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COFFEE CONSUMPTION AND THE INCIDENCE OF CORONARY HEART DISEASE

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Abstract We conducted a prospective investigation of the effect of coffee consumption on coronary heart disease in 1130 male medical students who were followed for 19 to 35 years. Changes in coffee consumption and cigarette smoking during follow-up were examined in relation to the incidence of clinically evident coronary disease in comparisons of three measures of coffee intake — base-line intake, average intake, and most recent intake reported before the manifestation of coronary disease. Clinical evidence of coronary disease included myocardial infarction, angina, and sudden cardiac death.

In separate analyses for each measure of coffee intake, the relative risks for men drinking five or more cups of coffee per day, as compared with nondrinkers, were approximately 2.80 for all three measures in the univariate analyses (maximum width of 95 percent confidence intervals, 1.27 to 6.51). After adjustment for age, current smoking, hypertension status, and base-line level of serum cholesterol, the estimated relative risk for men drinking five or more cups of coffee per day (using the most recent coffee intake measure), as compared with those drinking none, was 2.49 (maximum width of 95 percent confidence interval, 1.08 to 5.77). The association between coffee and coronary disease was strongest when the time between the reports of coffee intake and the coronary event was shortest.

These findings support an independent, dose-responsive association of coffee consumption with clinically evident coronary heart disease, which is consistent with a twofold to threefold elevation in risk among heavy coffee drinkers. (N Engl J Med 1986; 315:977-82.)

COFFEE consumption has long been suspected to be a contributing factor in the development of coronary heart disease, but strong, independent risks associated with coffee drinking have not yet been documented in well-designed prospective studies. Indeed, early case–control studies linking coffee intake to myocardial infarction[1,2] have not been consistently supported by several relevant case–control[3-6] and prospective[7-13] investigations with diverse design features. Nevertheless, it has not been possible to exclude coffee drinking as a potential coronary risk factor because of important methodologic differences among the various studies. In addition, recent epidemiologic evidence linking heavy coffee consumption to elevations in total serum cholesterol levels has renewed concern that coffee drinking may increase the risk of coronary heart disease.[14-20]

The major limitation of past prospective studies is that coffee consumption was measured at a time remote from the coronary event.[21] Changes over time in coffee consumption and in other important variables, most notably cigarette smoking, were not adequately considered. In this investigation, repeated measurements of coffee drinking and smoking during a long-term prospective study of medical students allowed the evaluation of changes in both these habits over time. Furthermore, this study examined and compared the potential risks of coronary disease associated with coffee drinking early in adulthood, with average coffee consumption during a 25-year period, and with the amount of coffee consumed during the years just before the manifestation of a first coronary event.

METHODS

Study Population

The data for this report came from the Precursors Study, a long-term prospective investigation of risk factors during early adulthood for later chronic diseases that was designed in 1946–1947 by one of us (C.B.T.).[22] The study population was 1130 white male medical students enrolled in the 1948 to 1964 graduating classes of the Johns Hopkins Medical School. The age range of the total cohort at the initial examination was 19 to 49 years (mean, 23). More than 95 percent of all eligible participants were enrolled. Before graduation, medical students completed questionnaires that elicited information on family history and habits of daily living, including the amount of coffee drunk and the number of cigarettes smoked per day. In addition, participants received a standardized medical examination that included determination of blood pressure and total serum cholesterol levels (classes of 1949 to 1964 only), as previously described.[22]

Subsequently, questionnaires were mailed to participants at five-year intervals in order to ascertain changes in personal habits. To

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date, as many as six measurements of coffee intake and exposure to cigarettes are available, representing up to 25 years of information on these habits during adulthood. (The questionnaires did not ask for information on the consumption of decaffeinated coffee or tea.) Participation has remained high during this period, with response rates that have ranged from 68 to 78 percent for the return of any one set of follow-up questionnaires. Less than 1 percent of the enrolled cohort has not provided information during subsequent data collection.

