COFFEE, CAFFEINE, AND CARDIOVASCULAR DISEASE IN MEN

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Abstract *Background.* For many years, an association between coffee consumption and the risk of coronary heart disease has been suspected. Although based on small numbers of end points, a prospective study has suggested a particularly strong association between recent coffee drinking and the incidence of cardiovascular disease.

Methods. We examined prospectively the relation of coffee consumption with the risk of myocardial infarction, need for coronary-artery bypass grafting or angioplasty, and risk of stroke in a cohort of 45,589 U.S. men who were 40 to 75 years old in 1986 and who had no history of cardiovascular disease.

Results. During two years of follow-up observation, 221 participants had a nonfatal myocardial infarction or died of coronary heart disease, 136 underwent coronary-artery surgery or angioplasty, and 54 had a stroke. Total coffee consumption was not associated with an increased risk of coronary heart disease or stroke. The age-adjusted relative risk for all cardiovascular disease among participants who drank four or more cups of coffee per day was 1.04 (95 percent confidence interval, 0.74 to 1.46). Increasing levels of consumption of caffeinated coffee were not associated with higher risks of cardiovascular disease. Higher consumption of decaffeinated coffee, however, was associated with a marginally significant increase in the risk of coronary heart disease (relative risk, 1.63; 95 percent confidence interval, 1.02 to 2.60). Finally, we observed no pattern of increased risk across the subgroups of participants with increasing intakes of caffeine from all sources. Adjustment for major cardiovascular-risk indicators, dietary intake of fats, and cholesterol intake did not materially alter these associations.

Conclusions. These findings do not support the hypothesis that coffee or caffeine consumption increases the risk of coronary heart disease or stroke. (N Engl J Med 1990; 323:1026-32.)

FOR many years, an association has been suspected between coffee drinking and cardiovascular disease, in particular coronary heart disease.[1-22] Studies have been inconsistent, however, fueling a debate about the hazards of coffee drinking.[23] Although findings in several case–control studies support an elevated risk of myocardial infarction among men and women with high coffee intakes,[2,3,9,18-20] others do not,[4,7,11] and reports of prospective studies show similarly conflicting results.[5,6,8-10,12-17,21,22] It has been suggested that some negative findings may be due to the relatively small size of most of the studies or the long time between the assessment of coffee intake and the occurrence of cardiovascular events.[9,11,14,24-27] In a study by LaCroix and coworkers,[14] of 1130 male medical students followed for up to 35 years, those who drank five or more cups of coffee daily were reported to have a 2.5-fold risk of coronary heart disease as compared with nondrinkers. This risk was greatest for coffee use reported within a few years before the event, and the authors speculated that the absence of a positive association in some other studies was due to an excessively long period between the assessment of coffee intake and the occurrence of cardiovascular events.[14]

Studies addressing the mechanisms by which coffee consumption increases cardiovascular disease also offer conflicting results. Coffee may raise serum cholesterol levels, although this effect is probably influenced by the brewing method.[28,29] In a preliminary report of a randomized trial, decaffeinated coffee increased levels of low-density lipoprotein cholesterol, and findings in a second double-blind study did not support an effect of caffeine.[30,31] Coffee may also raise blood pressure[32-34] and induce cardiac arrhythmias.[35] The best-known pharmacologically active substance in coffee is caffeine, but effects may be mediated by a variety of other substances.[34]

In this paper we examine the relation of coffee, caffeine, and tea intake with the incidence of coronary heart disease and cerebrovascular disease in a large cohort of U.S. men participating in the Health Professionals Follow-up Study.

METHODS

Population for Analysis

The Health Professionals Follow-up Study is a longitudinal study of risk factors for cardiovascular disease and cancer among 51,529 men in the United States who were 40 to 75 years of age in 1986. The study population consists of 29,683 dentists, 3745 optometrists, 2218 osteopathic physicians, 4185 pharmacists, 1600 podiatrists, and 10,098 veterinarians who returned a mailed questionnaire in 1986. These were 33 percent of the potentially eligible men to whom we initially mailed questionnaires. From the base-line questionnaire we obtained information on medical history, past and present smoking habits, and family history of coronary heart disease and stroke.

Among the 51,529 health professionals who returned the base-line questionnaire, a total of 4350 cohort members reported a history of cardiovascular disease, including 2290 with a previous myocardial infarction, 1875 with previous coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty, 2154 with angina pectoris, and 466 with a stroke or transient ischemic attack. For the present analysis, after excluding 222 men who did not provide data on coffee use and 1368 men who did not provide complete information on diet, height, and weight in 1986, we included the remaining 45,589 members of the cohort who were free of reported cardiovascular disease at the start of the follow-up period.

Assessment of Diet

As part of the base-line questionnaire, the participants completed a semiquantitative food-frequency questionnaire regarding the average use of 131 foods and beverages in the previous year. This questionnaire included questions about the use of caffeinated and

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decaffeinated coffee and tea. There were nine possible responses regarding the frequency with which subjects drank one cup of these beverages: never or less than once a month, one to three times a month, once a week, two to four times a week, five or six times a week, once a day, two to three times a day, four to five times a day, and six or more times a day. Nutrient intakes were computed from the reported frequency of consumption of each specified unit of food or beverage and the nutrient content of the specified portions.[36] Total caffeine intake was calculated by summing the amounts contained in the coffee, brownies, candies, chocolate and chocolate cookies, cocoa, cola beverages, and tea consumed by the subjects. The caffeine score was calculated with use of the caffeine content of the specified portion size for each food, multiplied by a weight proportional to its frequency of use, with once-daily use equal to 1.0.

