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Coffee Intake and Coronary Heart Disease

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ABSTRACT

We examined the risk of coronary heart disease (CHD) associated with coffee intake in 1040 male medical students followed for 28 to 44 years. During the follow-up, CHD developed in 111 men. The relative risks (95% confidence interval) associated with drinking 5 cups of coffee/d were 2.94 (1.27, 6.81) for baseline, 5.52 (1.31, 23.18) for average, and 1.95 (0.86, 4.40) for most recent intake after adjustment for baseline age, serum cholesterol levels, calendar time, and the time-dependent covariates number of cigarettes, body mass index, and incident hypertension and diabetes. Risks were elevated in both smokers and nonsmokers and were stronger for myocardial infarction. Most of the excess risk was associated with coffee drinking prior to 1975. The diagnosis of hypertension was associated with a subsequent reduction in coffee intake.

Negative results in some studies may be due to the assessment of coffee intake later in life or to differences in methods of coffee preparation between study populations or over calendar time. Ann Epidemiol 1994:4:425–433.

KEY WORDS: Coffee, coronary heart disease, epidemiology, prospective studies.

INTRODUCTION

Eighty percent of Americans drink coffee (1). Given this widespread use, it is important to define the risks and benefits associated with coffee drinking to better inform both health professionals and the public. Studies that have examined the risk of coronary heart disease and other cardiovascular diseases associated with coffee intake produced conflicting results, reporting both elevated risks and no risks (2–25).

Previously, we reported a strong, independent, dose–response relationship between coffee intake and the development of coronary heart disease in a cohort of white male medical students (16). That report was based on a relatively small number of coronary heart disease events, 51. We now report a reexamination of this issue in this cohort based on 8 additional years of follow-up. Because of the age structure of the cohort, a much larger number of events has occurred and adequate power is now available to examine this association separately for smokers and nonsmokers and for the more specific outcome, myocardial infarction. Because of changes in methods of coffee preparation over time, we hypothesized that most of the risk associated with coffee drinking would be present at an earlier calendar time. In addition, participants were enrolled at an average age of 22 years, prior to the development of cardiovascular disease. Examination of the characteristics of men who altered their coffee intake over the long period of follow-up and comparison of the effects of coffee drinking at different calendar times shed light on why some studies of middle-aged men demonstrated no harmful effect of coffee drinking.

METHODS

Study Population and Design

The Johns Hopkins Precursors Study was begun in 1947 by Caroline Bedell Thomas. The 1337 students who matriculated into the graduating classes of 1948 to 1964 of the Johns Hopkins University School of Medicine were eligible for the study. Between 1948 and 1964, 1160 male and 111 female students (95% of those eligible) were enrolled. In medical school, participants completed questionnaires about their medical history, family history, health, and dietary habits including coffee intake and cigarette smoking (26). Participants also underwent a standardized medical examination that included measurements of weight, height, and blood pressure. Total serum cholesterol level was deter-

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mined only in the classes of 1949 to 1964, and was converted to Abell-Kendell values (27, 28). The 1040 white men who provided coffee information while in medical school are the study population for the present analysis.

Definitions of Coffee Consumption

Coffee intake and cigarette smoking was assessed while the students were in medical school, every 5 years after graduation until 1984, and also in 1978 and 1986. Information on coffee consumption in medical school, 1978, and 1986 was obtained in response to an open-ended question. At the 5-year follow-ups, participants indicated their current intake on a checklist of items ranging from 0 to 7 or more cups a day. The questionnaires did not distinguish between caffeinated and decaffeinated coffee. Three measures of coffee consumption—early adult, average lifetime, and most recent (16)—ranging from 0 to 5 or more cups a day were calculated from the available information on coffee intake during 25 to 41 years of adulthood (16). Early adult consumption was defined as the coffee intake (usual number of cups/d) reported during the initial examination in medical school. Average coffee consumption for up to 38 years (from graduation in 1948 to 1986) of observation was computed as a weighted average of coffee drinking, prior to development of coronary disease, reported at each of the 10 possible time points with use of the following formula:

$$\text{Average Coffee Consumption} = \frac{\Sigma\,[(C_i) * (Y_i)]}{\text{Total person-y}}$$

where C_i refers to the reported coffee consumption (number of cups/d) at the midpoint of the ith interval, Y_i (years).