In addition, the incidence of disease events and mortality in this cohort were surveyed annually. The length of follow-up on each subject ranged from 19 to 35 years, depending on the subject's graduating class. During that time, 51 cases of coronary heart disease occurred in the cohort, including 21 cases of acute myocardial infarction, 21 cases of angina pectoris, and 9 sudden cardiac deaths. Nonfatal coronary events self-reported by the subjects and deaths from coronary heart disease were verified by reviews of medical records or death certificates in 76.5 percent of cases (100.0, 81.0, and 61.9 percent, respectively, for deaths, myocardial infarctions, and angina). Information on coffee consumption was available for 1040 participants, including 47 in whom coronary heart disease occurred. Multivariate analyses that included serum cholesterol levels (which were not obtained in the participants who had been enrolled in the 1948 graduating class) were based on 864 subjects, including 37 in whom coronary disease developed.

Definitions of Coffee Consumption

Three measures of coffee consumption were derived from the available information on coffee intake during 25 years of adulthood — early adult consumption, average consumption, and most recent consumption. Early adult consumption was defined as the coffee intake (usual number of cups drunk per day) reported during the initial examination in medical school. Average coffee consumption for up to 25 years of observation was computed as a weighted average of coffee drinking reported at each of the six time points, with use of the following formula:

$$\text{Average coffee consumption} = \frac{\Sigma\,[\text{coffee}_i\ (\text{years participating in interval}_i)]}{\text{total person-years}},$$

where coffee_i refers to the reported coffee consumption (number of cups per day) in the ith interval.

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 data were entered by averaging the quantity of coffee consumption reported at time points adjacent to the missing value.

Statistical Analysis

The relation between coffee consumption and the incidence of coronary heart disease during the 19- to 35-year follow-up period was first evaluated by an examination of Kaplan–Meier survival curves for each of four categories of coffee consumption (none, one to two cups daily, three to four daily, and five or more cups daily), with use of the base-line and average measures of coffee exposure.[23] The statistical difference between the four curves was assessed with a log-rank test with corresponding two-sided P values that were considered significant at or below the 0.05 level.[24] Since in relation to the most recent measure, subjects could change coffee-consumption groups at each time point, the unadjusted associations of the three measures of coffee exposure (early adult, average, and most recent) with the development of coronary disease were compared by entering each measure (zero to seven cups per day) into separate Cox proportional hazards models.[25]

Three multivariate Cox proportional hazards models were then developed to consider potential confounding variables for each measure of coffee intake. In an effort to replicate as nearly as possible the multivariate approach used in previous prospective investigations,[7-13] the model for base-line coffee consumption was adjusted for other variables measured in medical school, including age, systolic blood pressure, number of cigarettes smoked per day, and serum cholesterol level. Cox models for the average and the most recent coffee consumption used the full range of available data for the 25-year period, and they were developed with two special features. First, the models incorporated time-dependent exposure data on cigarette smoking and the presence of hypertension treated with medication, in addition to age and serum cholesterol level at base line. This allowed individual covariate attributes to change whenever new information was reported during the follow-up period. In time-dependent survival models, covariate characteristics of each new case of coronary heart disease were compared with characteristics of noncases at the time of the clinical event. Second, the models were constructed to consider potential cohort effects arising from differences in base-line risk factors, the secular decline in mortality due to coronary disease, or both.[26,27]

Finally, using available information on coffee consumption over time, we constructed multivariate Cox models to investigate various latency periods, or lag times, between coffee consumption and subsequent coronary disease. It was therefore possible in this study population to determine the single measurement of coffee consumption that was most strongly associated with the development of coronary disease. Estimates of relative risk and corresponding two-sided 95 percent confidence intervals relating coffee consumption to coronary heart disease were computed from the final multivariate Cox models.[25]