To evaluate the validity of the reported consumption of coffee and tea, as well as other dietary factors, 127 participants residing in eastern Massachusetts weighed and recorded all foods and beverages consumed at each meal for two one-week periods six to eight months apart; several weeks after the second period they completed another dietary questionnaire identical to the base-line questionnaire. The mean total consumption of coffee in cups per day was 1.83 on the base-line questionnaire, 1.56 according to the dietary records, and 1.75 on the repeat diet questionnaire. Spearman correlations were 0.82 between the dietary records and both the base-line and repeat questionnaires. For tea, the mean numbers of cups per day were 0.47 on the base-line questionnaire, 0.51 according to dietary records, and 0.55 on the repeat diet questionnaire. Spearman correlations were 0.68 between the dietary records and the base-line questionnaire and 0.75 between the records and the repeat questionnaire.

Morbidity and Mortality Follow-up

All members of the cohort received the first mailing of a biennial follow-up questionnaire in January 1988. Participants were asked whether they had experienced a myocardial infarction or cerebrovascular accident or had undergone coronary-artery surgery or angioplasty since January 1986. After up to six mailings, 96 percent of the population enrolled in 1986 returned the follow-up questionnaire.[37] Deaths were ascertained by reports of family members, from questionnaires returned by the postal system, or by reports from the participants' professional organizations. In addition, the vital status of nonresponding members of the cohort was assessed with the use of the computerized National Death Index. This method has previously been shown to be highly sensitive in identifying deaths in a similar study among women.[38]

When a report of myocardial infarction, stroke, or death from cardiovascular disease was identified from the questionnaire or vital records, we asked for permission from the participant (or next of kin for decedents) to obtain hospital records for confirmation of the self-reported disease. The primary end points for this study were fatal and nonfatal myocardial infarction, coronary-artery bypass grafting or percutaneous coronary angioplasty, total coronary heart disease, fatal and nonfatal stroke, and total cardiovascular disease. A definite myocardial infarction was classified according to the criteria of the World Health Organization and required symptoms and either typical electrocardiographic changes or elevation of serum cardiac enzyme levels.[39] A definite stroke was classified as confirmed if the criteria of the National Survey of Stroke were met.[40] Incident cases of nonfatal myocardial infarction and nonfatal stroke were classified as probable if hospital records could not be obtained but the event required hospitalization and was corroborated by additional information from a letter or telephone interview with the participant. Coronary-artery bypass grafting or percutaneous transluminal coronary angioplasty was based on self-report; hospital records obtained for a sample of half the men confirmed the self-report in 96 percent of the cases.

A death was considered due to myocardial infarction if confirmed by hospital records or autopsy reports. In addition, the event was recorded as a fatal myocardial infarction if coronary heart disease was listed on the death certificate as the underlying cause of death in the absence of another plausible cause, and if we obtained evidence from hospital records or interviews with the next of kin that the subject had been given a diagnosis of coronary heart disease before the terminal event but after entry into the study. At no time did we use death-certificate classification alone to categorize a death as due to coronary heart disease. Sudden death was defined as death occurring within an hour of the onset of symptoms in a man with no previous serious illness, for which no more plausible cause than coronary heart disease could be found. For this analysis, sudden cardiac death was included with fatal myocardial infarction. Fatal strokes were classified as definite if they were verified by hospital records or autopsy, or as probable if stroke was listed as the underlying cause on the death certificate. In this study, 81 percent of the nonfatal and fatal myocardial infarctions and 55 percent of the nonfatal and fatal strokes were classified as definite. In the primary analysis, definite and probable coronary and cerebrovascular end points were combined. For the present analysis, we considered only cases of cardiovascular disease that occurred during the first two years of follow-up — that is, between the return of the base-line questionnaire and January 1, 1988.

Statistical Analysis

For each participant, person-months of follow-up were counted from the date of the return of the 1986 questionnaire to January 1, 1988, or for those who had coronary heart disease or a stroke or who died from another cause, up to the date of the event. Each participant could contribute only one end point to the category of total coronary heart disease or total cardiovascular disease, the first event being counted. However, the data for one subject could be considered in more than one analysis of specific end points. Thus, the number of cases in analyses of total cardiovascular events was slightly smaller than the sum of the cases in analyses of specific end points. We allocated person-months of follow-up according to the 1986 exposure status and calculated incidence rates as the number of events divided by the person-time of follow-up. Incidence rates were age-adjusted by direct standardization, with the use of five-year age groups and the total cohort as the standard population.

Relative risks (incidence-rate ratios) were calculated as a measure of association by dividing the rate of disease among the exposed (coffee-drinking) groups by the rate among those who were not exposed.[41] Age-adjusted relative risks were calculated after stratification according to five-year age categories.[41] In addition, relative risks were adjusted for multiple variables simultaneously by means of logistic regression analysis.[42] The model contained terms for age (in five-year age categories), quintiles of Quetelet's index (weight in kilograms divided by the square of the height in meters), smoking habits (current smoker, classified according to the number of cigarettes smoked per day; former smoker; or never smoked), history of diabetes mellitus (yes or no), seven categories of alcohol use, parental history of myocardial infarction (in neither parent, in one or both parents before 61 years of age, or in one or both after 60 years of age), specific health profession of each subject, and quintiles of dietary intake of energy, cholesterol, and saturated, polyunsaturated, and monounsaturated fats. In an additional analysis, adjustments were made for histories of hypertension (yes or no) and hypercholesterolemia (yes or no), which could mediate an effect of coffee on cardiovascular disease.

