Coffee consumption and mortality in women with cardiovascular disease[1–3]

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ABSTRACT

Background: Coffee is commonly consumed among populations of all ages and conditions. The few studies that have examined the association between coffee consumption and mortality in patients with cardiovascular disease (CVD) have obtained conflicting results.

Objective: The objective was to assess the association between filtered caffeinated coffee consumption and all-cause and CVD mortality during up to 24 y of follow-up in women with CVD from the Nurses' Health Study.

Design: The Nurses' Health Study included 11,697 women. Coffee consumption was first assessed in 1980 with a food-frequency questionnaire (FFQ) and then repeatedly every 2–4 y. Cumulative consumption was calculated with all available FFQs from the diagnosis of CVD to the end of the follow-up in 2004 to assess long-term effects. In addition, the most recent coffee measurement was related to mortality in the subsequent 2 y to assess shorter-term effects. Analyses were performed by using Cox regression models.

Results: We documented 1159 deaths, of which 579 were due to CVD. The relative risks [RRs (95% CI)] of all-cause mortality across categories of cumulative coffee consumption [<1 cup (240 mL or 8 oz)/mo, 1 cup/mo to 4 cups/wk, 5–7 cups/wk, 2–3 cups/d, and ≥4 cups/d] were 1, 1.04 (0.86, 1.27), 1.13 (0.95, 1.36), 1.01 (0.86, 1.18), and 1.18 (0.89, 1.56), respectively (P for trend = 0.91). The RRs of CVD mortality across the same categories of coffee intake were 1, 0.99 (0.75, 1.31), 1.03 (0.80, 1.35), 0.97 (0.78, 1.21), and 1.25 (0.85, 1.84), respectively (P for trend = 0.76). Similarly, caffeine intake was not associated with total or CVD mortality. Finally, we observed no association of the most recent coffee and caffeine intakes with total and CVD mortality in the subsequent 2 y.

Conclusion: Consumption of filtered caffeinated coffee was not associated with CVD or all-cause mortality in women with CVD. *Am J Clin Nutr* 2011;94:218–24.

INTRODUCTION

Coffee is commonly consumed among populations of all ages and conditions. In healthy individuals, we have found that long-term coffee consumption does not increase the risk of coronary heart disease (CHD) (1), stroke (2), and premature death from cardiovascular disease (CVD) or all causes (3). In addition, coffee consumption has been associated with a lower risk of type 2 diabetes (4) and liver cancer (5, 6).

However, the few studies that have examined the association between coffee consumption and mortality in patients with CVD have obtained conflicting results. In a population-based case-control study, heavy coffee consumption was significantly related to a higher risk of sudden cardiac death (7). Another study, in patients hospitalized for acute myocardial infarction (AMI), found a strongly protective association between heavy coffee consumption and all-cause mortality after 90 d of follow-up but not after 4 y of follow-up (8). In addition, a 3-y study that assessed the association between the cumulative consumption of non-filtered coffee and the risk of a second CVD event observed no association (9). Finally, in a 10-y prospective study that followed patients after an acute AMI, filtered coffee consumption during the year preceding the coronary event was associated with lower all-cause mortality (10).

This study examined the association between filtered caffeinated coffee consumption and the risk of all-cause and CVD death during 24 y of follow-up in women with CVD. The main advantages of this study were the long follow-up, large cohort, and assessment of consumption of coffee both before and after the CVD event every 4 y; this allowed us to assess both long-term and shorter-term effects of coffee consumption.

SUBJECTS AND METHODS

Study population and design

The Nurses' Health Study (NHS) was established in 1976 (11). Information on the cohort, except for diet, has been updated every

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2 y. Dietary information was collected for the first time in 1980. We selected those women with a nonfatal CVD event diagnosed from 1976 through 2002, the last year for which coffee information was available at least once after the CVD event. We excluded participants with a history of cancer (except nonmelanoma skin cancer) in 1980 or before. Then, we examined the relation between coffee consumption after the CVD event and mortality up to 2004. The Harvard School of Public Health and Brigham and Women's Hospital Human Subjects Committee Review Board approved the study protocol.

