

Association of Coffee Consumption with Total and Cause-Specific Mortality in Three Large Prospective Cohorts

Running title: *Ding et al.; Coffee and Total and Cause-specific Mortality*

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Abstract

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 NHS 2, and 40,557 men in the Health Professionals Follow-up Study. Coffee consumption was assessed at baseline using a semi-quantitative 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 non-linearly associated with mortality. Compared to non-drinkers, coffee consumption one to five cups/d was associated with lower risk of mortality, while coffee consumption more than five cups/d was not associated with risk of mortality. However, when restricting to never smokers, compared to non-drinkers, the HRs of mortality were 0.94 (0.89 to 0.99) for ≤ 1 cup/d, 0.92 (0.87 to 0.97) for 1.1-3 cups/d, 0.85 (0.79 to 0.92) for 3.1-5 cups/d, and 0.88 (0.78 to 0.99) for > 5 cups/d (p for non-linearity = 0.32; p for trend < 0.001). Significant inverse associations were observed for caffeinated (p for trend < 0.001) and decaffeinated coffee (p for trend = 0.022). Significant inverse associations were observed between coffee consumption and deaths due to cardiovascular disease, neurological 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.

Key words: mortality; cardiovascular disease prevention

Introduction

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 ¹, liver cancer ², endometrial cancer ³, lethal prostate cancer ⁴, basal cell carcinoma of the skin ⁵, and neurological diseases ⁶, as well as with risk of cardiovascular disease (CVD) when consumed in moderation ⁷.

The association between coffee consumption and risk of total mortality has also been investigated. Recent studies showed 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 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.

Based on the results of previous studies, four questions remain unanswered: first, does a non-linear relationship exist between coffee consumption and risk of mortality, i.e., 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 non-linear association exists, is it truly a biological effect of coffee or is it an artifact due to 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 three 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 6,888 total deaths and extended to a younger cohort of nurses (Nurses' Health Study II). These cohorts provide measures of caffeinated and decaffeinated coffee consumption, extensive data on known or suspected confounders, and up to 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 30-55 y 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 25-42 y 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 40-75 y at baseline. The male participants returned a baseline questionnaire about detailed medical history, lifestyle, and usual diet. In all three cohorts, questionnaires were collected at baseline and biennially thereafter, to update information on lifestyle factors and the occurrence of chronic diseases. All of the three cohorts consist of approximate 95% Caucasians.

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 further 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 was collected every four years from the NHS II participants starting in 1991 and from the HPFS participants starting in 1986. In all 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 has been described in detail elsewhere²⁴⁻²⁷. 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 one year period²⁶. As mean coffee consumption did not change in NHS 2 and decreased slightly in NHS and HPFS over time (**Supplemental figure 1**), 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, and self-reported diagnosis of diseases, including hypertension, hypercholesterolemia, CVD, and cancer. For NHS and NHS 2 participants, we also ascertained data on menopausal status and postmenopausal hormone use. We calculated the Alternate Healthy Eating Index (aHEI) as an overall measure of diet quality using FFQ data²⁸.

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 more than 98% of the deaths in each cohort²⁹. A physician who was blinded to data on coffee consumption and other risk factors reviewed death certificates and medical records to classify the cause of death according to the eighth and ninth revisions of the *International Classification of Diseases*. Deaths were grouped into nine major categories (**Supplemental Table 1**).

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 (31 December 2012 for the NHS, 31 December 2012 for the NHS 2, and 31 December 2012 for the HPFS), whichever came first. We used Cox proportional hazards regression models to examine the association between coffee consumption (five categories) and risk of mortality. The regression models included calendar time in 2-y intervals as the time scale, and were stratified by age in years. In the multivariable analysis, we further adjusted for body mass index (BMI), physical activity, overall dietary pattern (aHEI), 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 status in both men and women, and 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 non-linear association between coffee consumption and risk of mortality, a likelihood ratio test (LRT) was used comparing the model with only the linear term of coffee consumption to the model with both the linear and the cubic spline terms, with *P* value < 0.05 denoting significant non-linearity. All 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 BMI ($\leq 25 \text{ kg/m}^2$, $> 25 \text{ kg/m}^2$), age ($\leq 70\text{y}$, $> 70\text{y}$), aHEI (\leq median score, $>$ median score), physical activity (\leq median, $>$ median), smoking status (never smokers, ever smokers), sex (male, 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 (LRT) 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 statistical tests were 2-sided and performed using SAS version 9.2 for UNIX (SAS Institute Inc).

Results

Coffee Consumption and Dietary and Lifestyle Factors

The percentages of never coffee drinkers were 12% in NHS, 30% in NHS 2, and 17% in HPFS. The percentages of those who drank more than 5 cups/d were 8% in NHS, 3% in NHS 2, 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 2, and HPFS respectively, while the proportions of never smokers among those who drank more than 5 cups/d were 24%, 35%, and 25% in NHS, NHS 2, 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 2, we documented 2,056 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 three 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 three 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 non-linear association between consumption of total, caffeinated, and decaffeinated coffee and all-cause mortality (P values for non-linearity using LRT < 0.001 ; P values for non-linear trend < 0.001) (**Table 2**). Relative to no consumption of coffee, the pooled

hazard ratio for death was 0.95 (95% CI: 0.91 to 0.99) for ≤ 1 cup of total coffee per day, 0.91 (95% CI: 0.88 to 0.95) for 1.1 - 3 cups per day, 0.93 (95% CI: 0.89 to 0.97) for 3.1 - 5 cups per day, and 1.02 (95% CI: 0.96 to 1.07) for > 5 cups per day. Similar results were found when caffeinated and decaffeinated coffee was examined separately. Examining the three cohorts individually, the non-linear associations between consumption of total coffee, caffeinated coffee, and decaffeinated coffee and risk of all-cause mortality were most pronounced in NHS (**Table 2, Supplemental figures 2 - 4**).

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

Coffee Consumption and Cause-specific Mortality

The association between coffee consumption and leading causes of mortality was further investigated (**Supplemental table 2**). In the whole population, coffee consumption was inversely associated with risk of mortality due to CVD, non-linearly associated with risk mortality due to type 2 diabetes, and positively associated with risks of mortality due to lung cancer and respiratory diseases (**Supplemental table 3**). However, when restricting to never smokers, coffee consumption was no longer associated with risk of mortality due to lung cancer and respiratory disease, but was inversely associated only with risks of mortality due to CVD, neurological

disease, and suicide. No associations of coffee consumption with risks of mortality due 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 due to lung cancer ($P < 0.0001$) and respiratory disease ($P < 0.05$), and inversely associated with mortality due to CHD, stroke, neurological disease, and type 2 diabetes ($P < 0.05$). However, after restricting to never smokers, the positive association disappeared for lung cancer and respiratory disease and significant inverse associations remained for mortality due to CHD, neurological disease, and suicide ($P < 0.05$) (**Figure 2**).

Stratified Analysis

Significant interactions were found between coffee consumption and risk of mortality by age (P for interaction = 0.003) and smoking (P for interaction = 0.015) (**Supplemental table 4**). 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 aHEI score, BMI, physical activity, sex, and cohort.

The proportional hazard assumption was violated in NHS (but not in NHS 2 or HPFS), with a stronger association between coffee consumption and mortality in earlier time intervals. However, non-linear associations between coffee consumption and risk of mortality were found in both subgroups stratified by time interval in NHS (**Supplemental table 5**). We further assessed the proportional hazard assumption among never smokers in NHS, and the proportional hazard assumption was no longer violated (P 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, 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 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 (**Supplemental table 6-7, Supplemental figure 5 - 9**).

To further evaluate whether the change of the association from non-linear in the whole population to inverse linear among never smokers was due 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 (**Supplemental table 8**).

Discussion

In this analysis of three large ongoing cohort studies, we observed a non-linear association between coffee consumption and risk of mortality in the overall population, with 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 to never smokers, it is likely that the non-linear association observed in the total population was due to the residual confounding by smoking. This was further strengthened by the observation that the positive association between coffee consumption and death due to lung

cancer and respiratory diseases in the overall population, for both of which smoking is an 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 due to the different composition of total mortality. For both caffeinated and decaffeinated coffee consumption, the non-linear associations in the total population and the inverse associations among the never smokers decreased the possibility that the non-linear association was due to 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 diabetes¹. 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, 31}
³²⁻³⁴³⁵. 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 vesicles³⁶; by reducing oxidative stress as a result of its antioxidant properties; and by reducing liver glucose output³⁷. In our study, an inverse association between coffee drinking and risk of mortality due to CVD was observed. Given that diabetes 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 (PD)^{6, 38, 39}, which is consistent with our finding of an inverse association between coffee consumption and risk of neurological mortality. In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) neurotoxin model of PD, caffeine was shown to attenuate MPTP - induced striatal dopamine loss, striatal dopamine transporter binding sites loss, and dopaminergic neurons loss, which might be mediated through A_{2A} adenosine receptors⁴⁰. Three published cohort studies have shown an inverse association between coffee consumption and risk of suicide^{17, 41, 42}, however, one study showed a J-shaped association where heavy coffee consumption was associated with a higher risk of suicide⁴³. 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 due to liver diseases^{2, 44-47}, however, no association of coffee consumption with risk of mortality due to liver diseases was found in our study, which might be due to 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 besides 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 A_{2A} receptor⁵⁰⁻⁵², 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 death⁵⁵⁻⁵⁷. One cohort study assessed the association of coffee consumption with total mortality in subsequent 2 years among CVD participants, and no association was found¹⁴. 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 a large number of deaths provided sufficient power to detect a non-linear 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 to multiple week diet records, and high reproducibility (Pearson correlation = 0.80) by comparing two consecutive FFQs²⁶. Moreover, coffee intake was also one of the food items showing the highest validity and reproducibility by the FFQs in Europe⁵⁸ 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, since our cohort participants comprise medical and health professionals and the vast 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 due to CVD, and neurological 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.