Most recent coffee consumption was defined as the last reported measure of coffee intake before the onset of clinical coronary disease among those with the disorder, in comparison with coffee consumption at the same time among those without the disease. To compute average and most recent coffee consumption among persons with one or more missing values, the quantity of coffee consumption reported at time points adjacent to the missing value was averaged.

Follow-up Procedures and Case Validation

The cohort has been followed with yearly questionnaires to detect cardiovascular disease in the participants and to update body weight and other risk factor information. Participants are known to accurately report cardiovascular disease (29), blood pressure, and body weight (30, 31). Response rates for any 5-year period ranged from 87 to 94%. Vital status of nonrespondents was ascertained by contacting family members, scanning obituaries, and searching the National Death Index. Vital status is known for more than 99% of the cohort. By using death certificates, hospital records, autopsy reports, and physician reports, cardiovascular diagnoses were assigned according to modified Lipid Research Clinics criteria by a committee of internists who were also trained in epidemiology (32). Information was reviewed by two physicians without knowledge of the participant's coffee intake. Disagreements were adjudicated by consensus of the entire committee. Diagnoses were classified by International Classification of Diseases, ninth revision (ICD-9) rubric. Coronary heart disease included myocardial infarction (ICD-9 410 and 412), sudden death (ICD-9 427.5 and 798.2), angina pectoris (ICD-9 413), and other symptomatic coronary disease requiring coronary artery bypass graft surgery (ICD 414).

Statistical Analysis

After examination of the distribution of all variables, the association of coffee drinking with possible confounders was assessed by χ^2 test and analysis of variance (ANOVA). The beginning of follow-up was defined as year of graduation and the end of follow-up, as December 31, 1992. Follow-up time since graduation was the time variable used in all survival analyses. The relation between coffee consumption in young adulthood and the incidence of coronary heart disease during the 28- to 44-year follow-up period was first evaluated by an examination of Kaplan-Meier survival curves for each of four categories of coffee consumption (none, 1 to 2 cups daily, 3 to 4 cups daily, and 5 or more cups daily) for the baseline and average measures of coffee exposure (33). The statistical difference between the four curves was assessed with a log-rank test (34). To estimate the risk associated with most recently reported coffee intake, where participants could change coffee consumption groups at each time data were collected, time-dependent covariates were used in a Cox proportional hazards model (35). Multivariate Cox proportional hazards models were developed to adjust for potential confounding variables for each measure of coffee intake. These models included variables measured in medical school—age, systolic blood pressure, body mass index, and serum cholesterol level—as well as time-dependent data on number of cigarettes smoked, body weight, and the incidence of hypertension and diabetes during follow-up. The models were stratified by calendar time periods to adjust for potential cohort effects arising from differences in baseline risk factors over time and the secular decline in mortality due to coronary disease (36, 37). To examine the hypothesis that exposure to coffee drinking at earlier calendar times was responsible for the observed association between baseline coffee drinking and coronary heart disease, time-dependent coffee intake was also modeled as three calendar time–specific variables: before 1975, 1975 to 1984, and after 1984. These cutpoints were chosen because methods of coffee preparation began to shift toward automatic drip coffee makers around 1975 and the previous report from this cohort included follow-up through 1984. Multivariate Cox models were also constructed to investi-

gate various latency periods between coffee consumption and subsequent coronary disease.

Coffee intake was modeled as both a continuous and a categorical variable. Both approaches yielded similar findings; results for coffee exposure as a categorical variable are presented for the main results. Estimates of relative risk and corresponding two-sided 95% confidence intervals (CIs) relating coffee consumption to coronary heart disease were computed from the Cox models (35). All tests of significance were two-tailed with an α level of 0.05.

