02 (1.01–1.03)	<0.001	<0.001
Age and smoking adjusted	1.00	0.94 (0.89–0.99)	0.82 (0.78–0.86)	0.81 (0.76–0.86)	0.92 (0.86–0.98)	0.98 (0.97–0.99)	<0.001	<0.001
Multivariate-adjusted model	1.00	0.94 (0.88–0.99)	0.90 (0.86–0.95)	0.93 (0.88–0.99)	1.02 (0.95–1.09)	1.00 (0.99–1.01)	<0.001	0.50
NHS II								
Age-adjusted	1.00	0.89 (0.79–1.00)	0.83 (0.74–0.92)	0.93 (0.80–1.07)	1.37 (1.12–1.67)	0.98 (0.95–1.01)	0.003	0.23
Age and smoking-adjusted	1.00	0.86 (0.76–0.97)	0.74 (0.66–0.83)	0.74 (0.64–0.86)	0.92 (0.75–1.13)	0.93 (0.90–0.96)	0.015	<0.001
Multivariate-adjusted model	1.00	0.91 (0.81–1.03)	0.84 (0.75–0.95)	0.86 (0.74–1.01)	1.02 (0.83–1.26)	0.96 (0.93–1.00)	0.17	0.03
HPFS								
Age-adjusted	1.00	1.06 (1.00–1.12)	1.05 (0.99–1.11)	1.09 (1.02–1.16)	1.30 (1.19–1.42)	1.02 (1.00–1.03)	0.98	0.007
Age and smoking-adjusted	1.00	1.00 (0.94–1.06)	0.95 (0.90–1.01)	0.94 (0.88–1.01)	1.05 (0.96–1.15)	0.98 (0.94–1.02)	0.24	0.36
Multivariate-adjusted model	1.00	1.00 (0.94–1.06)	0.97 (0.90–1.01)	0.95 (0.88–1.02)	1.02 (0.93–1.12)	0.99 (0.97–1.00)	0.13	0.04
Pooled								
Multivariate-adjusted model	1.00	0.95 (0.91–0.99)	0.91 (0.88–0.95)	0.93 (0.89–0.97)	1.02 (0.96–1.07)	0.98 (0.97–0.99)	<0.001	<0.001
Caffeinated coffee								
Cases/person-time	8615/1 454 869	10 105/1 404 192	8495/1 255 722	3304/419 049	1437/156 238			
NHS								
Multivariate-adjusted model	1.00	0.96 (0.92–1.00)	0.92 (0.89–0.96)	1.01 (0.96–1.07)	1.07 (0.99–1.14)	1.00 (0.99–1.01)	<0.001	0.78
NHS II								
Multivariate-adjusted model	1.00	0.97 (0.86–1.09)	0.91 (0.80–1.02)	0.99 (0.83–1.17)	1.11 (0.88–1.40)	0.99 (0.96–1.02)	0.38	0.47
HPFS								
Multivariate-adjusted model	1.00	1.00 (0.96–1.05)	0.94 (0.90–0.99)	1.00 (0.93–1.07)	1.11 (1.00–1.24)	0.99 (0.98–1.00)	0.046	0.11
Pooled								
Multivariate-adjusted model	1.00	0.97 (0.94–1.00)	0.93 (0.90–0.96)	1.00 (0.96–1.05)	1.08 (1.02–1.14)	0.98 (0.97–0.99)	0.015	<0.001
Decaffeinated coffee								
Cases/person-time	16 393/2 607 891	10 637/1 516 930	3777/445 908	1149/119 341				
NHS								
Multivariate-adjusted model	1.00	0.94 (0.90–0.97)	0.92 (0.87–0.96)	0.96 (0.89–1.04)		0.96 (0.95–0.98)	0.008	<0.001
NHS II								
Multivariate-adjusted model	1.00	0.83 (0.74–0.92)	0.86 (0.70–1.04)	0.93 (0.64–1.35)		0.92 (0.86–1.00)	0.009	0.035
HPFS								
Multivariate-adjusted model	1.00	0.91 (0.88–0.95)	0.92 (0.87–0.98)	0.91 (0.83–1.01)		0.97 (0.95–0.99)	0.006	0.014
Pooled								
Multivariate-adjusted model	1.00	0.92 (0.89–0.94)	0.91 (0.88–0.94)	0.94 (0.88–1.00)		0.96 (0.94–0.97)	<0.001	<0.001