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Circulation

Clinical Perspective

In 2014, we published a meta-analysis on *Circulation* (2014; 129: 643-659) showing that coffee consumption was non-linearly 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 non-linear association was due to a true biological effect or confounding of smoking is not known. In the current study, with 208,501 participants and 31,956 deaths in three large cohort studies, we prospectively examined the associations of coffee consumption with total mortality and cause-specific mortality. Our results showed a non-linear 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 due to CVD, neurological 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 non-linear association of coffee with total mortality might be due to the confounding of smoking.

Table 1. Age-adjusted baseline characteristics of participants by frequency of total coffee consumption (including caffeinated and decaffeinated coffee) in NHS, NHS 2, and HPFS.

	NHS (1984)					NHS 2 (1991)					HPFS (1986)				
	0	≤1	1.1 - 3	3.1-5	>5	0	≤1	1.1 - 3	3.1-5	>5	0	≤1	1.1 - 3	3.1-5	>5
Cups/d	0	≤1	1.1 - 3	3.1-5	>5	0	≤1	1.1 - 3	3.1-5	>5	0	≤1	1.1 - 3	3.1-5	>5
N	9,233	14,740	30,420	14,760	5,737	27,888	22,837	29,239	10,049	3,041	6,863	11,402	14,264	5,861	2,167
Age (year)	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/d)	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/d)	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 (serving/d)	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 (grams/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 (serving/d)	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 (serving/d)	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 (serving/d)	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 (serving/d)	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 (serving/d)	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/m ²)	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: alternative healthy eating index; BMI: body mass index.

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

Table 2. HRs (95% CI) for the association between consumption of total coffee, caffeinated coffee, and decaffeinated coffee and risk of mortality

Total coffee								
Intake (cups/d)	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	Per cup increase	P for non-linearity*	P for linear trend
Cases/Person-time	4,166/ 958,267	7,826/ 1,086,683	12,198/ 1,681,922	5,456/ 709,646	2,310/ 253,554			
<i>NHS</i>								
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
<i>NHS 2</i>								
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
<i>HPFS</i>								
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
<i>Pooled</i>								
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								
Intake (cups/d)	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	Per cup increase	P for non-linearity*	P for linear trend
Cases/Person-time	8,615/ 1,454,869	10,105/ 1,404,192	8,495/ 1,255,722	3,304/ 419,049	1,437/ 156,238			

<i>NHS</i>								
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
<i>NHS 2</i>								
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
<i>HPFS</i>								
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
<i>Pooled</i>								
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								
Intake (mg/d)	0	≤ 1 cup/d	1.1-3 cups/d	>3 cups/d		Per cup increase	P for non-linearity*	P for linear trend
Cases/Person-time	16,393/ 2,607,891	10,637/ 1,516,930	3,777/ 445,908	1,149/ 119,341				
<i>NHS</i>								
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
<i>NHS 2</i>								
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
<i>HPFS</i>								
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
<i>Pooled</i>								
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

* A likelihood ratio test was performed.

Multivariate-adjusted model: further adjusted for baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (aHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former (1 - 4 cigarettes/d), former (5 - 14 cigarettes/d), former (15 - 24 cigarettes/d), former (25 - 34 cigarettes/d), former (35 - 44 cigarettes/d), former (≥ 45 cigarettes/d), former (unknown cigarettes/d), current (1 - 4 cigarettes/d), current (5 - 14 cigarettes/d), current (15 - 24 cigarettes/d), current (25 - 34 cigarettes/d), current (35 - 44 cigarettes/d), current (≥ 45 cigarettes/d), current (unknown cigarettes/d)), 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.

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.

Total coffee								
Intake (cups/d)	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	Per cup increase	P for non-linearity*	P for linear trend
Cases/Person-time	2,190/ 704,010	3,032/ 638,687	3,759/ 779,966	1,211/ 262,069	313/ 67,238			
<i>NHS</i>								
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
<i>NHS 2</i>								
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
<i>HPFS</i>								
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
<i>Pooled</i>								
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								
Intake (cups/d)	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	Per cup increase	P for non-linearity*	P for linear trend
Cases/Person-time	3,702/ 962,732	3,637/ 771,531	2,409/ 542,629	595/ 138,375	162/ 36,700			
<i>NHS</i>								
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
<i>NHS 2</i>								
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

<i>HPFS</i>								
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
<i>Pooled</i>								
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								
Intake (mg/d)	0	≤ 1 cup/d	1.1-3 cups/d	>3 cups/d		Per cup increase	P for non-linearity*	P for linear trend
Cases/Person-time	5,436/ 1,423,563	3,775/ 799,017	1,084/ 191,219	210/ 38,171				
<i>NHS</i>								
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
<i>NHS 2</i>								
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
<i>HPFS</i>								
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
<i>Pooled</i>								
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

* A likelihood ratio test was performed.

Multivariate-adjusted model: further adjusted for baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (AHEI 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.

Table 4. Multivariate HRs (95% CI) for the association between consumption of total coffee and risk of cause-specific mortality among never smokers.

	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	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
<i>CHD mortality (1815 cases)</i>						
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
<i>Stroke mortality (656 cases)</i>						
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
<i>Colorectal cancer mortality (380 cases)</i>						
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
<i>Lung cancer mortality (217 cases)</i>						
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
<i>Pancreatic cancer mortality (321 cases)</i>						
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
<i>Breast cancer mortality (567 cases)</i>						
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
<i>Premenopausal breast cancer mortality (77 cases)</i>						
Multivariate-adjusted model	NA					
<i>Postmenopausal breast cancer mortality (490 cases)</i>						
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

<i>Ovary cancer mortality (250 cases)</i>						
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
<i>Endometrial cancer mortality (115 cases)</i>						
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
<i>Prostate cancer mortality (210 cases)</i>						
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

* A likelihood ratio test was performed.

The model adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (AHEI 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.

Figure Legends:

Figure 1. The association between coffee consumption and risk of mortality in the overall population and among never smokers pooled across the three cohorts. 1a. Total coffee consumption and risk of mortality 1b. Caffeinated coffee consumption and risk of mortality 1c. Decaffeinated coffee consumption and risk of mortality. Multivariate-adjusted models adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), smoking status (never, former (1 - 4 cigarettes/d), former (5 - 14 cigarettes/d), former (15 - 24 cigarettes/d), former (25 - 34 cigarettes/d), former (35 - 44 cigarettes/d), former (≥ 45 cigarettes/d), former (unknown cigarettes/d), current (1 - 4 cigarettes/d), current (5 - 14 cigarettes/d), current (15 - 24 cigarettes/d), current (25 - 34 cigarettes/d), current (35 - 44 cigarettes/d), current (≥ 45 cigarettes/d), current (unknown cigarettes/d)), overall dietary pattern (AHEI 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.

Figure 2. The association of a 1-cup per day increment in coffee consumption with risk of cause-specific mortality pooled across the three cohorts. The black squares stand for the overall population. The red squares stand for never smokers. * P value < 0.05. ** P value < 0.001. Multivariate-adjusted models adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²),

physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, \geq 27 MET-h/wk), smoking status (never, former (1 - 4 cigarettes/d), former (5 - 14 cigarettes/d), former (15 - 24 cigarettes/d), former (25 - 34 cigarettes/d), former (35 - 44 cigarettes/d), former (\geq 45 cigarettes/d), former (unknown cigarettes/d), current (1 - 4 cigarettes/d), current (5 - 14 cigarettes/d), current (15 - 24 cigarettes/d), current (25 - 34 cigarettes/d), current (35 - 44 cigarettes/d), current (\geq 45 cigarettes/d), current (unknown cigarettes/d)), overall dietary pattern (AHEI score, in quintiles), total energy intake (quintiles), sugar-sweetened beverages consumption (quintiles) and alcohol consumption (0, 0-5, 5-10, 10-15, \geq 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.