RESULTS

The characteristics, assessed in medical school, of the 1040 men in this study are given in Table 1. The average age at graduation was 26.3 years. The mean age of the cohort at the end of follow-up in 1992 was 62.0 years, with a range of 51 to 90. Most of the men (82%) drank coffee in medical school, with an average consumption of 2.3 cups/d. Only 44 (4.2%) of the participants were overweight, defined as body mass index above 27.9 kg/m^2; 38 (3.7%) had blood pressure levels higher than or equal to 160 mm Hg systolic and/or 95 mm Hg diastolic. About half of the men smoked in medical school.

Age, blood pressure, and serum cholesterol level were associated with coffee intake but without a clear dose–response relationship. Coffee drinkers were much more likely to smoke cigarettes. Adiposity and physical activity did not vary significantly among coffee-drinking categories.

Median follow-up time for this analysis was 32 years, yielding 32,601 person-years of observation. Over this period, 111 men experienced coronary heart disease events (24 fatal): 74 had myocardial infarctions (24 fatal); 34 had angina without myocardial infarction; and in 3, symptomatic coronary heart disease developed but did not meet the criteria for myocardial infarction or angina. The mean age at the time of a coronary heart disease event was 54 years.

Coffee consumption assessed in medical school was associated with coronary heart disease incidence over the course of follow-up (Figure 1). There was a strong dose–response relationship, with men who drank 5 or more cups/d having the highest risk. This excess risk was evident by 20 years of follow-up, corresponding to an average age of less than 46 years. By Kaplan-Meier analysis, the relative risk of developing coronary heart disease at 30 years of follow-up for coffee drinkers compared to nondrinkers was 2.5 for those who drank 1 to 2 cups a day, 3.7 for those who drank 3 to 4 cups a day, and 5.3 for those who had 5 or more cups a day. Average coffee consumption was also positively associated with the incidence of coronary heart disease in Kaplan-Meier analysis ($P < 0.007$).

To limit the possibility that the observed coffee–coronary heart disease relationship might be due to confounding by smoking, the analyses were repeated in the 420 men who were lifelong nonsmokers (i.e., who reported not smoking at baseline and over the duration of follow-up). The higher risk of coronary heart disease associated with higher coffee consumption at baseline was also present in the nonsmokers. The cumulative incidence of coronary heart disease at 35 years in lifetime nonsmokers rose from 3.1% in nondrinkers to 6.0% in those drinking 1 to 2 cups/d and 16.3% in those drinking 3 or more cups of coffee a day (test for trend, $P = 0.003$). A similar gradient of risk was seen among smokers (test for trend, $P = 0.02$).

In univariate proportional hazards analysis, the unadjusted relative risk of subsequent coronary heart disease associated with drinking 5 cups of coffee a day was 3.90 (95% CI: 1.81, 8.44) for baseline intake, 7.37 (95% CI: 1.79, 30.38) for average intake, and 1.83 (95%CI: 0.94, 3.56) for most recent consumption.

Coffee drinking has been suggested to increase the risk of coronary disease by raising serum cholesterol concentration and blood pressure. The increased risk of developing coronary disease associated with all three measures of coffee use

TABLE 1. Characteristics assessed in medical school of 1040 white men in the study cohort by baseline coffee intake: The Johns Hopkins Precursors Study

Characteristic	Total	Cups/d			
		0	1–1	3–4	⩾5
No. (%)	1040 (100)	188 (18.1)	474 (45.6)	243 (23.4)	35 (13.0)
Age at graduation (y)[a]	26.3 (2.4)	26.2 (2.3)	26.1 (2.3)	26.2 (2.0)	27.5 (3.0)[c]
Body mass index (kg/m^2)[a]	23.1 (2.6)	23.0 (2.5)	23.1 (2.4)	23.3 (3.0)	23.2 (2.7)
Systolic blood pressure (mm Hg)[a]	125 (14)	123 (14)	125 (13)	128 (15)	123 (14)[d]
Diastolic blood pressure (mm Hg)[a]	75 (10)	74 (9)	74 (10)	77 (10)	75 (9)[d]
Serum cholesterol (mg/dL)[a,b]	192.2 (31.4)	187.3 (29.3)	191.5 (31.7)	197.1 (29.0)	192.8 (36.1)[e]
Cigarette smokers (n (%))	506 (50)	44 (24)	211 (46)	147 (62)	104 (78)[c]

[a] Mean (standard deviation).
[b] Information on this variable was available only for 940 men. For all other variables in the tables, less than 2.0% were missing.
[c] $P < 0.0001$; all P values from analysis of variance and χ^2 analysis.
[d] $P < 0.01$.
[e] $P < 0.05$.

