The Confounded Relation of Coffee Drinking to Coronary Artery Disease

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After decades of conflicting studies, the relation of coffee drinking to coronary artery disease (CAD) risk remains unresolved. Using Cox proportional-hazards models with 5 covariates, 127,212 subjects who supplied baseline data at voluntary health examinations from 1978 to 1985 were studied. Subsequently, 8,357 subjects were hospitalized for CAD. Coffee drinking was unrelated to CAD risk in 58,888 never smokers, but in ex-smokers and current baseline smokers, daily coffee intake was associated with higher CAD risk. This disparity was generally consistent in stratified subgroups. In conclusion, this relation of coffee consumption to increased CAD risk only in smokers could be explained by incomplete control for smoking, by other traits of smokers, or by an adverse biologic interaction of a coffee ingredient with smoking effect on CAD. **(Am J Cardiol 2008;101:825–827)**

Conflicting reports have appeared about relations of coffee drinking to coronary artery disease (CAD).[1–8] Although coffee drinking is unrelated to total mortality[9,10] and may reduce the risk for several conditions,[10–15] concern persists about possible increased CAD risk. In a case-control analysis of 464 subjects with acute myocardial infarctions, we found no increased CAD risk for heavy coffee drinkers.[1] Later, we reported a cohort study of CAD hospitalizations with a mean follow-up period of 5 years and 1,914 patients with CAD that showed a slightly increased CAD risk in heavier coffee drinkers.[2] Here we present expanded data with 15 additional years of follow-up and 8,357 patients with CAD.

Methods and results

The study protocols were approved by the Institutional Review Board of the Kaiser Permanente Medical Care Program. We studied 127,212 subjects who voluntarily underwent health examinations[16] from 1978 to 1985. Examination questionnaire items included ethnicity, other demographics, habits, and medical history. One query was "Do you drink coffee?" with the following response options: "More than 6 cups per day," "4-6 cups per day," "1-3 cups per day," "less than 1 cup per day," and "never or seldom." There were no queries about type of coffee (e.g., caffeinated or not) or preparation method. Measurements included height, weight, and total blood cholesterol. Subjects were followed until December 31, 2004, death, or other health plan termination or first CAD hospitalization (International Classification of Diseases, Ninth Revision, codes 410 to 414; n = 8,537) at a program facility, yielding 2,618,523 person-years of observation. Table 1 lists selected distributions.

We used Cox proportional-hazards models determined by the PHREG procedure of SAS version 8 (SAS Institute Inc., Cary, North Carolina). Most multivariate models included age (×10 years), gender, race (referent = white; black, other), and cigarette smoking (referent = never; exsmoker, <1 pack/day, ≥1 pack/day). Coffee was studied categorically, with never or seldom as the referent and <1, 1 to 3, 4 to 6, and ≥6 cups/day or <1, 1 to 3, and ≥4 cups/day. Coffee was also studied as a continuous per cup per day variable, with these assigned numbers: 0 for never or seldom, 0.5 for <1 cup/day, 2.0 for 1 to 3 cups/day, 5.0 for 4 to 6 cups/day, and 7 for '6 cups/day. Although body mass index, education, and alcohol drinking were related to CAD, the inclusion of these in models had virtually no effect on coffee-CAD relations, and they were not included in final models. These analyses yielded estimates of relative risk (RR), 95% confidence intervals (CIs), and p values.

Disproportionate numbers of patients with CAD among heavier coffee drinkers, ex-smokers, and heavier smokers (Table 1) translated into higher unadjusted rates of CAD. For example, compared with an overall CAD crude rate of 3.2 per 1,000 person-years, the rates for ex-smokers, smokers of ≥1 pack/day, and drinkers of ≥4 cups of coffee/day were 4.3, 4.4, and 4.6 respectively. A multivariate model including all subjects showed a modest relation of heavier coffee drinking to higher CAD risk (Table 2). However, models stratified by smoking (Table 3) showed no relation of coffee to CAD risk in never smokers, with increased risk in smokers and ex-smokers. Figure 1 presents the coffee-CAD relation in all subjects, never smokers, and ever (baseline current plus ex-smokers) smokers, making it apparent that the relation of coffee to CAD in all subjects was due entirely to that of the ever smokers.