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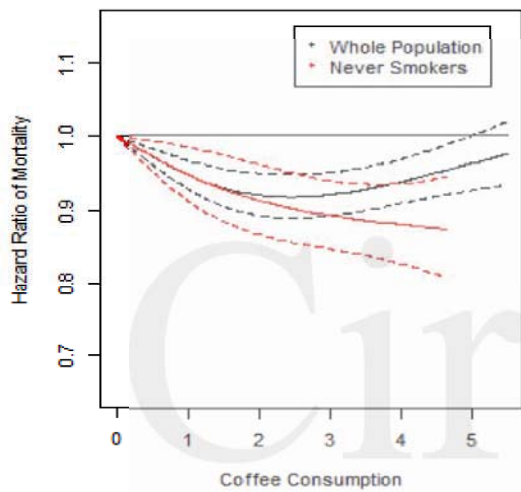


Figure 1a

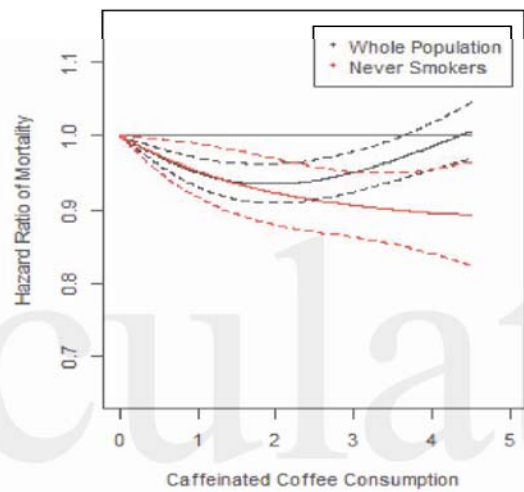


Figure 1b

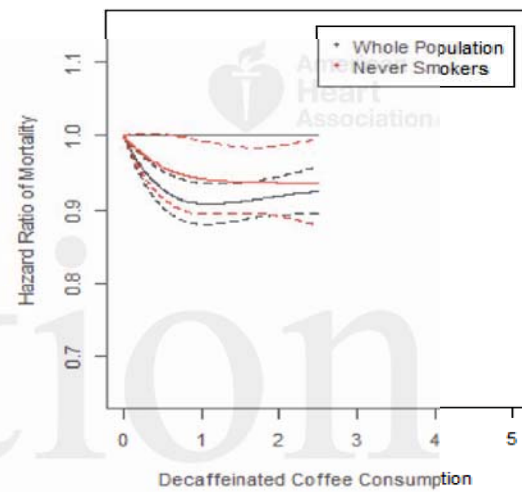


Figure 1c

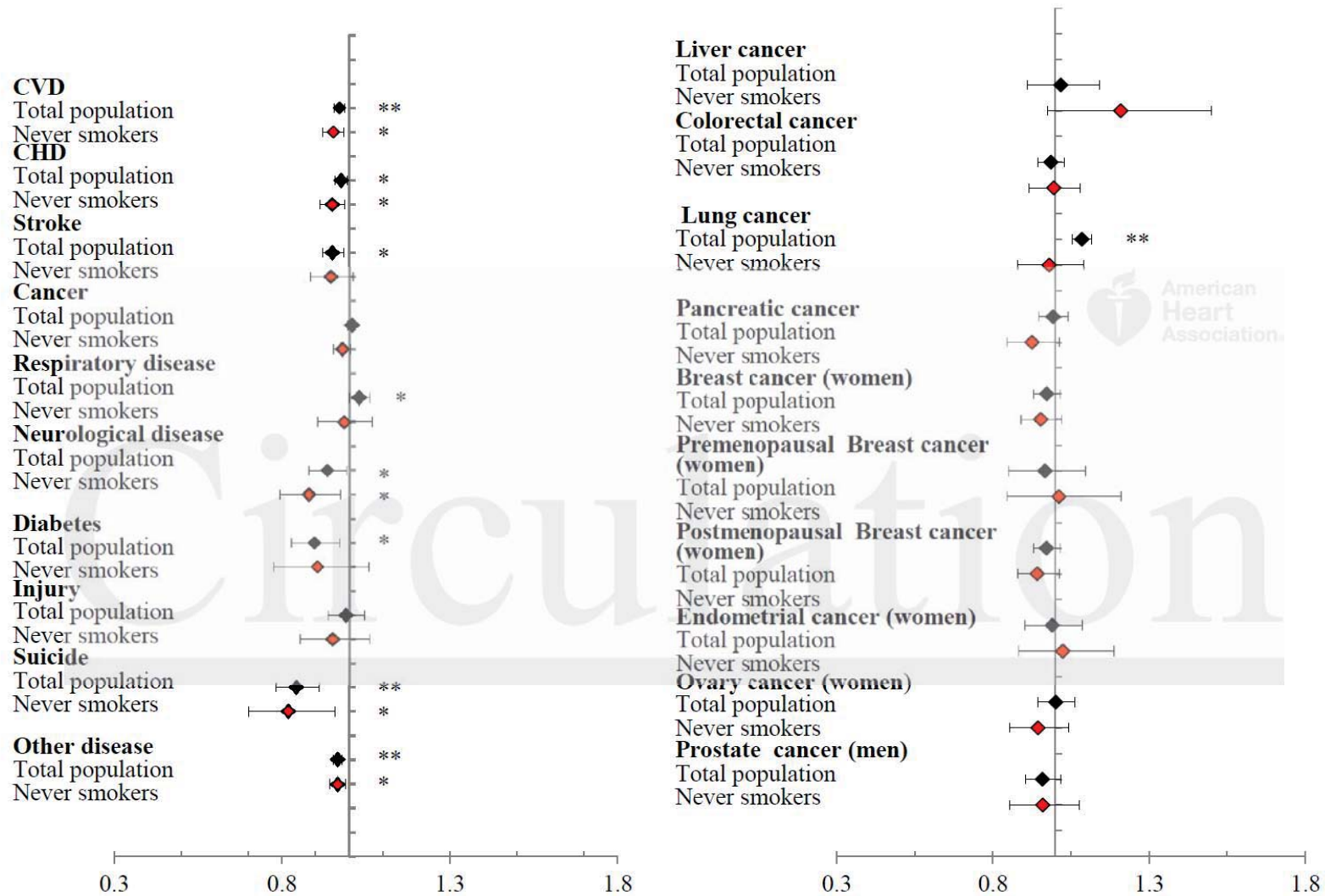


Figure 2.

Association of Coffee Consumption with Total and Cause-Specific Mortality in Three Large Prospective Cohorts

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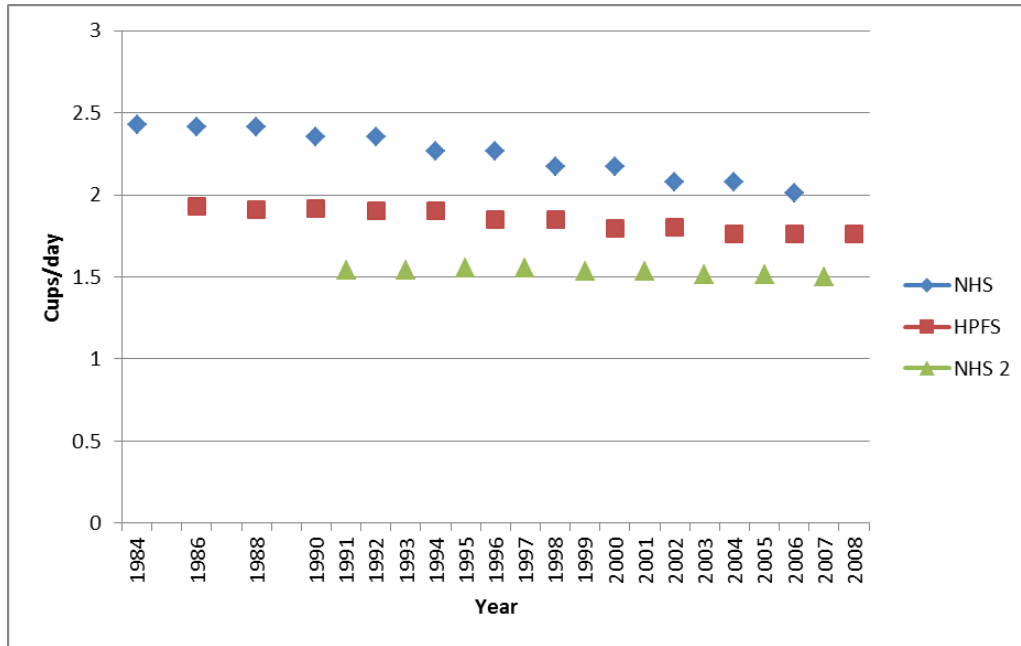
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SUPPLEMENTAL MATERIAL



Supplemental Figure 1. Mean coffee consumption in NHS, NHS 2, and HPFS over follow-up period.

Supplemental Table 1. Categories for causes of death.

Causes of death	ICD-8 code
Cardiovascular disease	390-458
Heart disease	390-429, 440-458
Stroke	430-438
Cancer	140-207
Colorectal cancer	153, 154
Lung cancer	162
Pancreatic cancer	157
Breast cancer	174
Ovary cancer	183
Prostate cancer	185
Respiratory disease	460-519
Diabetes	250
Neurological disease	290, 340, 342, 348
Injury	800-950, 959-999
Suicide	950-959
All other causes	The rest of the ICD codes

Supplemental Table 2. The disease composition of overall mortality.

