Association between coffee intake and coronary heart disease among postmenopausal women

By

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Even though this study is just a beginning in my academic career and more researches will be needed for this specific topic, I really hope my finding can contribute to improve prophylaxis and positively impact on public health.

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ABSTRACT

Background: Association between long-term habitual coffee intake and risk of coronary heart disease (CHD) among postmenopausal women is unclear.

Objective: The objective was to examine the dose-response relationship between total, caffeinated, and decaffeinated coffee intake and risk of CHD in a large cohort of postmenopausal women enrolled in the Women's Health Initiative (WHI).

Design: A substudy (Observational Study) in 86,459 postmenopausal women within the Women's Health Initiative (WHI) with measured coffee intake were followed for an average of 11.5 y for CHD events. The multivariable-adjusted models were computed by using Cox proportional hazards regression to evaluate the association between coffee intake and CHD.

Results: Of the 86,459 postmenopausal women, 5,899 CHD events occurred. Drinking ≥2 cups caffeinated coffee was significantly associated with reduced risk of CHD in a dose response manner. After fully adjusting for potential covariates, drinking 2-3 cups of caffeinated coffee was associated with a 8% reduction in the risk of CHD (HR: 0.92; 95% CI: 0.86, 0.98) while ≥ 4 cups/d of caffeinated coffee intake was associated with 13% of reduction in CHD risk (HR: 0.87; 95%CI: 0.78, 0.96), p trend =0.001. Decaffeinated coffee intake showed no clear association with CHD; however, there was no increased CHD risk with higher consumption.

Conclusion: Long-term caffeinated coffee intake (≥2 cups) may be beneficial on reducing CHD risk among postmenopausal women.

INTRODUCTION

Coronary Heart Disease (CHD) is the most common type of heart disease and the leading cause of mortality among women in the United States, accounting for about 1 in every 5 female deaths (1). Postmenopausal women have an accelerated risk of CHD and therefore menopause is considered a risk factor for CHD (2). The prevalence of CHD in women aged 45 to 54 years is 1 in 8 and increases to 1 in 3 among women over 65 years of age. Furthermore, women after menopause have a 31% higher risk of mortality from CHD compared to that of hip fracture and breast cancer (3).

Dietary habits may provide health benefits of reducing the risk of CHD (4). Coffee is among the most commonly consumed beverages worldwide and about 89% of American adults with equal prevalence in both sexes consume some caffeine on any given day (5). Beverages provide 98% of caffeine consumed, with coffee (~64%) as the predominant source in the adult US population (5). Despite its wide use, the nature of any association between coffee drinking and CHD risk remains unclear. In particular, the association of caffeinated and decaffeinated coffee with CHD among postmenopausal women who are at a high coronary risk, including any dose-response, needs further clarification. The literature addressing the coffee and CHD association is inconsistent in previous studies (6-29). Previous observational epidemiologic studies have shown both reduced risk (6-8, 13, 17, 20, 21, 23) and increased risk of CHD (10-13, 14-16), and no significant association (9-11, 18, 19, 22) from drinking coffee (6-23). Case-control studies are prone to report a positive trend or an excess risk between high consumption of coffee (> 4 cups/d) and CHD (10, 13). However, prospective cohort studies tend to show a U-shaped association (with the lowest risk at 3-5 cups/d) or an inverse relationship between moderate coffee consumption (2-6 cups/d) and the risk of incident CHD or death from CHD (6-8, 13, 17,

20, 21, 23). No evidence of increased harm or benefit from coffee drinking on CHD risk has also been reported (9-11, 18, 19, 22). Mixed results and a lack of evidence across studies were found when considering the effects of coffee on CHD risk factors and the sex difference (24-29). In addition, different study designs in previous literature make it even more difficult to provide public health recommendations regarding the health effects of coffee and CHD risk for postmenopausal women. Therefore, we examined the dose-response relationship between total, caffeinated, and decaffeinated coffee intake and risk of CHD in a large cohort of postmenopausal women enrolled in the Women's Health Initiative (WHI).

METHODS

Study Population

The Women's Health Initiative (WHI) is a large cohort study with 161,808 women enrolled that aims to assess influence of biological, physiological, genetic, and lifestyle factors on major health events including CHD. Those women were recruited from the 40 clinical centers throughout the United States and assigned to either the Observational Study (OS) or the Clinical Trial (CT) component. All women signed an informed consent at each of the 40 clinical centers. Only women in the OS sample had coffee consumption queried at baseline. Therefore, our analysis focused on 93,676 postmenopausal women in the WHI-OS aged between 50 and 79 years were enrolled from 1993 to 1998 and followed up for about the past 25 years. Women were eligible for the study if they were postmenopausal, willing to provide written informed consent for the pertinent study component, and residents in the study recruitment area for at least 3 years following enrollment. Women were excluded from the WHI if they had or if they were known to have medical conditions predictive of a survival time of less than 3 years, if they were active

participants in another randomized controlled clinical trial or had inconsistent adherence. Women who had implausible energy intake < 600 kcal/d or > 5,000 kcal/d were also excluded. A detailed description of the eligibility and exclusion criteria of the WHI study can be found elsewhere (4, 30, 31). CHD-free OS participants, excluding women with a history of self-reported CHD (myocardial infarction, coronary artery bypass surgery, and percutaneous transluminal coronary angioplasty) at baseline (n=3,230) were prospectively evaluated. In addition, women who had missing exposure data (n=3,580) or time to event (n=407) data (participants left the study before outcomes were collected) were excluded from the analysis. This resulted in 86,459 postmenopausal women in our analytic sample. The end of follow-up for the study was March 1, 2019.

Exposure measurements

Coffee drinking habits were measured in the WHI by using an OS questionnaire (Form 42) which asked participants about their usual consumption and preparation of coffee. Different types of coffee were asked regardless of the degree of caffeination. This questionnaire was administered only at baseline and asked to report how many cups were consumed per day [count tall (12 oz. or more) cups and espresso drinks made with double shots as 2 cups] and how they were made according to one or two of following brewing methods: drip, espresso, instant, boiled, percolated, and French press. The exact questions about coffee intake in the questionnaire were as follows: “How many cups of regular coffee (not decaf) do you usually drink each day?”, “How many cups of decaf coffee do you usually drink each day?”, and “How is the coffee usually made? (Mark one or two.)” The food and nutrient database was derived from the

University of Minnesota's Nutrition Coordinating Center (Minnesota Nutrition Data System for Research, version 2005).

