Coffee Drinking Is Dose-Dependently Related to the Risk of Acute Coronary Events in Middle-Aged Men[1]

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ABSTRACT Heavy coffee consumption has been associated with increased coronary heart disease (CHD) risk although many studies have not observed any relation. We studied the effect of coffee consumption, assessed with a 4-d food record, on the incidence of nonfatal acute myocardial infarction or coronary death in a cohort of 1971 men who were 42 to 60 y old and free of symptomatic CHD at baseline in 1984–1989. During a mean follow-up of 14 y, 269 participants experienced an acute coronary event. After adjustment for age, smoking, exercise ischemia, diabetes, income, and serum insulin concentration, the rate ratios (95% CIs) in daily nondrinkers and light (375 mL or less), moderate (reference level), and heavy (814 mL or more) drinkers were 0.84 (0.41–1.72), 1.22 (0.90–1.64), 1.00, and 1.43 (1.06–1.94). To address time dependence of the effect, the analysis was repeated for 75 CHD events that occurred during the first 5 y; the respective rate ratios were 0.42 (0.06–3.10), 2.00 (1.16–3.44), 1.00, and 2.07 (1.17–3.65). Further adjustment for serum HDL and LDL cholesterol concentration, diastolic blood pressure, maximal oxygen uptake, and waist-hip ratio slightly increased the rate ratio for heavy coffee intake. Neither the brewing method (boiling vs. filtering) nor the serum LDL cholesterol concentration had any impact on the risk estimates for coffee intake. In conclusion, heavy coffee consumption increases the short-term risk of acute myocardial infarction or coronary death, independent of the brewing method or currently recognized risk factors for CHD. J. Nutr. 134: 2381–2386, 2004.

KEY WORDS: • *adenosine* • *caffeine* • *cholesterol* • *coffee* • *coronary disease*

In the past 40 y, a suspected association between coffee drinking and coronary heart disease (CHD) was extensively studied but the evidence remains equivocal. A study of 45,589 men followed up for 2 y concluded that caffeinated coffee, as currently consumed by men in the United States, causes no substantial increase in the risk of CHD (1). Likewise, there was no evidence of a positive association between coffee consumption and 10-y incidence of CHD in a cohort of 85,747 middle-aged U.S. women (2). Two earlier U.S. studies, however, indicated that men drinking 5 or more cups of coffee daily had a 2-fold risk of myocardial infarction (3) or CHD (4); the risk was 3-fold among those drinking 10 cups or more (3) compared with nondrinkers.

A meta-analysis of 11 prospective studies found no association between coffee consumption and CHD occurrence (5). Another analysis of 8 case-control and 14 cohort studies found a homogeneous increased risk (rate ratio of 1.42 for 5 cups per d vs. none) in the case-control studies (6). Cohort studies showed lower but heterogeneous effect estimates (for 5 cups, rate ratios of 0.92 in 5 studies published up to 1981 and 1.27 in 9 studies published since 1986). Kawachi and co-workers (7) reported similar findings from their meta-analysis. The discrepancy in findings between case-control and cohort studies persists in studies published more recently (8–10).

The search for mechanisms of the suspected increase in CHD risk in heavy coffee drinkers has mainly concentrated on the association of coffee drinking with increased serum cholesterol concentrations (11). In particular, nonfiltered coffee increases serum LDL cholesterol concentration (12), due to lipid compounds in coffee that are retained by a paper filter.

We examined the dose-response relationship of the consumption of caffeine-containing coffee with the incidence of acute myocardial infarction or death from CHD in a cohort of middle-aged eastern Finnish men initially free from symptomatic CHD. Furthermore, we attempted to identify potential mediators of the observed coffee effects.

METHODS

Study population. The Kuopio Ischaemic Heart Disease Risk Factor Study is a population-based cohort study of 2682 men aged 42, 48, 54, or 60 y at the baseline examination carried out in 1984–1989. The study was approved by the University of Kuopio Research Ethics Committee; all participants gave written informed consent. We excluded 677 men with prevalent CHD at baseline, as defined earlier

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(13). Of the remaining 2005 men, data on coffee consumption and smoking were available from 1971 participants.