	NHS	NHS 2	HPFS	Total population
Cardiovascular disease	3844	211	3781	7836
Coronary heart disease	2545	157	2966	5668
Stroke	1062	43	750	1855
Other diseases	4667	680	2925	8272
Respiratory disease	1383	52	924	2359
Injury	144	10	500	654
Neurological disease	460	48	22	530
Suicide	84	98	192	374
Type 2 diabetes	214	32	92	338
Renal disease	48	3	26	77
Cancer	6624	922	3970	11516
Lung cancer	1596	107	745	2448
Breast cancer	961	261	0	1222
Premenopausal breast cancer	42	83	0	125
Postmenopausal breast cancer	911	178	0	1089
Colorectal cancer	549	69	417	1035
Pancreatic cancer	487	49	338	874
Non-Hodgkin lymphoma	398	54	295	747
Prostate cancer	0	0	572	572
Ovary cancer	496	82	0	578
Brain cancer	195	58	167	420
Leukemia	193	30	175	398
Myeloma	162	7	145	314
Renal cell cancer	142	10	119	271
Bladder cancer	107	5	160	272
Skin cancer	105	26	126	257
Endometrial cancer	211	31	0	242
Esophagus cancer	71	5	133	209
Stomach cancer	102	9	87	198
Head and neck cancer	83	8	84	175

Liver cancer	72	5	60	137
Gall bladder cancer	89	13	32	134
Small intestine cancer	26	8	9	43
Cervix cancer	28	11	0	39
Hodgkin lymphoma	14	4	11	29
Total mortality	17,468	2,056	12,432	31,956

Supplemental Table 3. HRs (95% CI) for the association between consumption of total coffee and risk of cause-specific mortality

	0 cup/d	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	P non-linearity*
CVD mortality (7836 cases)	1.00	1.01 (0.93, 1.09)	0.95 (0.87, 1.01)	0.88 (0.81, 0.96)	1.02 (0.91, 1.14)	0.49
<i>CHD mortality (5668 cases)</i>	1.00	0.98 (0.90, 1.07)	0.92 (0.85, 1.01)	0.90 (0.81, 0.99)	1.03 (0.91, 1.17)	0.21
<i>Stroke mortality (1855 cases)</i>	1.00	1.05 (0.89, 1.23)	0.95 (0.81, 1.11)	0.81 (0.67, 0.97)	1.00 (0.79, 1.25)	0.89
Cancer mortality (11,516 cases)	1.00	1.01 (0.94, 1.08)	1.01 (0.95, 1.08)	1.03 (0.95, 1.10)	1.16 (1.06, 1.27)	0.88
<i>Colorectal cancer mortality (1,035 cases)</i>	1.00	1.03 (0.83, 1.28)	0.95 (0.77, 1.17)	0.95 (0.75, 1.20)	0.94 (0.69, 1.29)	0.91
<i>Lung cancer mortality (2448 cases)</i>	1.00	1.03 (0.86, 1.23)	1.15 (0.98, 1.36)	1.39 (1.17, 1.65)	1.82 (1.51, 2.19)	0.39
<i>Pancreatic cancer mortality (874 cases)</i>	1.00	1.35 (1.05, 1.72)	1.17 (0.92, 1.49)	1.08 (0.83, 1.42)	1.25 (0.89, 1.74)	0.64
<i>Liver cancer (137 cases)</i>	1.00	1.72 (0.89, 3.33)	1.37 (0.71, 2.61)	1.76 (0.88, 3.52)	0.62 (0.19, 1.94)	0.53
<i>Breast cancer mortality (1222 cases)</i>	1.00	0.97 (0.81, 1.18)	0.97 (0.81, 1.16)	0.92 (0.75, 1.14)	1.00 (0.77, 1.31)	0.50
<i>Postmenopausal breast cancer mortality (1089 cases)</i>	1.00	0.96 (0.78, 1.19)	0.94 (0.78, 1.14)	0.93 (0.74, 1.16)	1.05 (0.80, 1.39)	0.80
<i>Ovary cancer mortality (578 cases)</i>	1.00	0.72 (0.54, 0.97)	0.88 (0.68, 1.14)	0.82 (0.61, 1.10)	0.90 (0.62, 1.31)	0.73
<i>Endometrial Cancer (242 cases)</i>	1.00	1.11 (0.70, 1.75)	1.19 (0.78, 1.82)	1.12 (0.69, 1.82)	1.18 (0.63, 2.21)	0.17
<i>Prostate cancer mortality (572 cases)</i>	1.00	0.76 (0.59, 0.98)	0.76 (0.59, 0.98)	0.73 (0.54, 1.00)	0.50 (0.30, 0.85)	0.08
Respiratory disease mortality (2,359 cases)	1.00	0.90 (0.77, 1.05)	0.84 (0.73, 0.97)	1.04 (0.89, 1.22)	1.32 (1.10, 1.58)	< 0.001

Neurological disease mortality (530 cases)	1.00	0.91 (0.68, 1.21)	0.80 (0.61, 1.04)	0.69 (0.50, 0.95)	0.60 (0.38, 0.94)	0.17
Diabetes mortality (338 cases)	1.00	0.90 (0.65, 1.24)	0.59 (0.43, 0.82)	0.65 (0.43, 0.97)	0.57 (0.32, 1.01)	0.03
Injury mortality (654 cases)	1.00	0.88 (0.68, 1.13)	0.91 (0.71, 1.16)	0.84 (0.62, 1.12)	0.98 (0.67, 1.44)	0.58
Suicide (374 cases)	1.00	1.10 (0.81, 1.48)	0.76 (0.56, 1.03)	0.58 (0.39, 0.86)	0.54 (0.31, 0.92)	0.70
Other disease mortality (8,272 cases)	1.00	0.88 (0.82, 0.95)	0.80 (0.75, 0.86)	0.81 (0.74, 0.87)	0.79 (0.71, 0.88)	< 0.001

* A likelihood ratio test was performed.

The model adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (AHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former (1 - 4 cigarettes/d), former (5 - 14 cigarettes/d), former (15 - 24 cigarettes/d), former (25 - 34 cigarettes/d), former (35 - 44 cigarettes/d), former (≥ 45 cigarettes/d), former (unknown cigarettes/d), current (1 - 4 cigarettes/d), current (5 - 14 cigarettes/d), current (15 - 24 cigarettes/d), current (25 - 34 cigarettes/d), current (35 - 44 cigarettes/d), current (≥ 45 cigarettes/d), current (unknown cigarettes/d)), 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.

Supplemental Table 4. Stratified analysis for the association between coffee consumption and risk of total mortality

	Categories of total coffee consumption					P for interaction†
	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	
Stratified by age						0.003
<i>Age ≤ 70 years</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.97 (0.92-1.03)	0.87 (0.83-0.92)	0.86 (0.81-0.92)	0.96 (0.88-1.04)	
<i>Age > 70 years</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.96 (0.91-1.01)	0.93 (0.89-0.98)	0.95 (0.89-1.00)	1.06 (0.99-1.14)	
Stratified by BMI						0.076
<i>BMI ≤ 25 kg/m²</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.93 (0.88-0.99)	0.92 (0.87-0.97)	0.93 (0.87-0.99)	1.03 (0.95-1.11)	
<i>BMI > 25 kg/m²</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.97 (0.92-1.02)	0.90 (0.86-0.95)	0.91 (0.86-0.97)	0.98 (0.91-1.05)	
Stratified by aHEI						0.96
<i>aHEI ≤ median level</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.95 (0.90-1.00)	0.90 (0.86-0.95)	0.92 (0.87-0.98)	1.00 (0.93-1.07)	
<i>aHEI > median level</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.95 (0.90-1.01)	0.92 (0.87-0.97)	0.94 (0.88-1.00)	1.04 (0.96-1.13)	
Stratified by physical activity						0.20
<i>Physical activity ≤ median level</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.91 (0.87-0.96)	0.88 (0.84-0.92)	0.92 (0.87-0.97)	1.00 (0.93-1.07)	

<i>Physical activity > median level</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	1.01 (0.94-1.07)	0.96 (0.91-1.02)	0.95 (0.88-1.02)	1.06 (0.97-1.16)	
Stratified by smoking status						< 0.001
<i>Never</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.94 (0.89-1.00)	0.92 (0.87-0.97)	0.85 (0.79-0.92)	0.88 (0.78-0.99)	
<i>Ever</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.96 (0.91-1.01)	0.92 (0.87-0.97)	0.96 (0.91-1.01)	1.04 (0.98-1.11)	
Stratified by sex						0.39
<i>Female</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.93 (0.88-0.97)	0.89 (0.85-0.93)	0.93 (0.88-0.98)	1.02 (0.95-1.08)	
<i>Male</i>						
Multivariate-adjusted hazard ratio (95% CI)	1.00	1.00 (0.94, 1.06)	0.97 (0.91, 1.03)	0.96 (0.90, 1.03)	1.05 (0.96, 1.14)	
Stratify by individual cohort (cohort effect)						
NHS						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.94 (0.88, 1.00)	0.90 (0.85, 0.95)	0.92 (0.88, 0.98)	1.02 (0.96, 1.10)	
NHS 2						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.92 (0.81, 1.04)	0.85 (0.75, 0.95)	0.86 (0.73, 1.01)	0.97 (0.78, 1.20)	
HPFS						

Multivariate-adjusted hazard ratio (95% CI)	1.00	1.00	0.97	0.96	1.05
		(0.94, 1.06)	(0.91, 1.03)	(0.90, 1.03)	(0.96, 1.14)

Abbreviations: CI, confidence interval; BMI, body mass index; aHEI, alternative health eating index

* Models were adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (AHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former (1 - 4 cigarettes/d), former (5 - 14 cigarettes/d), former (15 - 24 cigarettes/d), former (25 - 34 cigarettes/d), former (35 - 44 cigarettes/d), former (≥ 45 cigarettes/d), former (unknown cigarettes/d), current (1 - 4 cigarettes/d), current (5 - 14 cigarettes/d), current (15 - 24 cigarettes/d), current (25 - 34 cigarettes/d), current (35 - 44 cigarettes/d), current (≥ 45 cigarettes/d), current (unknown cigarettes/d)), 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.