Outcome measurements

Our primary outcome was CHD defined as the first occurrence of myocardial infarction (MI), coronary artery bypass graft (CABG), percutaneous transluminal coronary angioplasty (PTCA), or CHD death. A secondary outcome of "hard CHD" which is less prone to selection bias was also evaluated. Hard CHD is defined as non-fatal MI and fatal CHD death. All self-reported hospitalizations had medical records extracted including emergency room records, admission history and physicals, discharge summaries, progress notes, EKGs, cardiac enzymes, CABG, PTCA, chest x-rays, stress tests, coronary angiograms were reviewed annually by trained physician adjudicators for myocardial infarction, CABG or PTCA. Potential CHD death was based on death certificates, autopsy reports, coroners and next of kin reports, and all hospital records including electrocardiograms, laboratory test results, and reports from all relevant cardiac procedures near the time of death.

Statistical Analysis

In describing baseline characteristics, categorical variables and continuous variables according to coffee intake categories were presented as frequencies (and proportions) and means (and standard deviations), respectively. Coffee intake was divided into four groups of following frequency categories: (none, 1 cup/day, 2-3 cups/day, ≥ 4 cups/day). HRs (and 95% CI) for CHD according to the frequency categories of coffee intake were computed by using Cox proportional hazards regression. We performed a test for trend by treating coffee intake levels as a continuous

variable represented by its corresponding median and the Wald test was used to assess statistical significance. Potential covariates considered in the multivariable-adjusted models included age, race/ethnicity, education, family income, marital status, geographic region, BMI, cigarette smoking status, alcohol intake, total energy intake, leisure physical activity, postmenopausal hormone use, oral contraceptive use, history of diabetes mellitus, hysterectomy, a family history of CHD, blood pressure, hypertension, and dyslipidemia. We checked for multicollinearity among covariates and there was no correlation between covariates. Potential confounders were identified by previous studies and the existing literature and were associated with both the exposures of interest and CHD outcome and not in the causal pathway (7, 23, 32, 33). A minimally adjusted model that included age and total energy intake (Model 1) and a fully adjusted model (Model 2) that included all potential confounders not in the causal pathway were presented. As blood pressure, history of hypertension, and dyslipidemia might lie in the causal pathway as potential mediators, but also may represent confounders, a separate model (Model 3) including them was evaluated. To explore the mediating effect, the HR's for the exposure in the fully adjusted Cox model with each potential mediator individually included were compared. To examine potential effect modification of our associations, stratified analyses were performed according to history of dyslipidemia, hypertension, diabetes, and smoking status. Statistical analyses were performed using SPSS version 25.0.

RESULTS

From a total of 86,459 postmenopausal women free of CHD at baseline, 5,899 developed incident CHD after an average of 11.5 years (the maximum of 24 y) of follow-up in this study. Of coffee drinkers, 14,110 women drank a combination of both types of coffee, 34,023 drank

exclusively caffeinated coffee, and 12,501 drank exclusively decaffeinated coffee. From our analytic sample, 25,825 women did not report drinking coffee. We observed risk factors for CHD in the analytic sample as the following: older age, African Americans, less family income, higher BMI, present cigarette smoking, a history of dyslipidemia, hypertension, diabetes, hysterectomy, and family history of CHD (**Supplemental Table 1**). Women with higher consumption of caffeinated coffee were more likely to be white, living in the Midwest, current smokers, and moderate (1 to <7 drinks/week) or heavy (≥7 drinks/week) alcohol drinkers (**Table 1A**). Women in higher consumption of decaffeinated coffee tend to be white, presently married, living in the Midwest, former smokers, and moderate or heavy alcohol drinkers (**Table 1B**).

For the analyses on CHD risk, our results showed dose-response relationships, indicating inverse association between caffeinated coffee intake and risk of CHD (**Table 2**). After subdividing total coffee into different types of coffee intake, drinking ≥ 2 cups/d of caffeinated coffee showed inverse association of the risk of CHD across the different models. Drinking 2-3 cups/d and ≥ 4 cups of caffeinated coffee were significantly associated with reduced risk of CHD in a dose response manner. In the fully adjusted model (Model 2), drinking 2-3 cups of caffeinated coffee was associated with a 8% reduction in the risk of CHD (HR: 0.92; 95% CI: 0.86, 0.98) while ≥ 4 cups/d of caffeinated coffee intake was associated with a 13% reduction in CHD risk (HR: 0.87; 95%CI: 0.78, 0.96), p trend =0.001. For caffeinated coffee drinkers, risk of consuming 1 cup/d was not much different compared to none drinkers. We did not observe significant mediating effect between each potential mediator (blood pressure, hypertension, and dyslipidemia) and CHD risk among caffeinated drinkers (**Supplemental Table 2**). When we combined into two categories of caffeinated coffee, drinking ≥ 2 cups/d was significantly

lowered risk compared with none to 1cup/d of consumption in the minimally adjusted model (HR: 0.92; 95% CI: 0.87, 0.97) and the fully adjusted model (HR: 0.93; 95% CI: 0.87, 0.98). Individual point estimates after further adjusting for potential mediators (Model 3) were similar to the fully adjusted model with 2-3 cups/d (HR:0.93; 95% CI: 0.87, 1.00) and ≥ 4 cups/d (HR:0.92; 95% CI: 0.84, 1.02) of caffeinated coffee and their *p*-trend values were significant.(**Table 2**). For decaffeinated coffee, the results showed no clear association with CHD across the number of cups and the models; however, there was consistently no increased CHD risk with higher consumption of decaffeinated coffee.

When we stratified the incident CHD according to having history of dyslipidemia, hypertension, diabetes, and smoking individually at baseline, we did not observe the considerable modifying effect from each covariate in general (**Table 3**). Among caffeinated coffee drinkers, current smokers appeared to have significantly protective effect with a larger magnitude of an inverse association from drinking 2-3 cups/d (HR: 0.74; 95% CI: 0.57, 0.95). Decaffeinated coffee showed no significant results and no evidence of effect modification of HRs across the cups of coffee when stratified CHD by history of dyslipidemia, hypertension, diabetes, and smoking.

Our secondary analyses showed that the inverse trends were remained between caffeinated coffee and hard CHD while there was no significant mediating effect from blood pressure, hypertension, and dyslipidemia (**Supplemental Table 3 and Supplemental Table 4**). Drinking 2-3 cups/d of caffeinated coffee was associated with a 10% reduction in hard CHD risk (HR: 0.90; 95% CI: 0.83, 0.98) while ≥ 4 cups/d of caffeinated coffee intake was associated with a 15% reduction in hard CHD risk (HR:0.85; 95% CI: 0.75, 0.97), p trend =0.002. When we combined into two categories of caffeinated coffee, drinking ≥ 2 cups/d was significantly

associated with reduced risk in all models for hard CHD compared with none to 1cup/d of consumption; 0.91(95% CI: 0.85, 0.98) in the minimally adjusted model, 0.88 (95% CI: 0.81, 0.94) in the fully adjusted model, and 0.90 (95% CI: 0.84, 0.97) in the model with further adjustments for potential mediators.