Assessment of coffee intake and diet. Consumption of foods and beverages was assessed with an instructed and interview-checked 4-d food recording by household measures, including cups of coffee and tea. The volume of the cup mainly used by each participant was estimated by showing photographs of 4 different cup sizes generally available in Finland. In a subsample of 1002 men, the usual method of brewing coffee was determined during an interview of coffee-drinking habits. Dietary intake of foods and nutrients was calculated using NUTRICA software (National Public Health Institute).

Measurement of covariates. The examination protocol and measurements were fully described previously (13). Briefly, a participant was defined as a current smoker if he had ever smoked on a regular basis and had smoked within the past 30 d. The lifelong exposure to smoking was estimated as the product of years smoked and the number of cigarettes, cigars, and pipefuls smoked at baseline examination. Height and weight were measured in light clothing without shoes and BMI was calculated by dividing weight in kilograms by the square of the height in meters. Alcohol intake was measured with a recall of the frequency and usual amounts of alcoholic beverages consumed in the past 12 mo. Annual income was obtained from a self-administered questionnaire. Diabetes was defined as self-reported diabetes mellitus or fasting blood glucose of 6.1 mmol/L or more. Waist-hip ratio was defined as waist girth/hip circumference measured at the trochanter major.

The collection of blood specimens and assessment of blood glucose and leukocytes, serum lipids, blood pressure, and ischemia during the maximal exercise tolerance test (13); conditioning leisure-time physical activity and maximal oxygen uptake (14); and vitamin C concentration in plasma (15) was carried out as described previously. Plasma fibrinogen concentrations were determined based on clotting of diluted plasma with excess thrombin. The rate of the ADP-induced phase of aggregation was used as a measure of platelet aggregability. Serum insulin was determined with a commercial radioimmunoassay test kit (Novo Nordisk).

Ascertainment of CHD events. The collection of data on and classification of possible acute myocardial infarction and coronary death (here referred to as "acute coronary events") until the end of 1992 was previously described (13,16). From 1993, data on acute coronary events were obtained by computer linkage to the national hospital discharge registry; diagnostic information was collected from the hospitals and classified using identical diagnostic criteria. There were no losses to follow-up. In the case of multiple events in the same participant, the first event was considered the endpoint.

Statistical analysis. All analyses were performed with SPSS version 11.5 (SPSS). Data on the following were missing: cumulative smoking "dose" (cigarette years) for 39 men, physical activity for 8, BMI for 6, blood pressure for 11, LDL cholesterol for 39, HDL cholesterol for 28, serum insulin for 58, and maximal oxygen uptake for 195. In multivariate analyses, missing values were replaced with the respective mean; for diabetes, 18 missing values were coded as nondiabetic.

Mean daily coffee intake was divided into 4 categories: 0 (nondrinkers), 1 to 375 mL (light drinkers), 376 to 813 mL (moderate drinkers), and 814 mL and over (heavy drinkers). ANOVA and the chi-square test were used for testing for baseline differences in continuous and categorical variables, respectively, among the coffee intake categories. Cox proportional hazards regression was used to assess the association between coffee consumption and acute coronary events, using both the categorized and the continuous representations of coffee intake. For the latter analyses, coffee intake was scaled into cups by dividing by 125 mL, which is the coffee content in the most common cup size in this population. The appropriateness of the model was checked graphically by plotting the log[-log(survival)] curves versus log(time). Variable selection was done backward, based on change in any coffee estimate; if <10%, the variable was deleted, unless it contributed to model fit ($P < 0.10$ in the likelihood ratio test). To reduce multicollinearity, continuous variables were centered around their respective means; an eigenanalysis of the predictor correlation matrix did not indicate near collinearities. Modification of the coffee effect by smoking was examined by adding product terms and performing separate analyses in current smokers and nonsmokers. Statistical inference was based on 95% Wald CIs or two-sided P values.

RESULTS

Age was similar over categories of coffee consumption but the proportion of smokers increased with increasing coffee intake. Among coffee drinkers, intake of total and saturated fatty acids and daily total energy increased while leisure-time physical activity decreased with increasing coffee consumption; however, there was little difference in the BMI or maximal oxygen uptake. Serum LDL cholesterol concentration increased dose-dependently with increasing coffee intake. Blood pressure was highest in the light drinker category (**Table 1**).