Ascertainment of cardiovascular disease

Women with a nonfatal CVD event diagnosed from 1976 through 2002 were asked for permission to have their medical records reviewed by a physician, who had no knowledge of the participants' exposure status. The CVD events considered were MI, stroke, angina pectoris, coronary bypass, and coronary angioplasty. MI was classified as confirmed if the criteria of the World Health Organization were met, specifically, on the basis of symptoms and either electrocardiographic changes or elevated cardiac enzyme concentrations (12). Stroke was classified according to the criteria of the National Survey of Stroke (13), which required evidence of a neurologic deficit with sudden or rapid onset that persisted for >24 h. A pathologically confirmed cerebrovascular condition due to infection, trauma, or malignancy was excluded, as were "silent" strokes discovered only by radiologic imaging. For each type of stroke, the diagnosis was classified as confirmed when a computed tomography scan, magnetic resonance imaging, angiography, or surgery had confirmed the lesion. Computed tomography or magnetic resonance imaging reports were available for 89% of the participants with medical records. Cases in which medical record release was refused or when medical records were unavailable were classified as probable CHD or probable stroke of undetermined type. For these analyses, we included both confirmed and probable cases of CHD and stroke. Finally, information about angina pectoris, coronary bypass, and coronary angioplasty was self-reported. A total of 11,697 women had experienced a nonfatal CVD event (11.1% had a MI, 11.3% a stroke, 56.1% angina pectoris, and 21.4% a coronary bypass or coronary angioplasty).

Assessment of coffee consumption

Dietary questionnaires were sent to the participants in 1980, 1984, 1986, 1990, 1994, 1998, and 2002. In each questionnaire, participants were asked how often on average during the previous year they had drunk coffee or tea or consumed chocolate. The participants could choose from 9 responses. Using the US Department of Agriculture food-composition sources, supplemented with other sources, we estimated the caffeine content as 137 mg per 1 cup (240 mL or 8 oz) of coffee, 47 mg per 1 cup of tea, 46 mg per 1 can or a 355-mL (12-oz) bottle of soft drink, and 7 mg per 100-g (1-oz) serving of chocolate candy. We assessed the total intake of caffeine by summing the caffeine content for a unit of each food multiplied by a weight proportional to the frequency of its consumption. In our validation study, we obtained high correlations between consumption of coffee and other caffeinated beverages estimated from the food-frequency questionnaire and consumption estimated from repeated 1-wk dietary records (coffee, $r = 0.78$; tea, $r = 0.93$; and caffeinated soft drinks, $r = 0.85$) (14). Food-frequency questionnaires were also used to assess the consumption of other foods. Nutrient values were derived from the foods reported and were energy-adjusted by using the residual method (15).

Ascertainment of mortality

Deaths were reported by the next of kin or the postal authorities or were ascertained through the National Death Index. We estimated that death ascertainment was >98% complete (16). For all deaths, we sought death certificates and, when appropriate, requested permission from the next of kin to review medical records. The underlying cause of death was assigned according to the International Classification of Diseases, 8th Revision (ICD-8). The primary endpoint in this analysis was death from any cause. We also conducted analyses according to CVD mortality (ICD-8 codes 390.0 through 458.9 and 795.0–795.9).

Medical history, anthropometric data, and lifestyle factors

In the baseline questionnaire, we requested information about age, weight, height, smoking status, parental history of MI, menopausal status and use of hormone therapy, personal history of hypertension, hypercholesterolemia, type 2 diabetes, cancer, and medication use. This information, with the exception of height and parental history, has been updated in the biennial follow-up questionnaires. Body mass index was calculated as weight (in kg) divided by the square of height (in m). Physical activity was also assessed biennially and reported as the average time spent per week during the preceding year in specific activities (eg, walking outdoors, jogging, and bicycling). The time spent in each activity (in h/wk) was multiplied by its typical energy expenditure, expressed in metabolic equivalent tasks, and then summed over all activities to yield a metabolic equivalent task/h score. Standard portion sizes for alcoholic drinks were specified as a can/bottle or glass for beer, a 120-mL (4-oz) glass for wine, and one drink or shot for liquor. Detailed information on the validity and reproducibility of the information about self-reported weight, physical activity, and alcohol consumption from the questionnaires was reported elsewhere (17–19). In addition, self-reported diagnoses of hypertension, hypercholesterolemia, type 2 diabetes, and cancer have been found to be reliable in the NHS cohort (20, 21).