DISCUSSION

In this large cohort of postmenopausal women, coffee intake was inversely associated with risk of CHD. We found protective dose-response trends suggesting monotonically decreasing risk between caffeinated coffee and CHD risk from drinking ≥ 2 cups/d of coffee. This association was significantly shown in the minimally and fully adjusted model adjusting for all covariates without potential mediators (blood pressure, hypertension, and dyslipidemia). In addition, significantly stronger inverse association was observed for higher consumption with ≥ 4 cups/d of caffeinated coffee in the fully adjusted model. Our results were similar to previous meta-analyses of prospective cohort studies showing an inverse association with 2-6 cups/d or a U-shaped association with the lowest risk from 3-5 cups/d between coffee consumption and CHD (6-8, 13, 17, 20, 21, 23). Few studies have focused on women, but all presented similar results to our finding that moderate coffee drinking (US studies: 1-3 cups, European: 3-4 cups/d) was significantly associated with lowered CHD risk in both women and men (7). A Swedish study including older women aged 40-74 y demonstrated that coffee consumption did not increase MI risk and more than 5 cups/week was associated with reduced risk of MI but this did not reach statistical significance (34). The Iowa study focusing on postmenopausal women reported coffee consumption reduced risk of death attributed to inflammatory and cardiovascular diseases (29).

The authors suggested that coffee consumption may inhibit inflammation, thereby reducing CVD risk due to dietary antioxidants in coffee (29).

Coffee is a chemical mixture of various compounds that might explain both beneficial and detrimental effects on CHD. Its complex composition and impact on metabolic pathways in humans have been associated with mixed effects on coronary health. Coffee has numerous micronutrients other than caffeine such as phenolic phytochemicals, vitamin B3, magnesium, and potassium (37, 38) which can act as antioxidants and anti-inflammatory compounds (36-38). Potential deleterious effects of caffeine include its effects on platelet aggregation, cardiac arrhythmias, aortic stiffness, and decreased insulin sensitivity (6-8). Also, caffeine has been associated with higher sensitivity c-reactive protein level suggesting inflammation in blood and a higher homocysteine level leading to vascular endothelial dysfunction (6-8). Caffeine has been associated with, an elevated risk of hypertension, increased blood pressure, and serum total cholesterol level (6-8, 11, 23). However, caffeine content largely varies by how coffee was prepared (roasting and brewing) and different types of coffee beans used according to preparation preference by different countries and culture (7). In terms of bioavailability of caffeine, its half-life time extensively varies which depends on individuals including age, medication use, and oral contraceptive use (35, 38). Our results about beneficial effects on incident CHD from coffee drinking can be explained by mixture of these various compounds from coffee counterbalancing the potential detrimental effects of caffeine.

In this study, we did not observe significant mediating effect from the blood pressure and hypertension which are known to be risk factors for CHD. This finding is possibly explained by the difference in caffeine's acute but not chronic, effect on cardiovascular system (11, 39-42). The acutely elevated blood pressure from caffeine is transient where it acutely increases blood

pressure but then returns to the baseline (8, 35, 36). Several previous epidemiological studies noted that there is no evidence of coffee consumption on increased blood pressure and hypertension (35, 43-45). Moreover, polyphenols in phytochemicals might play a beneficial role in regulating blood pressure, oxidative stress, and chronic inflammation which are known CHD risk factors (43, 46). In this context, those presumed benefits from micronutrients possibly offset the harmful acute effects of caffeine on blood pressure in this long-term follow-up study (37, 47). Thus, habitual coffee drinkers rapidly adapt to caffeine effects with developed coffee tolerance and that might weaken acute pressor effect (48).

From our study, dyslipidemia did not significantly confound the inverse association between coffee and CHD. Previous studies reported that boiled coffee (unfiltered coffee) produces diterpenes including cafestol and kahweol that raise serum total cholesterol level thereby potentially increasing harm on coronary health (8, 37). However, the cholesterol-raising effect was not associated with coffee when the filtered brewing method was used (8, 37). Use of filtered brewing method can also be a possible explanation for the favorable effect of coffee (7, 12, 19, 29, 34). From previous studies, coffee intake was not associated with adversely modifying blood lipid profile (49, 51). In our cohort, women with higher consumption in both caffeinated and decaffeinated coffee used the drip brewing method, defined as coffee prepared in a coffee machine with a filter or by letting coffee drip into a cup from a coffee filter (50).

Our study has several strengths. First, a large study population of multiethnic women was evaluated. Second, our prospective study design measured multiple lifestyle factors and confounders to allow for potential confounding to accounted for. This prospective study design was suitable to capture the long-term effects of coffee intake, and less prone to recall and selection bias compared to a case-control study design.

Our study has several limitations. Due to the nature of our observational study, it is inferior to a case-cross over design at capturing recent coffee intake and its temporal effects on acute CHD event. There was a possibility of unmeasured confounding even after multivariable adjustment in our analyses to bias our results. Also, our association was possibly affected from confounding by indication in that the participants in the none coffee drinker group might have stopped drinking coffee prior to the study due to higher risk of CHD and therefore our inverse association may be attributed to the higher CHD risk in this group and not any beneficial effects of moderate caffeinated coffee consumption. In terms of brewing methods, we could not determine the different long-term effect between boiled coffee (unfiltered coffee) and filtered coffee on CHD development that can elucidate favorable effects from filtered coffee due to a small sample size of the boiled coffee drinkers. From a perspective of gene-environment interaction, our study did not consider different genotype that might explain individual coffee metabolizers and their effects on CHD in variations. We did not suffer from a large loss-to follow up, however, our results are not generalizable to older males and it is uncertain that these findings imply the same effects for younger women or older women with established CHD.

CONCLUSION

This study of postmenopausal women showed that long-term caffeinated coffee intake (≥2 cups) may be beneficial on reducing CHD risk. There was no evidence of harm for CHD from drinking total, caffeinated, and decaffeinated coffee. The results and conclusion should be taken with caution. Further studies and evidence are needed for the association.

