

# Coffee consumption and plasma total homocysteine: The Hordaland Homocysteine Study<sup>1-3</sup>

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**ABSTRACT** The health consequences of coffee drinking remain controversial. We report on an association between coffee consumption and the concentration of total homocysteine (tHcy) in plasma, a risk factor for cardiovascular disease and for adverse pregnancy outcome. The study population consisted of 7589 men and 8585 women 40–67 y of age and with no history of hypertension, diabetes, ischemic heart disease, or cerebrovascular disease. They were recruited from Hordaland county of western Norway in 1992–1993. Daily use of coffee was reported by 89.1% of the participants, of whom 94.9% used caffeinated filtered coffee. There was a marked positive dose-response relation between coffee consumption and plasma tHcy, which was stronger than the relation between coffee and total serum cholesterol. In 40–42-y-old men, mean tHcy was 10.1  $\mu\text{mol/L}$  for nonusers and 12.0  $\mu\text{mol/L}$  for drinkers of  $\geq 9$  cups of coffee/d. Corresponding tHcy concentrations in 40–42-y-old women were 8.2 and 10.5  $\mu\text{mol/L}$ , respectively. Although coffee drinking was associated with smoking and lower intake of vitamin supplements and fruit and vegetables, the coffee-tHcy association was only moderately reduced after these variables were adjusted for. The combination of cigarette smoking and high coffee intake was associated with particularly high tHcy concentrations. A strong inverse relation between tea and tHcy concentration in univariate analysis was substantially attenuated after smoking and coffee drinking were adjusted for. The results of the present report should promote future studies on tHcy as a possible mediator of adverse clinical effects related to heavy coffee consumption. *Am J Clin Nutr* 1997;65:136–43.

**KEY WORDS** Coffee, tea, plasma total homocysteine, cholesterol, cigarette smoking, population-based study

## INTRODUCTION

A series of observational studies (1–8) showed that elevated blood concentrations of homocysteine (Hcy includes both homocysteine and its oxidized species; the abbreviation tHcy refers to total homocysteine, which includes both protein-bound and non-protein-bound Hcy) are associated with an increased risk of cardiovascular disease. Recently, as part of a cardiovascular risk survey, we initiated a population-based prospective study on plasma tHcy and disease in Hordaland county of Western Norway. Baseline data from this 40–67-y-old population showed that tHcy in plasma is related to major components of the cardiovascular risk profile, including sex, age, cigarette smoking, exercise, blood pressure, and total

cholesterol (9). An unexpected finding during the analyses was that coffee consumption was associated with plasma tHcy, a relation that was not reported previously.

Some (10–17), but not all (18–22), studies have shown that coffee consumption is associated with increased risk of ischemic heart disease. One explanation for this relation is the cholesterol-raising effect of coffee (23). However, in some studies, coffee intake predicts coronary death (24), risk of myocardial infarction (14, 15), and clinically evident ischemic heart disease (12) independent of the coffee-cholesterol relation, suggesting that coffee may influence the development of heart disease by other mechanisms.

Adverse pregnancy outcome has also been related to coffee intake as well as to elevated plasma tHcy. Consumption of coffee or caffeine has been linked to congenital malformations (25), low birth weight (26–31), and fetal loss (32–34), and elevated tHcy concentrations have been associated with an increased risk of neural tube defects (35, 36), recurrent spontaneous abortion, or abruptio placentae (37, 38).

Thus, the available data suggest an association of heart disease and adverse pregnancy outcome with both tHcy and coffee consumption in some populations. A possible link between these two factors may point to pathogenetic processes, strategies for preventive measures, as well as the design of future studies on health implications of coffee consumption. As a first step to address these new perspectives, we analyzed the coffee-tHcy relation in a large community-based adult population.

## SUBJECTS AND METHODS

### Study population

The Hordaland Homocysteine Study cohort was established from April 1992 to April 1993 by the National Health Screen-

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ing Service in cooperation with the University of Bergen and local health services in Norway (9). The eligible population included all subjects who were 40–42 y of age in the county, a 2% random sample of residents aged 43–64 y in the city of Bergen, and all subjects who were 65–67 y of age in Bergen and three neighboring municipalities. A total of 24 815 subjects were invited to attend. The overall attendance rate was 72.7%. The study protocol was approved by the Regional Ethical Committee of Western Norway, whose directives are based on the Helsinki Declaration.