* † Likelihood ratio tests were performed.

Supplemental Table 5. The tests of proportional hazard assumption in NHS, NHS 2, and HPFS.

	Categories of total coffee consumption					P _{interaction} †
	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	
Stratified by follow-up time in NHS						< 0.001
< 20 years						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.93 (0.85, 1.02)	0.87 (0.80, 0.94)	0.84 (0.76, 0.92)	0.89 (0.79, 0.99)	
≥ 20 years						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.94 (0.87, 1.01)	0.93 (0.87, 0.99)	1.00 (0.92, 1.07)	1.12 (1.02, 1.22)	
Stratified by follow-up time in NHS2						0.49
< 14 years						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.92 (0.74, 1.13)	0.99 (0.81, 1.21)	0.96 (0.74, 1.25)	1.04 (0.72, 1.48)	
≥ 14 years						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.91 (0.78, 1.06)	0.78 (0.67, 0.91)	0.83 (0.68, 1.00)	1.01 (0.78, 1.31)	
Stratified by follow-up time in HPFS						0.53
< 20 years						
Multivariate-adjusted hazard ratio (95% CI)	1.00	1.00 (0.92, 1.09)	0.96 (0.88, 1.04)	0.93 (0.85, 1.03)	1.00 (0.88, 1.14)	
≥ 20 years						
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.98 (0.90, 1.07)	0.95 (0.87, 1.03)	0.96 (0.87, 1.06)	1.03 (0.90, 1.17)	

* Models were adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (AHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former (1 - 4 cigarettes/d), former (5 - 14 cigarettes/d), former (15 - 24 cigarettes/d), former (25 - 34 cigarettes/d), former (35 - 44 cigarettes/d), former (≥ 45 cigarettes/d), former (unknown cigarettes/d), current (1 - 4 cigarettes/d), current (5 - 14 cigarettes/d), current (15 - 24 cigarettes/d), current (25 - 34 cigarettes/d), current (35 - 44 cigarettes/d), current (≥ 45 cigarettes/d), current (unknown cigarettes/d)), 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.

* † Likelihood ratio tests were performed.

Supplemental Table 6. Sensitivity analyses for the association between coffee consumption and total mortality in the overall population, and pooled multivariate-adjusted hazard ratio was shown.

	Categories of total coffee					P _{non-linearity*}
	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	
Using cumulative coffee consumption, and stopping updating after cancer and diabetes	1.00	0.96 (0.92, 1.00)	0.89 (0.86, 0.92)	0.91 (0.87, 0.95)	0.94 (0.88, 0.99)	< 0.001
Using cumulative coffee consumption, and further stopping updating after hypertension, hypercholesterolemia, and CVD	1.00	0.96 (0.92, 1.00)	0.89 (0.86, 0.92)	0.91 (0.87, 0.95)	0.97 (0.92, 1.03)	< 0.001
Continue updating after diagnosis of chronic disease with 4-year lag	1.00	0.99 (0.96, 1.04)	0.93 (0.88, 0.97)	0.94 (0.89, 0.98)	0.94 (0.87, 1.00)	< 0.001
Continue updating after diagnosis of chronic disease adjusting for time-varying hypercholesterolemia	1.00	1.02 (0.97, 1.06)	0.92 (0.88, 0.96)	0.92 (0.87, 0.96)	0.86 (0.80, 0.92)	0.04
Using baseline exposure with exclusion of hypertension and hypercholesterolemia at baseline	1.00	0.98 (0.93, 1.02)	0.93 (0.88, 0.97)	0.95 (0.91, 1.00)	1.04 (0.98, 1.10)	< 0.001

	Categories of caffeinated coffee					
	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	
Using cumulative coffee consumption, and stopping updating after cancer and diabetes	1.00	0.98 (0.95, 1.01)	0.93 (0.90, 0.96)	0.98 (0.94, 1.03)	0.98 (0.91, 1.04)	< 0.001
Using cumulative coffee consumption, and further stopping updating after hypertension, hypercholesterolemia, and CVD	1.00	0.98 (0.95, 1.01)	0.91 (0.88, 0.94)	0.98 (0.94, 1.03)	1.02 (0.96, 1.09)	< 0.001
Continue updating after diagnosis of chronic disease with 4-year lag		1.00	0.95	0.99	0.98	0.014
Continue updating after diagnosis of chronic disease adjusting for time-varying hypercholesterolemia	1.00	(0.97, 1.04)	(0.92, 0.99)	(0.95, 1.03)	(0.91, 1.07)	
Using baseline exposure with exclusion of hypertension and hypercholesterolemia at baseline	1.00	0.98 (0.95, 1.01)	0.93 (0.90, 0.96)	1.00 (0.96, 1.06)	1.10 (1.03, 1.14)	< 0.001
	Categories of decaffeinated coffee					
	0	≤ 1 cup/d	1.1-3 cups/d	>3 cups/d		

Using cumulative coffee consumption, and stopping updating after cancer and diabetes	1.00	0.89 (0.86, 0.91)	0.87 (0.84, 0.90)	0.94 (0.88, 0.99)	< 0.001
Using cumulative coffee consumption, and further stopping updating after hypertension, hypercholesterolemia, and CVD	1.00	0.86 (0.86, 0.88)	0.84 (0.82, 0.88)	0.95 (0.88, 1.01)	< 0.001
Continue updating after diagnosis of chronic disease with 4-year lag	1.00	0.90 (0.88, 0.92)	0.89 (0.87, 0.93)	0.91 (0.85, 0.98)	< 0.001
Continue updating after diagnosis of chronic disease adjusting for time-varying hypercholesterolemia	1.00	0.90 (0.87, 0.92)	0.88 (0.86, 0.92)	0.90 (0.84, 0.97)	< 0.001
Using baseline exposure with exclusion of hypertension and hypercholesterolemia at baseline	1.00	0.93 (0.89, 0.96)	0.93 (0.89, 0.97)	0.93 (0.86, 1.00)	< 0.001

Models were adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (AHEI score, in quintiles), total energy intake (quintiles), smoking status (never, former (1 - 4 cigarettes/d), former (5 - 14 cigarettes/d), former (15 - 24 cigarettes/d), former (25 - 34 cigarettes/d), former (35 - 44 cigarettes/d), former (≥ 45 cigarettes/d), former (unknown cigarettes/d), current (1 - 4 cigarettes/d), current (5 - 14 cigarettes/d), current (15 - 24 cigarettes/d), current (25 - 34 cigarettes/d), current (35 - 44

cigarettes/d), current (≥ 45 cigarettes/d), current (unknown cigarettes/d), 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.

* A likelihood ratio test was performed.

Supplemental Table 7. Sensitivity analyses for the association between coffee consumption and total mortality among never smokers, and pooled multivariate-adjusted hazard ratio was shown.

	Categories of total coffee					P _{non-linearity*}
	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	
Using cumulative coffee consumption, and stopping updating after cancer and diabetes	1.00	0.93 (0.87, 0.99)	0.89 (0.83, 0.95)	0.83 (0.76, 0.90)	0.83 (0.72, 0.96)	0.26
Using cumulative coffee consumption, and further stopping updating after hypertension, hypercholesterolemia, and CVD	1.00	0.93 (0.87, 0.99)	0.89 (0.83, 0.95)	0.84 (0.78, 0.91)	0.85 (0.74, 0.97)	0.87
Continue updating after diagnosis of chronic disease with 4-year lag	1.00	0.96 (0.90, 1.03)	0.93 (0.88, 1.00)	0.80 (0.73, 0.86)	0.85 (0.72, 1.00)	0.25
Continue updating after diagnosis of chronic disease adjusting for time-varying hypercholesterolemia	1.00	0.99 (0.93, 1.06)	0.91 (0.85, 0.96)	0.79 (0.73, 0.85)	0.73 (0.61, 0.87)	0.30
Using baseline exposure with exclusion of hypertension and hypercholesterolemia at baseline	1.00	0.95 (0.87, 1.01)	0.93 (0.88, 1.00)	0.82 (0.75, 0.89)	0.91 (0.79, 1.04)	0.88

	Categories of caffeinated coffee					
	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d	
Using cumulative coffee consumption, and stopping updating after cancer and diabetes	1.00	1.00 (0.95, 1.05)	0.91 (0.86, 0.96)	0.87 (0.79, 0.95)	0.80 (0.65, 0.99)	0.34
Using cumulative coffee consumption, and further stopping updating after hypertension, hypercholesterolemia, and CVD	1.00	1.00 (0.93, 1.05)	0.88 (0.83, 0.93)	0.89 (0.82, 0.98)	0.79 (0.66, 0.97)	0.91
Continue updating after diagnosis of chronic disease with 4-year lag	1.00	0.99 (0.94, 1.05)	0.90 (0.85, 0.96)	0.85 (0.76, 0.94)	0.81 (0.63, 1.06)	0.084
Continue updating after diagnosis of chronic disease adjusting for time-varying hypercholesterolemia	1.00	0.99 (0.94, 1.05)	0.89 (0.84, 0.94)	0.80 (0.72, 0.88)	0.77 (0.59, 1.01)	0.07
Using baseline exposure with exclusion of hypertension and hypercholesterolemia at baseline	1.00	0.97 (0.92, 1.02)	0.92 (0.87, 0.99)	0.85 (0.76, 0.94)	0.94 (0.78, 1.12)	0.91
	Categories of decaffeinated coffee					
	0	≤ 1 cup/d	1.1-3 cups/d	>3 cups/d		