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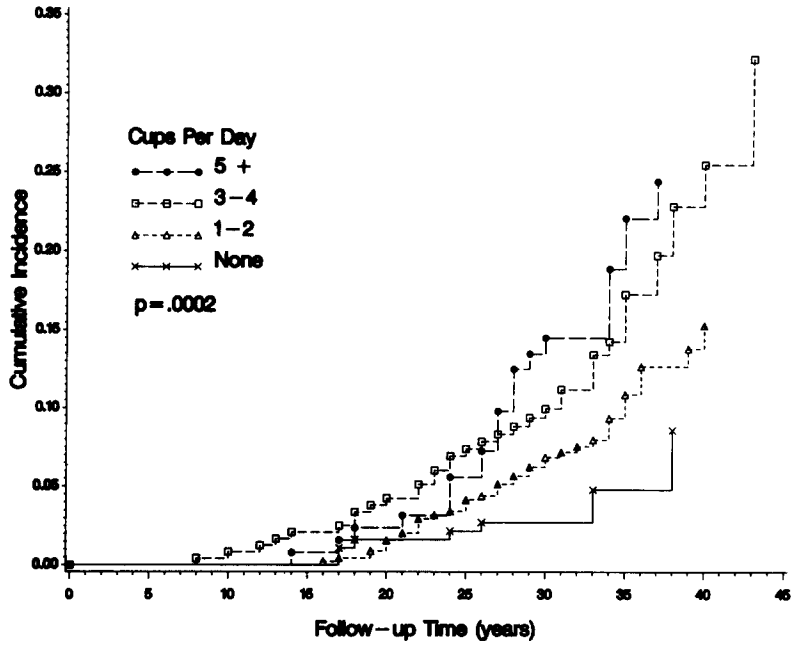

FIGURE 1. Cumulative incidence (%) of coronary heart disease by baseline coffee intake in 1040 white men.

was not altered, however, by adjusting for the development of hypertension, baseline blood pressure, or serum cholesterol level in bivariate Cox models. After simultaneous adjustment for age, baseline serum cholesterol level, and the time-dependent covariates number of cigarettes smoked, body mass index, and incidence of hypertension and diabetes assessed over follow-up (Table 2), a stepwise increase in risk was seen with higher levels of exposure for all three measures of coffee intake. Because coffee drinking and cigarette smoking were associated at baseline and many of the men quit smoking over the course of follow-up, the risk associated with baseline coffee consumption was higher when smoking status was included as a time-dependent covariate rather than as a fixed, baseline value. The weakest risk estimates were associated with most recent coffee intake and this measure was no longer statistically significantly associated with coronary heart disease after adjustment. Coffee intake measured 5 to 10 years prior to a coronary heart disease event did impart an increased risk of coronary disease, more so for 10 years prior than 5 years before an event.

When myocardial infarction, a more specific category than overall coronary heart disease, was used as the end point, the risk associated with coffee use was also apparent and was more pronounced for baseline and average coffee intake (Table 3). The risk of myocardial infarction was high-

TABLE 2. Relative risk (95% confidence interval) of developing coronary heart disease by categories of coffee drinking during 28 to 44 years of follow-up in 935 white men, using Cox proportional hazards analysis: The Johns Hopkins Precursors Study

