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Coffee Intake and Elevated Cholesterol and Apolipoprotein B Levels in Men

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Abstract

Coffee intake from three-day diet records was studied in association with plasma lipoprotein concentrations in a cross-sectional sample of 77 middle-aged American men to determine the significance and form of their interrelationships. The number of cups consumed per day correlated positively with levels of apolipoprotein B ($r = .27$, $P \leq 0.01$) and became more strongly correlated when adjusted for age, cigarette use, adiposity, aerobic capacity, nutrient intake, and stress. Coffee intake also correlated with total cholesterol and low-density lipoprotein (LDL) cholesterol levels when adjusted for these confounding factors. Graphic analyses revealed that plasma concentrations of apolipoprotein B and LDL-cholesterol were unrelated to intake of up to 2 cups of coffee per day and positively associated with intake exceeding 2 to 3 cups. These results suggest that male heavy coffee drinkers have lipoprotein profiles suggestive of increased cardiovascular disease risk, although the causality remains to be determined.

INTRODUCTION

Coffee intake is reported to be associated with elevated plasma cholesterol concentrations in some European and Commonwealth populations [1–5]. Studies on Americans, however, have generally failed to substantiate the coffee-cholesterol connection [6–8]. It has been proposed that the lower levels of coffee consumption or that differences in brewing procedures of Americans vs Europeans may partly account for these discrepant results.

A relationship between coffee intake and the potential for increased cardiovascular risk would be more strongly supported if the level of consumption was shown to be associated with elevated plasma levels of apolipoprotein (apo) B or low-density lipoprotein (LDL) cholesterol, because these lipoprotein components are thought to be more directly involved with the atherosclerotic process than is the total amount of cholesterol in plasma [9]. Thus far, coffee studies have primarily focused only on total cholesterol levels as a risk factor.

In this report we demonstrate, in a sample of American male university employees, a significant association between coffee intake of more than 2 cups per day and elevated plasma concentrations of total cholesterol, LDL-cholesterol, and apo B. The resolution of the coffee-lipoprotein association is enhanced through graphic methods and also by the availability of comprehensive data on coffee intake and factors that could potentially confound the coffee-lipoprotein relationship, namely (1) recorded three-day coffee intake as opposed to questionnaires that broadly categorize usual intake, (2) direct assessment of fasting lipoprotein cholesterol concentrations, (3) adiposity directly measured by hydrostatic weighing instead of estimated by a body mass index, (4) aerobic physical fitness measured by maximum oxygen uptake (VO₂ max) during a treadmill test to exhaustion, (5) dietary assessment by three-day

records, and (6) a comprehensive psychological profile of the subjects for those personality traits that are usually associated with stress. The significant association observed between coffee and lipoprotein concentrations in these men could not be attributed to effects caused by age, cigarette smoking, adiposity, aerobic fitness, or other dietary factors or to any of the psychological variables.

METHODS

Subjects and Measurements

Our report focuses on the baseline measurements of 77 sedentary men, aged 30 to 55 years, who later participated in an exercise trial [10]. The subjects were selected to be free of known cardiovascular disease or abnormalities, acute illness or active chronic systemic disease, and medication use likely to interfere with their lipid metabolism. We also required that all participants had resting blood pressures below 160/100 mm Hg, body weight less than 140% of "ideal" weight (according to the 1959 Metropolitan Insurance Company [New York] standards), plasma total cholesterol level below 300 mg/dL, and plasma triglyceride concentrations below 500 mg/dL [10]. Fasting lipid and lipoprotein cholesterol concentrations were determined by the methods of the Lipid Research Clinics [11], and fasting apo A-I, A-II, B, and D levels were determined in total plasma by radioimmunoassay or radial immunodiffusion methods [12–15]. The VO₂ max was defined as the peak value measured during the last two minutes of a graded exercise test to exhaustion [16]. Body composition was evaluated by hydrostatic weighing [17]. Mean total caloric and nutrient intakes were determined from three-day records, using the computerized food composition tables of the Nutrition Coding Center (Minneapolis) and an analysis program.

Type A behavior was assessed from a structured interview. A rater trained in the standardized Western Collaborative Group Study procedures [18] assigned each participant a rating from one of four categories of coronary-prone behavior: A1 (greatest coronary-prone behavior) and A2, X, or B (least coronary-prone behavior). Pencil and paper assessment instruments were used to measure hostility (Cook-Medley hostility scale [19]), anxiety (Thurstone activity scale [20] and the trait form of the Spielberger State-Trait Anxiety Inventory [21]), and depression (from the Minnesota Multiple Personality Inventory [22]).