In the present report we used the baseline data of this cohort. Because disease, use of medication, and changes in lifestyle may influence tHcy concentrations, we excluded 1866 participants who in the questionnaires reported a previous diagnosis of ischemic heart disease, cerebrovascular disease, hypertension, or diabetes mellitus. One patient with homocystinuria was also excluded. Thus, a total of 16 175 subjects with data on plasma tHcy and coffee consumption were included in the present study; 96.2% belonged to the four main age-sex groups, ie, 40–42-y-old and 65–67-y-old men and women.

### Data collection

Data were collected using questionnaires, clinical examination, and blood samples. A mailed questionnaire, completed at home and collected on the examination day, provided information about age; personal history of cardiovascular disease, hypertension, and diabetes mellitus; current and former smoking habits; physical activity; coffee consumption; and preference for type of fat usually eaten on bread and for cooking. The subjects received an extended questionnaire on the day of examination. This was later filled in at home by 86% of those who attended. It covered more detailed information about medical history, lifestyle, use of alcohol, tea consumption, and frequency of intake of various food items and vitamin supplements.

Information about coffee consumption included the amount and type of coffee. Participants were classified into five groups according to number of cups (the volume of a cup was self-reported and idiomatic) consumed per day: 0, < 1, 1–4, 5–8, and  $\geq 9$ . Coffee type was classified into four separate categories as boiled, filtered, instant, or decaffeinated. If a person marked more than one type of coffee, all types marked were registered. Tea consumption was classified into five groups: 0, < 1, 1–2, 3–7, and  $\geq 8$  cups/d. Smoking habits were classified into five categories: never smokers, exsmokers, current light smokers (1–9 cigarettes/d), moderate smokers (10–19 cigarettes/d), and heavy smokers ( $\geq 20$  cigarettes/d).

Two scores were created to assess differences in intake of folate among the participants. A fruit-vegetable score was based on the sum of frequencies of intake of fruit and vegetables. The highest of four categories represented subjects consuming both fruit and vegetables  $\geq 6$  d/wk (38%), whereas the lowest category represented those whose intake of fruit and vegetables was once a week or less (4.3%).

A vitamin supplement score was based on frequency and seasonal variation in intake of vitamin supplements. The lowest of five categories included subjects who never used vitamin supplements (34%), whereas the highest category represented those who took vitamins 6–7 d/wk during the whole year (14%). Among those taking vitamins,  $\approx 80\%$  reported use of B and/or multivitamin combinations. In Norway, these contain

either no or 100  $\mu\text{g}$  folic acid per tablet. Other types of vitamin supplements do not contain folic acid.

Plasma folate was determined in a subsample ( $n = 329$ ) and showed significant correlations with the vitamin supplement score ( $r = 0.31$ ) and the fruit-vegetable score ( $r = 0.12$ ). No significant correlation was observed between these scores and plasma cobalamin. A summary score based on the vitamin supplement score, the fruit-vegetable score, and intake of oranges, fruit juices, eggs, and meat showed a higher correlation with plasma folate ( $r = 0.45$ ). Because this summary score did not improve the correlation with plasma tHcy ( $r = 0.21$ ) compared with a combination of the fruit-vegetable and vitamin supplement scores ( $r = 0.23$ ), minimally affected the results, and decreased the number of subjects with complete data, it was not used.

### Biochemical determinations

A detailed description of blood sample collection, preparation of plasma and serum, transport, storage and analytical procedures was given previously (9). In brief, blood was drawn from nonfasting subjects and the plasma samples were stored in our laboratory at  $-20^\circ\text{C}$  until analyzed. Plasma tHcy was determined by using HPLC with fluorescence detection (39, 40). The precision (CV) of the assay is  $< 3\%$ . Serum total cholesterol was measured with enzymatic methods at the Department of Clinical Chemistry, Ullevål Hospital, Oslo.

### Statistical analyses

The concentration of tHcy showed a marked, positively skewed distribution. To better satisfy the assumption of a normally distributed dependent variable, multiple-linear-regression and covariance analyses were carried out with the logarithm of tHcy. Thus, geometric means of tHcy are presented. Adjusted mean concentrations of plasma tHcy and serum cholesterol were estimated by using analysis of covariance.