Measure of coffee consumption	Cups of coffee/d				P value[a]
	0	1–2	3–4	5+	
Baseline[b]	1.0	165	2.51	2.39	0.03
(n = 921, events = 93)		(0.76, 3.59)	(1.13, 5.57)	(1.02, 5.62)	
Baseline[c]	1.0	1.70	3.02	2.94	0.002
(n = 933, events = 95)		(0.78, 3.68)	(1.37, 6.65)	(1.27, 6.81)	
Average[c]	1.0	2.83	4.00	5.52	0.002
(n = 933, events = 95)		(0.64, 12.53)	(0.96, 16.77)	(1.31, 23.18)	
Most recent[c]	1.0	1.56	1.72	1.95	0.14
(n = 933, events = 95)		(0.70, 3.48)	(0.78, 3.79)	(0.86, 4.40)	
5 y prior[c]	1.0	1.48	1.58	2.22	0.05
(n = 929, events = 95)		(0.60, 3.66)	(0.65, 3.83)	(0.91, 5.42)	
10 y prior[c]	1.0	4.26	5.01	5.66	0.03
(n = 914, events = 93)		(1.00, 18.10)	(1.19, 21.06)	(1.34, 23.96)	

[a] Test for trend.
[b] Adjusted for age at graduation, baseline serum cholesterol, number of cigarettes, and calendar time.
[c] Adjusted for age at graduation, baseline serum cholesterol, calendar time and time-dependent hypertension status, number of cigarettes, diabetes, and body mass index.

TABLE 3. Relative risk (95% confidence interval) of myocardial infarction by categories of coffee drinking during 28 to 44 years of follow-up in 935 white men, using Cox proportional hazards analysis: The Johns Hopkins Precursors Study

Measure of coffee consumption	Cups of coffee/d				P value[a]
	0	1–2	3–4	5+	
Baseline[b]	1.0	1.92	2.31	3.42	0.02
(n = 921, events = 59)		(0.65, 5.62)	(0.76, 7.04)	(1.10, 10.60)	
Baseline[c]	1.0	2.05	3.17	4.59	0.001
(n = 933, events = 61)		(0.70, 6.03)	(1.05, 9.59)	(1.51, 13.94)	
Average[c]	1.0	3.21	5.57	8.50	0.002
(n = 933, events = 61)		(0.39, 26.58)	(0.74, 42.21)	(1.12, 64.30)	
Most recent[c]	1.0	0.51	1.08	1.54	0.03
(n = 933, events = 61)		(0.21, 1.30)	(0.48, 2.45)	(0.67, 3.52)	
5 y prior[c]	1.0	0.64	1.53	1.94	0.001
(n = 929, events = 61)		(0.21, 1.99)	(0.57, 4.11)	(0.71, 5.29)	
10 y prior[c]	1.0	1.82	2.08	2.57	0.12
(n = 916, events = 61)		(0.52, 6.40)	(0.60, 7.16)	(0.74, 8.91)	

[a] Test for trend.
[b] Adjusted for age at graduation, baseline serum cholesterol, number of cigarettes, and calendar time.
[c] Adjusted for age at graduation, baseline serum cholesterol, calendar time and time-dependent hypertension status, number of cigarettes, diabetes, and body mass index.

est for average coffee intake but not significantly more so than for other measures of coffee intake (see Table 3).

Average and most recent coffee consumption were associated with baseline coffee intake. To determine which measure was most strongly associated with coronary heart disease incidence, bivariate Cox models containing baseline coffee use and either average intake or most recent intake were constructed. Baseline coffee intake continued to demonstrate the same degree of risk and statistical significance after adjustment for either average or most recent intake while the effect of these latter two variables was greatly diminished (data not shown). Thus, coffee drinking in early adulthood had all the predictive power contained in the average and most recent intake measures. When analyses were performed by calendar time of coffee assessment, the risk associated with coffee drinking before 1975 was markedly higher than that in later time periods (Table 4). The same trend was seen in adjusted analyses (see Table 4) and when myocardial infarction was used as the outcome (not shown).

TABLE 4. Relative risk (RR) (95% confidence interval (CI)) of developing coronary heart disease for men drinking 5 or more cups of coffee/d compared to nondrinkers, by calendar time of coffee exposure using Cox proportional hazards analysis: The Johns Hopkins Precursors Study

Time of exposure	Unadjusted RR (95% CI)	Adjusted[a] RR (95% CI)
Before 1975	2.72 (1.22, 6.06)	2.43 (1.00, 5.92)
1975–1984	1.21 (0.60, 2.44)	1.42 (0.64, 3.15)
After 1984	1.33 (0.55, 3.26)	1.36 (0.54, 3.40)
P[b]	0.03	0.11

[a] Adjusted for age at graduation, baseline serum cholesterol, calendar time and time-dependent hypertension status, number of cigarettes, diabetes, and body mass index.
[b] Test of whether the risk associated with coffee drinking varied over calendar time. Both coffee intake and calendar time were modeled as continuous variables.