Statistical Procedures

The coffee-lipoprotein relationships are assessed by Pearson's correlation coefficient and by partial correlations that adjust for age, fitness, cigarette smoking, diet, alcohol intake, and psychological variables.

Because the assumption of multivariate normality may not hold for our data, the standard estimates of significance and confidence intervals for partial correlations were verified by permutation test [23] and bootstrap resampling procedures [24], respectively. First, adjusted coffee intake and adjusted lipoprotein concentration were obtained from the residuals of separate regression equations that predicted coffee intake and lipoprotein concentrations from the adjustment variables. To determine a nonparametric significance level, we randomly permuted, 1,000 times, the adjusted coffee values among the adjusted lipoprotein concentrations to obtain 1,000 partial correlation coefficients under the null hypotheses of zero partial correlation. A two-tailed nonparametric significance level for testing whether the observed partial correlation was different from zero was then obtained by doubling the proportion of times that the correlations for the permuted data exceeded the partial correlation of the original (unpermuted) data [24]. To construct a nonparametric 95% confidence interval for a partial correlation coefficient, we constructed 1,000 "bootstrapped" data sets by sampling 77 bivariate observations, with replacement from the original 77 adjusted observations.

Correlations were calculated for the 1,000 bootstrapped samples, which were then arranged in ascending order. The 25th and 975th largest correlations approximate a nonparametric 95% confidence interval [24].

The associations between coffee intake and plasma lipoprotein concentrations are graphically displayed by a scatterplot smoothing procedure described by Cleveland [25], using half of the data to smooth each point. The method offers considerable flexibility over linear regression because it does not assume a simple straight-line fit between coffee intake and lipoprotein concentration and thus may reveal important nonlinear relationships. Smoothed scatterplots are applied to the original data values and also to the data after adjustment for age, diet, cigarette smoking, adiposity, aerobic fitness, and psychological variables to determine whether nonlinearity could be ascribed to linear interactions with other variables. Bootstrap resampling was used to help distinguish nonlinearity from random variation.

RESULTS

Sixty-nine (89.6%) of 77 men reported drinking coffee during the three-day period. Those who drank coffee reported consuming an average of 2.6 cups/day (1 cup=8 fl oz), with a maximum of 7.5 cups/day. Ninety-one percent of the coffee consumed was prepared from regular grounds. Because instant and decaffeinated coffee constituted less than 9% of the total coffee intake, and because intakes of tea and other foods or medication that contain caffeine were too small for meaningful analyses (approximately 10% of total caffeine intake and did not correlate significantly with any of the lipoprotein concentrations), our analyses focus specifically on mean daily coffee intake prepared from regular grounds. One third (22) of the 66 regular-ground coffee drinkers added a dairy creamer to their coffee, 20 men (30%) added nondairy creamer, and 28 men (42%) added sugar or honey. The physiological, psychological, and dietary characteristics of this sample of 77 men are summarized in Table 1.

Coffee intake did not correlate with age, percent body fat, VO_2 max, alcohol intake, percent calories due to protein, or any of the four pencil and paper psychological variables. Analysis of variance revealed no significant association between type A behavior and coffee intake. There was a weak tendency for those men who drank more cups of coffee per day also to smoke more cigarettes per day ($r = 0.22$, $P \leq 0.06$) and to consume a greater proportion of their total calorie intake from fat ($r = 0.21$, $P \leq 0.06$) than from carbohydrates ($r = -0.20$, $P \leq 0.08$).

Coffee Intake vs Apo B Level

Table 1 reveals that plasma concentrations of apo B were positively correlated with daily reported intake of regular coffee ($r = 0.27$, $P \leq 0.05$). The coffee-apo B association continued to be significant when adjusted for age, number of cigarettes smoked per day, percent body fat, dietary variables, alcohol intake, and various psychological profiles (Table 2).

The smoothed scatterplot of Fig 1 reveals no increase in apo B levels in association with coffee intake for consumption of less than 2 cups/day, but a pronounced increase in apo B concentration with coffee intake greater than 2.5 to 3 cups/day. Figure 2 (top) suggests that this threshold effect was not due to an association of coffee intake or apo B concentration with some other measured variable. To generate the curve of Fig 2 (top), we first used stepwise regression to select a set of adjustment covariates among the various fitness, adiposity, dietary, psychological, and other variables measured. In combination with coffee intake, the variables number of cigarettes smoked per day, alcohol intake, and percent of total calories from sucrose were the most significant predictors of apo B concentration, accounting for 22% of its total variance. Both coffee intake and apo B concentration were then adjusted to their expected levels for a nonsmoker with average intakes of alcohol and sucrose. Applying the scatterplot smoothing procedure to the adjusted data (Fig 2 [top]) revealed no association below intake of

2 cups of coffee per day, but a positive association between coffee and apo B concentration above intake of 2.5 to 3 cups/day.