To examine whether the effects of coffee drinking were modified by age and smoking habits, age-adjusted relative risks were calculated separately for participants younger than 60 years of age and those who were 60 or older. In addition, all analyses were repeated after the exclusion of events occurring during the first year of follow-up to address the possible effect of subclinical cardiovascular symptoms on the dietary patterns, and when only definite events were included.

Results

Among the 45,589 men free of diagnosed coronary heart disease and cerebrovascular diseases at the start of the study, 181 participants experienced a nonfatal myocardial infarction, 136 underwent coronary-artery surgery or angioplasty, and 54 had a stroke during two years of follow-up. In addition, 40 men died of myocardial infarction or sudden death. Table 1 presents the general characteristics, the prevalence of cardiovascular-risk indicators, and the intake of fat

Table 1. Characteristics of the Participants, According to Their Consumption of Coffee.*

Characteristic	Total Group (N = 45,589)	No Coffee (N = 7592)	Any Coffee (N = 37,997)	Caffeinated Coffee† (N = 31,679)	Decaffeinated Coffee† (N = 23,215)
Age (yr)	54.5±0.04	52.1±0.11	55.0±0.05	54.1±0.08	56.6±0.13
Quetelet's index‡	25.5±0.02	25.2±0.04	25.6±0.02	25.7±0.03	25.2±0.04
Current smoker (%)	10	4	11	12	9
History of hypertension (%)	20	17	21	20	22
History of hypercholesterolemia (%)	11	11	11	10	12
Family history of CHD (%)§	0.3	0.3	0.3	0.3	0.3
Diabetes mellitus (%)	2.6	2.0	2.7	2.6	2.8
Fat intake (g/day)					
Total	70.4	68.1	70.9	72.2	70.1
Saturated	24.7	23.6	24.8	25.4	24.3
Polyunsaturated	13.5	13.3	13.6	13.7	13.6
Cholesterol intake (mg/day)	327.2	302.9	331.4	339.0	325.0
Caffeine intake (mg/day)	236.7	52.6	268.6	312.3	211.1

*All values are standardized according to the age distribution of the cohort. Plus–minus values are means ±SEM.

†The use of caffeinated and the use of decaffeinated coffee are not mutually exclusive.

‡Values are the weight in kilograms divided by the square of the height in meters.

§Subject's father or mother had a myocardial infarction before the age of 61. CHD denotes coronary heart disease.

and caffeine according to coffee consumption. Of the participants, 83 percent drank coffee, and 69 percent reported the use of caffeinated coffee. Those who did not drink coffee were slightly younger and leaner than coffee consumers. Coffee consumers were more than twice as likely to smoke as those who did not drink coffee, but the proportion of smokers in the group as a whole was only 10 percent. Other characteristics were similar among the groups.

Total coffee consumption (caffeinated plus decaffeinated) was not associated with an increased risk of nonfatal myocardial infarction and fatal coronary heart disease, total coronary heart disease, stroke, or total cardiovascular disease (Table 2). As compared with the men who consumed no coffee, the age-adjusted relative risk of total cardiovascular disease among those who drank four or more cups per day was 1.04 (95 percent confidence interval, 0.74 to 1.46). Some suggestion of a trend for an increasing risk of having coronary-artery bypass grafting and coronary angioplasty with increasing consumption of coffee was observed; however, this was limited to an association with decaffeinated coffee (see next paragraph). After adjustment for present and past smoking habits, diabetes mellitus, alcohol use, dietary intake of cholesterol and saturated, monounsaturated, and polyunsaturated fat, family history of coronary heart disease, and profession, the relative risk of total cardiovascular disease among those consuming four or more cups of coffee per day was 0.90 (95 percent confidence interval, 0.67 to 1.22). Those with a total consumption of six or more cups of coffee per day had a relative risk of total cardiovascular disease of 0.65 (95 percent confidence interval, 0.31 to 1.35).

Men drinking caffeinated coffee had no increases in the risk of cardiovascular disease with higher intakes (Table 3). Rather, the estimates of relative risk were below 1.0 for total coronary heart disease and total cardiovascular disease in those drinking four or more cups of caffeinated coffee per day. There was a posi-

Table 2. Age-Standardized Incidence Rates and Relative Risks of Cardiovascular End Points, According to Total Coffee Consumption.

Variable*	Coffee Consumption				Trend	
	None (N = 7592)	≤1 cup/day (N = 13,048)	2–3 cups/day (N = 16,009)	≥4 cups/day (N = 8940)	chi†	P value
Nonfatal myocardial infarction and fatal CHD						
Incidence/10^6 person-yr (cases)	363 (34)	300 (63)	281 (75)	367 (49)		
Age-adjusted relative risk†	1.0	0.83	0.76	1.03	0.14	0.89
Multivariate relative risk (95% CI)‡	1.0	0.60 (0.38–0.96)	0.98 (0.71–1.35)	1.08 (0.72–1.60)		
CABG and PTCA						
Incidence/10^6 person-yr (cases)	167 (16)	148 (32)	243 (62)	208 (26)		
Age-adjusted relative risk†	1.0	0.85	1.45	1.28	2.44	0.01
Multivariate relative risk (95% CI)‡	1.0	0.86 (0.50–1.46)	1.22 (0.82–1.81)	0.95 (0.56–1.61)		
Total CHD						
Incidence/10^6 person-yr (cases)	539 (50)	448 (95)	524 (137)	575 (75)		
Age-adjusted relative risk†	1.0	0.84	0.98	1.15	1.01	0.31
Multivariate relative risk (95% CI)‡	1.0	0.71 (0.50–1.01)	1.06 (0.83–1.36)	1.00 (0.73–1.37)		
Fatal and nonfatal stroke						
Incidence/10^6 person-yr (cases)	80 (8)	108 (23)	70 (18)	45 (5)		
Age-adjusted relative risk†	1.0	1.28	0.83	0.50	−1.82	0.07
Multivariate relative risk (95% CI)‡	1.0	0.58 (0.25–1.36)	0.68 (0.36–1.31)	0.48 (0.18–1.31)		
Total cardiovascular disease						
Incidence/10^6 person-yr (cases)	589 (57)	556 (118)	590 (154)	613 (79)		
Age-adjusted relative risk†	1.0	0.93	0.99	1.04	1.35	0.18
Multivariate relative risk (95% CI)‡	1.0	0.70 (0.51–0.97)	1.00 (0.79–1.26)	0.90 (0.67–1.22)		