Multivariate-adjusted model was further adjusted for baseline disease status (hypertension, hypercholesterolemia, diabetes mellitus), BMI (<20.9, 21.0–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m²), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 MET-h/wk), overall dietary pattern (aHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former [1–4 cigarettes per day], former [5–14 cigarettes per day], former [15–24 cigarettes per day], former [25–34 cigarettes per day], former [35–44 cigarettes per day], former [45 or more cigarettes per day], former [unknown cigarettes per day], current [1–4 cigarettes per day], current [5–14 cigarettes per day], current [15–24 cigarettes per day], current [25–34 cigarettes per day], current [35–44 cigarettes per day], current [45 or more cigarettes per day], current [unknown cigarettes per day]), sugar-sweetened beverage consumption (quintiles), and alcohol consumption (0, 0–5, 5–10, 10–15, ≥15 g/d). We additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (yes vs no) for women. Caffeinated and decaffeinated coffee adjusted for each other. aHEI indicates alternative healthy eating index; BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; MET, metabolic equivalent; NA, not applicable; and NHS, Nurses' Health Study.

*A likelihood ratio test was performed.

nonlinear associations between consumption of total coffee, caffeinated coffee, and decaffeinated coffee and risk of all-cause mortality were most pronounced in NHS (Table 2 and Figures II through IV in the online-only Data Supplement).

Because smoking is a strong confounder of the coffee-mortality relationship, we repeated the analysis among never smokers only. In this analysis, 10 505 deaths were documented during 2 451 970 person-years of follow-up after pooling data

Figure 1. The association between coffee consumption and risk of mortality in the overall population and among never smokers pooled across the 3 cohorts. **A**, Total coffee consumption and risk of mortality. **B**, Caffeinated coffee consumption and risk of mortality. **C**, Decaffeinated coffee consumption and risk of mortality. Multivariate-adjusted models adjusted for age, baseline disease status (hypertension, hypercholesterolemia, and diabetes mellitus), body mass index (BMI; <20.9, 21.0–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, and ≥35.0 kg/m²), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, and ≥27.0 metabolic equivalents-h/wk), smoking status (never, former [1–4 cigarettes per day], former [5–14 cigarettes per day], former [15–24 cigarettes per day], former [25–34 cigarettes per day], former [35–44 cigarettes per day], former [45 or more cigarettes per day], former [unknown cigarettes per day], current [1–4 cigarettes per day], current [5–14 cigarettes per day], current [15–24 cigarettes per day], current [25–34 cigarettes per day], current [35–44 cigarettes per day], current [45 or more cigarettes per day], current [unknown cigarettes per day]), overall dietary pattern (Alternate Healthy Eating Index score, in quintiles), total energy intake (quintiles), sugar-sweetened beverages consumption (quintiles), and alcohol consumption (0, 0–5, 5–10, 10–15, ≥15 g/d). We additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (yes vs no) for women. Caffeinated and decaffeinated coffee adjusted for each other.

from the 3 cohorts. Overall, the association of total coffee, caffeinated coffee, and decaffeinated coffee consumption with risk of all-cause mortality changed from a nonlinear association in the overall population to a linear inverse association when restricting to never smokers (total coffee: *P* value for nonlinearity = 0.32, *P* value for linear trend < 0.001; caffeinated coffee: *P* value for nonlinearity = 0.40, *P* value for linear trend < 0.001; decaffeinated coffee: *P* value for nonlinearity = 0.18, *P* value for linear trend = 0.02; Table 3 and Figure 1).