To determine that the observed threshold level for the coffee-apo B relationship was not the consequence of random variation, the scatterplot smoothing procedure was applied to 20 bootstrapped data sets. The set of 20 curves (not displayed) showed no clear association between coffee intake and apo B concentration for low-intake levels, and all 20 curves exhibited a positive coffee-apo B association above a threshold level that varied from 1.5 to 3.5 cups/day. The consistent form of all 20 bootstrap curves supports the conclusion that the coffee-apo B association is nonlinear.

Coffee Intake vs LDL-Cholesterol Level

Levels of LDL-cholesterol correlated positively with percent body fat and correlated negatively with the trait anxiety score but were not significantly correlated with other variables, including coffee intake (Table 1). However, adjustment for the number of cigarettes smoked per day and other variables yielded significant partial correlations between LDL-cholesterol concentration and coffee intake (Table 2).

Stepwise regression analyses revealed that, in association with coffee intake, the variables number of cigarettes smoked per day, the amount of dietary sucrose, alcohol intake, and percent body fat were the most significant predictors of LDL-cholesterol concentration in plasma, accounting for 27% of its total variance. Figure 2 (center) displays graphically the relationship between the LDL-cholesterol concentration and coffee, when both coffee intake and LDL-cholesterol concentration are adjusted to the sample averages of the best predictor variables. There is no clear association below 2 cups/day and a tendency for increased LDL-cholesterol concentrations above 2 cups/day. Coffee's association with LDL-cholesterol concentration does not appear to be as strong as does its association with apo B among these higher coffee drinkers (compare Fig 2, center and top).

Coffee intake vs Total Cholesterol Concentration

Total plasma cholesterol concentration showed a generally weaker association with coffee intake than did apo B or LDL-cholesterol, perhaps reflecting its heterogeneous origin from several lipoprotein species. Table 1 shows that total cholesterol concentration in plasma correlated positively and significantly with percent body fat and alcohol (the latter association partly reflecting an association between high-density lipoprotein cholesterol and alcohol) and negatively with cigarettes smoked per day (also in part due to lower concentrations of high-density lipoprotein cholesterol for smokers than nonsmokers) and with the trait anxiety score. As observed for LDL-cholesterol levels, total cholesterol concentration is positively associated with coffee intake when adjusted for the number of cigarettes smoked per day, fitness, adiposity, age, diet, and psychological variables. Stepwise regression selected cigarettes smoked per day, dietary intake of alcohol, proportion of calories due to sucrose and protein, and percent body fat as the best predictors of total cholesterol concentration when included with coffee intake. Together, these variables accounted for 37% of the variance in total plasma cholesterol concentrations. Figure 2 (bottom), which displays the adjusted total cholesterol concentration-coffee association, reveals the same basic characteristics of the curves of Fig 2 (top and center), but with somewhat less definition.

Coffee Intake Concentrations of Other Plasma Lipoproteins and Apolipoproteins

Coffee intake was positively correlated with plasma concentrations of triglycerides ($r = 0.23$, $P \leq 0.04$) and very-low-density cholesterol ($r = 0.21$, $P \leq 0.06$), but not with the concentrations of high-density lipoprotein cholesterol ($r = -0.03$) or apolipoproteins A-I ($r = 0.01$), A-II ($r = 0.01$), or D ($r = 0.04$) in plasma.

COMMENT

The Tromso Study [1] report of a significant coffee-cholesterol association precipitated much discussion of other factors that could potentially induce such an association without coffee being causal. Modest [26] proposed that stress could induce an apparent relationship between coffee and cholesterol given (1) plasma cholesterol concentrations are purported to be higher for individuals under stress and (2) stressful conditions are likely to increase coffee intake. Roeckel [27] speculated that cream added to coffee could increase plasma cholesterol concentrations and Ockene et al [28] suggested that heavy coffee drinkers may have diets that differ in many other ways from those of persons who drink less. The Tromso Study did not include comprehensive diet records or detailed psychological tests, but on the basis of their available data the authors of the report concluded that these factors were unlikely to have induced the coffee-lipoprotein associations [29].