Statistical analysis

We calculated person-years of exposure from the date of CVD diagnosis to the date of death, or 1 June 2004, whichever came first. To represent long-term or habitual intake, and to account for changes in coffee consumption, we used the cumulative average coffee consumption from all available dietary questionnaires from the diagnosis of CVD through the end of follow-up (22). To assess the shorter-term effect of coffee, we related the first available measure of coffee consumption after the CVD event to mortality in the following 2 y.

Participants were classified into 5 groups according to levels of coffee consumption. We used Cox proportional hazards models to investigate the association between categories of coffee consumption and death from all causes and from CVD. To control as finely as possible for confounding by age and calendar time, we

stratified the analysis jointly by age in months at the start of follow-up and calendar year of the current questionnaire cycle. We used hazard ratios to estimate relative risks (RRs) in each category of coffee consumption in comparison with participants in the lowest category. Multivariable models were adjusted for smoking, body mass index, physical activity, alcohol intake, parental history of MI, menopausal status and use of hormone therapy, hypertension, hypercholesterolemia, type 2 diabetes, cancer, and medication use, specifically aspirin, diuretics, β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other blood pressure medication, statins and other cholesterol-lowering drugs, insulin, and oral hypoglycemic medication. Last, analyses were also adjusted for dietary factors, including multivitamin use, vitamin E supplement use, total energy intake, glycemic load, folate intake, and quintiles of polyunsaturated, saturated, total n−3, and *trans* fat intakes. To test for a linear dose-response relation, we modeled coffee consumption as a continuous variable by using the median value of each category of coffee consumption. We did similar analyses with total caffeine intake.

Finally, we examined the change in coffee consumption after the CVD event, which might have confounded the association if this change was associated with the severity of the disease. In this scenario, participants with the most severe events would have decreased their coffee consumption the most so they would be classified in the lower categories of consumption, producing an underestimation of risk in the highest categories. This effect can be assessed because all participants included in our analysis were free of CVD at the beginning of the NHS, so we have before and after event measurements of coffee consumption.

The analyses were performed by using SAS software (version 9.1; SAS Institute Inc, Cary, NC). This manuscript follows the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) recommendations (23). The authors had full access to the data and take responsibility for its integrity.

RESULTS

In this population of 11,697 women who experienced a nonfatal CVD event, caffeinated coffee was consumed by 62% of the subjects after the CVD event. The characteristics of the study participants, by the amount of coffee consumed, are shown in **Table 1**. After the diagnosis of CVD, coffee consumption was directly associated with smoking and alcohol intake. In addition, women who drank more coffee were less likely to have a parental history of MI, hypertension, hypercholesterolemia, or type 2 diabetes. Similarly, medication use was less frequent among those women who consumed more coffee. In addition, women in the higher categories of coffee consumption tended to have a diet higher in saturated and *trans* fats, a lower glycemic load, and a lower folate content. Finally, women who reported a higher consumption of caffeinated coffee had a lower consumption of decaffeinated coffee.

During follow-up, we documented 1159 deaths, of which 579 were due to CVD. Habitual coffee consumption was not associated with the risk of total death, either in the analyses adjusted for age and smoking or in the analyses adjusted for all potential confounders (**Table 2**). For the relation between coffee and CVD mortality, the results were similar. We also assessed the association between total caffeine intake and mortality without finding any excess risk of mortality at any intake (**Table 3**). Finally, we assessed the association between coffee and caffeine intakes and all-cause and CVD mortality during the 2 y after the CVD event. No evidence of a shorter-term adverse effect of coffee or caffeine was found (**Tables 4** and **5**).

Although coffee intakes before and after CVD were highly correlated (r = 0.87), we performed a sensitivity analyses to address the possibility of a decrease in coffee consumption after the CVD event related to the severity of the disease. First, we restricted the analyses of habitual coffee consumption and mortality to participants who reported a stable coffee consumption, defined as a change of <1 cup/d between the last assessment before the CVD event and the first assessment after the event. In this population (88% of the participants), the results were similar to those in the main analysis: the RRs of all-cause mortality across categories of cumulative coffee consumption were 1, 1.11 (95% CI: 0.88, 1.39), 1.10 (0.89, 1.36), 0.89 (0.73, 1.10), and 1.22 (0.85, 1.75), respectively (P for trend = 0.75). The RRs of CVD mortality across the same categories of coffee intake were 1, 1.10 (0.80, 1.52), 0.96 (0.70, 1.32), 0.89 (0.66, 1.20), and 1.18 (0.69, 2.00), respectively (P for trend = 0.56).