During a mean follow-up of 14 y, 269 participants experienced an acute coronary event. Among coffee drinkers, univariate analysis unveiled a *J*-shape relationship between coffee intake and CHD incidence. Adjustment for age and smoking slightly reduced the effect estimate for heavy drinkers; further adjustment for other potential confounders and intermediate variates had no influence on the rate ratio estimates (**Table 2**). In the final model, the hazard rate of acute coronary events was 43% (95% CI, 5 to 94%) higher in heavy coffee drinkers compared with moderate drinkers.

Time dependence of the association was investigated by repeating the analyses for the first 2.5 and 5 y of follow-up when 39 and 75 participants, respectively, experienced an acute coronary event. During the first 2.5 y, light drinkers had a 1-fold and heavy drinkers a nearly 2-fold increase in the CHD event rate, compared with moderate drinkers (**Table 3**). During 5 y of follow-up, the adjusted rate ratios (95% CIs) of acute coronary events were 1.93 (1.12 to 3.32) and 2.15 (1.20 to 3.83) in light and heavy drinkers, respectively, compared with moderate drinkers. The effect estimates tended to be higher among smokers than nonsmokers, but a model with product terms for smoking and coffee intake did not indicate deviation from multiplicativity. Analyses treating coffee intake as continuous confirmed the results of the categorical analysis, implying a *U*-shape dose-response relationship (**Fig. 1**).

Brewing method. To investigate the effect of the brewing method, the analyses were repeated in a subsample of 1002 men from whom information on the usual method of brewing coffee at home was available. The brewing method (boiling vs. filtering) did not have any impact on the rate ratio estimates for coffee intake or model fit. The point estimate of the rate ratio for use of boiled coffee ranged between 0.67 and 1.2, depending on covariates included and the duration of follow-up.

DISCUSSION

In this population-based cohort of middle-aged men initially free of symptomatic CHD, we found an independent, *U*-shape dose-response relationship between consumption of caffeine-containing coffee and the incidence of acute myocardial infarction or coronary death during a follow-up time of 5 y. Even during a mean follow-up of 14 y, the incidence of acute coronary events remained elevated among heavy coffee drinkers compared with moderate drinkers.

At 5 y, adjustment for age and smoking decreased the rate ratio estimate for heavy compared with moderate drinkers from 2.30 to 2.05. Adjustment for ischemia in exercise test, diabetes, income, and serum insulin concentration did not

TABLE 1

Demographic, lifestyle, and clinical characteristics of the study participants, according to their mean daily consumption of coffee[1]