Our more complete dietary and psychological assessments enable us to address the issues raised by Modest, Roeckel, and Ockene et al more directly. First, the psychological parameters usually associated with stress, ie, anxiety, hostility, depression, and type A behavior, were only weakly associated with lipoprotein concentrations, showed no association with coffee intake, and did not account for our observed coffee-lipoprotein associations. Second, a comprehensive adjustment of both coffee intake and lipoprotein concentrations for effects caused by the intake of alcohol; protein; saturated, monounsaturated, and polyunsaturated fat; sucrose; starch; other carbohydrates; and cholesterol during the three-day recording period strengthened, rather than weakened, the coffee-lipoprotein associations. These dietary adjustments controlled for the addition of any real or artificial cream to coffee.

In his criticism of the Tromso report, Modest [26] cites several studies that show associations between stressful situations and elevated cholesterol. However, several of the studies cited were not controlled for coffee intake. Excessive coffee intake may have accompanied stress experienced by medical students before taking a major medical school examination [30] and the stress experienced by tax accountants before meeting major tax deadlines [31], thus potentially confounding the reputed stress-cholesterol relationship.

There are several cross-sectional studies, some involving much larger samples than our study of 77 men, that do not find a significant coffee-cholesterol association [6–8,32] as well as several population studies that agree with our results [1–5]. These differences may in part be due to methodological differences across studies, including the following:

1. **Choice of Variables.** Total cholesterol concentration showed a generally weaker association with coffee in our data than did concentrations of LDL-cholesterol or apo B. With few exceptions [1,3], most studies have focused only on total plasma cholesterol concentrations.
2. **Measurement of Coffee Intake.** Questionnaires that assess usual coffee intake in broadly defined categories may be less sensitive than diet records that directly record the number of cups consumed per day. The cut-points that define the categories may also affect the sensitivity of the questionnaire's measurement. For example, a significant coffee-cholesterol association was shown in a group of vegetarians studied by Sacks et al [33] when coffee intake was divided into 2 cups/day or less and more than 2 cups/day. This division corresponds to the level above which coffee intake appears to be positively associated with elevated apo B, LDL-cholesterol, and total cholesterol concentrations (Fig 2). Significant differences ($P \leq .05$) in apo B, LDL-cholesterol, and total cholesterol concentrations were also achieved for our data when the men were divided into groups of coffee intake above ($n = 40$) and below ($n = 37$)

2 cups and analyzed by the more traditional approach of analysis of covariance to adjust for cigarette use.

3. **Adjustment for Cigarette Smoking.** A moderate correlation between cigarette intake and coffee consumption has been reported [6], and adjustment for the number of cigarettes smoked per day can alter inferences regarding coffee's relationship with other variables [6]. Bjelke's [2] observation of a cholesterol-coffee association was not adjusted for cigarettes smoked per day. In another study, Heyden et al [34] concluded that a synergistic relationship exists between coffee intake and cigarette smoking because coffee drinkers who consumed more than 5 cups/day had higher cholesterol concentrations than did those who drank fewer than 5 cups/day only if they also smoked. Our results suggest, however, that the coffee-cholesterol association is not limited to smokers.

We agree with the proposition of Thelle et al [29], Kovar et al [7], and Shekelle and colleagues [8] that in addition to methodological variation, true interpopulation differences may exist, including, for example, variations in brewing procedures. Thelle et al reported that most Norwegians prepared boiled coffee. The coffee-cholesterol association is evidently not restricted to boiled coffee, however, because most of the participants of our study probably brewed drip coffee. Variations in brewing procedures will affect caffeine content. On the average, drip-brewed coffee contains more caffeine (179 mg/8-oz cup) than either percolated (118 mg/8-oz cup) or instant coffee (106 mg/8-oz cup) [35], and these levels will further depend on coffee variety and strength. The caffeine content can vary from 90 to 282 mg for an 8-oz cup of drip-brewed coffee, from 62 to 269 mg for percolated coffee, and from 46 to 282 mg for instant [35].

Limitations and Caveats

Our analyses suggest that coffee intake exceeding 2.5 to 3 cups per day is associated with elevated plasma concentrations of three well-established cardiovascular risk factors: total cholesterol, LDL-cholesterol, and apo B concentrations in a sample of sedentary, middle-aged men. The causality of the coffee-lipoprotein relationships are not proved by these cross-sectional associations and remain to be determined in controlled clinical trials. We also emphasize caution in extrapolating these coffee-lipoprotein associations to the general population, given the more selected nature and modest size of our sample.

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Fig 1. Smoothed scatterplot of plasma apolipoprotein B (apo B) concentration vs regular coffee intake in 77 middle-aged American men. The plot shows no relationship between apo B and coffee below 2 to 2.5 cups/day and positive association above this level.

