Coffee Drinking and Mortality in Ten European Countries – the EPIC Study

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Abstract

**Background:** How coffee consumption relates to mortality in diverse European populations, with variable coffee preparation methods and customs, is unclear.

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

**Design:** Prospective cohort study.

**Setting:** Ten European countries.

**Participants:** A total of 521,330 individuals enrolled in the European Prospective Investigation into Cancer and Nutrition (EPIC).

**Main outcome measure:** Hazard ratios (HRs) and 95% confidence intervals (CIs) estimated using multivariable Cox proportional hazards models. The association of coffee with serum biomarkers of liver function, inflammation, and metabolic health was evaluated in the EPIC Biomarkers sub-cohort (n=14,800).

**Results:** During a mean follow-up of 16.4 years, 41,693 deaths occurred. Compared with non-consumers, participants in the highest quartile of coffee consumption experienced statistically significant lower all-cause mortality (Men: HR=0.88, 95%CI: 0.82-0.95; P-trend<0.001; Women: HR=0.93, 95%CI: 0.87-0.98; P-trend=0.009). Inverse associations were also observed for digestive disease mortality for men (HR=0.41, 95%CI: 0.32-0.54; P-trend<0.0001) and women (HR=0.60, 95%CI: 0.46-0.78; P-trend<0.0001). Among women only, there was a statistically significant inverse association between coffee and circulatory disease mortality, (HR=0.78, 95%CI: 0.68-0.90; P-trend<0.001), cerebrovascular disease mortality (HR=0.70, 95%CI: 0.55-0.90; P-trend=0.002), and a positive association between
coffee and ovarian cancer mortality (HR 1.31, 95% CI: 1.07-1.61; P-trend 0.02). In the EPIC-biomarkers sub-cohort, higher coffee consumption was associated with lower serum alkaline phosphatase, alanine transaminase, aspartate transaminase, and C-reactive protein.

Limitation: Reverse causality may have led to spurious findings; however, results did not differ following exclusion of participants who died within 8-years of baseline. The study is also limited by a single assessment of coffee drinking habits.

Conclusions: Overall, coffee drinking was associated with reduced risk of mortality from various causes. This relationship did not vary by country where coffee preparation and drinking habits may differ.
Introduction

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

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

We investigated the association of coffee consumption with all-cause and cause-specific mortality in the European Prospective Investigation into Cancer and Nutrition (EPIC) – a large multi-national cohort that captured country-specific coffee preparation methods. In addition, to gain insight into potential biological mechanisms, we investigated the association of coffee with selected serum biomarkers of liver function, inflammation, and metabolic health.

Methods

Study population

EPIC is a multicenter prospective cohort of 521,330 participants, mostly aged 35 years or
above, who were recruited in 1992-2000 predominantly from the general population of 10 European countries (Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden and United Kingdom) (18, 19). Written informed consent was provided by all study participants and ethical approval for the EPIC study was provided from the International Agency for Research on Cancer and local participating centers. Exclusions prior to the onset of the analyses included: participants who reported cancer (n=22,537), heart disease (n=12,619), stroke (n=3,683), or diabetes (n=12,461); participants in the highest and lowest 1% of the distribution for the ratio between energy intake to estimated energy requirement (n=8,828); and those with missing coffee consumption and follow-up information (n=9,459). The final analytic dataset, therefore, included 451,743 participants (130,662 men, 321,081 women).

Diet, lifestyle, and anthropometric information

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

Liver function, circulatory disease, and metabolic biomarker measurement

Baseline data on serum albumin, alkaline phosphatase(ALP), alanine transaminase(ALT), aspartate transaminase(AST), gamma-glutamyltransferase(GGT), hs-C-reactive protein
(CRP), glycated hemoglobin (HbA1c), high density lipoprotein cholesterol (HDL-C), and lipoprotein(a) were available for the EPIC Biomarkers’ sub-cohort of 16,775 randomly-selected participants (See Table S1 for measurement method details). After applying the same exclusion criteria used in the main coffee-mortality analyses, 14,800 participants remained.