Second, we studied the relation between coffee consumption before the CVD event and mortality after the CVD event. We found no association for all-cause or CVD mortality [RRs of all-cause mortality: 1, 1.04 (0.81, 1.33), 1.01 (0.83, 1.23), 0.94 (0.77, 1.16), 1.29 (0.94, 1.77), respectively; P for trend = 0.38]. Finally, to account for disease severity, the RRs of mortality by coffee or caffeine intake were adjusted for the type of CVD event diagnosed; we observed no substantial change in results after adjustment (data not shown). Because of the small sample size for different groups of CVD patients, it was not possible to separately assess the effect of coffee on mortality for each group. To complete the analyses, we calculated the full adjusted RRs for the association between categories of decaffeinated and all-cause mortality, with the following results: 1.0, 0.97 (0.82, 1.15), 0.99 (0.82, 1.20), 1.04 (0.87, 1.24), 0.98 (0.57, 1.69), respectively (P for trend = 0.71).

DISCUSSION

In this cohort of US women with a diagnosis of CVD, we found no association between long-term filtered caffeinated coffee consumption and risk of all-cause or CVD mortality. Neither was shorter-term coffee consumption associated with mortality in these women.

Several studies have examined the association of coffee with mortality in patients with CVD and have obtained conflicting results. de Vreede-Swagemakers et al (7), in a retrospective case-control study of patients with coronary artery disease, found that heavy coffee consumption (>10 cups/d) was associated with sudden cardiac death (RR: 55.7; 95% CI: 6.4, 482.8). However, the type of study design and the small sample size may limit the validity of the results. Mukamal et al (8) examined the association of interest in a cohort of 1902 patients with confirmed AMI. After 4 y, the RRs of all-cause mortality for consumption of 0, 1–7, 8–14, and >14 cups/wk were 1, 1.03 (0.72, 1.47), 1.39 (0.94, 2.06), and 1.52 (1.03, 2.26). This increase in risk was not seen during the first 90 d of follow-up, during which those with a higher coffee consumption showed a lower mortality. However, in a different cohort of 1369 patients hospitalized with

TABLE 1
Baseline characteristics of women with cardiovascular disease, by filtered caffeinated coffee consumption, after a cardiovascular disease event in the Nurses' Health Study[1]