*CHD denotes coronary heart disease, CI confidence interval, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†A chi value of more than 1.96 denotes a P value of less than 0.05. The sign of the chi value indicates the direction of the trend.

‡Adjusted for age (in five-year age categories), quintiles of Quetelet's index, smoking habits (current smoker [number of cigarettes smoked], former smoker, or never smoked), history of diabetes mellitus (yes or no), quintiles of alcohol use, parental history of myocardial infarction (none, one or both parents before 61 years of age, or one or both parents after 60 years of age), specific health profession, and quintiles of dietary intake of energy, cholesterol, and saturated, monounsaturated, and polyunsaturated fat.

Table 3. Age-Standardized Incidence Rates and Relative Risks of Cardiovascular End Points, According to the Consumption of Caffeinated Coffee.*

VARIABLE	CAFFEINATED COFFEE				TREND	
	NONE (N = 13,056)	≤1 CUP/DAY (N = 16,015)	2–3 CUPS/DAY (N = 10,679)	≥4 CUPS/DAY (N = 4986)	CHI†	P VALUE
Nonfatal myocardial infarction and fatal CHD						
Incidence/10^6 person-yr (cases)	339 (64)	275 (70)	326 (52)	337 (25)		
Age-adjusted relative risk†	1.0	0.83	0.95	0.98	0.14	0.89
Multivariate relative risk (95% CI)‡	1.0	0.83 (0.59–1.17)	0.97 (0.66–1.42)	1.01 (0.62–1.65)		
CABG and PTCA						
Incidence/10^6 person-yr (cases)	191 (37)	179 (46)	241 (38)	136 (10)		
Age-adjusted relative risk†	1.0	0.85	1.24	0.74	0.13	0.90
Multivariate relative risk (95% CI)‡	1.0	0.85 (0.55–1.29)	1.20 (0.76–1.90)	0.66 (0.32–1.34)		
Total CHD						
Incidence/10^6 person-yr (cases)	533 (101)	454 (116)	568 (90)	471 (35)		
Age-adjusted relative risk†	1.0	0.86	1.06	0.90	0.32	0.75
Multivariate relative risk (95% CI)‡	1.0	0.84 (0.64–1.10)	1.04 (0.78–1.40)	0.84 (0.56–1.25)		
Fatal and nonfatal stroke						
Incidence/10^6 person-yr (cases)	95 (18)	79 (20)	70 (12)	36 (2)		
Age-adjusted relative risk†	1.0	0.83	0.83	0.34	−1.39	0.16
Multivariate relative risk (95% CI)‡	1.0	0.67 (0.35–1.30)	0.71 (0.33–1.53)	0.28 (0.06–1.26)		
Total cardiovascular disease						
Incidence/10^6 person-yr (cases)	612 (116)	533 (136)	590 (102)	494 (36)		
Age-adjusted relative risk†	1.0	0.88	0.99	0.82	−0.24	0.81
Multivariate relative risk (95% CI)‡	1.0	0.83 (0.65–1.07)	1.00 (0.79–1.26)	0.74 (0.50–1.09)		

*Numbers are slightly smaller than for total coffee consumption because of missing data on consumption of specific type of coffee. CHD denotes coronary heart disease, CI confidence interval, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†A chi value of more than 1.96 denotes a P value of less than 0.05. The sign of the chi value indicates the direction of the trend.

‡Adjusted for age (in five-year age categories), quintiles of Quetelet's index, smoking habits (current smoker [number of cigarettes smoked], former smoker, or never smoked), history of diabetes mellitus (yes or no), quintiles of alcohol use, parental history of myocardial infarction (none, one or both parents before 61 years of age, or one or both parents after 60 years of age), specific health profession, and quintiles of dietary intake of energy, cholesterol, and saturated, monounsaturated, and polyunsaturated fat. For the analysis of caffeinated-coffee use, adjustments were made for the consumption of decaffeinated coffee through the use of a common reference category of no coffee consumption.

tive trend, however, toward an association between a higher consumption of decaffeinated coffee and coronary-artery bypass grafting and coronary angioplasty, and there was a slight and marginally significant increase in the risk of coronary heart disease and total cardiovascular disease with increased consumption (Table 4). Because fewer participants drank decaffeinated than caffeinated coffee, the confidence intervals for the estimates for decaffeinated coffee were wider. Multivariate analysis changed the risk estimates only slightly. No apparent association was observed between the consumption of tea and

Table 4. Age-Standardized Incidence Rates and Relative Risks of Cardiovascular End Points, According to the Consumption of Decaffeinated Coffee.*