Coffee Consumption and Cause-Specific Mortality

The association between coffee consumption and leading causes of mortality was further investigated (Table II in the online-only Data Supplement). In the whole population, coffee consumption was inversely associated with risk of mortality attributed to CVD, nonlinearly associated with risk mortality attributed to type 2 diabetes mellitus, and positively associated with risk of mortality attributed to lung cancer and respiratory diseases (Table III in the online-only Data Supplement). However, when restricting to never smokers, coffee consumption was no longer associated with risk of mortality attributed to lung cancer and respiratory disease but was inversely associated only with risks of mortality attributed to CVD, neurologic disease, and suicide. No associations of coffee consumption with risks of mortality attributed to colorectal cancer and breast cancer were found (Table 4).

In the total population, a 1-cup-per-day increment in coffee consumption was positively associated with mortality attributed to lung cancer (*P*<0.0001) and respiratory disease (*P*<0.05) and inversely associated with mortality attributed to CHD, stroke, neurologic disease, and type 2 diabetes mellitus (*P*<0.05). However, after restricting to never smokers, the positive association disappeared for lung cancer and respiratory disease and significant inverse associations remained for

mortality attributed to CHD, neurologic disease, and suicide (*P*<0.05; Figure 2).

Stratified Analysis

Significant interactions were found between coffee consumption and risk of mortality by age (*P* value for interaction = 0.003) and smoking (*P* value for interaction = 0.015; Table IV in the online-only Data Supplement). The association appeared to be stronger among those aged <70 years than older individuals and was stronger among never smokers than smokers. There were no significant differences in the associations between coffee consumption and risk of total mortality when stratified by Alternate Healthy Eating Index score, body mass index, physical activity, sex, and cohort.

The proportional hazard assumption was violated in NHS (but not in NHS II or HPFS), with a stronger association between coffee consumption and mortality in earlier time intervals. However, nonlinear associations between coffee consumption and risk of mortality were found in both subgroups stratified by time interval in NHS (Table V in the online-only Data Supplement). We further assessed the proportional hazard assumption among never smokers in NHS, and the proportional hazard assumption was no longer violated (*P* value for interaction = 0.60).

Sensitivity Analysis

We further evaluated the association between coffee consumption and mortality using cumulatively updated coffee consumption and stopping updating of coffee consumption when intermediate diseases developed (hypertension, hypercholesterolemia, type 2 diabetes mellitus, cancer, and CVD); using time-varying coffee consumption with 4-year lag; using time-varying coffee consumption adjusting for hypercholesterolemia as a time-varying covariate; and using baseline coffee consumption excluding the hypertensive

Table 3.   HRs (95% CI) for the Association Between Consumption of Total Coffee, Caffeinated Coffee, and Decaffeinated Coffee and Risk of Mortality Among Never Smokers