	Coffee consumption[2]				
	<1 cup/mo	1 cup/mo to 4 cups/wk	5–7 cups/wk	2–3 cups/d	≥4 cups/d
No. of participants	4415	1508	2341	2838	595
Age (y)	68 ± 8[3]	67 ± 8	68 ± 8	66 ± 8	62 ± 9
Current smoker (%)	7	7	9	18	31
BMI (kg/m^2)	27.3 ± 5.7	27.5 ± 5.8	27.3 ± 5.7	26.9 ± 5.4	26.6 ± 5.8
Physical activity (MET-h/wk)	15.1 ± 18.4	14.9 ± 19.9	15.0 ± 21.1	14.7 ± 21.1	14.7 ± 21.8
Alcohol intake (g/d)	3.2 ± 8.0	3.6 ± 8.1	4.8 ± 9.3	5.9 ± 11.1	3.9 ± 8.1
Parental history of MI (%)	83	83	83	81	82
Postmenopausal hormone use (%)	29	28	30	31	39
Hypertension (%)	73	73	73	68	61
Hypercholesterolemia (%)	76	78	77	74	67
Diabetes (%)	22	21	22	18	14
Cancer (%)	17	17	18	17	19
Medication use (%)[4]					
Aspirin	68	69	67	67	68
Diuretics	18	20	19	18	15
β Blockers	33	33	34	30	24
Calcium channel blockers	24	24	25	23	23
ACE inhibitors	17	15	16	15	12
Other blood pressure medication	13	12	12	11	9
Statins	36	35	35	32	26
Other cholesterol-lowering drugs	6	6	7	6	5
Insulin	6	7	6	5	3
Oral hypoglycemic drugs	9	8	9	8	5
Dietary factors					
Multivitamin use (%)	55	54	51	51	50
Vitamin E supplement use (%)	37	37	36	33	31
Polyunsaturated fat (% of energy)	5.5 ± 1.8	5.6 ± 1.6	5.6 ± 1.7	5.7 ± 1.7	5.8 ± 1.9
Saturated fat (% of energy)	9.1 ± 3.2	9.5 ± 3.0	9.6 ± 3.0	10.0 ± 3.1	10.8 ± 3.3
n−3 Fatty acids (% of energy)	0.66 ± 0.28	0.67 ± 0.26	0.67 ± 0.26	0.66 ± 0.23	0.65 ± 0.25
trans Fat (% of energy)	1.5 ± 0.7	1.6 ± 0.7	1.6 ± 0.7	1.7 ± 0.7	1.8 ± 0.7
Glycemic load	116 ± 24	114 ± 22	112 ± 22	110 ± 22	107 ± 23
Folate (μg/d)	445 ± 185	439 ± 177	428 ± 162	419 ± 171	396 ± 170
Caffeine (mg/d)	42 ± 61	78 ± 66	151 ± 68	308 ± 141	557 ± 212
Decaffeinated coffee (cups/d)	0.87 ± 1.19	0.79 ± 1.09	0.40 ± 0.82	0.38 ± 0.89	0.28 ± 0.90

[1] The data correspond to different periods based on the diagnosis of cardiovascular disease during follow-up (1980–2004) and were directly standardized to the age distribution of the entire cohort (except for age). MI, myocardial infarction; MET-h, metabolic equivalent hours; ACE, angiotensin-converting enzyme.
[2] 1 cup = 240 mL.
[3] Mean ± SD (all such values).
[4] One or more times per week.

a confirmed first AMI followed over 10 y in Sweden, Mukamal et al (10) found that the RRs of all-cause mortality for 0, 1–2, 3–4, 5–6, and ≥7 cups/d were 1, 0.68 (0.45, 1.02), 0.56 (0.37, 0.85), 0.53 (0.34, 0.83), and 0.58 (0.34, 0.98), respectively; thus, they concluded that coffee consumed at the time of hospitalization was inversely associated with subsequent postinfarction mortality. Last, Silletta et al (9), in a follow-up study of 11,231 patients with recent MI, found that after 3.5 y the RRs of having a second CVD event (fatal and nonfatal) for 0, <2, 2–4, and >4 cups/d were 1, 1.02 (0.87, 1.20), 0.91 (0.75, 1.09), and 0.88 (0.64, 1.20), respectively. Their conclusion was that moderate coffee consumption was not associated with an increase in CVD events. The type of coffee consumed was mainly espresso. Our study extends the previous findings because it assessed coffee as commonly consumed in the United States (mostly drip-filtered coffee), considered both the long- and the shorter-term effects of coffee, and examined coffee consumption before the CVD event.

Case-control studies and cohort studies have found discrepant results on the effects of coffee on health (24). Whereas case-control studies mostly found an increased risk of CVD and death among regular coffee drinkers, cohort studies have found no evidence of a detrimental effect of coffee. An emerging hypothesis considers that coffee might have an acute detrimental effect in triggering coronary events among susceptible patients, but would not produce any long-term effect among the nonsusceptible population (25). In this scenario, case-control studies query coffee consumption before the event and may also capture the acute effects of coffee among individuals who drink this beverage occasionally. In contrast, most cohort studies link habitual consumption, not occasional consumption, with CVD events. Habitual consumers may be less sensitive to the acute

TABLE 2
Relative risks (RRs) and 95% CIs for all-cause and cardiovascular disease mortality, by cumulative filtered caffeinated coffee consumption, in women with cardiovascular disease