		Coffee intake category[2]				
	Total group	None	Light	Moderate	Heavy	*P* value
n	1971	77	456	1087	351	—
Median coffee consumption, *mL*	556	0	269	588	950	—
Age, *y*	52.5 ± 5.3	52.2 ± 5.0	52.9 ± 5.3	52.5 ± 5.3	51.9 ± 5.4	0.067
Current smoker, %	30	10	24	28	48	<0.001
Packyears among smokers, *y*	28.4 ± 18.3	52.5 ± 52.0	25.2 ± 20.0	26.8 ± 16.4	31.7 ± 16.4	<0.001
Physical activity, *kJ/d*	581 ± 707	632 ± 895	613 ± 789	601 ± 698	467 ± 549	0.010
Ischemia in exercise electrocardiogram, %	18	21	20	17	17	0.159
Family history of CHD, %	46	47	46	46	46	0.960
Diabetes, %	5.2	6.7	6.2	4.7	5.1	0.336
Serum glucose concentration, *mmol/L*	4.7 ± 1.0	4.7 ± 0.9	4.7 ± 0.9	4.7 ± 1.0	4.7 ± 1.1	0.937
Serum insulin concentration, *pmol/L*	77 ± 45	66 ± 35	82 ± 54	77 ± 44	72 ± 36	0.003
Income, *thousand Finnish Marks*	130 ± 74	131 ± 71	139 ± 75	131 ± 75	114 ± 67	<0.001
Alcohol intake, *g/wk*	73 ± 115	69 ± 180	78 ± 128	70 ± 99	76 ± 125	0.547
Total fat intake, *% energy*	39.7 ± 5.9	38.4 ± 6.5	39.0 ± 6.0	39.7 ± 5.8	40.8 ± 5.6	<0.001
Saturated fat intake, *% energy*	19.4 ± 4.1	18.6 ± 4.8	18.9 ± 4.1	19.2 ± 4.0	20.5 ± 4.2	<0.001
Daily total energy intake, *MJ*	10.8 ± 2.7	11.6 ± 3.5	9.9 ± 2.3	10.8 ± 2.6	12.0 ± 3.1	<0.001
Daily tea consumption, *mL*	110 ± 194	333 ± 343	193 ± 249	78 ± 146	50 ± 115	<0.001
Daily total water intake, *L*	2.35 ± 0.60	2.25 ± 0.74	2.08 ± 0.52	2.33 ± 0.55	2.78 ± 0.57	<0.001
Plasma vitamin C, *μmol/L*	48 ± 23	51 ± 24	49 ± 23	48 ± 23	44 ± 24	0.002
BMI, *kg/m²*	26.7 ± 3.5	26.0 ± 3.5	26.9 ± 3.8	26.8 ± 3.5	26.4 ± 3.2	0.042
Waist-hip ratio	0.94 ± 0.06	0.93 ± 0.05	0.95 ± 0.06	0.94 ± 0.06	0.94 ± 0.06	0.365
Systolic blood pressure, *mm Hg*	134 ± 17	131 ± 18	136 ± 18	134 ± 16	133 ± 16	0.008
Diastolic blood pressure, *mm Hg*	89 ± 10	86 ± 11	90 ± 11	89 ± 10	88 ± 10	<0.001
Serum LDL cholesterol, *mmol/L*	4.01 ± 0.99	3.66 ± 1.05	3.92 ± 0.98	4.01 ± 0.98	4.18 ± 0.99	<0.001
Serum HDL cholesterol, *mmol/L*	1.31 ± 0.29	1.36 ± 0.32	1.31 ± 0.30	1.31 ± 0.29	1.29 ± 0.29	0.433
Plasma fibrinogen, *g/L*	2.97 ± 0.55	2.92 ± 0.49	2.95 ± 0.54	2.95 ± 0.54	3.08 ± 0.58	0.001
Platelet aggregation velocity, *mV/s*	0.13 ± 0.12	0.13 ± 0.11	0.12 ± 0.12	0.13 ± 0.12	0.14 ± 0.12	0.492
Maximal oxygen uptake, *L/min*	2.55 ± 0.60	2.63 ± 0.51	2.48 ± 0.57	2.57 ± 0.59	2.54 ± 0.67	0.057
Blood leukocyte count, 10^9*/L*	5.6 ± 1.6	5.2 ± 1.4	5.5 ± 1.5	5.5 ± 1.6	6.0 ± 1.7	<0.001

[1] Values are means ± SD unless otherwise indicated.
[2] Light, 1–375 mL; moderate, 376–813 mL; and heavy, >814 mL.

influence the estimate; further adjustment for diastolic blood pressure, serum HDL and LDL cholesterol concentration, maximal oxygen uptake, and waist-hip ratio increased the rate ratio to 2.15. Smoking is a strong confounder of the coffee-CHD relation; however, residual confounding alone (by smoking or any other factor taken into account) is unlikely to explain all of the remaining excess incidence. Despite a relatively small number of events and consequently wide CIs, these findings are consistent with a moderate to substantial effect of heavy coffee intake on CHD risk. In light vs. moderate drinkers, the corresponding change in estimate after adjustment was from 2.01 to 1.93, indicating relative independence of the effect estimate from the factors considered covariates.

Such a *U*-shape relation between coffee intake and CHD incidence was not previously noted, except for a recent report

TABLE 2

Rate ratios of acute myocardial infarction or coronary death during a mean follow-up of 14 y in middle-aged men initially free from symptomatic CHD, according to mean daily consumption of coffee[1]

	Coffee intake category[2]			
	None (*n* = 77)	Light (*n* = 456)	Moderate (*n* = 1087)	Heavy (*n* = 351)
Number of events	8	65	134	62
Person-time, *y*	1026	5865	14,731	4430
RR for coffee alone[3]	0.86 (0.42–1.75)	1.23 (0.91–1.65)	1.00	1.55 (1.15–2.10)
RR, adjusted for age and smoking	0.85 (0.42–1.74)	1.25 (0.93–1.68)	1.00	1.45 (1.07–1.96)
RR, adjusted for confounders[4]	0.84 (0.41–1.72)	1.22 (0.90–1.64)	1.00	1.43 (1.06–1.94)
RR, adjusted for confounders[4] and intermediate variates[5]	1.12 (0.55–2.29)	1.24 (0.92–1.67)	1.00	1.43 (1.05–1.94)