Assessment of mortality

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

Statistical analysis

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

To account for between-country variability in volume and concentration of the type of coffee locally consumed, total, caffeinated and decaffeinated coffee were modelled using country-specific quartiles among coffee consumers, and then compared against non-consumers.
Analyses using cup-size categories (non-consumers, <1, 1-<2, 2-<3, and 3+ cups/day) were also undertaken. Trend tests across exposure groups were calculated by entering the category variables into the Cox models as a continuous term. Continuous models (HR expressed per cup/day; 1 cup=237 mL) were also used. The multivariable models were adjusted for a set of a priori-determined covariates that included body mass index (BMI: <22, 22-24.9, 25-29.9, 30-34.9, 35+ kg/m²); physical activity (inactive, moderately inactive, moderately active, active); smoking status and intensity (never; current, 1-15 cigarettes/day; current, 16-25 cigarettes/day; current, 25+ cigarettes/day; former, quit ≤10 years; former, quit 11-20 years; former, quit 20+ years; current, pipe/cigar/occasional; current/former); smoking duration (<10, 10-<20, 20-<30, 30-<40, 40+ years); education (none/primary school completed, technical/professional school, secondary school, longer education - including university); menopausal status (premenopausal, postmenopausal, perimenopausal); ever use of oral contraceptives; ever use of menopausal hormone therapy; alcoholic drinks (non-consumers, <5, 5-14.9, 15-29.9, or 30+ g of ethanol/day), total energy (kcal/day) red and processed meats, and fruit and vegetables (all g/day). Further adjustment for dietary intakes of fiber, calcium, fish, soft drinks, and NSAID use resulted in virtually unchanged risk estimates, so these variables were not included in the final multivariable models.

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

Liver function, inflammation, and metabolic biomarker measurements

In the EPIC biomarkers sub-cohort, mean levels of serum liver function, inflammatory, and metabolic biomarkers were calculated for coffee consumption categories. For biomarker values that were non-normally distributed, data were log-transformed and geometric means were calculated for each coffee consumption category (see Figure 3A footnote for multivariable adjustments). Also in the sub-cohort, Cox proportional hazards models, using the same criteria as the coffee-mortality analyses, were used to assess the relationships between serum levels (sex-specific quartiles) of albumin, ALP, ALT, AST, GGT, CRP, HbA1c, HDL-C, and lipoprotein(a) with all-cause mortality (see Figure S2 footnote for multivariable adjustments).

All statistical tests were two-sided and a $P$-value of <0.05 was considered statistically significant.

Role of the Funding Source

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

After a mean follow-up of 16.4 years, 18,302 and 23,391 deaths were recorded among men and women, respectively. Of the total 41,693 deaths: 18,003 were from cancer; 9,106 from circulatory diseases; 2,380 from cerebrovascular diseases; 3,536 from ischemic heart disease; 1,213 from digestive diseases; 1,589 from respiratory diseases; 1,571 from external causes; and 418 from suicide. The mortality rates, age-adjusted to European standard populations (23), were 118 and 78 deaths per 10,000 person-years in men and women, respectively. Intakes of coffee by daily volume consumed were highest in Denmark (median 900 mL/day for men and women) and were lowest in Italy (median 91 mL/day for men and 93 mL/day for women; Table S2). Compared to non-consumers, individuals with higher reported coffee intakes were more likely to be younger and current smokers, and reported higher intakes of red and processed meats and alcohol; with lower consumption of fruit and vegetables (Table 1).

Coffee consumption and all-cause mortality

High coffee consumers had lower all-cause mortality risks compared to non-consumers after adjustments for smoking and other covariates in the multivariable models (Men: HR comparing highest quartile of coffee consumption with non-consumers=0.88; 95%CI: 0.82-0.95; P-trend<0.001; Women: HR=0.93; 95% CI: 0.87-0.98; P-trend=0.009; Table 2). When cup-size categories were used, similar inverse associations were observed for men (≥3 cups/day vs. non-consumers, HR=0.82, 95%CI: 0.76-0.89; P-trend<0.001) and women (≥3 cups/day vs. non-consumers, HR=0.92, 95%CI: 0.87-0.98; P-trend<0.001) (data not tabulated). There was no evidence of heterogeneity by country for the association between coffee consumption and all-cause mortality (P-heterogeneity 0.71 for men and 0.37 for women). Overall, similar inverse associations and linear trends were observed for consumption of caffeinated and decaffeinated coffee, albeit in men, the association of caffeinated coffee with all-cause mortality was less pronounced than for decaffeinated
coffee, with a statistically significant lower risk not observed in the highest quartile of consumption (Tables S3 and S4).