	Cumulative coffee consumption[1]					
	<1 cup/mo	1 cup/mo to 4 cups/wk	5–7 cups/wk	2–3 cups/d	≥4 cups/d	*P* for trend
Death from all causes						
Person-years	15,811	8036	9959	21,803	2923	
No. of deaths	285	162	207	438	67	
Age- and smoking-adjusted RR	1.0	1.07 (0.88, 1.30)	1.07 (0.89, 1.28)	0.95 (0.81, 1.11)	1.16 (0.88, 1.53)	0.53
Multivariable-adjusted RR[2]	1.0	1.04 (0.86, 1.27)	1.13 (0.95, 1.36)	1.01 (0.86, 1.18)	1.18 (0.89, 1.56)	0.91
Death from cardiovascular disease						
No. of deaths	147	81	98	217	36	
Age- and smoking-adjusted RR	1.0	1.04 (0.79, 1.36)	0.99 (0.77, 1.28)	0.89 (0.72, 1.11)	1.13 (0.78, 1.66)	0.43
Multivariable-adjusted RR[2]	1.0	0.99 (0.75, 1.31)	1.03 (0.80, 1.35)	0.97 (0.78, 1.21)	1.25 (0.85, 1.84)	0.76

[1] 1 cup = 240 mL.

[2] Adjusted for age (5-y categories), smoking status (never, past, or current: 1–14, 15–24, or ≥25 cigarettes/d), BMI (in kg/m^2; <23.0, 23.0–24.9, 25.0–27.9, 28.0–29.9, or ≥30.0), physical activity (<1.5, 1.0–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 metabolic equivalent hours/wk), alcohol intake (never or 0.1–4.9, 5.0–14.9, or ≥15.0 g/d), parental history of myocardial infarction, menopausal status and use of hormone therapy (premenopausal, postmenopausal without hormone therapy, postmenopausal with past hormone therapy, or postmenopausal with current hormone therapy), hypertension, hypercholesterolemia, type 2 diabetes, medication use (aspirin, diuretics, β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other blood pressure medications, statins, other cholesterol-lowering drugs, insulin, or oral diabetic medications), and dietary factors (daily multivitamin and vitamin E supplement use, total energy intake, glycemic load, folate intake, and quintiles of polyunsaturated, saturated, total n−3, and *trans* fat intakes).

effects of coffee. We could not test the acute effects of coffee in the hours after consumption, when coffee may trigger a nonfatal MI or a stroke (26, 27); instead, we tried to evaluate this hypothesis by examining the relation between coffee consumption and mortality within the 2 y after the assessment, as a proxy of an acute effect, and found no evidence of detrimental effects on mortality.

We examined the effect of a change in coffee consumption after the CVD event by using various sensitivity analyses. To our knowledge, this is the first study that examined this. Because these analyses produced consistent results with the main analysis, it is unlikely that changes in coffee consumption are confounding the association, at least for long-term consumption. Our analyses were also adjusted for medication use, which was updated repeatedly during the follow-up. The percentages of individuals receiving drug treatment during the 2-y period after the CVD event are shown in Table 1. The values may seem low because *1*) a high proportion of patients had angina pectoris and did not require several of the medications considered and *2*) strong clinical evidence on the beneficial effects of angiotensin-converting enzyme inhibitors date from 1991 (28) and of statins date from 1994 (29), which implies that current standard CVD treatments were set long after the start of cohort follow-up.

The metabolic and CVD effects of coffee are a topic of active research. In the long-term, substances in coffee other than caffeine might affect some metabolic pathways, for example by improving glucose metabolism and decreasing inflammation and

TABLE 3
Relative risks (RRs) and 95% CIs for all-cause and cardiovascular disease mortality, by quintile (Q) of cumulative total caffeine consumption, in women with cardiovascular disease

	Cumulative caffeine consumption					
	Q1	Q2	Q3	Q4	Q5	*P* for trend
Death from all causes						
Person-years	11,690	11,718	11,708	11,748	11,669	
No. of deaths	212	227	234	251	235	
Age- and smoking-adjusted RR	1.0	1.05 (0.87, 1.26)	1.03 (0.86, 1.25)	1.11 (0.92, 1.33)	0.97 (0.80, 1.17)	0.94
Multivariable-adjusted RR[1]	1.0	1.00 (0.83, 1.21)	1.04 (0.86, 1.26)	1.11 (0.92, 1.34)	0.94 (0.77, 1.14)	0.88
Death from cardiovascular disease						
No. of deaths	112	119	111	118	119	
Age- and smoking-adjusted RR	1.0	1.04 (0.80, 1.35)	0.93 (0.71, 1.21)	0.99 (0.76, 1.29)	0.94 (0.72, 1.22)	0.51
Multivariable-adjusted RR[1]	1.0	0.99 (0.76, 1.29)	0.90 (0.69, 1.18)	0.99 (0.76, 1.30)	0.95 (0.72, 1.25)	0.70