	0 Cups per Day	1.0 or Less Cups per Day	1.1–3.0 Cups per Day	3.1–5.0 Cups per Day	More Than 5.0 Cups per Day	Per Cup Increase	P for Nonlinearity*	P for Linear Trend
Total coffee								
Cases/person-time	2190/704 010	3032/638 687	3759/779 966	1211/262 069	313/67 238			
NHS								
Age-adjusted model	1.00	0.92 (0.85–0.99)	0.80 (0.74–0.86)	0.73 (0.66–0.80)	0.76 (0.65–0.88)	0.93 (0.91–0.95)	0.09	< 0.001
Multivariate-adjusted model	1.00	0.92 (0.85–0.99)	0.88 (0.81–0.95)	0.84 (0.76–0.92)	0.82 (0.71–0.96)	0.96 (0.95–0.98)	0.09	< 0.001
NHS II								
Age-adjusted model	1.00	0.84 (0.71–0.98)	0.84 (0.72–0.98)	0.76 (0.60–0.97)	0.85 (0.55–1.32)	0.95 (0.91–1.00)	0.20	0.07
Multivariate-adjusted model	1.00	0.89 (0.76–1.05)	0.98 (0.84–1.15)	0.88 (0.69–1.13)	0.91 (0.59–1.42)	1.00 (0.95–1.05)	0.77	0.96
HPFS								
Age-adjusted model	1.00	0.99 (0.90–1.08)	0.96 (0.88–1.05)	0.83 (0.73–0.95)	1.06 (0.84–1.33)	0.96 (0.94–0.99)	0.20	0.005
Multivariate-adjusted model	1.00	0.98 (0.89–1.08)	0.97 (0.88–1.06)	0.84 (0.73–0.97)	0.98 (0.78–1.24)	0.96 (0.94–0.99)	0.38	0.009
Pooled								
Multivariate-adjusted model	1.00	0.94 (0.89–0.99)	0.92 (0.87–0.97)	0.85 (0.79–0.92)	0.88 (0.78–0.99)	0.97 (0.95–0.98)	0.32	< 0.001
Caffeinated coffee								
Cases/person-time	3702/962 732	3637/771 531	2409/542 629	595/138 375	162/36 700			
NHS								
Multivariate-adjusted model	1.00	0.95 (0.89–1.01)	0.89 (0.83–0.96)	0.84 (0.75–0.94)	0.82 (0.67–1.00)	0.96 (0.94–0.98)	0.34	< 0.001
NHS II								
Multivariate-adjusted model	1.00	0.99 (0.85–1.15)	1.07 (0.90–1.27)	1.05 (0.78–1.42)	1.04 (0.60–1.81)	1.02 (0.98–1.08)	0.95	0.42
HPFS								
Multivariate-adjusted model	1.00	1.03 (0.95–1.11)	0.92 (0.84–1.02)	0.95 (0.80–1.14)	1.06 (0.78–1.44)	0.97 (0.95–1.00)	0.76	0.08
Pooled								
Multivariate-adjusted model	1.00	0.98 (0.93–1.03)	0.92 (0.87–0.97)	0.89 (0.81–0.97)	0.90 (0.77–1.06)	0.97 (0.95–0.99)	0.40	< 0.001
Decaffeinated coffee								
Cases/person-time	5436/1 423 563	3775/799 017	1084/191 219	210/38 171				
NHS								
Multivariate-adjusted model	1.00	0.97 (0.91–1.03)	0.92 (0.85–1.00)	0.97 (0.82–1.14)		0.97 (0.93–1.00)	0.56	0.03
NHS II								
Multivariate-adjusted model	1.00	0.82 (0.70–0.95)	0.87 (0.65–1.16)	0.70 (0.33–1.47)		0.93 (0.83–1.04)	0.06	0.21
HPFS								
Multivariate-adjusted model	1.00	0.96 (0.88–1.03)	0.94 (0.83–1.06)	0.70 (0.52–0.95)		0.98 (0.93–1.02)	0.61	0.33
Pooled								
Multivariate-adjusted model	1.00	0.95 (0.91–0.99)	0.93 (0.86–0.99)	0.89 (0.77–1.02)		0.97 (0.94–0.99)	0.18	0.02

Multivariate-adjusted model was further adjusted for baseline disease status (hypertension, hypercholesterolemia, diabetes mellitus), BMI (<20.9, 21.0–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m²), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 MET-h/wk), overall dietary pattern (aHEI score, in quintiles), total energy intake (quintiles), sugar-sweetened beverage consumption (quintiles), and alcohol consumption (0, 0–5, 5–10, 10–15, ≥15 g/d). We additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (yes vs no) for women. Caffeinated and decaffeinated coffee adjusted for each other. aHEI indicates alternative healthy eating index; BMI, body mass index; CI, confidence interval; HPFS, Health Professionals Follow-up Study; HR, hazard ratio; MET, metabolic equivalent; NA, not applicable; and NHS, Nurses' Health Study.