Results

The base-line characteristics of the study cohort, according to medical school class year, are presented in Table 1 to show secular differences in risk-factor profiles at entry into the study. The percentage of nonsmokers at base line was much lower among participants entering in the earlier class years (39.2 percent), as compared with the later years (53.7 percent). This suggested a secular decline in smoking among young adults that coincided with a statement by the Surgeon General on smoking in 1957.[28] Mean coffee consumption at base line was identical in the two class groups (2.3 cups per day). Age-adjusted serum cholesterol levels at base line were moderately elevated among coffee drinkers, as compared with nondrinkers (219.4 mg per deciliter, or 5.7 mmol per liter, among nondrinkers vs. 225.0 mg per deciliter, or 5.8 mmol per liter, 231.5 mg per deciliter, or 5.9 mmol per liter, and 223.0 mg per deciliter, or 5.8 mmol per liter, respectively, among those drinking one to two, three to four, and five or more cups daily).

Table 1. Base-Line Characteristics of the Precursors Study Cohort, According to Class-Year Groups.

Base-Line Characteristic	Class Group		Total
	1948–1956	1957–1964	
No. of subjects	593	537	1130
Mean (±SD) age	24.3–3.1	22.4–1.9	23.4–2.8
Mean no. (±SD) of cups of coffee per day	2.3–1.8	2.3–1.8	2.3–1.8
Smoking variables — % (no.)			
Nonsmokers	39.2 (205)	53.7 (257)	46.1 (462)
Smokers (cigarettes per day)			
1–10	23.5 (123)	19.6 (94)	21.7 (217)
11–19	13.0 (68)	5.6 (27)	9.5 (95)
20–39	22.2 (116)	18.2 (87)	20.2 (203)
>40	2.1 (11)	2.9 (14)	2.5 (25)
Unknown*	— (70)	— (58)	— (128)
Mean (±SD) serum cholesterol — mg/dl	228.4–43.8	222.6–38.4	225.3–41.1

*Not included in percentages.

In the total cohort, coffee consumption increased markedly in the first 10 years of follow-up and declined slightly at each subsequent measurement. The proportion of heavy coffee drinkers (those drinking five or more cups per day) was lowest at base line (13.8 percent), highest at the 10th year of follow-up (28.6 percent), and at an intermediate level (21.7 percent) at the 25th year. Average coffee consumption was most strongly associated with coffee intake (r = 0.94) at the 10th year of follow-up (in mid-adulthood) but was also highly correlated with the latest measure of coffee intake (r = 0.81).

In contrast, the percentage of subjects who were smokers at the time of the initial examination and who remained smokers at each subsequent evaluation declined steadily, from 53.0 percent at base line to 13.5 percent by the 25th year of follow-up. Coffee drinking was strongly associated with current smoking habits throughout the follow-up period (Fig. 1). Nonsmokers consistently reported the lowest mean coffee intake (about 2.3 cups per day) throughout the 25-year period, whereas subjects who continued to smoke throughout the follow-up period reported the highest coffee consumption (about 3.8 cups per day). Subjects who quit smoking (about 40 percent of the cohort) continued to drink more coffee than those who had never smoked, but drank less coffee than current smokers (about 3.0 cups per day). Persons who reported at least two changes in smoking status ("switchers") drank more coffee on the average than former smokers but less than current smokers.

Cumulative incidence rates of coronary heart disease over time, according to categories of base-line coffee consumption, are presented in Table 2. At the 30-year follow-up, subjects who drank five or more cups of coffee per day had the highest cumulative incidence of coronary disease (10.7 percent), as compared with subjects who drank three to four cups per day (8.8 percent), one to two cups per day (5.1 percent), or no coffee (1.6 percent; log-rank chi-square, 8.34; P = 0.04). Cumulative incidence rates for categories of average coffee consumption (data not shown) were similar to those shown in Table 2, with incidence rates of 0.8, 5.9, 6.3, and 9.6 percent, respectively, at the 30-year follow-up for those who drank no coffee, one to two cups, three to four cups, and five or more cups daily (log-rank chi-square, 7.20; P = 0.07).