Most previous studies of coffee and coronary heart disease, prospective and otherwise, were conducted in middle-aged individuals. To compare our data with those from studies that enrolled persons in midlife, mean coffee consumption by age group was calculated. Figure 2 shows the mean coffee intake by age during the follow-up period. Overall, average cups consumed per day rose until age 40, after which it fell. The correlation between coffee intake measured at the ages of 25 to 29 years and subsequent assessments fell over time (see Figure 2). This observed decline in coffee intake at older ages may have been due to a decrease in intake by men who perceived themselves to be at high risk of coronary heart disease. In fact, men who reported a diagnosis of hypertension over the course of follow-up significantly decreased their coffee intake afterward ($P < 0.004$). This phenomenon would result in a differential shift of high-risk men to lower levels of coffee intake, thereby minimizing any association between coffee drinking measured later in life and coronary heart disease. Even if the change in amount of coffee consumed over follow-up was nondifferential, midlife intake was a poor measure of intake in early adulthood.

DISCUSSION

These results demonstrate a strong, independent dose–response relationship between coffee intake and the subsequent development of coronary heart disease in this cohort. This increased risk associated with coffee use was also present in lifetime nonsmokers, thus eliminating cigarette use as a confounding variable. The risk estimates for the various

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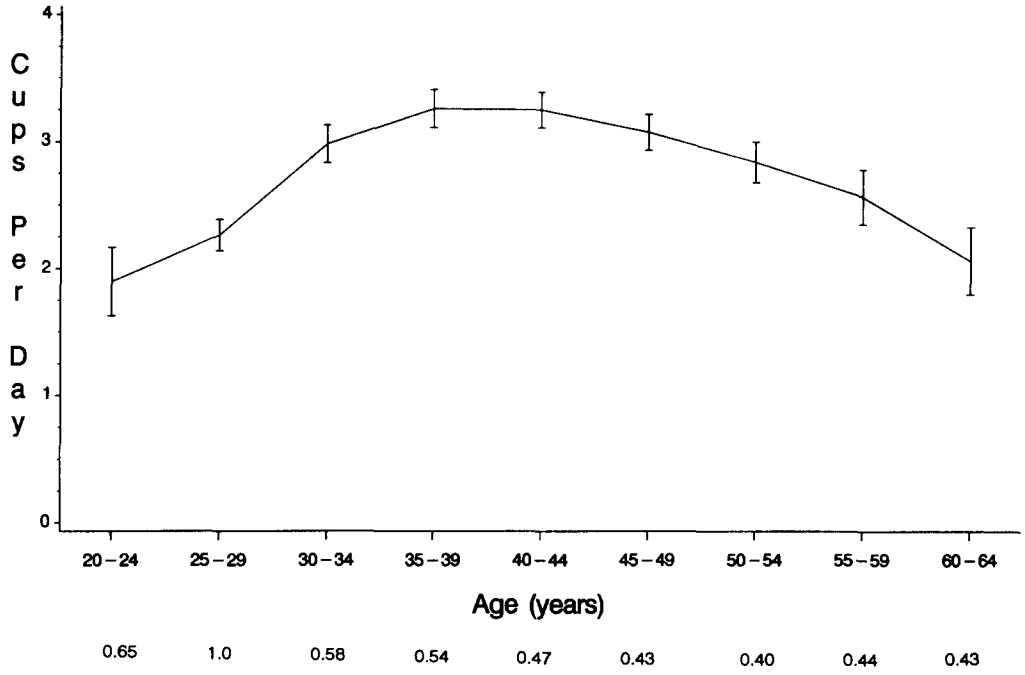