*A likelihood ratio test was performed.

or hypercholesterolemia cases at baseline. The associations between consumption of total coffee, caffeinated coffee, and decaffeinated coffee and risk of mortality did not change substantially in these analyses (Tables VI and VII in the online-only Data Supplement and Figures V through IX in the online-only Data Supplement). To further evaluate whether the change of the association from nonlinear in the whole population to inverse linear among never smokers was attributed to the differences in the composition of total mortality between the overall population and never smokers,

Cox models with inverse probability weighting were applied in the never smokers assessing the association between coffee consumption and risk of mortality and the results did not change substantially (Table VIII in the online-only Data Supplement).

Discussion

In this analysis of 3 large ongoing cohort studies, we observed a nonlinear association between coffee consumption and risk of mortality in the overall population, with

Table 4. Multivariate HRs (95% CI) for the Association Between Consumption of Total Coffee and Risk of Cause-Specific Mortality Among Never Smokers
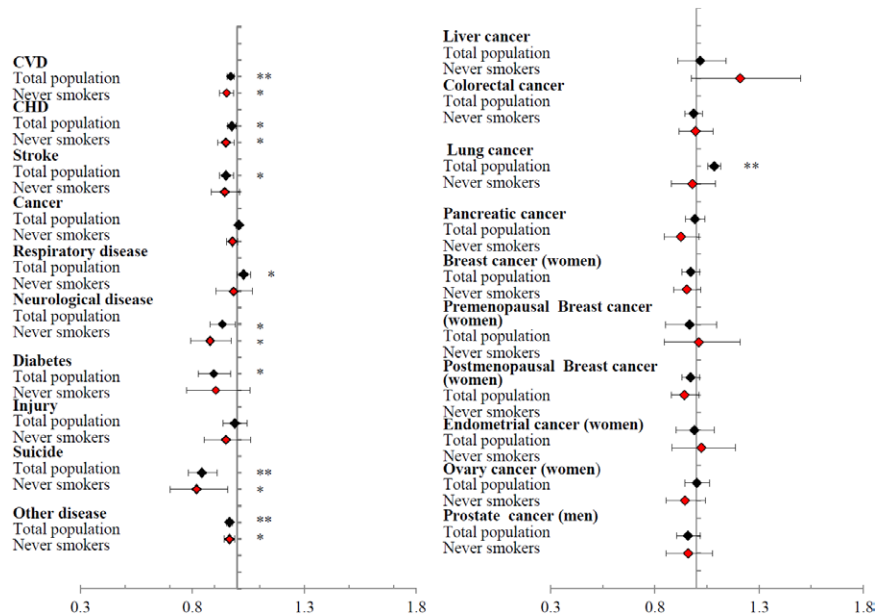
Variable	0	1.0 or Less Cups per Day	1.1–3.0 Cups per Day	3.1–5.0 Cups per Day	More Than 5.0 Cups per Day	*P* for Nonlinearity*
CVD mortality (2587 cases)						
Multivariate-adjusted model	1.00	0.95 (0.85–1.07)	0.94 (0.84–1.05)	0.81 (0.70–0.95)	0.91 (0.71–1.17)	0.77
CHD mortality (1815 cases)						
Multivariate-adjusted model	1.00	0.90 (0.78–1.03)	0.90 (0.79–1.03)	0.81 (0.68–0.98)	0.89 (0.66–1.20)	0.90
Stroke mortality (656 cases)						
Multivariate-adjusted model	1.00	1.04 (0.82–1.31)	1.01 (0.80–1.27)	0.76 (0.56–1.04)	0.93 (0.56–1.54)	0.81
Cancer mortality (3664 cases)						
Multivariate-adjusted model	1.00	0.99 (0.90–1.09)	0.99 (0.90–1.08)	0.88 (0.77–0.99)	0.84 (0.68–1.03)	0.34
Colorectal cancer mortality (380 cases)						
Multivariate-adjusted model	1.00	0.88 (0.65–1.19)	0.92 (0.69–1.23)	0.92 (0.63–1.33)	0.94 (0.51–1.75)	0.78
Lung cancer mortality (217 cases)						
Multivariate-adjusted model	1.00	1.11 (0.73–1.69)	1.14 (0.76–1.71)	1.15 (0.70–1.90)	0.89 (0.37–2.12)	0.32
Pancreatic cancer mortality (321 cases)						
Multivariate-adjusted model	1.00	1.47 (1.04–2.06)	1.10 (0.78–1.55)	1.06 (0.69–1.62)	0.41 (0.15–1.14)	0.056
Breast cancer mortality (567 cases)						