Using cumulative coffee consumption, and stopping updating after cancer and diabetes	1.00	0.92 (0.87, 0.96)	0.90 (0.84, 0.95)	0.93 (0.81, 1.08)	0.016
Using cumulative coffee consumption, and further stopping updating after hypertension, hypercholesterolemia, and CVD	1.00	0.90 (0.86, 0.95)	0.89 (0.84, 0.95)	0.97 (0.85, 1.12)	0.008
Continue updating after diagnosis of chronic disease with 4-year lag	1.00	0.95 (0.90, 0.99)	0.97 (0.91, 1.03)	0.91 (0.76, 1.09)	0.22
Continue updating after diagnosis of chronic disease adjusting for time-varying hypercholesterolemia	1.00	0.94 (0.90, 0.98)	0.92 (0.87, 0.98)	0.89 (0.75, 1.06)	0.20
Using baseline exposure with exclusion of hypertension and hypercholesterolemia at baseline	1.00	0.95 (0.90, 0.99)	0.93 (0.87, 0.99)	0.87 (0.74, 1.04)	0.17

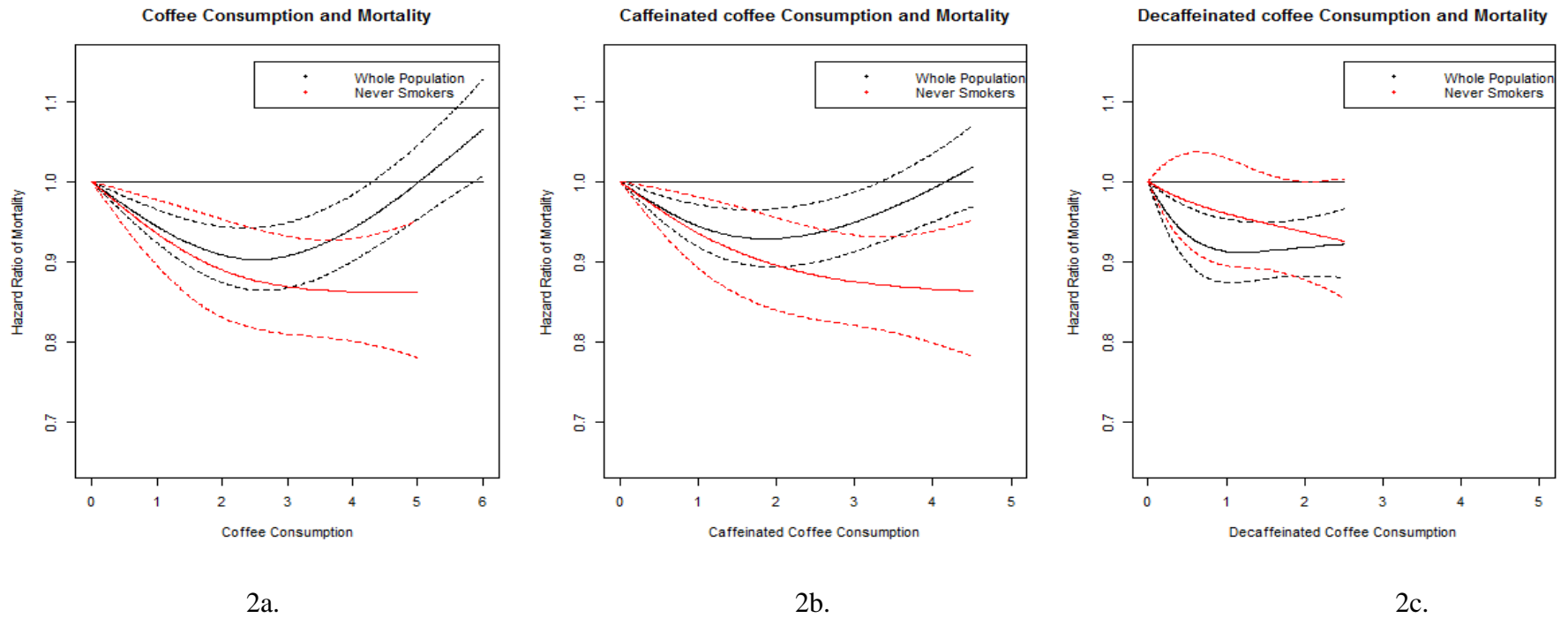
* A likelihood ratio test was performed.

Supplemental Table 8. The association between coffee consumption and risk of total mortality among never smokers by Cox model with inverse probability weighting.

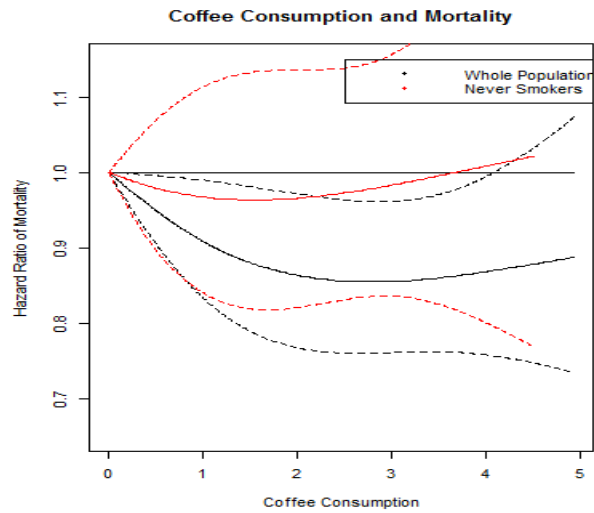
Total coffee					
Intake (cups/d)	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.95 (0.90, 1.00)	0.93 (0.87, 0.98)	0.86 (0.80, 0.93)	0.87 (0.77, 0.98)
Caffeinated coffee					
Intake (cups/d)	0	≤ 1 cup/d	1.1-3 cups/d	3.1-5 cups/d	>5 cups/d
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.97 (0.94, 1.02)	0.92 (0.87, 0.96)	0.90 (0.82, 0.98)	0.89 (0.76, 1.05)
Decaffeinated coffee					
Intake (mg/d)	0	≤ 1 cup/d	1.1-3 cups/d	>3 cups/d	
Multivariate-adjusted hazard ratio (95% CI)	1.00	0.95 (0.91, 0.99)	0.93 (0.87, 0.99)	0.89 (0.78, 1.03)	

The model adjusted for age, baseline disease status (hypertension, hypercholesterolemia, diabetes), BMI (< 20.9, 21-22.9, 23-24.9, 25-29.9, 30-34.9, ≥ 35 kg/m²), physical activity (< 3, 3-8.9, 9-17.9, 18-26.9, ≥ 27 MET-h/wk), overall dietary pattern (AHEI 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.

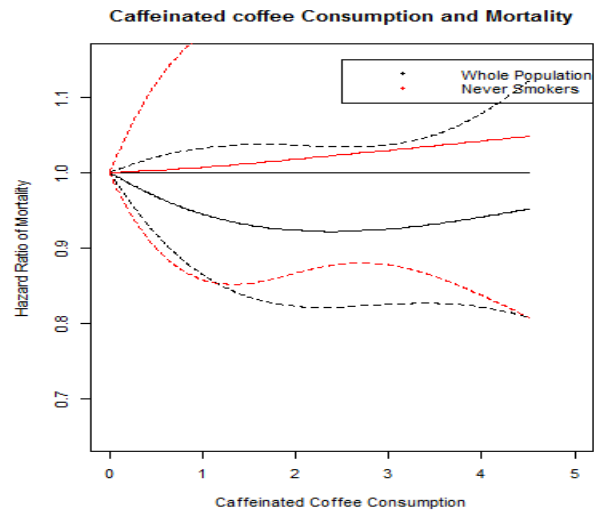
For the weight calculation, the weight for the non-cases was 1, while the weights for the death cases were calculated in a way that the composition of the total mortality among the never smokers was the same as the overall population.



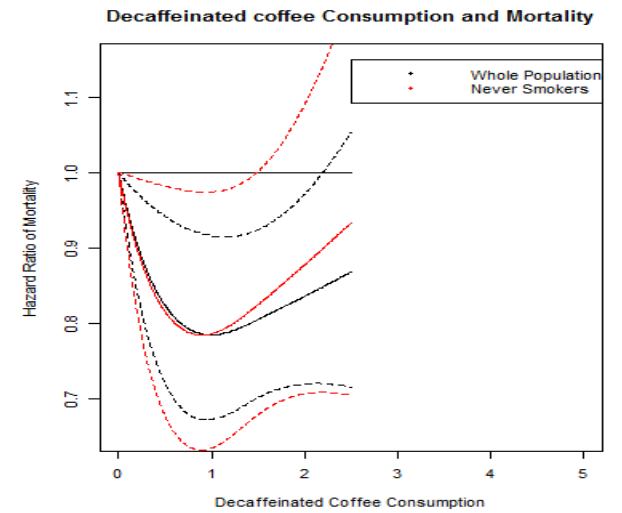
Supplemental Figure 2. Baseline coffee consumption and risk of mortality in the overall population and among never smokers in NHS. 2a. Total coffee consumption and risk of mortality. 2b. Caffeinated coffee consumption and risk of mortality. 2c. Decaffeinated coffee consumption and risk of mortality.