VARIABLE	DECAFFEINATED COFFEE				TREND	
	NONE (N = 21,111)	≤1 CUP/DAY (N = 16,865)	2–3 CUPS/DAY (N = 4839)	≥4 CUPS/DAY (N = 1512)	CHI†	P VALUE
Nonfatal myocardial infarction and fatal CHD						
Incidence/10^6 person-yr (cases)	340 (100)	282 (76)	321 (26)	539 (12)		
Age-adjusted relative risk†	1.0	0.83	0.94	1.54	0.37	0.71
Multivariate relative risk (95% CI)‡	1.0	0.90 (0.66–1.22)	0.95 (0.61–1.48)	1.55 (0.85–2.81)		
CABG and PTCA						
Incidence/10^6 person-yr (cases)	167 (48)	228 (58)	227 (18)	348 (8)		
Age-adjusted relative risk†	1.0	1.30	1.53	2.06	2.07	0.04
Multivariate relative risk (95% CI)‡	1.0	1.35 (0.92–1.97)	1.22 (0.70–2.10)	1.74 (0.81–3.73)		
Total CHD						
Incidence/10^6 person-yr (cases)	503 (148)	483 (134)	549 (44)	386 (20)		
Age-adjusted relative risk†	1.0	0.98	1.08	1.71	1.55	0.12
Multivariate relative risk (95% CI)‡	1.0	1.06 (0.84–1.35)	1.04 (0.74–1.47)	1.63 (1.02–2.60)		
Fatal and nonfatal stroke						
Incidence/10^6 person-yr (cases)	73 (21)	90 (24)	56 (4)	115 (2)		
Age-adjusted relative risk†	1.0	1.23	0.71	1.20	−0.09	0.93
Multivariate relative risk (95% CI)‡	1.0	1.31 (0.71–2.42)	0.86 (0.31–2.33)	1.16 (0.26–5.10)		
Total cardiovascular disease						
Incidence/10^6 person-yr (cases)	572 (167)	587 (158)	596 (47)	1002 (22)		
Age-adjusted relative risk†	1.0	1.03	1.03	1.67	1.43	0.15
Multivariate relative risk (95% CI)‡	1.0	1.10 (0.88–1.38)	1.01 (0.72–1.40)	1.58 (1.01–2.48)		

*Numbers are slightly smaller than for total coffee consumption because of missing data on the consumption of specific types of coffee. CHD denotes coronary heart disease, CI confidence interval, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†A chi value of more than 1.96 denotes a P value of less than 0.05. The sign of the chi value indicates the direction of the trend.

‡Adjusted for age (in five-year age categories), quintiles of Quetelet's index, smoking habits (current smoker [number of cigarettes smoked], former smoker, or never smoked), history of diabetes mellitus (yes or no), quintiles of alcohol use, parental history of myocardial infarction (none, one or both parents before 61 years of age, or one or both parents after 60 years of age), specific health profession, and quintiles of dietary intake of energy, cholesterol, and saturated, monounsaturated, and polyunsaturated fat. For the analysis of decaffeinated-coffee use, adjustments were made for the consumption of caffeinated coffee through the use of a common reference category of no coffee consumption.

the risk of any cardiovascular end point (data not shown); however, only 664 men drank four or more cups of tea per day.

Although histories of hypercholesterolemia and hypertension were associated with an increased risk of cardiovascular disease, they were not related to coffee or caffeine intake; thus, the inclusion of these variables in the multivariate model did not change the risk estimates for coffee or caffeine intake. Similarly, including categories of physical activity assessed on the baseline questionnaire did not alter associations with coffee consumption. The findings were also essentially the same when we limited the analyses to definite end points (relative risk of any coronary heart disease among those drinking four or more cups of caffeinated coffee per day, 0.89; 95 percent confidence interval, 0.57 to 1.40). The associations were not materially altered when events occurring before January 1, 1987, were disregarded: the relative risks of any coronary heart disease were 0.81 among those drinking four or more cups of caffeinated coffee per day (95 percent confidence interval, 0.48 to 1.36) and 1.71 among men drinking four or more cups of decaffeinated coffee per day (95 percent confidence interval, 0.95 to 3.06).

We also examined total caffeine intake and observed no pattern of higher risk across categories of increasing intake from all sources (Table 5). As indicated in Figure 1, the relation of total coffee use to the incidence of total cardiovascular disease was not modified appreciably by age.

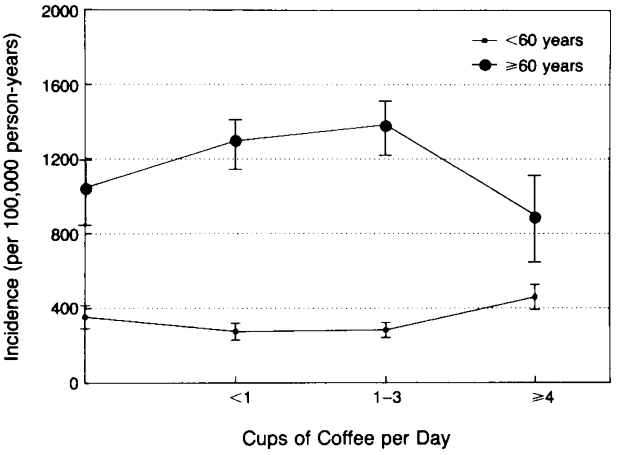

Figure 1. Incidence Rates of Total Cardiovascular Disease, According to Coffee Consumption among Men Younger Than 60 and Those 60 or Older.
The error bars denote means ±SEM.