Multivariate-adjusted model	1.00	0.96 (0.76–1.22)	0.91 (0.72–1.14)	0.79 (0.58–1.07)	0.62 (0.36–1.09)	0.84
Premenopausal breast cancer mortality (77 cases)						
Multivariate-adjusted model	NA					
Postmenopausal breast cancer mortality (490 cases)						
Multivariate-adjusted model	1.00	0.94 (0.72–1.21)	0.83 (0.64–1.07)	0.79 (0.57–1.08)	0.67 (0.38–1.18)	0.57
Ovary cancer mortality (250 cases)						
Multivariate-adjusted model	1.00	0.73 (0.50–1.05)	0.85 (0.61–1.19)	0.51 (0.31–0.83)	0.63 (0.30–1.33)	0.71
Endometrial cancer mortality (115 cases)						
Multivariate-adjusted model	1.00	0.99 (0.55–1.80)	1.24 (0.72–2.15)	0.90 (0.43–1.85)	2.17 (0.94–5.05)	0.26
Prostate cancer mortality (210 cases)						
Multivariate-adjusted model	1.00	0.75 (0.51–1.10)	0.87 (0.59–1.28)	0.74 (0.42–1.29)	0.83 (0.30–2.35)	0.42
Respiratory disease mortality (385 cases)						
Multivariate-adjusted model	1.00	0.91 (0.67–1.23)	0.88 (0.66–1.19)	0.94 (0.65–1.36)	0.62 (0.30–1.31)	0.31
Neurological disease mortality (243 cases)						
Multivariate-adjusted model	1.00	0.91 (0.62–1.32)	0.80 (0.55–1.15)	0.63 (0.39–1.01)	0.79 (0.38–1.62)	0.83
Diabetes mortality (128 cases)						
Multivariate-adjusted model	1.00	0.96 (0.59–1.56)	0.67 (0.40–1.11)	0.76 (0.38–1.49)	0.76 (0.26–2.20)	0.19
Injury mortality (233 cases)						
Multivariate-adjusted model	1.00	1.01 (0.70–1.46)	0.90 (0.62–1.31)	0.71 (0.42–1.22)	1.28 (0.62–2.65)	0.28
Suicide mortality (134 cases)						
Multivariate-adjusted model	1.00	1.36 (0.88–2.10)	0.73 (0.45–1.21)	0.64 (0.30–1.35)	0.80 (0.24–2.65)	0.58
Other disease mortality (3108 cases)						
Multivariate-adjusted model	1.00	0.86 (0.77–0.95)	0.81 (0.73–0.90)	0.81 (0.71–0.93)	0.94 (0.76–1.16)	0.011

The model was adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes mellitus), BMI (<20.9, 21.0–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m²), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 MET-h/wk), overall dietary pattern (aHEI score, in quintiles), total energy intake (quintiles), sugar-sweetened beverage consumption (quintiles), and alcohol consumption (0, 0–5, 5–10, 10–15, ≥15 g/d). We additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (yes vs no) for women. Caffeinated and decaffeinated coffee adjusted for each other. aHEI indicates alternative healthy eating index; BMI, body mass index; CHD, congenital heart defect; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; and NA, not applicable.