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TABLE 1A
Baseline characteristics according to categories of caffeinated coffee intake

	Caffeinated coffee intake				
	None	**1 cup/d**	**2-3 cups/d**	**≥4 cups/d**	***P* value[1]**
	n=38326	n=14811	n=25022	n=8300	
Sociodemographic [*n* (%)]					
Age					
<50-59	12690(33.1)	4398(29.7)	8160(32.6)	2892(34.8)	<0.001
60-69	16545(43.2)	6517(44.0)	11139(44.5)	3822(46.0)	
70-79+	9091(23.7)	3896(26.3)	5723(22.9)	1586(19.1)	
Race/Ethnicity					
American Indian or Alaskan Native	144(0.4)	66(0.4)	118(0.5)	42(0.5)	<0.001
Asian or Pacific Islander	1226(3.2)	656(4.4)	561(2.2)	80(1.0)	
Black or African American	4170(10.9)	1252(8.5)	1165(4.7)	162(2.0)	
Hispanic/Latina	1172(3.1)	773(5.2)	996(4.0)	206(2.5)	
White (not of Hispanic origin)	31075(81.3)	11834(80.1)	21851(87.6)	7720(93.2)	
Other	435(1.1)	184(1.2)	261(1.0)	70(0.8)	
Education					
less than HS graduate	1778(4.6)	743(5.0)	1216(4.9)	408(4.9)	<0.001
HS graduate	6018(15.7)	2283(15.4)	3988(15.9)	1529(18.4)	
some college	13471(35.1)	5299(35.8)	9222(36.9)	3154(38.0)	
college graduate	16731(43.7)	6366(43.0)	10430(41.7)	3146(37.9)	
missing/not reported	328(0.9)	120(0.8)	166(0.7)	63(0.8)	
Family income					
<$20,000	5516(15.6)	2141(15.6)	3424(14.7)	1236(16.0)	<0.001
$20,000-$74,999	22406(63.3)	8705(63.4)	14970(64.2)	5064(65.4)	
≥$75,000	7465(21.1)	2887(21.0)	4918(21.1)	1447(18.7)	
Marital status					
Never married	1915(5.0)	669(4.5)	1120(4.5)	391(4.7)	

Divorced/separated	12222(32.0)	4873(33.1)	8190(32.9)	2779(33.6)	0.002
Presently married	24023(63.0)	9186(62.4)	15608(62.6)	5089(61.6)	
U.S. Region					
Midwest	8676(22.6)	2692(18.2)	5269(21.1)	2496(30.1)	<0.001
Northeast	8152(21.3)	3783(25.5)	6128(24.5)	7465(21.3)	
South	10019(26.1)	4049(27.3)	6387(25.5)	1681(20.3)	
West	11479(30.0)	4287(28.9)	7238(28.9)	2358(28.4)	
Physiologic [*n* (%)]					
BMI					
<18.00	291(0.8)	106(0.7)	148(0.6)	70(0.8)	<0.001
18.00-24.99	15490(40.6)	6040(41.0)	9961(40.0)	3228(39.1)	
25.00-29.99	12390(32.5)	5037(34.2)	8714(35.0)	2959(35.8)	
30+	9950(26.1)	3557(24.1)	6090(24.4)	2005(24.3)	
Systolic blood pressure					
≤120 mm Hg	15215(39.8)	5676(38.4)	10106(40.4)	3752(45.2)	<0.001
120-140 mm Hg	15211(39.7)	5954(40.2)	10133(40.5)	3169(38.2)	
>140 mm Hg	7846(20.5)	3163(21.4)	4752(19.0)	1372(16.5)	
Diastolic blood pressure					
<90 mm Hg	35677(93.2)	13777(93.2)	23498(94.0)	7873(95.0)	<0.001
90+ mm Hg	2597(6.8)	1008(6.8)	1488(6.0)	417(5.0)	
Lifestyle					
Smoking status [*n* (%)]					
Never-smoker	21786(57.5)	7783(53.3)	11136(45.1)	3033(37.0)	<0.001
Former smoker	14702(38.8)	6156(42.2)	11690(47.4)	3798(46.3)	
Current smoker	1390(3.7)	657(4.5)	1862(7.5)	1366(16.7)	
Alcohol intake [*n* (%)]					
Non-drinker	13887(36.5)	4043(27.5)	5484(22.0)	1968(23.8)	<0.001
Light drinker	12572(33)	4860(33.1)	7399(29.7)	2531(30.7)	

Moderate drinker	8211(21.6)	3933(26.7)	7634(30.7)	2400(29.1)	
Heavy drinker	3388(8.9)	1867(12.7)	4376(17.6)	1357(16.4)	
Total energy intake [*n* (%)]					
600-1499 kcal/day	19540(53.2)	7517(52.7)	12066(49.8)	3587(44.6)	<0.001
1500-1999 kcal/day	10315(28.1)	4104(28.8)	7159(29.6)	2386(29.7)	
2000-2499 kcal/day	4452(12.1)	1694(11.9)	3237(13.4)	1271(15.8)	
2500-2999 kcal/day	1556(4.2)	609(4.3)	1137(4.7)	486(6.0)	
3000-5000 kcal/day	876(2.4)	336(2.4)	613(2.5)	308(3.8)	
Physical activity (MET-h[3]/wk)	14.1(14.7)[2]	13.4(13.9)	13.7(14.3)	13(14.1)	<0.001
Postmenopausal hormone use [*n* (%)]					
Never used hormones	11224(29.8)	4255(29.3)	7402(30.1)	2792(34.3)	<0.001
Past hormone user	7977(21.2)	2942(20.2)	5130(20.9)	1752(21.5)	
Current hormone user	18438(49.0)	7345(50.5)	12036(49.0)	3597(44.2)	
Oral contraceptive use [*n* (%)]					
Yes	15518(40.5)	5757(38.9)	10367(41.4)	3541(42.7)	<0.001
Medical history [n (%)]					
Dyslipidemia					
Yes	5712(14.9)	2219(15.0)	3259(13.0)	870(10.5)	<0.001
Hypertension					
Yes	13128(34.3)	5174(34.9)	7626(30.5)	2066(24.9)	<0.001
Diabetes mellitus					
Yes	1641(4.3)	561(3.8)	783(3.1)	216(2.6)	<0.001
Hysterectomy					
Yes	16480(43.0)	6237(42.1)	10029(40.1)	3057(36.8)	<0.001
Family history of CHD					
Yes	4492(11.7)	1593(10.8)	2957(11.8)	1028(12.4)	0.001

[1]Calculated by using one-way analysis of variance (ANOVA) for a continuous variable and chi-square tests for categorical variables.
[2]Mean (SD).
[3]MET-h, metabolic equivalent task hours.