[1] The 95% CIs for the rate ratios are given in parentheses.
[2] Light, 1–375 mL; moderate, 376–813 mL; and heavy, >814 mL.
[3] RR, rate ratio derived from Cox proportional hazards models.
[4] Age, packyears of smoking, ischemia in exercise test, diabetes, income, and serum insulin concentration. Physical activity; family history of CHD; intake of alcohol, tea, saturated fat, total energy, and total water; serum glucose and plasma vitamin C concentration; and year of baseline examination did not influence estimates for coffee or model fit.
[5] Diastolic blood pressure, serum HDL and LDL cholesterol concentration, maximal oxygen uptake, and waist-hip ratio. BMI, systolic blood pressure, plasma fibrinogen concentration, platelet aggregation velocity, and white blood cell count did not influence estimates for coffee or model fit.

TABLE 3

Rate ratios of acute myocardial infarction or coronary death during the first 2.5 and 5 y of follow-up in middle-aged men initially free from symptomatic CHD, according to mean daily consumption of coffee[1]

	Coffee intake category[2]							
	None (n = 77)		Light (n = 456)		Moderate (n = 1087)		Heavy (n = 351)	
	2.5 y	5 y	2.5 y	5 y	2.5 y	5 y	2.5 y	5 y
Number of events	0	1	12	24	14	29	13	21
Person-time, *y*	192	379	1119	2187	2690	5316	858	1672
RR for coffee alone[3]	—	0.48 (0.07–3.56)	2.06 (0.95–4.46)	2.01 (1.17–3.46)	1.00	1.00	2.92 (1.37–6.20)	2.30 (1.31–4.04)
RR, adjusted for age and smoking	—	0.41 (0.05–3.05)	2.10 (0.97–4.53)	2.04 (1.18–3.50)	1.00	1.00	2.57 (1.20–5.52)	2.05 (1.16–3.62)
RR, adjusted for confounders[4]	—	0.42 (0.06–3.10)	2.07 (0.96–4.48)	2.00 (1.16–3.44)	1.00	1.00	2.55 (1.18–5.49)	2.07 (1.17–3.65)
RR, adjusted for confounders[4] and intermediate variates[5]	—	0.66 (0.09–4.91)	1.92 (0.89–4.19)	1.93 (1.12–3.32)	1.00	1.00	2.77 (1.27–6.03)	2.15 (1.20–3.83)

[1] The 95% CIs for the rate ratios are given in parentheses.
[2] Light, 1–375 mL; moderate, 376–813 mL; and heavy, >814 mL.
[3] RR, rate ratio derived from Cox proportional hazards models.
[4] Age, packyears of smoking, ischemia in exercise test, diabetes, income, and serum insulin concentration.
[5] Diastolic blood pressure, serum HDL and LDL cholesterol concentration, maximal oxygen uptake, and waist-hip ratio.

of a *J*-shape effect of coffee consumption on the risk of developing acute coronary syndromes in a case-control study carried out in Greece (17). Earlier studies may have failed to correctly identify the shape of the association due to imprecise measurement of coffee intake (18). Our finding of increased risk among heavy coffee drinkers is in agreement with the results of several case-control studies (see 6,9,10), as well as those from the Precursors study (4,19), the Chicago Western Electric Company study (20), and a Norwegian cohort study (21). In contrast, the Framingham study (22), the Health Professionals Follow-up study (1), and the Nurses' Health study (2) found no appreciable increase in CHD risk with increasing coffee consumption. The analysis of the Framingham data (22) treated coffee intake as a continuous variable without any higher-order terms in the regression model. A similar approach in analyzing our data would have resulted in a lack of any association between coffee and CHD. The findings of Grobbee and co-workers (1) were criticized for not fully exploring the dose-response relation beyond 5 cups per d, due to lack of data in higher consumption categories (23). In the present study, 40% of participants consumed 5 cups or more daily.