3a.

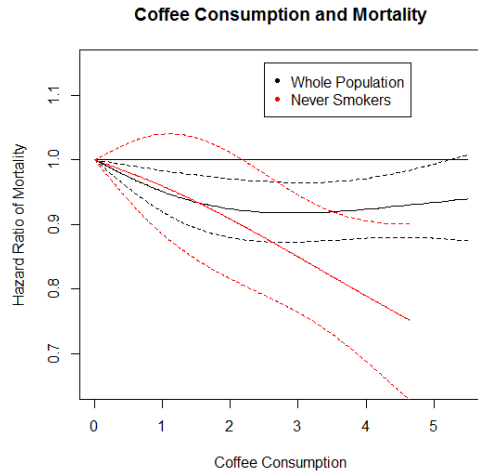


3b.

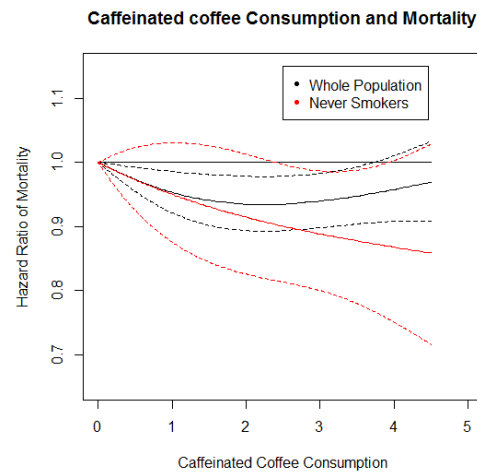


3c.

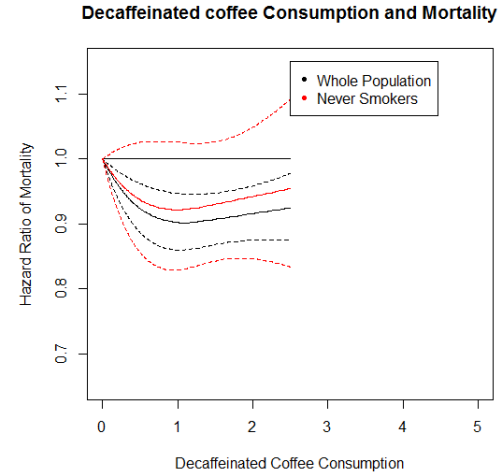
Supplemental Figure 3. Baseline coffee consumption and risk of mortality in the overall population and among never smokers in NHS 2. 3a. Total coffee consumption and risk of mortality. 3b. Caffeinated coffee consumption and risk of mortality. 3c. Decaffeinated coffee consumption and risk of mortality.



4a.

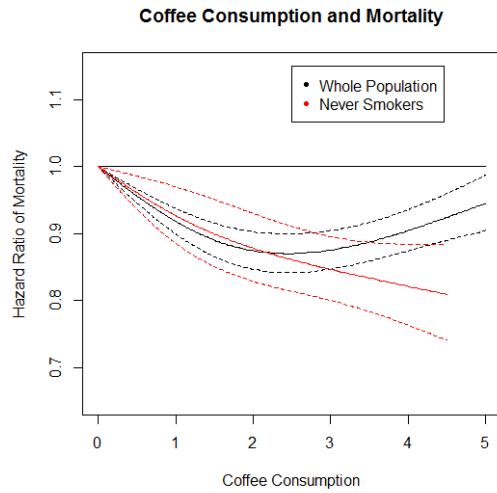


4b.

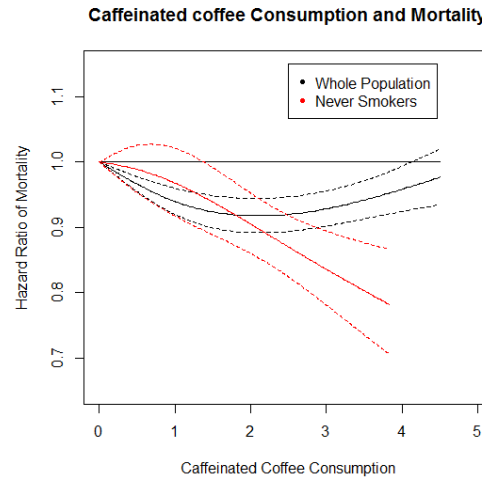


4c.

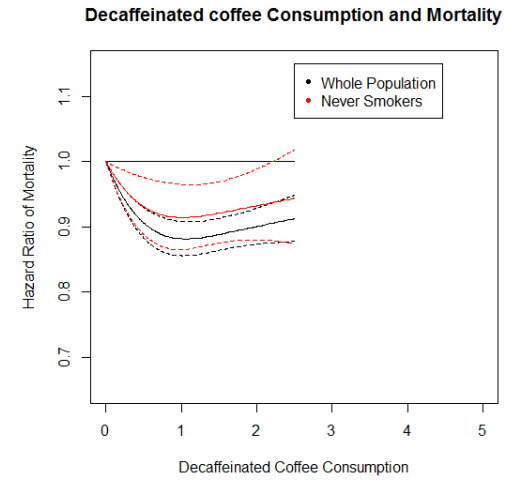
Supplemental Figure 4. Baseline coffee consumption and risk of mortality in the overall population and among never smokers in HPFS. 4a. Total coffee consumption and risk of mortality. 4b. Caffeinated coffee consumption and risk of mortality. 4c. Decaffeinated coffee consumption and risk of mortality.



5a.

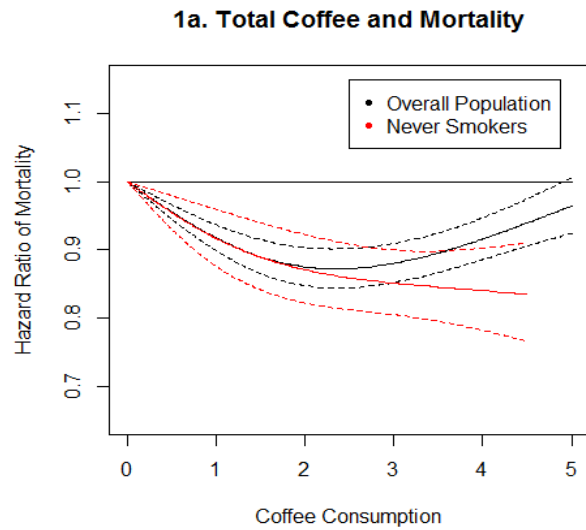


5b.

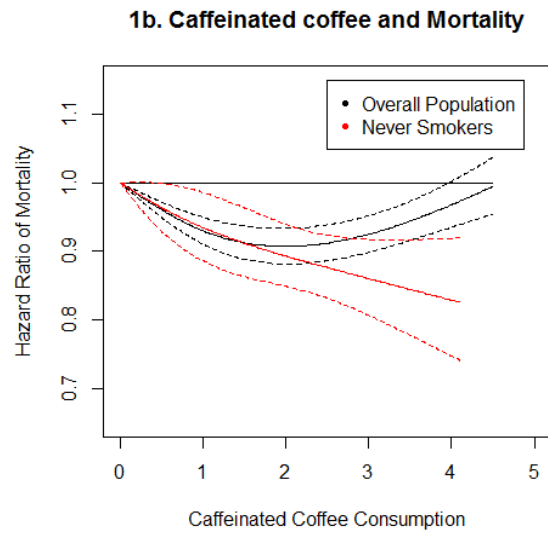


5c.

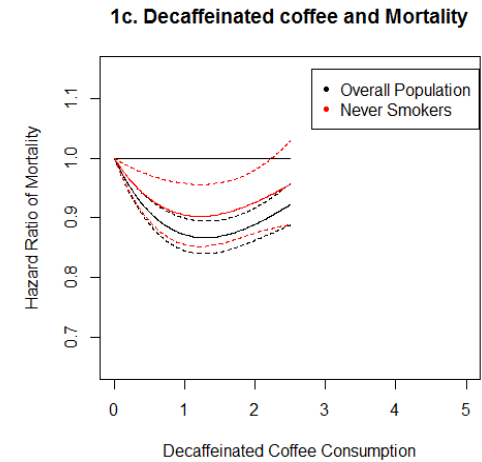
Supplemental Figure 5. Cumulative coffee consumption and stopping updating when cancer and diabetes develop, and risk of mortality in the overall population and among never smokers by pooled across the three cohorts. 5a. Total coffee consumption and risk of mortality. 5b. Caffeinated coffee consumption and risk of mortality. 5c. Decaffeinated coffee consumption and risk of mortality.



6a.