*A likelihood ratio test was performed.

moderate coffee consumption being associated with lower mortality risk and high coffee consumption not being associated with mortality risk. Given that this association became linear and inverse after restricting it to never smokers, it is likely that the nonlinear association observed in the total population was attributed to the residual confounding by smoking. This was further strengthened by the observation that the positive association between coffee consumption and death attributed to lung cancer and respiratory diseases in the overall population, for both of which smoking is an

Figure 2. The association of a 1-cup-per-day increment in coffee consumption with risk of cause-specific mortality pooled across the 3 cohorts. The black squares stand for the overall population. The red squares stand for never smokers. *$P<0.05$, **$P<0.001$. Multivariate-adjusted models adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes mellitus), body mass index (BMI; <20.9, 21.0–22.9, 23.0–24.9, 25.0–29.9, 30.0–34.9, ≥35.0 kg/m²), physical activity (<3.0, 3.0–8.9, 9.0–17.9, 18.0–26.9, ≥27.0 metabolic equivalents-h/wk), smoking status (never, former [1–4 cigarettes per day], former [5–14 cigarettes per day], former [15–24 cigarettes per day], former [25–34 cigarettes per day], former [35–44 cigarettes per day], former [45 or more cigarettes per day], former [unknown cigarettes per day], current [1–4 cigarettes per day], current [5–14 cigarettes per day], current [15–24 cigarettes per day], current [25–34 cigarettes per day], current [35–44 cigarettes per day], current [45 or more cigarettes per day], current [unknown cigarettes per day]), overall dietary pattern (Alternate Healthy Eating Index score, in quintiles), total energy intake (quintiles), sugar-sweetened beverages consumption (quintiles), and alcohol consumption (0, 0–5, 5–10, 10–15, ≥15 g/d). We additionally adjusted for menopausal status (yes vs no) and postmenopausal hormone use (yes vs no) for women. Caffeinated and decaffeinated coffee adjusted for each other.

important risk factor, disappeared when restricting to never smokers. The inverse association between coffee consumption and risk of mortality did not change substantially when using a weighted Cox model among never smokers, excluding the possibility that the different associations in overall population and never smokers were because of the different compositions of total mortality. For both caffeinated and decaffeinated coffee consumption, the nonlinear associations in the total population and the inverse associations among the never smokers decreased the possibility that the nonlinear association was because of the biological effect of caffeine.

Our results for the associations between coffee consumption and cause-specific mortality are consistent with the associations between coffee consumption and cause-specific diseases from previous studies. Numerous prospective cohort studies have shown coffee consumption to be associated with lower risk of type 2 diabetes mellitus.[1] There are several plausible biological mechanisms that could explain this observation. The chlorogenic acid, lignans, quinides, trigonelline, and magnesium in coffee reduce insulin resistance and systematic inflammation.[30–35] Chlorogenic acid may have this putative effect by reducing glucose absorption in the intestine by competitively inhibiting glucose-6-phosphate translocase and reducing sodium-dependent glucose transport in the brush border membrane vesicles[36]; by reducing oxidative stress as a result of its antioxidant properties; and by reducing liver glucose output.[37] In our study, an inverse association between coffee drinking and risk of mortality because of CVD was observed. Given that diabetes mellitus and CVD share common disease pathways, the mechanism of inverse association between coffee consumption and risk of CVD mortality might be similar to that for diabetes mortality. Studies have also shown coffee consumption to be associated with a lower risk of Parkinson's diseases,[6,38,39] which is consistent with our finding of an inverse association between coffee consumption and risk of neurologic mortality. In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxin model of Parkinson's diseases, caffeine was shown to attenuate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine–induced striatal dopamine loss, striatal dopamine transporter binding sites loss, and dopaminergic neurons loss, which might be mediated through A_{2A} adenosine receptors.[40] Three published cohort studies have shown an inverse association between coffee consumption and risk of suicide[17,41,42]; however, 1 study showed a J-shaped association where heavy coffee consumption was associated with a higher risk of suicide.[43] Our study had shown an inverse association of both caffeinated and decaffeinated coffee consumption with risk of suicide in both the whole population and never smokers, indicating that coffee consumption might have antidepressant effects. Studies have shown an inverse association between coffee consumption and risk of liver diseases or risk of mortality because of liver diseases[2,44–47]; however, no association of coffee consumption with risk of mortality because of liver diseases was found in our study, which might be because of the limited power given the small

number of cases. Previous cohort studies showed no association between coffee consumption and risk of colorectal cancer,[48,49] which was consistent with our results.