TABLE 1B
Baseline characteristics according to categories of decaffeinated coffee intake

	Decaffeinated coffee intake				
	None	**1 cup/d**	**2-3 cups/d**	**≥4 cups/d**	***P* value[1]**
	n=59848	n=12818	n=11123	n=2670	
Sociodemographic [n (%)]					
Age					
<50-59	20237(33.8)	3801(29.7)	3283(29.5)	819(30.7)	<0.001
60-69	25826(43.2)	5792(45.2)	5140(46.2)	1265(47.4)	
70-79+	13785(23.0)	3225(25.2)	2700(24.3)	586(21.9)	
Race/Ethnicity					
American Indian or Alaskan Native	255(0.4)	54(0.4)	50(0.5)	11(0.4)	<0.001
Asian or Pacific Islander	2038(3.4)	334(2.6)	133(1.2)	18(0.7)	
Black or African American	5299(8.9)	890(7.0)	503(4.5)	57(2.1)	
Hispanic/Latina	2375(4.0)	437(3.4)	284(2.6)	51(1.9)	
White (not of Hispanic origin)	49035(82.2)	10930(85.5)	10015(90.3)	2500(93.7)	
Other	670(1.1)	145(1.1)	105(0.9)	30(1.1)	
Education					
less than HS graduate	2944(4.9)	612(4.8)	495(4.5)	94(3.5)	<0.001
HS graduate	9590(16)	1965(15.3)	1816(16.3)	447(16.7)	
some college	21875(36.6)	4426(34.5)	3891(35.0)	954(35.7)	
college graduate	24955(41.7)	5716(44.6)	4845(43.6)	1157(43.3)	
missing/not reported	484(0.8)	99(0.8)	76(0.7)	18(0.7)	
Family income					
<$20,000	9089(16.4)	1685(14.2)	1229(11.9)	314(12.8)	<0.001
$20,000-$74,999	35325(63.6)	7504(63.1)	6699(65.0)	1617(65.9)	
≥$75,000	11108(20.0)	2703(22.7)	2384(23.1)	522(21.3)	
Marital status					
Never married	2938(4.9)	616(4.8)	433(3.9)	108(4.1)	<0.001
Divorced/separated	20341(34.1)	3865(30.3)	3067(27.7)	791(29.7)	
Presently married	36291(60.9)	8277(64.9)	7578(68.4)	1760(66.2)	
U.S. Region					

Midwest	13091(21.9)	2588(20.2)	2634(23.7)	820(30.7)	<0.001
Northeast	13164(22.0)	3415(26.6)	2710(24.4)	539(20.2)	
South	15326(25.6)	3419(26.7)	2808(25.2)	583(21.8)	
West	18267(30.5)	3396(26.5)	2971(26.7)	728(27.3)	
Physiologic [*n* (%)]					
BMI					
<18.00	463(0.8)	83(0.7)	50(0.5)	19(0.7)	<0.001
18.00-24.99	23625(39.7)	5421(42.5)	4602(41.6)	1071(40.3)	
25.00-29.99	19898(33.4)	4328(33.9)	3903(35.3)	971(36.5)	
30+	15565(26.1)	2927(22.9)	2513(22.7)	597(22.5)	
Systolic blood pressure					
≤120 mm Hg	23817(39.8)	5198(40.6)	4557(41.0)	1177(44.1)	<0.001
120-140 mm Hg	24007(40.2)	5035(39.3)	4393(39.5)	1032(38.7)	
>140 mm Hg	11949(20.0)	2567(20.1)	2158(19.4)	459(17.2)	
Diastolic blood pressure					
<90 mm Hg	55782(93.3)	12053(94.2)	10448(94.1)	2542(95.3)	<0.001
90+ mm Hg	3986(6.7)	742(5.8)	657(5.9)	125(4.7)	
Lifestyle					
Smoking status [*n* (%)]					
Never-smoker	31248(52.9)	6540(51.7)	4985(45.4)	965(36.7)	<0.001
Former smoker	23925(40.5)	5558(44.0)	5420(49.4)	1443(54.8)	
Current smoker	3934(6.7)	543(4.3)	574(5.2)	224(8.5)	
Alcohol intake [*n* (%)]					
Non-drinker	18675(31.4)	3424(26.9)	2637(23.8)	646(24.3)	<0.001
Light drinker	18899(31.8)	4191(32.9)	3447(31.2)	825(31.1)	
Moderate drinker	14423(24.3)	3604(28.3)	3382(30.6)	769(29.0)	
Heavy drinker	7455(12.5)	1520(11.9)	1598(14.4)	415(15.6)	
Total energy intake [*n* (%)]					
600-1499 kcal/day	29505(51.3)	6383(51.6)	5513(51.1)	1309(50.2)	<0.001
1500-1999 kcal/day	16349(28.4)	3600(29.1)	3247(30.1)	768(29.4)	
2000-2499 kcal/day	7411(12.9)	1572(12.7)	1346(12.5)	325(12.5)	
2500-2999 kcal/day	2679(4.7)	523(4.2)	456(4.2)	130(5.0)	
3000-5000 kcal/day	1542(2.7)	296(2.4)	218(2.0)	77(3.0)	

Physical activity (MET-h[3]/wk)	13.5(14.5)[2]	14.1(14.0)	14.7(14.2)	15.1(14.5)	<0.001
Postmenopausal hormone use [*n* (%)]					
Never	18192(30.9)	3626(28.8)	3074(28.2)	781(30.0)	<0.001
Past	12286(20.9)	2650(21.1)	2315(21.2)	550(21.1)	
Current	28335(48.2)	6296(50.1)	5509(50.6)	1276(48.9)	
Oral contraceptive use [*n* (%)]					
Yes	24580(41.1)	4979(38.8)	4507(40.5)	1117(41.8)	<0.001
Medical history [n (%)]					
Dyslipidemia					
Yes	8107(13.5)	1882(14.7)	1695(15.2)	376(14.1)	<0.001
Hypertension					
Yes	19419(32.4)	4217(32.9)	3595(32.3)	763(28.6)	<0.001
Diabetes mellitus					
Yes	2314(3.9)	435(3.4)	365(3.3)	87(3.3)	0.002
Hysterectomy					
Yes	25065(41.9)	5245(40.9)	4465(40.1)	1028(38.5)	<0.001
Family history of CHD					
Yes	6906(11.5)	1479(11.5)	1337(12.0)	348(13.0)	0.062

[1]Calculated by using one-way analysis of variance (ANOVA) for a continuous variable and chi-square tests for categorical variables.
[2]Mean (SD).
[3]MET-h, metabolic equivalent task hours.