The increased CAD risk for heavier coffee drinkers among smokers was slightly stronger in women; for example, for ever smokers reporting ≥4 cups of coffee/day, the RR was 1.3 (95% CI 1.1 to 1.6, p = 0.001) for women and

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Table 1
Selected traits of study population and subjects with coronary artery disease

Group	Total Study Population*		Subjects With CAD n (%)
	n (%)	Mean Age (yrs)	
Gender/ethnicity			
All (total)	127,212 (100.0%)	40.7	8,357 (100.0%)
Men	56,211 (44.2%)	41.4	4,980 (59.6%)
Women	71,001 (55.8%)	40.0	3,377 (40.4%)
Black	34,269 (26.9%)	38.4	2,210 (26.4%)
White	71,109 (55.9%)	42.7	5,019 (60.0%)
Other ethnicity	21,834 (17.2%)	38.4	1,128 (13.5%)
Coffee (cups/day)†			
Never or seldom	34,264 (26.9%)	35.0	1,453 (17.4%)
<1	17,837 (14.0%)	38.1	957 (11.5%)
1–3	52,895 (41.6%)	43.2	3,872 (46.3%)
4–6	15,383 (12.1%)	45.0	1,373 (16.4%)
≥6	5,451 (4.3%)	45.9	586 (7.0%)
≥4	20,834 (16.4%)	45.2	1,959 (23.4%)
Cigarette smoker (packs/day)†			
Never	60,878 (47.9%)	39.4	3,242 (38.8%)
Ex-smoker	28,286 (22.2%)	44.8	2,469 (29.5%)
<1	21,347 (16.6%)	37.8	1,287 (15.4%)
≥1	11,743 (9.2%)	41.1	1,034 (12.3%)

* 1978 to 1985 examinees.
† Percentages do not add up to 100.0% because of missing values.

Table 2
Relative risk for coronary artery disease hospitalization according to coffee drinking*

Group (cups/day)	RR	95% CI	p Value
Never or seldom	1.00	Referent	—
<1	1.02	0.94–1.10	0.7
1–3	1.03	0.97–1.09	0.4
4–6	1.08	1.00–1.07	0.05
≥6	1.21	1.10–1.34	0.0002
≥4†	1.12	1.04–1.20	0.003
Per cup per day†	1.02	1.01–1.03	0.0001

* Among 123,016 subjects, of whom 8,357 had CAD; models included age, gender, ethnicity, smoking, and coffee consumption.
† Separate models.

1.2 (95% CI 1.0 to 1.29, p = 0.02) for men. It was similar for several ethnic groups and for those hospitalized for acute myocardial infarctions or other CAD diagnoses (data not shown). The relation was slightly stronger later in the follow-up years; for ever smokers reporting ≥4 cups of coffee/day, the RR of CAD <10 years from baseline was 1.2 (95% CI 1.0 to 1.3, p = 0.07), whereas at ≥10 years, the RR was 1.3 (95% CI 1.2 to 1.5, p <0.001). Covariate relations to risk for CAD were as expected, showing increased risk associated with age, male gender, and smoking; for example, the RR for CAD for ≥1 pack/day was 1.8 (95% CI 1.7 to 1.9, p <0.001). Control for total cholesterol or blood glucose had little effect; for example, among all smokers, the RR per cup per day was 1.05 (95% CI 1.04 to 1.07) with neither controlled, 1.05 (95% CI 1.03 to 1.06) with cholesterol controlled, and 1.05 (95% CI 1.03 to 1.07) with blood glucose controlled. Control for history of diabetes mellitus also had little effect (data not shown).

Table 3
Adjusted* relative risk for coronary artery disease by coffee drinking within smoking strata

Coffee (cups/day)	Never Smoked	Ex-Smoker	<1 Pack/Day	≥1 Pack/Day
<1 cup/day	1.02	0.98	0.92	0.97
1–3	1.05	0.96	0.98	1.01
4–6	0.99	1.06	1.13	1.13
≥6	1.02	1.23†	1.11‡	1.32†
≥4	1.00	1.10	1.12	1.21
Per cup per day	1.00	1.03†	1.03	1.04‡

* Compared with nondrinkers of coffee; models included age, gender, ethnicity, smoking, and coffee consumption.
† p <0.05; ‡ p <0.01.