Our results showed similar associations of caffeinated and decaffeinated coffee consumption with risk of total and cause-specific mortality in both the overall population and never smokers, further showing that other components in coffee than caffeine might play a beneficial role mediating the association between long-term coffee consumption and risk of mortality. However, short-term metabolic studies have shown that caffeine could acutely increase blood pressure by antagonizing the adenosine A1 and A2A receptors[50–52] and could also acutely adversely affect arterial stiffness and endothelium-dependent vasodilation.[53,54] Case crossover studies showed that coffee consumption transiently increased the risk of nonfatal myocardial infarction, ischemic stroke onset, and sudden cardiac death.[55–57] One cohort study assessed the association of coffee consumption with total mortality in subsequent 2 years among CVD participants, and no association was found.[14] However, it is still difficult to differentiate acute effects from long-term effects of habitual coffee consumption.

Our analysis has several strengths. The large sample size, long follow-up time, and large number of deaths provided sufficient power to detect a nonlinear association in the overall population and to perform further analyses among never smokers. The large number of deaths also allowed us to conduct analyses on cause-specific mortality. In addition, we had detailed measures of both caffeinated and decaffeinated coffee consumption, as well as other dietary and lifestyle factors.

Several potential limitations also need to be considered. First, given the observational nature of the study design, we could not directly establish a cause-effect relationship between coffee and mortality. Second, assessment of coffee intake was based on FFQs and thus measurement errors are inevitable. However, our validation studies have demonstrated high validity (Pearson correlation = 0.74) of the coffee intake by the FFQs as compared with multiple-week diet records and high reproducibility (Pearson correlation = 0.80) by comparing 2 consecutive FFQs.[26] Moreover, coffee intake was also one of the food items showing the highest validity and reproducibility by the FFQs in Europe[58] and Asia,[59,60] indicating that coffee was a beverage less prone to misreporting. In addition, the use of the repeated measures of diet not only represented long-term habitual intake but also reduced the influences of measurement errors. Finally, because our cohort participants are composed of medical and health professionals and the majority of them are white, the results may not be generalizable to other populations.

In conclusion, regular consumption of coffee was inversely associated with risk of total mortality and mortality attributed to CVD and neurologic disease. Similar associations of caffeinated and decaffeinated coffee consumption with risk of total and cause-specific mortality were found. Results from this and previous studies indicate that coffee consumption can be incorporated into a healthy lifestyle.

Disclosures

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CLINICAL PERSPECTIVE

In 2014, we published a meta-analysis in *Circulation* (2014;129:643–659) showing that coffee consumption was nonlinearly associated with risk of cardiovascular disease (CVD): moderate coffee consumption was associated with lower risk of CVD, with the lowest CVD risk at 3 to 5 cups per day, and heavy coffee consumption was not associated with risk of CVD. However, whether the nonlinear association was because of a true biological effect or confounding of smoking is not known. In the current study, with 208 501 participants and 31 956 deaths in 3 large cohort studies, we prospectively examined the associations of coffee consumption with total mortality and cause-specific mortality. Our results showed a nonlinear association of coffee consumption with total mortality in the whole population. When restricting to never smokers, coffee consumption was associated with lower risk of total mortality and mortality attributed to CVD, neurologic diseases, and suicide. No association of coffee consumption with cancer mortality was found. The present study provides strong evidence that long-term heavy consumption of coffee is not associated with risk of mortality and the nonlinear association of coffee with total mortality might be because of the confounding of smoking.

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