FIGURE 2. Mean coffee consumption by age over 28 to 44 years of follow-up in 1040 white men. Vertical bars indicate 95% confidence interval. Correlation coefficients for coffee intake assessed at age 25 to 29 years with coffee intake at other ages are given below the figure (all *Ps* < 0.0001).

measures of coffee intake were similar and not statistically different, although the risk was highest for coffee intake 10 years prior to an event. Average coffee intake, an average of multiple reports, minimized regression-dilution bias because it was a more precise estimate than the one-time baseline assessment. Thus, average intake yielded stronger risk estimates than did measures of baseline or most recent coffee consumption. When the risk associated with the various measures of coffee drinking was tested, however, baseline coffee intake appeared to contain all of the predictive power of the other two measures of coffee intake. Most of the excess risk associated with coffee drinking was accounted for by coffee intake prior to 1975. This result is consistent with the weaker risk estimates for most recent intake and coffee drinking 5 years prior to an event than for baseline and average intake.

Differences in the risk estimates between this report and the previous are primarily due to use of coffee intake as a categorical, rather than a continuous, measure in the present analysis (16). When coffee intake is analyzed as a continuous variable, results are very consistent with those for follow-up through 1984, even though most recent coffee intake was interpreted as being more important. There are several reasons for the differences in inferences drawn from these data. Unlike our previous analysis, coffee consumption measured in young adulthood continued to be associated with coronary heart disease after adjustment for other cardiovascular risk factors, probably reflecting the greater statistical power of the present analysis to detect associations (16). The previous analysis, however, did not formally compare the different measures of coffee intake. In addition, multivariate models examining baseline intake did not contain time-dependent cigarette smoking. Including change in cigarette smoking during follow-up serves to strengthen the risk estimates associated with baseline coffee drinking.

Coffee can cause gastrointestinal symptoms that could be misdiagnosed as angina pectoris. Such misclassification of coffee drinkers as having coronary disease would artifactually increase the risk associated with coffee intake. The risk associated with coffee use was as strong or stronger for myocardial infarction than for all types of coronary heart disease combined, however, indicating that the observed association was unlikely to be due to misdiagnosis.

Several aspects of the present analysis strongly support a causal association between coffee exposure and the development of coronary heart disease. Coffee intake was assessed in youth before subclinical cardiovascular disease, which may affect health behaviors, was likely to be present. In addition, the association was independent of other cardiovascular risk factors, present in nonsmokers as well as smokers, and stronger with increasing coffee use. Coffee drinkers tend to have "atherogenic" life-styles, with lower levels of physical activity and diets higher in fat (38–40). However, adjustment for baseline age, blood pressure, serum cholesterol level, and calendar time or the development of hypertension and diabetes and change in smoking status and body mass index over follow-up did not materially affect the risk estimates associated with coffee drinking, suggesting that the increased risk is not mediated through these factors. The lack of information on dietary intake of fat and cholesterol is a limitation of the present study. Serum cholesterol level at baseline is a strong predictor of subsequent coronary heart disease in this cohort (28). Confounding due to higher fat and cholesterol intake in persons drinking more coffee

should have been reduced by adjusting for serum cholesterol level, although there may be additional mechanisms by which dietary cholesterol increases the risk of coronary disease (41). In addition, some residual confounding due to change in serum cholesterol over follow-up may be present. For confounding to explain the observed association between baseline coffee intake and coronary heart disease, however, the confounding variable would have to have a relative risk much higher than observed for coffee drinking *and* be tightly linked with coffee drinking.

The mechanisms by which coffee exposure might increase the risk of coronary disease are uncertain. The strong association of baseline coffee intake with coronary disease over 20 years later in the present study is consistent with a chronic effect of coffee, perhaps on atherogenesis. Caffeine appears not to be the culprit (42, 43). The most plausible hypothesis for a coffee–coronary disease link at present is a recently identified fraction in boiled coffee that raises serum lipid levels (42, 43). This material has been demonstrated to raise serum cholesterol and its effect is reduced by filtering. Most of the risk associated with coffee drinking was for intake assessed before 1975, prior to the widespread popularity of automatic drip coffee makers in the United States. Although method of preparation was not ascertained in the present study, most of the coffee consumed at baseline was almost certainly percolated and unfiltered. Similarly, given the calendar time, it is likely that most of the baseline intake represented caffeinated, not decaffeinated, coffee. The strong influence of calendar time on the association of coffee drinking with coronary heart disease is consistent with secular trends in the method of coffee preparation. Differences in coffee preparation between populations and over time also may explain some of the disparity in results between studies. A recent meta-analysis offers support for this interpretation (44). Cohort studies with longer follow-up, thus being initiated earlier in calendar time, showed a tendency to demonstrate a higher risk of coronary heart disease associated with coffee drinking.