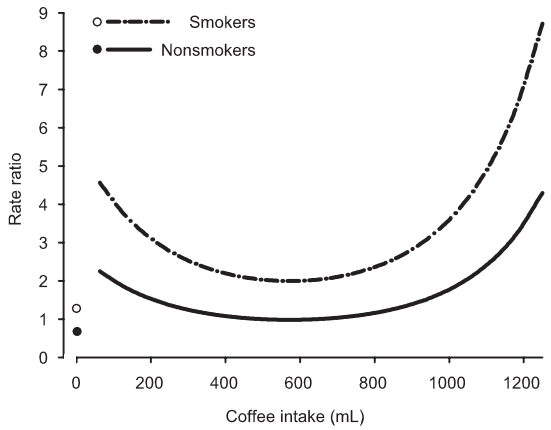

FIGURE 1 Rate ratios of acute coronary events during the first 5 y of follow-up in 1943 middle-aged men initially free from symptomatic CHD, according to mean daily coffee consumption (range truncated at 1250 mL) and smoking. Rate ratios predicted from Cox proportional hazards model including terms for coffee intake and coffee intake squared (for the latter, $P = 0.007$, likelihood ratio test) with age, packyears of smoking, ischemia in exercise test, diabetes, income, serum insulin concentration, diastolic blood pressure, serum HDL and LDL cholesterol concentration, maximal oxygen uptake, and waist-hip ratio as covariates.

Our data are limited for studying the effect of no vs. any coffee, since <4% of the men were nondrinkers of coffee at baseline, and there were only 1 and 8 events among nondrinkers during 5 and 14 y of follow-up, respectively. During a mean follow-up of 14 y, the risk in nonconsumers of coffee was 16% lower to 12% higher (depending on covariates included in the model) than that in moderate coffee drinkers, but the estimates are imprecise. Another limitation is the fact that in Finland the consumption of decaffeinated coffee is minimal and our findings are confined to caffeine-containing coffee.

At 5 y, men drinking 375 mL of coffee or less daily had an elevated incidence of acute coronary events when compared with moderate drinkers. The higher incidence in the low-intake category may not reflect a true effect of coffee but rather decreased coffee intake among men with underlying disease, who would also be at higher risk for the outcome. Of the participants, 31% reported having reduced their coffee intake in the past 10 y. Nevertheless, they had a risk of acute coronary events very similar to that of men whose consumption had remained stable or increased; adding an indicator variate for having reduced coffee intake had no effect on the coffee estimates. Furthermore, drinkers of 375 mL or less were physically as active as moderate drinkers and considerably more active than heavy drinkers. In addition, at baseline the prevalence rate of symptomatic CHD was between 24 and 26% in all coffee categories and there was no difference in coffee intake between participants without and those with symptomatic CHD (data not shown).

In addition to the *J*-shape relationship observed in the CARDIO2000 case-control study (17), some previous but so far unnoticed evidence of a *U*-shape association can be found. The 8-y follow-up data from the Chicago Western Electric Company study (24) show (unadjusted) relative risks of 2.9, 1.4, 1.0, 1.1, and 2.3 in drinkers of 0, 1 to 49, 50 to 99, 100 to 149, and >150 cups/mo, respectively, for nonfatal myocardial infarction and coronary death. Adjustment for smoking would

likely lower the estimate for the highest intake category but, concomitantly, the estimated excess risk for no coffee or 1 to 49 cups/mo would increase. Similar findings were reported from Scotland (25).

One explanation suggested for the discrepancy between findings in case-control and cohort studies is that coffee drinking has mainly acute or short-term effects, which the cohort studies with extended follow-up have missed (4,6,7). We analyzed our data separately for the first 2.5 and 5 y of follow-up and found a considerably stronger relation than thereafter, which supports the hypothesized short-term effect of coffee on CHD risk. An alternative explanation, that those at the highest risk have reduced their coffee intake, could explain the finding of increased risk in the low-intake category but not that among heavy consumers.

The decline in risk associated with coffee intake up to 500–600 mL per d could reflect a protective effect of moderate consumption. Chlorogenic and caffeic acids have antioxidant properties (26), and coffee drinking clearly increases plasma antioxidant capacity (27). In populations with high per capita coffee consumption (like the Nordic countries), coffee is actually the major contributor to the total intake of antioxidants (28).