Discussion

Our findings among 45,589 men 40 to 75 years of age, with more than 70,000 person-years of follow-up, indicate that the use of caffeinated coffee and the total intake of caffeine do not appreciably increase the risk of coronary heart disease or stroke. By contrast, a high consumption of decaffeinated coffee was associated with a moderate and marginally significant increase in risk of coronary heart disease.

Several previous reports suggesting an association between coffee consumption and coronary heart disease stem from studies among hospitalized patients and control subjects.[2,3,9,18-20] In these studies, it is difficult to exclude the possibility that reported coffee use before hospitalization is subject to recall and selection bias. The prospective design of the present study greatly reduced the possibility of biased reporting of coffee use or other characteristics because this infor-

Table 5. Age-Standardized Incidence Rates and Relative Risks of Cardiovascular End Points, According to the Consumption of Caffeine.*

Variable	Caffeine Consumption (mg/day)					Trend	
	0–74	75–148	149–285	286–491	492–1786	chi†	P value
Nonfatal myocardial infarction and fatal CHD							
Incidence/10^6 person-yr (cases)	315 (42)	344 (50)	275 (40)	325 (45)	326 (44)		
Age-adjusted relative risk†	1.00	1.13	0.88	1.03	1.04	0.11	0.91
Multivariate relative risk (95% CI)‡	1.00	1.03 (0.68–1.56)	0.85 (0.55–1.31)	0.96 (0.62–1.48)	0.98 (0.63–1.53)		
CABG and PTCA							
Incidence/10^6 person-yr (cases)	139 (19)	210 (29)	236 (35)	166 (23)	230 (30)		
Age-adjusted relative risk†	1.00	1.46	1.69	1.20	1.76	1.20	0.23
Multivariate relative risk (95% CI)‡	1.00	1.42 (0.81–2.49)	1.64 (0.94–2.84)	1.17 (0.64–2.14)	1.49 (0.82–2.71)		
Total CHD							
Incidence/10^6 person-yr (cases)	454 (61)	553 (79)	513 (75)	491 (68)	556 (74)		
Age-adjusted relative risk†	1.00	1.23	1.14	1.08	1.23	0.83	0.41
Multivariate relative risk (95% CI)‡	1.00	1.17 (0.84–1.63)	1.10 (0.78–1.54)	1.01 (0.71–1.43)	1.11 (0.78–1.57)		
Fatal and nonfatal stroke							
Incidence/10^6 person-yr (cases)	110 (15)	109 (15)	66 (10)	51 (7)	55 (7)		
Age-adjusted relative risk†	1.00	0.98	0.63	0.47	0.51	−2.16	0.03
Multivariate relative risk (95% CI)‡	1.00	0.89 (0.43–1.85)	0.57 (0.25–1.30)	0.43 (0.17–1.09)	0.45 (0.18–1.16)		
Total cardiovascular disease							
Incidence/10^6 person-yr (cases)	556 (75)	647 (92)	579 (85)	542 (75)	603 (80)		
Age-adjusted relative risk†	1.00	1.13	1.04	0.97	1.10	0.65	0.52
Multivariate relative risk (95% CI)‡	1.00	1.11 (0.82–1.51)	1.01 (0.74–1.38)	0.90 (0.65–1.25)	0.97 (0.70–1.35)		

*CHD denotes coronary heart disease, CI confidence interval, CABG coronary-artery bypass grafting, and PTCA percutaneous transluminal coronary angioplasty.

†A chi value of more than 1.96 denotes a P value of less than 0.05. The sign of the chi value indicates the direction of the trend.

‡Adjusted for age (in five-year age categories), quintiles of Quetelet's index, smoking habits (current smoker [number of cigarettes smoked], former smoker, or never smoked), history of diabetes mellitus (yes or no), quintiles of alcohol use, parental history of myocardial infarction (none, one or both parents before 61 years of age, or one or both parents after 60 years of age), specific health profession, and quintiles of dietary intake of energy, cholesterol, and saturated, monounsaturated, and polyunsaturated fat.

mation was collected before the diagnosis of cardiovascular disease. Most other prospective studies have not observed coffee intake to be associated with the risk of fatal coronary heart disease.[4,6,8,9,12,13,15,16,21] Our data confirm these reports for total coffee consumption and extend the findings to nonfatal coronary heart disease and cerebrovascular disease.

In our analysis, drinking four or more cups of decaffeinated coffee per day was associated with a moderate elevation in the risk of all cardiovascular end points (multivariate relative risk, 1.58). This finding was unexpected and requires further study. In a recent randomized trial,[30] the consumption of three to six cups of decaffeinated coffee per day did raise the levels of low-density lipoprotein cholesterol. For the time being there seems to be little merit in switching from caffeinated coffee to decaffeinated coffee as a means of reducing the risks of cardiovascular disease.

A possible limitation of our data is the relatively short follow-up period and the fact that the data on coffee use refer to the patterns of consumption within one to three years of the symptoms of coronary heart disease or stroke. Several authors, however, have suggested that the adverse effects of coffee on the cardiovascular system may be particularly evident within the four-year period before a cardiovascular event.[9,11,14,24-27] This hypothesis of a short-term effect derives from the relatively consistent absence of coffee-induced effects on cardiovascular disease in studies in which the intake was assessed long before the coronary events, and from the elevated risks reported in several case–control studies. In a prospective study, recent coffee-drinking habits appeared to be associated with a 2.5-fold increased risk of combined nonfatal and fatal coronary heart disease; however, the study included only 51 cases of coronary heart disease and only 21 cases of myocardial infarction, and thus the confidence intervals around the estimates of relative risk were wide.[14] All subjects in our study who reported previous cardiovascular disease at the start of the follow-up period were excluded from the analysis. We further limited the possibility of an effect of existing subclinical disease on coffee use by ignoring cardiovascular events that occurred in the first year of follow-up; this analysis yielded results that were essentially unchanged.