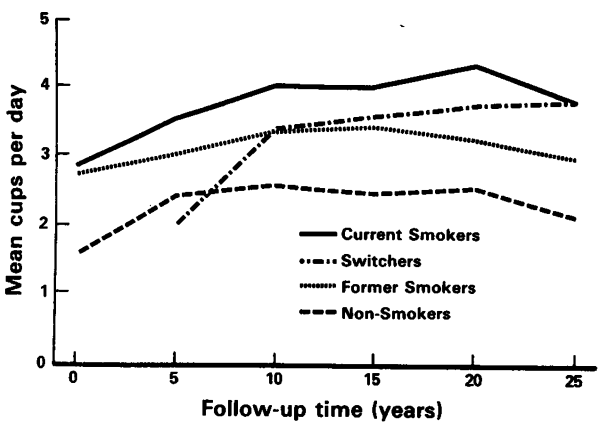

Figure 1. Coffee Consumption (Mean Number of Cups per Day) in Relation to Smoking Habits during 25 Years of Follow-up. "Switchers" denotes persons who reported at least two changes in smoking status.

Table 2. Cumulative Incidence of Coronary Heart Disease at Various Follow-up Times, According to Coffee Consumption at Base Line.

Base-Line Coffee Consumption	Subjects at Risk	No. of Coronary Events	Cumulative Incidence of Coronary Heart Disease		
			Year of Follow-up (t_i)		
			20	25	30
cups per day			*percent of subjects*		
0	189	4	1.6	1.6	1.6
1–2	474	17	2.0	3.1	5.1
3–4	243	17	3.8	7.5	8.8
≥5	134	9	3.0	5.1	10.7
Total	1040	47			
No. of subjects contributing person-years at t_i			930	582	290

Regardless of the measure of coffee consumption used, univariate analyses found that heavy coffee drinkers were almost three times more likely to have coronary heart disease than were nondrinkers. Relative-risk estimates comparing heavy coffee drinkers (five or more cups per day) with nondrinkers were nearly identical in terms of base-line (relative risk, 2.83; 95 percent confidence interval, 1.43 to 5.59), average (relative risk, 2.87; confidence interval, 1.27 to 6.51), and most recent coffee consumption (relative risk, 2.77; confidence interval, 1.37 to 5.59).

Table 3 shows the relative risks relating coffee consumption to the incidence of coronary disease after adjustment for other important risk factors. When base-line coffee consumption was adjusted for other variables measured concomitantly, including age, number of cigarettes smoked per day, and serum cholesterol level, the relative risk decreased to 1.77 (95 percent confidence interval, 0.79 to 3.98) for heavy coffee drinkers. Systolic blood pressure in medical school was not significantly associated with the development of coronary heart disease and therefore was not retained in the final Cox model.

In contrast, the elevated risk of coronary disease associated with average and most recent coffee consumption persisted after adjustment for other coronary risk factors. Both types of exposure to coffee were controlled for age, current number of cigarettes smoked per day, current hypertension status (treated vs. untreated), and serum cholesterol level at base line, with use of Cox models extended for time-dependent variables. The major difference introduced by the use of time-dependent models, as compared with the model

for base-line coffee consumption, was the consideration of changes in smoking habits and the occurrence of hypertension in the cohort. When these two factors were taken into account, the relative risks in the comparisons between heavy coffee drinkers and nondrinkers remained significantly elevated at 2.77 and 2.49, respectively, for average and most recent coffee consumption. Age, serum cholesterol level, and current hypertension were all important predictors of coronary disease in the time-dependent models. Although current cigarette smoking was retained in all models, it was not a significant predictor of coronary disease, reflecting the small number of subjects in the cohort who continued to smoke.

The time interval between reported coffee consumption and the manifestation of coronary disease was examined within the same time-dependent, multivariate survival model by manipulation of the coffee intake measure included in the model, from most recent consumption to consumption 10 years before the coronary event (Table 4). A 10-year lag time between reported coffee intake and coronary disease substantially diminished the association observed when heavy coffee drinkers were compared with nondrinkers, from a relative risk of 2.49 to a relative risk of 1.89, which was no longer statistically significant.