TABLE 2
HRs (and 95% CIs) for CHD according to total coffee, caffeinated, and decaffeinated coffee.[1]

			Model 1[2]		Model 2[3]		Model 3[4]	
	No. of cases	Person-years	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend
Total coffee[5]								
None	1762	297683	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cup/d	977	147438	1.04 (0.96, 1.13)	0.012	1.06 (0.98, 1.15)	0.004	1.03 (0.95, 1.12)	0.056
2-3 cups/d	1958	332524	0.96 (0.89, 1.02)		0.96 (0.89, 1.03)		0.96 (0.89, 1.03)	
≥4 cups/d	1202	217532	0.93 (0.86, 1.00)		0.90 (0.83, 0.98)		0.93 (0.86, 1.01)	
Caffeinated coffee								
None	2680	442112	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cup/d	1073	168946	1.02 (0.95, 1.10)	0.020	1.05 (0.97, 1.13)	0.001	1.04 (0.96, 1.12)	0.030
2-3 cups/d	1618	288533	0.92 (0.86, 0.98)		0.92 (0.86, 0.98)		0.93 (0.87, 1.00)	
≥4 cups/d	528	95586	0.94 (0.85, 1.03)		0.87 (0.78, 0.96)		0.92 (0.84, 1.02)	
Decaffeinated coffee								
None	4067	686377	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cups/d	872	148586	0.96 (0.89, 1.03)	0.333	0.98 (0.90, 1.05)	0.494	0.97 (0.90, 1.05)	0.599
2-3 cups/d	775	129050	0.96 (0.89, 1.04)		0.97 (0.90, 1.06)		0.98 (0.90, 1.06)	
≥4 cups/d	185	31164	0.96 (0.83, 1.12)		0.96 (0.82, 1.12)		0.97 (0.83, 1.14)	

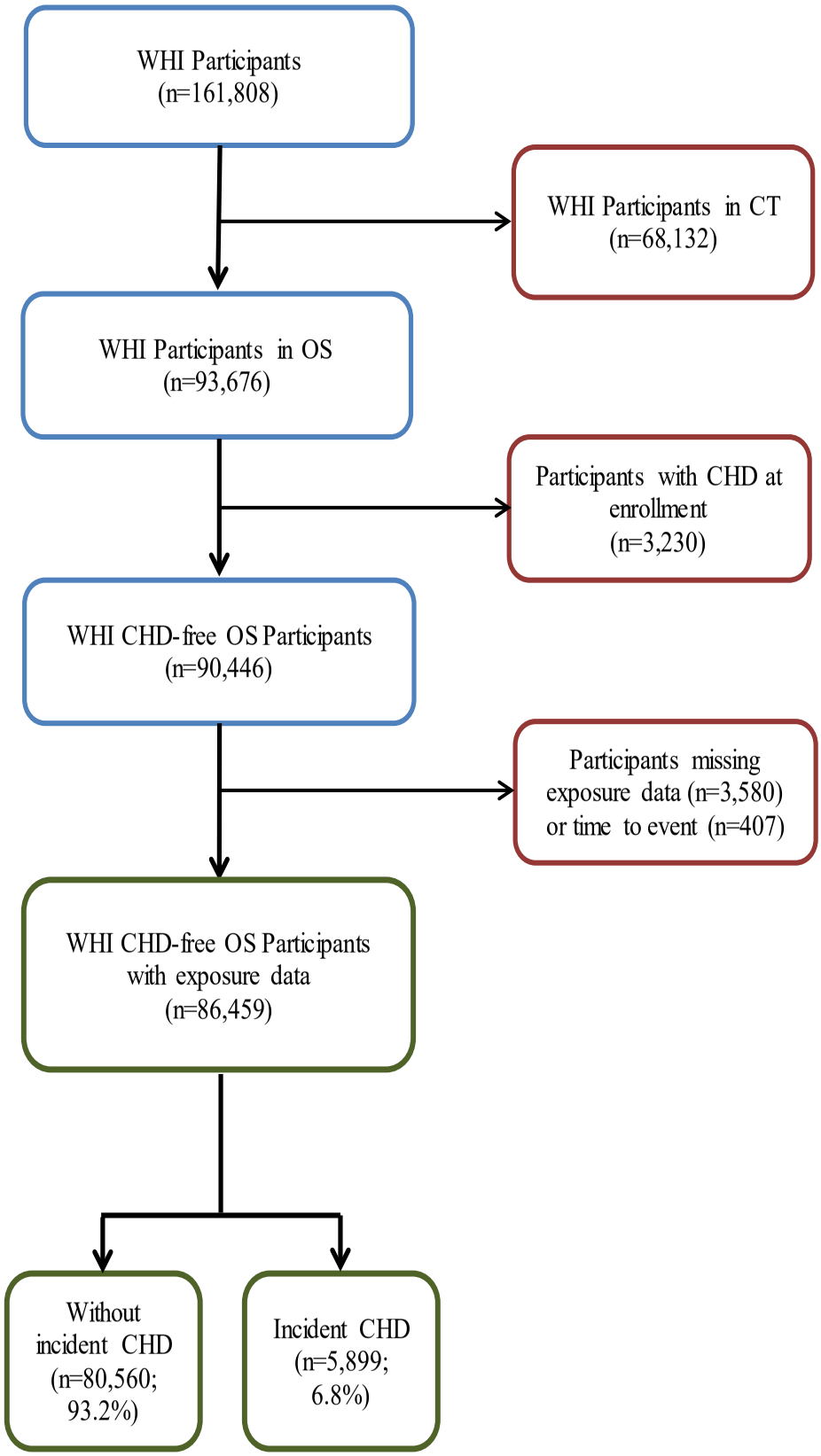
[1]Total coffee, caffeinated, and decaffeinated coffee were measured at baseline.
[2]Model 1 was adjusted for age and total energy intake.
[3]Model 2 was adjusted for model 1 plus race, education, family income, marital status, U.S. region, BMI, smoking status, alcohol intake, physical activity, postmenopausal hormone use, oral contraceptive use, diabetes mellitus, hysterectomy, and family history of CHD.
[4]Model 3 was adjusted for model 2 plus blood pressure, hypertension, and dyslipidemia.
[5]It is based on women who had a combination of caffeinated and decaffeinated coffee or either type of exclusive drinkers.