The complex pharmacologic effects of caffeine may provide another explanation. In caffeine-naive individuals, acute caffeine ingestion increases blood pressure, cardiac output, and circulating catecholamine and renin levels, along with other acute effects (29). During repeated dosing, tolerance to these neurohumoral effects develops in the course of 1 to 4 d (30). However, it is not exactly known how frequently and how much caffeine is needed for tolerance to develop or remain; furthermore, tolerance does not develop for all effects of caffeine. Caffeine withdrawal effects may occur as early as 12 h after the last dose (31). Rather than a protective effect of moderate coffee intake, the observed higher incidence of CHD events in light drinkers could result from an adverse effect of intermittent consumption of caffeine. Over 40% of the men in the low coffee intake category did not drink coffee on every day of the 4-d recording period. These men may lack complete tolerance to caffeine, which is compatible with the finding of the highest mean blood pressure in the low coffee intake category despite similar BMI with moderate coffee consumers. Consequently, caffeine ingestion preceding an episode of myocardial ischemia may be sufficient to trigger an acute coronary event.

Although heavy coffee consumers most likely have caffeine tolerance, high concentrations of caffeine may have adverse effects locally in the ischemic myocardium. Adenosine may play an important role in the modulation of coronary circulation and the reactivity of inflammatory cells and platelets during periods of myocardial ischemia (32). Caffeine is a nonselective adenosine receptor blocking agent (33), capable of blocking the beneficial effects of adenosine during myocardial ischemia. The concentration-dependent metabolism of caffeine (33) may play a further role in that there is a threshold before these effects are manifested. The finding that tea drinking does not have adverse effects on heart disease risk (34) does not refute this hypothesis, because the caffeine concentration in tea is considerably lower than that in coffee; thus it is difficult to reach high concentrations of caffeine by drinking tea only.

Coffee intake is known to increase serum homocysteine concentrations and a short-term association of homocysteine with the risk of CHD was suggested (35). In our study, homocysteine data were available only from 332 subjects and we were not able to control for it in these analyses. In a previous case-control analysis nested in this cohort, however, plasma total homocysteine concentration was not associated with CHD (36).

Our data fail to prove any major role of currently recognized biological risk factors of CHD—body adiposity, blood pressure, serum cholesterol or plasma fibrinogen concentrations, or platelet aggregability at baseline—as mediators of the coffee-CHD relation. Since the finding in the Tromsø Heart study of elevated serum cholesterol levels in coffee drinkers (11), increased LDL cholesterol concentration has been considered a likely mechanism of elevated CHD risk among heavy coffee drinkers. We observed a monotonic, positive dose-response between coffee intake and serum LDL cholesterol, as expected, because one third of the study participants drank boiled nonfiltered coffee. Adjustment for serum LDL cholesterol concentration, however, did not change the estimate of the excess risk associated with heavy coffee intake compared with moderate intake. The lack of importance of this effect was further confirmed in a subgroup analysis among men with data on the usual brewing method, which failed to show any effect of the brewing method (boiled vs. filtered).

In conclusion, our findings support the hypothesis that heavy consumption of caffeine-containing coffee (daily amounts exceeding 800 mL) causes a substantial increase in the risk of acute myocardial infarction in middle-aged men free from symptomatic CHD. The potential effect of coffee is more likely acute than chronic and cannot be explained by currently recognized biological risk factors of CHD. The dose-response relationship between coffee intake and the risk of CHD is more complex than previously recognized, because intermittent drinking or daily intake of only small amounts of coffee may also increase the risk of CHD events compared with daily drinking of moderate amounts (400–800 mL). Further research to characterize the relationship is warranted.

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ERRATUM

WALTER C. RUSSELL, M. WRIGHT TAYLOR AND JAMES V. DERBY, JR. The folic acid requirement of turkey poults on a purified diet.

Journal of Nutrition vol. 34, no. 6, December, 1947. Page 632: second line from top of page to be changed to —

100 gm of purified diet (1.5 mg per kilo) for optimum growth

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ERRATUM

Chakrabarty, Krishna, and Gilbert A. Leveille 1968 Influence of periodicity of eating on the activity of various enzymes in adipose tissue, liver and muscle of the rat. J. Nutr., *96:* 76–82. In tables 1, 2, and 3, pages 78 and 79, headings immediately above columns of data should read *milliunits/mg protein* [2] instead of *units/mg protein* [2].