Discussion

Our findings support a strong, positive, dose-responsive, independent association between the risk of clinically evident coronary disease and coffee consumption in this group of predominantly nonsmoking men. The magnitude of the relation suggests a twofold to threefold elevation in the risk of clinical coronary disease associated with heavy coffee drinking. The association observed was strongest when the time between reported coffee intake and the coronary event was shortest.

The results of previous epidemiologic studies that examined coffee drinking as a potential coronary risk factor have not confirmed a consistent positive association, nor have they established that such consumption poses no risk.[1-13,29] The present findings are in agreement with two earlier case–control studies that showed a twofold to threefold increased risk of acute myocardial infarction associated with heavy coffee consumption just before hospital admission for myocardial infarction.[1,2] Also consistent with the present study was a recent report of a positive association between coffee consumption and mortality due to coronary disease among a predominantly nonsmoking cohort of male Seventh-Day Adventists who were followed for 21 years.[29] In three other prospective studies, coffee was positively and significantly associated with coronary events or mortality in univariate analyses.[7,9,10] However, the association was explained in each report by the confounding effects of other risk factors, primarily smoking.

Three additional prospective investigations found no association between coffee and coronary disease, regardless of whether the effects of other coronary risk factors were taken into account.[8,11,12] However, the comparison group in each of these studies contained a substantial number of coffee drinkers (e.g., persons consuming less than five cups per day[11]) rather than the completely unexposed segment of the cohort that consisted of nondrinkers alone.

Although most previous prospective studies have not supported a positive association between coffee drinking and coronary disease, those investigations differed from the present study in that they employed only a single measure of coffee consumption, which was distant in time from the first manifestations of coronary events. When this analytic approach is applied to our base-line coffee-consumption measure, our study also shows no independent association between coffee drinking and coronary disease. However, if coffee-drinking habits changed during the follow-up intervals and if it is the acute or cumulative effects (rather than the remote effects) of coffee that promote

Table 3. Relative Risks Relating Coffee Consumption to Incidence of Coronary Heart Disease during 19 to 35 Years of Follow-up.

Measure of Coffee Consumption	Cups of Coffee per Day			
	0	1–2	3–4	≥5
		relative risk (95 percent confidence interval)		
Base line*	1.0	1.19 (0.93–1.51)	1.49 (0.85–2.63)	1.77 (0.79–3.98)
Average†	1.0	1.36 (1.02–1.81)	2.04 (1.04–4.01)	2.77 (1.06–7.26)
Most recent†	1.0	1.32 (1.02–1.69)	1.90 (1.05–3.41)	2.49 (1.08–5.77)

*Relative risks estimated from a Cox proportional hazards model, with adjustment for base-line age, the number of cigarettes smoked per day at base line, and base-line serum cholesterol level.

†Relative risks estimated from a Cox proportional hazards model, with adjustment for base-line age, base-line serum cholesterol level, and time-dependent changes in current smoking and hypertension status (treated vs. untreated).

Table 4. Relative Risks Relating Coffee Consumption at Various Times to Incidence of Coronary Heart Disease during 19 to 35 Years of Follow-up.

Measure of Coffee Consumption*	Cups of Coffee per Day			
	0	1–2	3–4	≥5
		relative risk (95 percent confidence interval)†		
Most recent	1.0	1.32 (1.02–1.69)	1.90 (1.05–3.41)	2.49 (1.08–5.77)
5 years before	1.0	1.31 (1.02–1.68)	1.87 (1.04–3.36)	2.44 (1.05–5.66)
10 years before	1.0	1.21 (0.94–1.55)	1.56 (0.87–2.79)	1.89 (0.82–4.34)

*Time of measurement of coffee consumption in relation to the first manifestation of coronary disease among those with the disease, as compared with coffee consumption at the same time among those without the disease.