TABLE 3
Associations of coffee intake and CHD stratified by history of dyslipidemia, hypertension, diabetes, and smoking

	Total coffee HR (95% CI)[3]				***P*-trend**
	None	1 cup/d	2-3 cups/d	≥4 cups/d	
Dyslipidemia					
No	1.0 (Reference)	1.06 (0.96, 1.17)	0.97 (0.90, 1.05)	0.94 (0.86, 1.03)	0.19
Yes		1.00 (0.84, 1.19)	0.93 (0.80, 1.08)	0.88 (0.74, 1.05)	0.11
Hypertension					
No	1.0 (Reference)	1.05 (0.93, 1.20)	0.94 (0.85, 1.04)	0.93 (0.84, 1.04)	0.14
Yes		1.02 (0.91, 1.14)	1.00 (0.91, 1.11)	0.97 (0.86, 1.09)	0.28
Diabetes					
No	1.0 (Reference)	1.09 (0.99, 1.19)	0.97 (0.90, 1.05)	0.93 (0.86, 1.01)	0.16
Yes		0.86 (0.67, 1.11)	0.92 (0.75, 1.13)	0.83 (0.64, 1.07)	0.09
Smoking					
No[1]	1.0 (Reference)	1.04 (0.95, 1.13)	1.00 (0.93, 1.08)	1.00 (0.92, 1.09)	0.17
Yes[2]		0.91 (0.64, 1.29)	0.75 (0.57, 0.99)	0.74 (0.56, 0.97)	0.04
	Caffeinated coffee HR (95% CI)				***P*-trend**
	None	1 cup/d	2-3 cups/d	≥4 cups/d	
Dyslipidemia					
No	1.0 (Reference)	1.06 (0.97, 1.15)	0.94 (0.87, 1.01)	0.89 (0.80, 1.00)	0.01
Yes		1.03 (0.88, 1.21)	0.88 (0.76, 1.02)	0.83 (0.65, 1.06)	0.04
Hypertension					
No	1.0 (Reference)	1.03 (0.92, 1.15)	0.90 (0.82, 1.00)	0.95 (0.83, 1.09)	0.14
Yes		1.06 (0.95, 1.17)	0.96 (0.87, 1.06)	0.86 (0.73, 1.00)	0.05
Diabetes					
No	1.0 (Reference)	1.06 (0.98, 1.15)	0.92 (0.86, 0.99)	0.87 (0.78, 0.97)	<0.01
Yes		1.00 (0.79, 1.26)	0.91 (0.74, 1.13)	0.84 (0.60, 1.19)	0.25
Smoking					
No[1]	1.0 (Reference)	1.05 (0.97, 1.14)	0.96 (0.90, 1.03)	0.97 (0.87, 1.08)	0.26
Yes[2]		0.93 (0.68, 1.27)	0.74 (0.57, 0.95)	0.78 (0.58, 1.03)	0.06

	Decaffeinated coffee HR (95% CI)				*P*-trend
	None	1 cup/d	2-3 cups/d	≥4 cups/d	
Dyslipidemia					
No	1.0 (Reference)	0.97 (0.88, 1.06)	0.95 (0.86, 1.04)	1.02 (0.86, 1.21)	0.56
Yes		1.00 (0.85, 1.17)	1.04 (0.88, 1.24)	0.72 (0.49, 1.04)	0.37
Hypertension					
No	1.0 (Reference)	0.93 (0.83, 1.04)	0.95 (0.85, 1.07)	1.01 (0.82, 1.24)	0.64
Yes		1.01 (0.91, 1.12)	0.99 (0.88, 1.11)	0.93 (0.74, 1.18)	0.58
Diabetes					
No	1.0 (Reference)	0.99 (0.92, 1.08)	0.98 (0.90, 1.07)	0.97 (0.83, 1.14)	0.67
Yes		0.82 (0.63, 1.07)	0.87 (0.67, 1.14)	0.76 (0.42, 1.36)	0.14
Smoking					
No[1]	1.0 (Reference)	0.97 (0.89, 1.05)	1.00 (0.92, 1.09)	0.99 (0.84, 1.17)	0.90
Yes[2]		1.01 (0.74, 1.37)	0.80 (0.57, 1.12)	1.06 (0.66, 1.69)	0.73

[1]Either never or former smokers were analyzed.
[2]Current smokers were analyzed.
[3]It is based on women who had a combination of caffeinated and decaffeinated coffee or either type of exclusive drinkers.



Supplemental Figure 1
Flowchart of the analytic sample.

Supplemental Table 1
Baseline characteristics stratified by CHD status

	No CHD	CHD	*P*-value[1]
	n=80560	n=5899	
Sociodemographic [*n* (%)]			
Age			
<50-59	27208(33.8)	932(15.8)	<0.001
60-69	35313(43.8)	2710(45.9)	
70-79+	18039(22.4)	2257(38.3)	
Race/Ethnicity			
American Indian or Alaskan Native	336(0.4)	34(0.6)	<0.001
Asian or Pacific Islander	2443(3.0)	80(1.4)	
Black or African American	6202(7.7)	547(9.3)	
Hispanic/Latina	2960(3.7)	187(3.2)	
White (not of Hispanic origin)	67503(84.0)	4977(84.7)	
Other	898(1.1)	52(0.9)	
Education			
less than high school graduate	3760(4.7)	385(6.5)	<0.001
High school graduate	12661(15.7)	1157(19.6)	
some college	28853(35.8)	2293(38.9)	
college graduate	34662(43.0)	2011(34.1)	
missing/not reported	624(0.8)	53(0.9)	
Family income			
<$20,000	11141(14.9)	1176(21.6)	<0.001
$20,000-$74,999	47535(63.6)	3610(66.3)	
≥$75,000	16057(21.5)	660(12.1)	
Marital status			
Never married	3874(4.8)	221(3.8)	<0.001

Divorced/separated	25742(51.3)	2322(51.8)	
Presently married	50584(63.1)	3322(56.6)	
U.S. Region			
Midwest	18376(22.8)	1452(24.6)	<0.001
Northeast	20694(25.7)	1442(24.4)	
South	17748(22.0)	1385(23.5)	
West	23742(29.5)	1620(27.5)	
Physiologic [*n* (%)]			
BMI			
<18.00	583(0.7)	32(0.5)	<0.001
18.00-24.99	32862(41.0)	1857(31.7)	
25.00-29.99	27036(33.7)	2064(35.2)	
30+	19691(24.6)	1911(32.6)	
Systolic blood pressure			
<= 120 mm Hg	30907(40.5)	3842(38.2)	<0.001
120-140 mm Hg	30322(39.7)	4145(41.2)	
>140 mm Hg	15058(19.7)	2075(20.6)	
Diastolic blood pressure			
<90 mm Hg	75442(93.8)	5383(91.5)	<0.001
90+ mm Hg	5007(6.2)	503(8.5)	
Lifestyle			
Smoking status [*n* (%)]			
Never-smoker	41001(51.5)	2737(47.1)	<0.001
Former smoker	33749(42.4)	2597(44.7)	
Current smoker	4801(6.0)	474(8.2)	
Alcohol intake [*n* (%)]			
Non-drinkers	23277(29.1)	2105(35.9)	<0.001
Light drinkers	25453(31.8)	1909(32.6)	
Moderate drinkers	20968(26.2)	1210(20.7)	