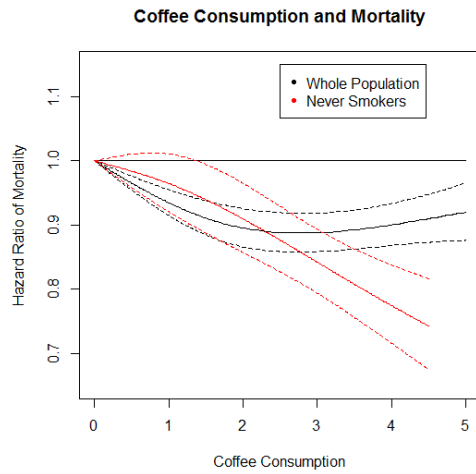


6b.

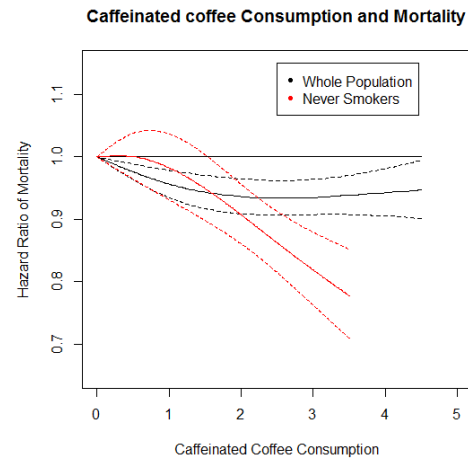


6c.

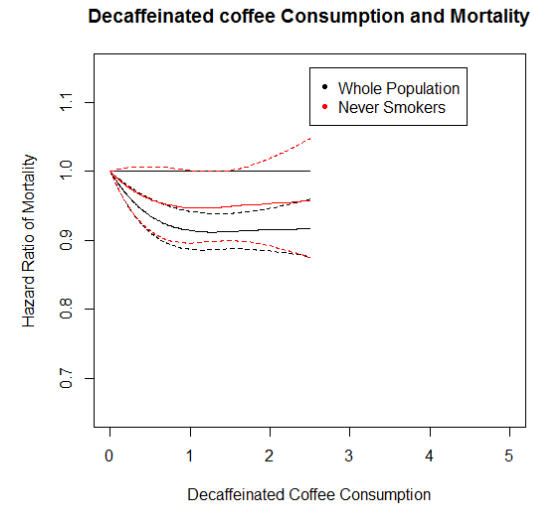
Supplemental Figure 6. Cumulative coffee consumption and further stopping updating when hypertension, hypercholesterolemia develop, and risk of mortality in the overall population and among never smokers by pooled across the three cohorts. 6a. Total coffee consumption and risk of mortality. 6b. Caffeinated coffee consumption and risk of mortality. 6c. Decaffeinated coffee consumption and risk of mortality.



7a.

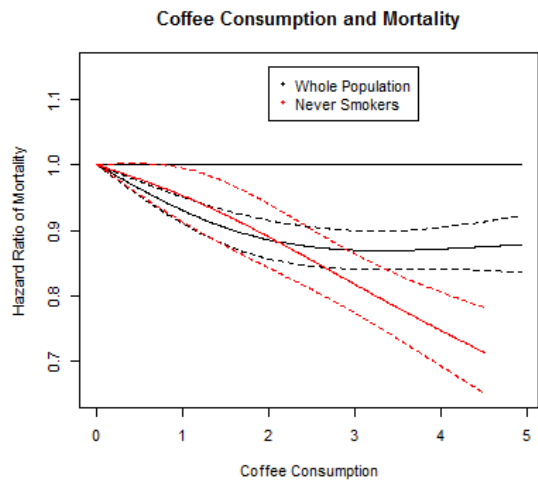


7b.

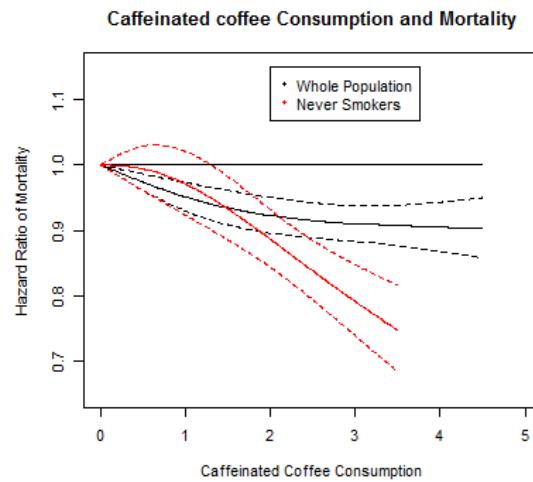


7c.

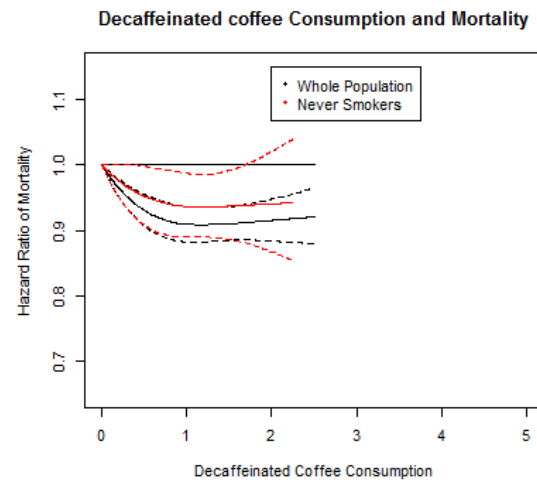
Supplemental Figure 7. Continue updating coffee consumption after diagnosis of chronic disease with 4-year lag and risk of mortality in the overall population and among never smokers pooled across the three cohorts. 7a. Total coffee consumption and risk of mortality. 7b. Caffeinated coffee consumption and risk of mortality. 7c. Decaffeinated coffee consumption and risk of mortality.



8a.

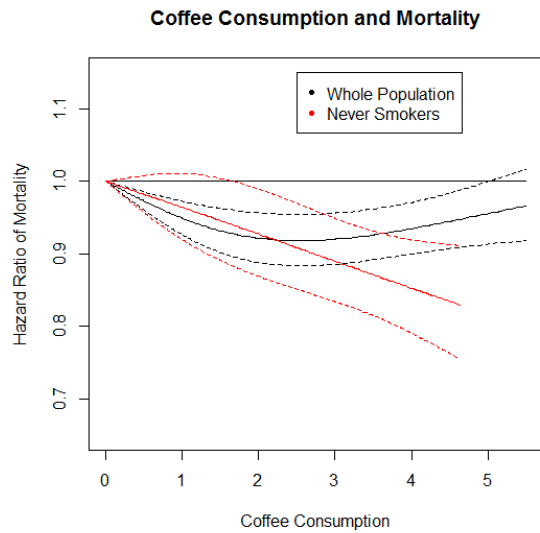


8b.

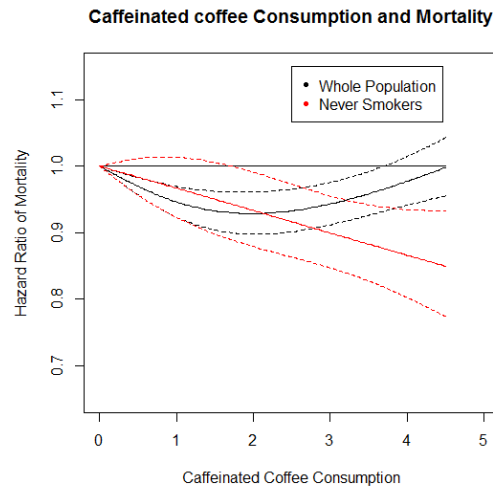


8c.

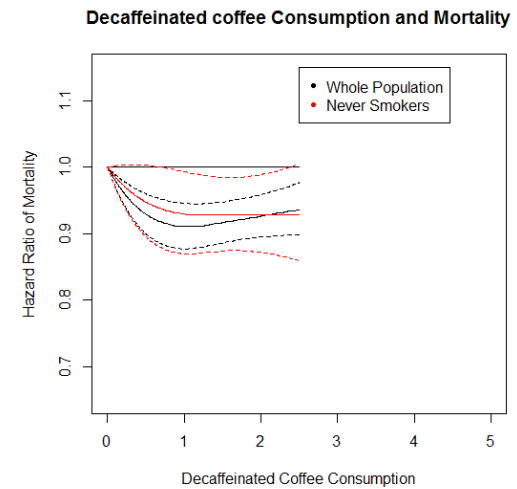
Supplemental Figure 8. Continue updating coffee consumption after diagnosis of chronic disease adjusting for hypercholesterolemia as a time varying covariates and risk of mortality in the overall population and among never smokers pooled across the three cohorts. 8a. Total coffee consumption and risk of mortality. 8b. Caffeinated coffee consumption and risk of mortality. 8c. Decaffeinated coffee consumption and risk of mortality.



9a.



9b.



9c.

Supplemental Figure 9. Baseline coffee consumption and risk of mortality in the overall population and among never smokers further excluding hypertension, hypercholesterolemia, and diabetes cases at baseline, pooled across the three cohorts. 9a. Total coffee consumption and risk of mortality. 9b. Caffeinated coffee consumption and risk of mortality. 9c. Decaffeinated coffee consumption and risk of mortality.