†Relative risks estimated from a Cox proportional hazards model, with adjustment for base-line age, base-line serum cholesterol level, and time-dependent changes in current smoking and hypertension status (treated vs. untreated).

coronary events, then the base-line measures may have misrepresented the actual consumption of coffee during the years just before the manifestation of coronary disease.

Indeed, the results of the present study demonstrate that the coffee consumption that was reported nearest in time to the first manifestation of coronary heart disease was associated with a significant elevation in risk, whereas consumption more than 5 to 10 years before the event was not a significant predictor. Similarly, a series of Swedish men who survived an acute myocardial infarction reported higher coffee consumption just before hospitalization than was reported during base-line evaluations of men of similar age who were followed for 12 years in a community population.[13] Four previous prospective studies that found no association between coffee and coronary heart disease measured coffee consumption only once — 8 to 17 years before the end of the follow-up period.[7,8,10,12] In these studies, the interval between the measurement of coffee intake and the manifestation of coronary disease may have been too long for an association to be observed.

Changes over time in other risk factors, particularly smoking, have also not been considered in previous prospective studies. In adult populations with growing numbers of subjects who have quit smoking, the measure of smoking at base line may greatly overestimate actual exposure to cigarettes as follow-up time increases.[30] Controlling for past, rather than for current, smoking habits could affect the ability to distinguish the risk associated with smoking among current smokers from the risk associated with continued heavy coffee drinking among former smokers. In the present study, the prevalence of cigarette smoking declined dramatically during the 25-year observation period, whereas coffee consumption remained higher among former smokers than among subjects who had never smoked. These trends are consistent with smoking patterns in other contemporary white-collar populations[31,32] and with patterns of coffee consumption among former smokers in a national sample.[33] In this study, cigarette smoking among men was also found to be unrelated to subsequent coronary disease — a finding consistent with the results of two other prospective studies.[29,34] Since the epidemiologic evidence linking smoking to coronary disease is overwhelming,[35] these findings are more likely to be a reflection of the low prevalence of smoking in these cohorts than of a true lack of association.

The present study did not control for the effects of other life-style or personality factors that may be associated with both heavy coffee consumption and the development of coronary disease. Among the most important factors not considered here was an atherogenic diet (including a high intake of total and saturated fat and cholesterol), which has been shown to be more common among men who drink a great deal of coffee than among other men.[14] In addition, heavy coffee consumption may occur more frequently in combination with a number of risk-producing habits or exposures, such as a sedentary life style or high levels of occupational stress.

Although this investigation was prospective and had features that overcome some of the limitations of earlier studies, the findings must be considered preliminary until they are replicated in other long-term studies with similar data-collection strategies. Furthermore, the applicability of these results to other racial groups, to women, and to other occupational groups remains to be determined by means of studies of more heterogeneous populations. In addition, the number of coronary events on which these findings are based was small and thus did not allow separate consideration of specific manifestations of coronary disease. A potential bias in our classification of coronary end points exists, in that the unverified cases of angina reported by our subjects (15.7 percent of the total case group) could have been due to sources of chest pain other than coronary disorders.

Finally, the biologic plausibility of an association between coffee and coronary disease has not been elucidated by this investigation. Coffee, because it is a stimulant, may promote arrhythmias leading to acute coronary events in the presence of underlying atherosclerotic disease.[36] The recent findings linking coffee intake to elevations in total serum cholesterol,[14-20] including those from one randomized intervention trial,[17] offer another possible explanation. In future studies the measurement and description of exposure to coffee can be improved by including more precise quantification of the volume of coffee drunk (e.g., ounces per day), the method of brewing used, the amounts of caffeinated and decaffeinated coffee consumed, and the substances added to coffee, such as cream and sugar. In the light of their implications for the 80 percent of adults in the United States who drink coffee regularly,[33] the present findings suggest a need for further investigation of the link between coffee and coronary disease.

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