Adjusted cumulative incidence curves for all-cause mortality by coffee consumption categories are presented in Figure S1. For men, compared to non-consumers of coffee, the cumulative incidence of death until age 80 years was 3.1% (95% CI: 1.74-4.53) and 2.2% (95% CI: 0.80-3.68) lower among those in the third and highest quartile of coffee consumption, respectively. For women, the cumulative incidence of death until age 80 years was 1.4% (95% CI:0.55-2.28) and 0.8% (95% CI:-0.12-1.69) lower among those in the third and highest quartile of coffee consumption when compared against non-coffee consumers.

**Coffee consumption and cause-specific mortality**

Strong inverse associations were observed between coffee consumption and risks of digestive disease deaths for men (Q4 vs. non-consumers/Q1, HR=0.41, 95%CI: 0.32-0.54; P-trend<0.0001) and women (Q4 vs. non-consumers/Q1, HR=0.60, 95%CI: 0.46-0.78; P-trend<0.0001) (Table 2). Similar strength inverse associations were observed when cup-size categories were used (data not shown). Just over one-third of digestive disease deaths were due to liver disease. There was a statistically significant inverse association between coffee and liver disease deaths (sexes combined: Q4 vs. non-consumers, HR=0.20, 95%CI: 0.13-0.29), whereas the results of non-liver digestive disease deaths were inconclusive (sexes combined: Q4 vs. non-consumers, HR 0.81, 95% CI: 0.56-1.16). There was a strong, inverse association between deaths from liver cirrhosis and coffee drinking (sexes combined: Q4 vs. non-consumers, HR 0.21 95% CI: 0.13-0.34). Similar inverse associations were observed for alcoholic and non-alcoholic cirrhosis (data not shown).

Consumption of coffee was also inversely associated with circulatory diseases; this relationship was more pronounced in women and the inverse associations were stronger for deaths from cerebrovascular disease (Q4 vs. non-consumers, HR=0.70, 95%CI: 0.55-0.90;
P-trend=0.002) (Table 2). In general, the associations between coffee and cause-specific mortality were weakened when caffeinated and decaffeinated coffee were analyzed separately, albeit associations were in the same direction for both coffee types (Tables S3 and S4). The association of coffee drinking with cancer-related death was not statistically significant in men whereas in women a positive association was found (Q4 vs. non-consumers, HR=1.12, 95%CI: 1.02-1.23; P-trend=0.001). In further analyses by cancer site, we observed a statistically significant positive association between coffee and ovarian cancer-specific mortality (Q4 vs. non-consumers, HR=1.31, 95% CI, 1.07-1.61; P-trend=0.02) in a multivariable model that included smoking and other risk factors (Table S5).

In men, there were statistically significant inverse associations between low-medium consumption of coffee and lung cancer mortality (Table S5). Coffee drinking was inversely associated with liver cancer mortality in both men and women. Respiratory disease mortality was not related to coffee consumption in the full models (Table 2). Coffee consumption was not associated with deaths from external causes; however, an inverse relationship was observed between suicide and coffee for men, but not women (Table 2).

Subgroup and sensitivity analyses

Smoking was the most influential confounder for the all-cause mortality analyses (Table 2); however, because smoking is positively associated with both coffee consumption and risk of death, confounding in this case would obscure a possible reduction in risk associated with coffee. As expected, statistical adjustment for smoking strengthened the association between coffee and reduced risk of death. Further, coffee drinking was inversely associated with all-cause mortality among never smokers, and across subgroups of other mortality risk factors (Figure 1). Similarly, among never smokers, coffee drinking was inversely associated with deaths caused by cancer, circulatory diseases, digestive diseases, and respiratory diseases (Table S6).
The associations of coffee with all-cause mortality did not differ according to follow-up time categories (Table S7) and were virtually unchanged when deaths which occurred during the first 5 and 8 years of follow-up were excluded (Tables S8 and S9). Similar associations were also observed when analyses were limited to individuals who reported being in ‘excellent’ or ‘good’ health at baseline (Table S10), and when analyses were limited to sole consumers of caffeinated and decaffeinated coffee only (data not shown). The sensitivity analysis on possible impact of residual confounding found that an unmeasured confounder would need to be strongly associated with all-cause mortality (HR=<0.75) and substantially imbalanced between never consumers and high consumers of coffee (>20% difference in prevalence) to attenuate the upper confidence interval limit to above 1.00. (Table S11).