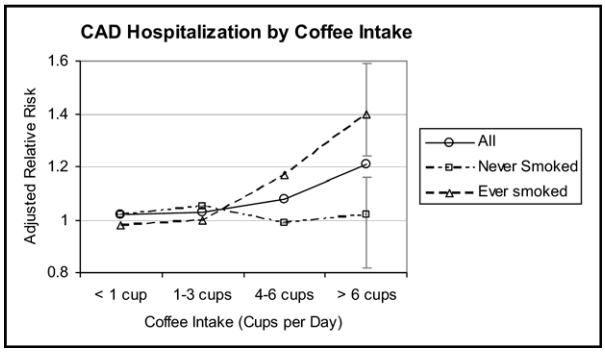

Figure 1. Adjusted RR for coffee intake categories compared with subjects reporting coffee intake never or seldom among all subjects, those reporting that they never smoked, and those reporting ever smoking (past or current baseline smoking).

Discussion

These data about the coffee-CAD relation indicate that a trait related to smoking but not to coffee alone is involved. Because smoking is a strong CAD predictor, residual confounding by incomplete control for smoking is a likely explanatory factor. The known correlation of smoking and coffee drinking in this study population[12] makes it plausible that there might be coffee-correlated variation in amount or intensity of smoking within smoking categories. A second type of confounding might arise from other user traits of smokers unfavorable for CAD risk, such as dietary or exercise habits. User traits might better explain the increased coffee-associated risk for ex-smokers, many of whom may have quit smoking because of concerns about illness or symptoms. If persistent, user traits might also help account for the increasing strength of the coffee-CAD relation in smokers after 10 years of follow-up.

A third possible factor is a biologic coffee-smoking interaction with an additive or synergistic effect. Thus, in some way, coffee might act as a promoter or facilitator of the adverse effects of smoking on atherothrombotic disease. It is not clear that nicotine has the dominant role in the promotion of atherogenesis by cigarette smoking, but it may be relevant that nicotine and caffeine are metabolized sub-

stantially by the hepatic cytochrome P450 1A1 enzyme.[17,18] The induction of this enzyme may thus be related to the strong correlation of smoking with coffee drinking. Caffeine clearance is increased by >50% in smokers, except in the presence of liver cirrhosis.[18] By diminishing the physiologic effect of nicotine, coffee drinking might facilitate increased cigarette smoking, which in turn might potentiate the promotion of CAD by some component of tobacco smoke other than nicotine.

Our data can be compared with those from a cohort study among male and female health professionals recently reported by Lopez-Garcia et al.[6] Those investigators found a strong smoking-coffee association, and they studied smoking strata separately. In that analysis, female smokers reporting ≥4 cups of coffee/day had an RR of CAD of 1.0 (95% CI 0.8 to 1.3), and male smokers had an RR of 1.4 (95% CI 0.9 to 2.2). Although Lopez-Garcia et al[6] interpreted their data as showing no coffee-CAD effect, this coffee-CAD relation in male smokers was similar to our data, albeit not statistically significant. The disparity for female smokers between the studies may be more apparent than real, in view of the presence of overlapping CIs. Additionally, Lopez-Garcia et al[6] controlled for dietary factors and hormone replacement therapy, which we were not able to do.

The importance of smoking as a confounder of studies of coffee and CAD has been noted for decades.[18–20] There are 2 other potentially important associations. The first has to do with cholesterol. Reports that low-density-lipoprotein cholesterol is increased by a lipid-soluble ingredient (cafestol) in boiled coffee have fueled concern about increased CAD risk.[6] However, probably because filter paper removes cafestol, and boiled coffee is not popular in our study population, cholesterol seems to play little role in the present analysis. The second is the mounting evidence that coffee protects against type 2 diabetes mellitus. This might translate into protection against CAD, but we found no evidence that blood glucose levels or diabetes history played a role in our data. Confounding by smoking or traits of smokers remains the dominant factor in our data about coffee and CAD. We conclude that independent of smoking, coffee drinking is unrelated to CAD risk.

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