Confounding may have been a problem in the analysis of some previous prospective studies. Coffee drinkers are more likely to smoke than those who do not drink coffee,[43] and they may have higher intakes of total and saturated fat and cholesterol.[44] Adjustments for the intake of fat and cholesterol did not materially change our findings, however. Most cohorts of men studied thus far included large proportions of smokers. Since the rates of smoking among men have decreased markedly over the past decades, a measure of smoking status at the start of a follow-up period a decade or more long may not provide adequate control for smoking as a confounding factor. In our study, only 10.1 percent of the members of the cohort were current smokers (Table 1), and the data on both smoking habits and coffee use refer to a period less than three years before the event. As discussed by Rosenberg et al., another concern is the possibility that risk estimates in some of the previous reports have been overadjusted when variables that may influence the effect of coffee on cardiovascular disease, such as blood pressure and serum lipid levels, were included in the multivariate models.[19] In our study, we analyzed the data both with and without the inclusion of these variables, with no appreciable change in the results.

The present study provides data from a very large cohort. The findings indicate that a substantial adverse effect of coffee use on the incidence of cardiovascular disease is unlikely. There remains the possibility of a threshold effect of coffee for its effect on the heart and the vessels; a very high coffee consumption may increase individual risk.[2,3,17,20] In the Western Electric Company Study, mortality from coronary heart disease was increased in those drinking more than six cups per day when compared with all others.[17] In the Western Electric cohort, however, coffee-drinking habits appear to have been somewhat atypical, since only 68 participants (3.5 percent) reported no intake of coffee. In a recent report from a Scandinavian study of middle-aged men, drinking nine cups of coffee per day or more was associated with a risk of myocardial infarction 2.2 times that of drinking less than one cup.[23] Only 2.9 percent of men in the Health Professionals Follow-up Study drank six or more cups of coffee per day. Even for this group, however, the relative risk of cardiovascular disease was not increased. A second restriction of our data is that no women were included in the cohort. Although there is little previous evidence to suggest a different association between coffee and cardiovascular risk among women as compared with men, the findings may not apply to women. In a recent case–control study in women, a nonsignificant increase in the risk of nonfatal myocardial infarction (relative risk, 1.72; confidence interval, 0.92 to 3.23) was noted in women who drank more than three cups of coffee per day relative to women who never drank coffee.[20] As indicated by the low prevalence of cigarette smoking and relatively low intake of dietary cholesterol, the population of health professionals in our study is not strictly representative of men as a whole in the United States. However, we have no reason to believe that the effect of coffee consumption on the incidence of cardiovascular disease would be substantially different in this relatively low risk population.

In summary, our data support the conclusion that caffeinated coffee as it is currently consumed by men in the United States causes no substantial increase in the risk of coronary heart disease or stroke.