Serum levels of liver, inflammation and metabolic biomarkers by coffee consumption

Compared to non-coffee and/or low consumers, higher coffee consumers had statistically significantly lower mean levels of the liver enzymes ALP, ALT, AST, and GGT, lower levels of CRP, and higher serum albumin (all P-trends<0.05; Table 3). For women only, higher coffee consumption was correlated with lower serum HbA1c, lipoprotein(a), and higher HDL-C. A total of 891 all-cause deaths were recorded in the EPIC-Biomarkers sub-cohort. Serum levels of ALP, AST, GGT, and CRP were associated with all-cause mortality when the highest and lowest quartiles were compared (Figure S2). Higher serum levels of albumin and ALT were associated with lower all-cause mortality.

Discussion

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

Consistent with the current investigation, prospective studies in Japan and the U.S. have published inverse associations between coffee consumption and all-cause mortality (10-12, 15, 16, 24). Previous European studies were of much smaller size and based within individual countries, where coffee intakes and preparation methods are relatively homogenous. In contrast, our analysis of EPIC data from 10 European countries with ~42,000 documented deaths would have captured the inter-country coffee preparation methods and customs unlike any other study to date. Similar to the findings from the analysis from the NIH-AARP cohort (10), our observed inverse association between coffee and all-cause mortality was consistent across subgroups of other lifestyle, anthropometric and dietary variables and was apparent for both caffeinated and decaffeinated coffee. The findings for caffeinated and decaffeinated coffee should, however, be interpreted cautiously as data on decaffeinated coffee consumption was not collected by all EPIC centers. Further, the analyses may be contaminated by participants habitually consuming both types of coffee. Nevertheless, in sensitivity analyses where only sole-consumers of caffeinated or decaffeinated coffee were analyzed, the associations remained essentially unaltered.

Our results revealed that coffee consumption was strongly inversely associated with liver disease mortality. Previous studies have reported inverse associations between coffee and both alcoholic and non-alcoholic cirrhosis development (25-27). With the largest number of liver disease cases to date, our results are consistent with these smaller studies. Serum levels of several indicators of altered hepatic function-including the enzymes ALP, ALT, AST, and GGT were lower among coffee drinkers compared to non-consumers/low consumers in the current analysis - observations that were consistent with prior data (25, 28); suggesting that coffee drinking may potentially have beneficial effects on hepatic function and health. Experimental evidence suggests that caffeine has anti-fibrogenic effects on hepatocytes and
hepatic stellate cells by lowering proliferation, stimulating apoptosis, and inhibiting adhesion (29-31). Coffee has also been demonstrated to impede progression of fatty liver disease by reducing fat accumulation, oxidative stress and liver inflammation in murine models (32), and a possible beneficial role for coffee on liver disease progression in hepatitis-C patients has also been reported (33).

The observed inverse associations between coffee drinking and mortality from circulatory disease are also consistent with the prior NIH-AARP analysis (10). We note that this relation was stronger among women than men with the difference between sexes driven by a strong inverse association for cerebrovascular mortality risk in women; a finding consistent with previous studies which reported lower incidence of stroke in women consuming coffee (34, 35). Interestingly, levels of HDL-C, which has been inversely related to risks of stroke and other circulatory disease outcomes (36), were higher among coffee drinkers compared to non-consumers in women in our analysis, but not in men. Further, among women only, lipoprotein(a), CRP, and HbA1c – factors that have been positively associated with cardiovascular disease outcomes (37-40) - were generally lower among coffee drinkers compared to non-consumers. Given that the inverse relation between coffee drinking and circulatory disease mortality was primarily restricted to females, it may be hypothesized that this association might be driven by female-specific beneficial effects of coffee on lipid, inflammatory, and metabolic profiles.