Published studies concerning coffee and coronary disease show both positive and negative results. Since publication of our previous analysis, three subsequent prospective studies (17–19) found similar, independent associations between coffee drinking and coronary disease. One of these was a repeat study of Kaiser-Permanente health maintenance organization (HMO) enrollees for whom the previous study findings had been negative (6, 19). The authors attributed this reversal to the use of a more sensitive measure of coffee intake. Another positive report was from the Western Electric Study, where a previous examination of this issue in a subset of the cohort also had showed no independent relationship between coffee and coronary disease (3, 17). Three case–control studies since 1986 also demonstrated an independent relationship of coffee drinking and coronary disease (20–22). One of these, a study in women under age 50, demonstrated a statistically significant trend of increased risk of myocardial infarction with higher coffee intake that had not been seen in a previously published interim analysis (9, 20). In contrast to these results, three recently reported prospective studies (23–25) reported no association of coffee use with coronary heart disease. In a reanalysis from the Framingham Study (24), coffee was not related to the incidence of cardiovascular disease, similar to previous analyses (10). There was also no relationship of coffee intake to either myocardial infarction or coronary death in 6765 Swedish men followed for 7.1 years (23). A prospective study initiated in 1986 of 45,589 middle-aged male health professionals, a white-collar group similar to that in the present study, who were followed for 2 years, likewise found no association between coffee intake and coronary heart disease (25). While the large size of that study population makes it unlikely that a true association was not detected, the cohort was considerably older than the Precursors Study cohort at inception. The age range at entry was 40 to 75 years, with an average of 54.5 years, compared to 22 years in the Precursors Study. Age-stratified analyses were performed for men younger than 60 years old, an age when most of the coronary disease events had already occurred in the present study. Thus, many men may have already decreased their coffee intake, as appears to have occurred with aging in the Precursors Study cohort. This change in behavior may be across the board or might be based on self-perceived risk, the presence of subclinical cardiovascular disease, or popular media reports of a possible harmful effect of coffee drinking. In a survey of 697 medical specialists in 1987, 75% recommended decreasing caffeine intake for a variety of conditions, including coronary disease (45). A systematic decrease in coffee intake by high-risk men would mask an association of coffee drinking with coronary disease. The relatively low initial response rate (33%) in the Health Professionals Follow-up Study and the knowledge associated with being a health professional may have increased the likelihood that this occurred. For example, only 2.9% of the men drank 6 or more cups a day (25). In the present study, the percentage drinking 5 or more cups a day at baseline was only slightly less than that in a representative US sample (16.8%) of professional men aged 20 to 44 years in 1976 (1). In addition to secular trends in techniques of coffee preparation, the assessment of coffee drinking before midlife and the occurrence of most of the coronary disease events at a relatively early age in the present study may explain the discrepancy between our results and those of other studies that enrolled persons in midlife.

Public health and clinical recommendations regarding coffee drinking should be based on the totality of evidence available from rigorously conducted studies, not on the results of a single study (44, 46). The present study adds important new information regarding the risk associated with coffee drinking over the life course. It demonstrates that

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coffee intake assessed at a young age and earlier calendar time periods is an independent risk factor for coronary heart disease. Our results are generally consistent with those from studies that showed little increased risk of coffee drinking in midlife. It suggests that in future studies of the risk of coffee drinking, method of preparations should be assessed as well as lifetime history of coffee intake. These results should stimulate further investigation into the mechanism of the association between coffee drinking and coronary heart disease, especially the role of coffee preparation.

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