[1] Adjusted for age (5-y categories), smoking status (never, past, or current: 1–14, 15–24, or ≥25 cigarettes/d), BMI (in kg/m^2; <23.0, 23.0–24.9, 25.0–27.9, 28.0–29.9, or ≥30.0), physical activity (<1.5, 1.0–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 metabolic equivalent hours/wk), alcohol intake (never or 0.1–4.9, 5.0–14.9, or ≥15.0 g/d), parental history of myocardial infarction, menopausal status and use of hormone therapy (premenopausal, postmenopausal without hormone therapy, postmenopausal with past hormone therapy, or postmenopausal with current hormone therapy), hypertension, hypercholesterolemia, type 2 diabetes, medication use (aspirin, diuretics, β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other blood pressure medications, statins, other cholesterol-lowering drugs, insulin, or oral diabetic medications), and dietary factors (daily multivitamin and vitamin E supplement use, total energy intake, glycemic load, folate intake, and quintiles of polyunsaturated, saturated, total n−3, and *trans* fat intakes).

TABLE 4
Relative risks (RRs) and 95% CIs for all-cause and cardiovascular disease (CVD) mortality, by caffeinated coffee consumption during the 2 y after the CVD event, in women with cardiovascular disease

	Coffee consumption during the 2 y after the CVD event[1]					
	<1 cup/mo	1 cup/mo to 4 cups/wk	5–7 cups/wk	2–3 cups/d	≥4 cups/d	*P* for trend
Death from all causes						
Person-years	8756	2664	4689	4561	1064	
No. of deaths	129	39	82	52	13	
Age- and smoking-adjusted RR	1.0	1.01 (0.70, 1.45)	1.12 (0.84, 1.48)	0.72 (0.52, 1.00)	0.77 (0.42, 1.43)	0.09
Multivariable-adjusted RR[2]	1.0	1.08 (0.74, 1.57)	1.12 (0.83, 1.50)	0.77 (0.55, 1.09)	0.70 (0.37, 1.32)	0.11
Death from CVD						
No. of deaths	57	16	32	21	7	
Age- and smoking-adjusted RR	1.0	0.97 (0.55, 1.72)	1.05 (0.67, 1.63)	0.66 (0.39, 1.12)	0.89 (0.37, 2.14)	0.35
Multivariable-adjusted RR[2]	1.0	0.93 (0.51, 1.68)	1.01 (0.63, 1.64)	0.70 (0.40, 1.23)	0.81 (0.31, 2.14)	0.41

[1] 1 cup = 240 mL.

[2] Adjusted for age (5-y categories), smoking status (never, past, or current: 1–14, 15–24, or ≥25 cigarettes/d), BMI (in kg/m^2; <23.0, 23.0–24.9, 25.0–27.9, 28.0–29.9, or ≥30.0), physical activity (<1.5, 1.0–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 metabolic equivalent hours/wk), alcohol intake (never or 0.1–4.9, 5.0–14.9, or ≥15.0 g/d), parental history of myocardial infarction, menopausal status and use of hormone therapy (premenopausal, postmenopausal without hormone therapy, postmenopausal with past hormone therapy, or postmenopausal with current hormone therapy), hypertension, hypercholesterolemia, type 2 diabetes, medication use (aspirin, diuretics, β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other blood pressure medications, statins, other cholesterol-lowering drugs, insulin, or oral diabetic medications), and dietary factors (daily multivitamin and vitamin E supplement use, total energy intake, glycemic load, folate intake, and quintiles of polyunsaturated, saturated, total n−3, and *trans* fat intakes).

endothelial dysfunction (30–32). These mechanisms can counterbalance some of the potential short-term harmful effects of caffeine, such as the stimulation of the release of adrenaline, an inhibitor of insulin activity, and the acute increase in blood pressure and homocysteine concentrations (33–35). Indeed, chlorogenic acid and other phenolic compounds in coffee, magnesium, trigonelline, and quinides might account for beneficial effect of coffee on certain health outcomes (30–32).