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

We also report a statistically significant inverse relationship between coffee consumption and death from suicide for men, but not women. Coffee consumption was previously reported to be associated with lower suicide risk in a pooled analysis of two U.S cohorts (44), while a Finnish study reported higher suicide risk among heavy coffee consumers (45). Overall, our analysis only included 418 suicides, and importantly we lacked information on other factors related to suicide risk, such as antidepressant medication use and mental health status which may confound the coffee-suicide relationship.

Our prospective study was the largest to date to investigate the coffee-mortality relationship, and we controlled for important potential confounding factors. However we recognize that the associations may be biased due to residual confounding. In our analyses, smoking was the most important and influential confounder of the coffee-mortality relationship. However, the large number of participants and recorded deaths meant that our analyses could be restricted to never smokers. Generally, although residual confounding cannot be excluded as a potential explanation of our findings, our data revealed limited evidence that our results were the result of confounding bias due to smoking or other established mortality risk factors. Reverse causality, whereby participants experiencing early disease symptoms at baseline may have recorded lower coffee consumption; may have also been a source of bias in our analysis. However, we excluded participants who self-reported previous ill-health.

Further, similar associations were observed when the analyses were limited to those individuals who self-reported being in 'excellent' or 'good' health at baseline, and when participants who died during the first 5 and 8 years of follow-up were excluded. An additional limitation is that coffee consumption information was only measured once at baseline and it is possible that changes in consumption may have occurred during the follow-up period. However, other studies in Western populations which measured diet repeatedly over the study follow-up period have recorded relatively stable coffee consumption patterns over time.
indicating that a single measure likely captures medium to long-term drinking habits (11). Finally, as coffee drinking was self-reported some degree of measurement error is likely.

In summary, our results suggest that higher levels of coffee drinking are associated with lower risks of death from a variety of causes and specifically from digestive and circulatory diseases. The consistency of the results of this European study with those from other cohort studies around the world, as well as biomarker data that indicate coffee drinkers have a more favorable liver function and inflammatory biomarker profile than non-consumers/low consumers, offers support to the hypothesis that coffee may confer health benefits. Since coffee is so ubiquitously consumed, and intakes are modifiable, the potentially beneficial clinical implications of coffee consumption should be given careful consideration.
Tables and Figures:

Table 1. Baseline characteristics of study participants by categories (non-consumers plus country specific quartiles) of daily coffee consumption.

Table 2. Associations of daily coffee consumption and all-cause and cause-specific mortality among men and women.

Table 3. Multivariable-adjusted mean serum levels of liver function, circulatory disease, and metabolic biomarkers across coffee consumption categories among men and women (n=14,800).

Figure 1. Subgroup analysis of the associations of daily coffee consumption and all-cause mortality among men and women.

Supplementary Materials / Appendix:

Table S1. Analytical methods used to measure the liver function, circulatory disease and metabolic biomarkers.

Table S2. Descriptive information of the European Prospective Investigation into Cancer and Nutrition study participant countries.

Table S3. Multivariable associations of daily caffeinated coffee consumption and all-cause and cause-specific mortality.

Table S4. Multivariable associations of daily decaffeinated coffee consumption and all-cause and cause-specific mortality.

Table S5. Associations of daily coffee consumption and overall and individual cancer mortality.

Table S6. Associations of daily coffee consumption and cause-specific mortality by smoking status.

Table S7. Associations of daily coffee consumption and all-cause mortality by follow-up time categories.

Table S8. Multivariable associations of daily coffee consumption and all-cause and cause-specific mortality among men and women after deaths which occurred during the first 5 years of follow-up (n=5,247) were excluded.

Table S9. Multivariable associations of daily coffee consumption and all-cause and cause-specific mortality among men and women after deaths which occurred during the first 8 years of follow-up (n=10,790) were excluded.

Table S10. Associations of daily coffee consumption and all-cause and cause-specific mortality among participants who self-reported being in ‘excellent’ or ‘good’ health at baseline (n=119,609).

Table S11. A sensitivity analysis to assess the possible impact of an unmeasured confounder on the observed coffee consumption and all-cause mortality relationship.
**Figure S1.** Adjusted cumulative incidence of all-cause mortality, by coffee consumption categories among men and women.

**Figure S2.** Multivariable associations of serum liver function, circulatory disease, and metabolic biomarkers and all-cause mortality (n=1,597 deaths) among men and women using sex specific quartiles.

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