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References

1. Paul O, Lepper MH, Phelan WH, et al. A longitudinal study of coronary heart disease. Circulation 1963; 28:20-31.
2. Coffee drinking and acute myocardial infarction: report from the Boston Collaborative Drug Surveillance Program. Lancet 1972; 2:1278-81.
3. Jick H, Miettinen OS, Neff RK, Shapiro S, Heinonen OP, Slone D. Coffee and myocardial infarction. N Engl J Med 1973; 289:63-7.
4. Klatsky AL, Friedman GD, Siegelaub AB. Coffee drinking prior to myocardial infarction: results from the Kaiser-Permanente Epidemiologic Study of Myocardial Infarction. JAMA 1973; 226:540-3.
5. Hrubec Z. Coffee drinking and ischaemic heart-disease. Lancet 1973; 1:548.
6. Dawber TR, Kannel WB, Gordon T. Coffee and cardiovascular disease: observations from the Framingham Study. N Engl J Med 1974; 291:871-4.
7. Hennekens CH, Drolette ME, Jesse MJ, Davies JE, Hutchison GB. Coffee drinking and death due to coronary heart disease. N Engl J Med 1976; 294:633-6.
8. Yano K, Rhoads GG, Kagan A. Coffee, alcohol and risk of coronary heart disease among Japanese men living in Hawaii. N Engl J Med 1977; 297:405-9.
9. Wilhelmsen L, Tibblin G, Elmfeldt D, Wedel H, Werkö L. Coffee consumption and coronary heart disease in middle-aged Swedish men. Acta Med Scand 1977; 201:547-52.
10. Heyden S, Tyroler HA, Heiss G, Hames CG, Bartel A. Coffee consumption and mortality: total mortality, stroke mortality, and coronary heart disease mortality. Arch Intern Med 1978; 138:1472-5.
11. Rosenberg L, Slone D, Shapiro S, Kaufman DW, Stolley PD, Miettinen OS. Coffee drinking and myocardial infarction in young women. Am J Epidemiol 1980; 111:675-81.
12. Murray SS, Bjelke E, Gibson RW, Schuman LM. Coffee consumption and mortality from ischemic heart disease and other causes: results from the Lutheran Brotherhood Study, 1966–1978. Am J Epidemiol 1981; 113:661-7.
13. Welin L, Svärdsudd K, Tibblin G, Wilhelmsen L. Coffee, traditional risk factors, coronary heart disease, and mortality. In: McMahon B, Sugimura T, eds. Coffee and health. Banbury report 17. Cold Spring Harbor, N.Y.: Cold Spring Harbor Laboratory, 1984:219-29.
14. LaCroix AZ, Mead LA, Liang K-Y, Thomas CB, Pearson TA. Coffee consumption and the incidence of coronary heart disease. N Engl J Med 1986; 315:977-82.
15. Jacobsen BK, Bjelke E, Kvale G, Heuch I. Coffee drinking, mortality, and cancer incidence: results from a Norwegian prospective study. J Natl Cancer Inst 1986; 76:823-31.
16. Yano K, Reed DM, MacLean CJ. Coffee consumption and the incidence of coronary heart disease. N Engl J Med 1987; 316:946.
17. LeGrady D, Dyer AR, Shekelle RB, et al. Coffee consumption and mortality in the Chicago Western Electric Company Study. Am J Epidemiol 1987; 126:803-12.
18. Rosenberg L, Werler MM, Kaufman DW, Shapiro S. Coffee drinking and myocardial infarction in young women: an update. Am J Epidemiol 1987; 126:147-9.
19. Rosenberg L, Palmer JR, Kelly JP, Kaufman DW, Shapiro S. Coffee drinking and nonfatal myocardial infarction in men under 55 years of age. Am J Epidemiol 1988; 128:570-8.
20. La Vecchia C, Gentile A, Negri E, Parazzini F, Franceschi S. Coffee consumption and myocardial infarction in women. Am J Epidemiol 1989; 130:481-5.
21. Wilson PW, Garrison RJ, Kannel WB, McGee DL, Castelli WP. Is coffee consumption a contributor to cardiovascular disease? Insights from the Framingham Study. Arch Intern Med 1989; 149:1169-72.
22. Tverdal A, Stensvold I, Solvoll K, Foss OP, Lund-Larsen P, Bjartveit K. Coffee consumption and death from coronary heart disease in middle aged Norwegian men and women. BMJ 1990; 300:566-9.
23. Lehman BA. A tempest in a coffee pot. Boston Globe. November 27, 1989:25.
24. Sawicki P, Berger M. Coffee consumption and the incidence of coronary heart disease. N Engl J Med 1987; 316:946.
25. Robertson D, Frölich JC, Carr RK, et al. Effects of caffeine on plasma renin activity, catecholamines and blood pressure. N Engl J Med 1978; 298:181-6.
26. Rotenberg FA, DeFeo JJ. The effects of caffeine on cardiac irritability. Fed Proc 1976; 35:384. abstract.
27. Greenland S. Quantitative methods in the review of epidemiologic literature. Epidemiol Rev 1987; 9:1-30.
28. Thelle DS, Heyden S, Fodor JG. Coffee and cholesterol in epidemiological and experimental studies. Atherosclerosis 1987; 67:97-103.
29. Bak AAA, Grobbee DE. The effect on serum cholesterol levels of coffee brewed by filtering or boiling. N Engl J Med 1989; 321:1432-7.
30. Superko HR, Bortz W, Albers JJ, Wood PD. Lipoprotein and apolipoprotein changes during a controlled trial of caffeinated and decaffeinated coffee drinking in men. Circulation 1989; 80:Suppl II:II-86. abstract.
31. Bak AAA, Grobbee DE. Effects of caffeine on blood pressure and serum lipids: results from a double blind study. Am J Clin Nutr (in press).
32. Lang T, Degoulet P, Aime F, et al. Relation between coffee drinking and blood pressure: analysis of 6,321 subjects in the Paris region. Am J Cardiol 1983; 52:1238-42.
33. Bak AA, Grobbee DE. A randomized study on coffee and blood pressure. J Hum Hypertens 1990; 4:259-64.
34. Whitsett TL, Manion CV, Christensen HD. Cardiovascular effects of coffee and caffeine. Am J Cardiol 1984; 53:918-22.
35. Prineas RJ, Jacobs DR Jr, Crow RS, Blackburn H. Coffee, tea and VPB. J Chronic Dis 1980; 33:67-72.
36. Willett WC, Sampson L, Stampfer MJ, et al. Reproducibility and validity of a semiquantitative food frequency questionnaire. Am J Epidemiol 1985; 122:51-65.
37. Rimm EB, Stampfer MJ, Colditz GA, Giovannucci E, Willett WC. Effectiveness of various mailing strategies among nonrespondents in a prospective cohort study. Am J Epidemiol 1990; 131:1068-71.
38. Stampfer MJ, Willett WC, Speizer F, et al. Test of the National Death Index. Am J Epidemiol 1984; 119:837-9.
39. Rose GA, Blackburn H. Cardiovascular survey methods. 2nd ed. Monograph series no. 58. Geneva: World Health Organization, 1982.
40. Walker AE, Robins M, Weinfeld FD. National survey of stroke: clinical findings. Stroke 1981; 12:Suppl I:I13-I44.
41. Rothman KJ. Modern epidemiology. Boston: Little, Brown, 1986.
42. Truett J, Cornfield J, Kannel W. A multivariate analysis of the risk of coronary heart disease in Framingham. J Chronic Dis 1967; 20:511-24.
43. Jacobsen BK, Thelle DS. The Tromsø Heart Study: is coffee drinking an indicator of a life style with high risk for ischemic heart disease? Acta Med Scand 1987; 222:215-21.
44. Haffner SM, Knapp JA, Stern MP, Hazuda HP, Rosenthal M, Franco LJ. Coffee consumption, diet, and lipids. Am J Epidemiol 1985; 122:1-12.