This study had several strengths. First, we had multiple repeated measurements of coffee consumption and could thus account for changes in intake over the years after a diagnosis of CVD. Second, the long follow-up and the large number of events provided statistical power to show even modest detrimental effects of coffee. On the other hand, some measurement error in the assessment of coffee consumption may have occurred because consumption was self-reported; however, results from our validation study indicate that coffee was among the foods most accurately reported in the dietary questionnaire (14). In addition, some residual confounding may still exist, although we controlled for potential confounders with greater detail than in earlier studies because information on risk factors was updated every 2 y. However, it is still a cause of concern that high coffee consumers tend to be healthier and to have less biological risk factors (9, 10); this is difficult to address because mediation and reverse causation are difficult to disentangle. Finally, because our study was conducted among health care professionals, extrapolation of results to the general population should be made with caution.

TABLE 5
Relative risks (RRs) and 95% CIs for all-cause and cardiovascular disease (CVD) mortality, by quintile (Q) of total caffeine consumption during the 2 y after the CVD event, in women with cardiovascular disease

	Caffeine consumption during the 2 y after the CVD event					
	Q1	Q2	Q3	Q4	Q5	*P* for trend
Death from all causes						
Person-years	4349	4343	4345	4352	4344	
No. of deaths	62	61	68	73	51	
Age- and smoking-adjusted RR	1.0	0.95 (0.67, 1.36)	1.05 (0.74, 1.48)	1.11 (0.78, 1.57)	0.74 (0.51, 1.09)	0.16
Multivariable-adjusted RR[1]	1.0	0.97 (0.67, 1.41)	1.09 (0.76, 1.56)	1.03 (0.72, 1.49)	0.69 (0.46, 1.03)	0.03
Death from CVD						
No. of deaths	25	28	29	28	23	
Age- and smoking-adjusted RR	1.0	1.09 (0.63, 1.88)	1.17 (0.68, 2.01)	1.07 (0.62, 1.86)	0.88 (0.48, 1.58)	0.32
Multivariable-adjusted RR[1]	1.0	1.17 (0.66, 2.09)	1.26 (0.71, 2.25)	1.02 (0.56, 1.83)	0.85 (0.45, 1.62)	0.17

[1] Adjusted for age (5-y categories), smoking status (never, past, or current: 1–14, 15–24, or ≥25 cigarettes/d), BMI (in kg/m^2; <23.0, 23.0–24.9, 25.0–27.9, 28.0–29.9, or ≥30.0), physical activity (<1.5, 1.0–5.9, 6.0–11.9, 12.0–20.9, or ≥21.0 metabolic equivalent hours/wk), alcohol intake (never or 0.1–4.9, 5.0–14.9, or ≥15.0 g/d), parental history of myocardial infarction, menopausal status and use of hormone therapy (premenopausal, postmenopausal without hormone therapy, postmenopausal with past hormone therapy, or postmenopausal with current hormone therapy), hypertension, hypercholesterolemia, type 2 diabetes, medication use (aspirin, diuretics, β blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, other blood pressure medications, statins, other cholesterol-lowering drugs, insulin, or oral diabetic medications), and dietary factors (daily multivitamin and vitamin E supplement use, total energy intake, glycemic load, folate intake, and quintiles of polyunsaturated, saturated, total n−3, and *trans* fat intakes).

In conclusion, in this large cohort of women with CVD, long-term consumption of filtered caffeinated coffee was not associated with an increase in mortality. In addition, the analysis of coffee consumption in relation to mortality in the subsequent 2 y suggests a lack of shorter-term detrimental effects of filtered coffee on mortality in women with CVD.

The authors' responsibilities were as follows—EL-G, FR-A, TYL, KJM, FBH, and RMvD: study concept and design, data analysis, data interpretation, and critical revision of the manuscript for important intellectual content; FBH: data acquisition; EL-G: draft of the manuscript; EL-G and TYL: statistical expertise; FBH: funding; FR-A and FBH: administrative, technical, or material support; and RMvD: study supervision. No conflicts of interest were reported.

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