Heavy drinkers	10353(12.9)	635(10.8)	
Total energy intake [*n* (%)]			
600-1499 kcal/day	39779(51.3)	2931(51.8)	0.109
1500-1999 kcal/day	24940(28.9)	3054(27.5)	
2000-2499 kcal/day	9918(12.8)	736(13.0)	
2500-2999 kcal/day	3504(4.5)	284(5.0)	
3000-5000 kcal/day	1978(2.5)	155(2.7)	
Physical activity (MET-h[3]/wk)	14(1447.1)[2]	12(1318.1)	<0.001
Postmenopausal hormone use [*n* (%)]			
Never used hormones	23725(30.0)	1948(33.8)	<0.001
Past hormone user	16363(20.7)	1438(25.0)	
Current hormone user	39043(49.3)	2373(41.2)	
Oral contraceptive use [*n* (%)]			
Yes	33336(41.4)	1847(31.3)	<0.001
Medical history [*n* (%)]			
Dyslipidemia			
Yes	10770(13.4)	1290(21.9)	<0.001
Hypertension			
Yes	24940(31.0)	3054(51.8)	<0.001
Diabetes			
Yes	2545(3.2)	656(11.1)	<0.001
Hysterectomy			
Yes	33061(41.0)	2742(46.5)	<0.001
Family history of CHD			
Yes	9148(11.4)	922(15.6)	<0.001

[1]Calculated by using one-way analysis of variance (ANOVA) for a continuous variable and chi-square tests for categorical variables.
[2]Mean (SD).
[3]MET-h, metabolic equivalent task hours.

Supplemental Table 2
HRs (and 95% CIs) for CHD according to individual mediators (blood pressure, hypertension, and dyslipidemia)

	Model 1[1]		Model 2[2]		Model 3[3]	
Caffeinated coffee	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend
None	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cup/d	1.05 (0.97, 1.13)	<0.001	1.04 (0.96, 1.12)	0.002	1.05 (0.97, 1.13)	<0.001
2-3 cup/d	0.92 (0.86, 0.98)		0.93 (0.87, 1.00)		0.92 (0.86, 0.99)	
≥4 cup/d	0.88 (0.80, 0.98)		0.91 (0.82, 1.01)		0.88 (0.80, 0.98)	

[1]Model 1 was adjusted for covariates in the fully adjusted model (Model 2 from Table 3) plus blood pressure.
[2]Model 2 was adjusted for covariates in the fully adjusted model (Model 2 from Table 3) plus hypertension.
[3]Model 3 was adjusted for covariates in the fully adjusted model (Model 2 from Table 3) plus dyslipidemia.

Supplemental Table 3
HRs (and 95% CIs) for hard CHD according to total coffee, caffeinated, and decaffeinated coffee.[1]

	Model 1[2]		Model 2[3]		Model 3[4]	
	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend
Total coffee[5]						
None	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cup/d	1.02 (0.92, 1.12)	0.001	1.03 (0.93, 1.15)	<0.001	1.03 (0.90, 1.12)	0.002
2-3 cups/d	0.89 (0.82, 0.97)		0.89 (0.82, 0.98)		0.90 (0.82, 0.98)	
≥4 cups/d	0.87 (0.79, 0.96)		0.84 (0.75, 0.93)		0.86 (0.78, 0.96)	
Caffeinated coffee						
None	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cup/d	1.04 (0.95, 1.14)	0.060	1.06 (0.96, 1.17)	0.002	1.05 (0.96, 1.12)	0.029
2-3 cups/d	0.91 (0.84, 0.99)		0.90 (0.83, 0.98)		0.91 (0.84, 1.00)	
≥4 cups/d	0.94 (0.83, 1.06)		0.85 (0.75, 0.97)		0.90 (0.79, 1.03)	
Decaffeinated coffee						
None	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cups/d	0.88 (0.80, 0.97)	0.003	0.89 (0.81, 0.99)	0.009	0.89 (0.80, 0.99)	0.013
2-3 cups/d	0.83 (0.75, 0.92)		0.84 (0.75, 0.94)		0.84 (0.75, 0.94)	
≥4 cups/d	0.92 (0.76, 1.12)		0.93 (0.76, 1.14)		0.94 (0.77, 1.15)	

[1]Total coffee, caffeinated, and decaffeinated coffee were measured at baseline.
[2]Model 1 was adjusted for age and total energy intake.
[3]Model 2 was adjusted for model 1 plus race, education, family income, marital status, U.S. region, BMI, smoking status, alcohol intake, physical activity, postmenopausal hormone use, oral contraceptive use, diabetes mellitus, hysterectomy, and family history of CHD.
[4]Model 3 was adjusted for model 2 plus blood pressure, hypertension, and dyslipidemia.
[5]It is based on women who had a combination of caffeinated and decaffeinated coffee or either type of exclusive drinkers.

Supplemental Table 4
HRs (and 95% CIs) for hard CHD according to individual mediators (blood pressure, hypertension, and dyslipidemia)

	Model 1[1]		Model 2[2]		Model 3[3]	
Caffeinated coffee	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend	HR (95% CI)	*P*-trend
None	1.0 (Reference)		1.0 (Reference)		1.0 (Reference)	
1 cup/d	1.06 (0.96, 1.17)	0.004	1.05 (0.96, 1.16)	0.025	1.06 (0.97, 1.17)	0.003
2-3 cup/d	0.90 (0.83, 0.98)		0.91 (0.84, 1.00)		0.90 (0.83, 0.99)	
≥4 cup/d	0.86 (0.76, 0.98)		0.90 (0.79, 1.02)		0.86 (0.75, 0.98)	

[1]Model 1 was adjusted for covariates in the fully adjusted model (Model 2 from Table 3) plus blood pressure.
[2]Model 2 was adjusted for covariates in the fully adjusted model (Model 2 from Table 3) plus hypertension.
[3]Model 3 was adjusted for covariates in the fully adjusted model (Model 2 from Table 3) plus dyslipidemia.