Fig 2. Smoothed scatterplot of plasma apolipoprotein B (top), LDL-cholesterol (center), and total cholesterol (bottom) concentrations vs coffee intake after adjustment for number of cigarettes smoked per day, age, percent body fat, maximum oxygen uptake, and other dietary factors as required.

Table 1

Sample Distribution and Pearson's Correlation Coefficient for Plasma Concentrations in 77 Middle-aged Men

Variables	Mean $\pm$ SD	Pearson's Correlation Coefficient		
		Apolipoprotein B (mg/dL)	Low-Density Lipoprotein Cholesterol (mg/dL)	Total Cholesterol (mg/dL)
Coffee (cups/day)	2.1 $\pm$ 1.6	0.27 [†]	0.18	0.17
No. of cigarettes/day	2.8 $\pm$ 8.0	-0.19	-0.24 [†]	-0.28 [†]
Age (yr)	45.8 $\pm$ 5.9	0.12	0.10	0.10
Body fat (%)	21.7 $\pm$ 5.7	0.18	0.26 [†]	0.27 [†]
Maximum oxygen uptake (mL/kg/min)	34.8 $\pm$ 6.3	-0.05	0.05	0.08
Dietary protein (g/1,000 kcal)	39.6 $\pm$ 6.2	0.08	0.08	0.09
Dietary fat (g/1,000 kcal)	45.0 $\pm$ 7.4	-0.10	-0.10	-0.16
Dietary carbohydrates (g/1,000 kcal)	95.2 $\pm$ 20.2	-0.09	-0.07	-0.12
Dietary alcohol (g/1,000 kcal)	8.0 $\pm$ 8.4	0.21	0.17	0.31 [†]
Dietary cholesterol (g/1,000 kcal)	189.5 $\pm$ 82.3	-0.03	0.10	0.06
Cook-Medley hostility scale	15.3 $\pm$ 8.1	0.04	-0.07	-0.03
Thurstone anxiety scale	68.1 $\pm$ 8.6	0.08	0.10	0.10
Trait anxiety	35.9 $\pm$ 8.4	-0.10	-0.27 [†]	-0.26 [†]
Personality inventory-depression	10.2 $\pm$ 6.1	-0.12	-0.20	-0.22

* Sample distributions for lipoprotein concentrations (milligrams per deciliter) in plasma were as follows: apolipoprotein B, 82.6 $\pm$ 17.3; low-density lipoprotein cholesterol, 146.0 $\pm$ 27.3; and total cholesterol, 214.2 $\pm$ 30.8. The sample distribution for coronary-prone (type A) behavior was as follows: A1 (20 men), A2 (30 men), X (nine men), and B (12 men). Six men did not have structured interviews and, therefore, were not rated.

[†] $P \leq 0.05$.

Table 2

Partial Correlation Analyses for Regular Coffee Intake vs Apolipoprotein B, Low-Density Lipoprotein Cholesterol, and Total Cholesterol Concentrations in Plasma (Milligrams per Deciliter) in 77 Middle-Aged Men

Partial Correlation Analyses	Coffee vs Concentrations of		
	Apolipoprotein B	Low-Density Lipoprotein Cholesterol	Total Cholesterol
Unadjusted	0.27*	0.18	0.18
95% Confidence interval [†]	0.05–0.46	–0.03–0.39	–0.05–0.40
$P_t^{\ddagger}$	0.009	0.051	0.057
Adjusted for number of cigarettes per day, age, percent body fat	0.35*	0.28*	0.29*
95% Confidence interval [†]	0.10–0.55	0.07–0.48	0.07–0.51
$P_t^{\ddagger}$	0.002	0.010	0.005
Adjusted for number of cigarettes per day and diet [§]	0.34*	0.28*	0.30*
95% Confidence interval [†]	0.14–0.52	0.11–0.45	0.10–0.49
$P_t^{\ddagger}$	0.002	0.010	0.007
Adjusted for number of cigarettes per day and psychological variables //	0.32*	0.27*	0.29*
95% Confidence interval [†]	0.07–0.53	0.00–0.51	0.05–0.51
$P_t^{\ddagger}$	0.005	0.016	0.017

* Designates when a partial correlation was also significant ($P \leq 0.05$) by the standard parametric method.

[†] Determined by 1,000 bootstrapped samples.

[‡] Determined by 1,000 permutations of the adjusted values.

[§] Dietary variables include grams per 1,000 kilocalories of protein, saturated fat, monounsaturated fat, polyunsaturated fat, alcohol, sucrose, starch, and other carbohydrates excluding fiber, and dietary cholesterol.

// Psychological variables are Cook-Medley hostility scale, Thurstone activity scale, trait anxiety inventory, personality inventory of depression, and type A behavior.