To assess the simultaneous relation among the various predictors of tHcy, and to provide effect estimates adjusted for other factors, multiple-linear-regression models were used. Here, log tHcy or cholesterol was the dependent variable whereas the independent variables were represented in the models as indicator variables denoting membership in one of five categories for coffee use, tea consumption, cigarette smoking, and vitamin supplement score, and in one of four groups for the fruit-vegetable score. Thus, each regression coefficient estimated the difference in tHcy or cholesterol between the reference category and the other categories for each variable. Confidence intervals for the tHcy coefficients were computed on the logarithmic scale and transformed back to the original scale. Effects of different types of coffee were studied with indicator variables for each of the nonfiltered coffee types. Persons who had indicated more than one type of coffee were excluded from this analysis.

Because multiple linear regression is a tool for statistical inference on location shifts of a normally distributed dependent variable, this technique cannot detect a selective influence of an independent variable on high or low values of the dependent variable. To explore this possibility, we performed a series of logistic regressions at different cutpoints for the binary dependent variable, tHcy. The independent variables were again

represented in the model by using zero-one indicators. Thus, the odds ratio for a defined level of the independent variable approximates the adjusted risk, relative to its reference level, of having tHcy below or above the chosen cutpoint.

All multivariate models were repeated with additional adjustment for body mass index, exercise in leisure time, alcohol consumption, and type of fat used on bread and in cooking. This additional adjustment influenced the results minimally.

The analyses were performed with the statistical packages BMDP (41) and S-PLUS (42). All tests were two-tailed, and a  $P$ -value  $< 0.05$  was considered significant.

## RESULTS

Coffee intake decreased with age and was highest in men (Table 1). A total of 89.1% of the participants drank at  $\geq 1$  cup of coffee/d. With increasing coffee consumption we observed a strong increase in plasma tHcy concentration in the four main sex and age groups. There was a stronger dose-response relation between coffee and tHcy than between coffee and total serum cholesterol (Table 1, Figure 1). At age 40–42 y, the percentage increase in mean tHcy concentration from coffee abstainers to heavy coffee consumers ( $\geq 9$  cups/d) was 18.4% for men and 28.9% for women (Table 1). The corresponding increase in mean serum cholesterol concentrations (Figure 1) was from 5.40 to 5.84 mmol/L in men (8.1% increase) and from 5.16 to 5.77 mmol/L in women (11.8% increase).

Among the coffee users, the proportions drinking filtered, boiled, instant, and decaffeinated coffee were 94.9%, 2.4%, 3.9%, and 1.6%, respectively. The coffee-tHcy relation did not differ significantly among the three types of caffeinated coffee, whereas no significant association was observed between decaffeinated coffee and tHcy. Only 36.0% drank tea daily, and among these, 78.4% were also daily coffee consumers. Only 0.9% drank neither coffee nor tea. Tea intake increased with age and was highest in women. In univariate analyses, consumption of tea showed a strong inverse relation to plasma tHcy that was substantially attenuated after adjustment for coffee and smoking.

Selected characteristics of 40–42-y-old men and women according to the number of cups of coffee they drank per day are listed in Table 2. Significant positive correlations ( $P < 0.01$ ) were found with cigarette smoking and alcohol consumption, and negative correlations ( $P < 0.01$ ) with exercise and

with consumption of fruit and vegetables, vitamin supplements, and tea. The correlations were strong with smoking ( $r = 0.36$  for men,  $r = 0.30$  for women) and with tea ( $r = -0.34$  for men,  $r = -0.37$  for women), whereas the relations with the other variables were weak ( $r < 0.10$ ). In the group aged 65–67 y, correlations between coffee consumption and the other variables tended to be weaker.

Potential confounding from various variables was assessed both by stratification and multivariate techniques. To study the influence of smoking on the coffee-tHcy relation, univariate analyses were repeated in nonsmokers and current smokers. A highly significant association between coffee dose and tHcy was noted in smokers as well as in nonsmokers in all main sex and age groups (Figure 2). At age 40–42 y, men and women who were heavy coffee consumers and heavy smokers had plasma tHcy concentrations that were 2.2 and 3.0  $\mu\text{mol/L}$  higher, respectively, than those of abstainers from both coffee and smoking.

The univariate analysis was also repeated among subjects with different vitamin intake scores. In these analyses, the coffee-tHcy association was clearly shown in both users and nonusers of vitamin supplements, and in subjects with either a high or low frequency of intake of fruits and vegetables.

The results from multivariate-linear-regression analyses are shown in Table 3, and are presented as the estimated mean differences in tHcy and total cholesterol concentrations associated with sex and age, tea and coffee intake, and smoking habits. The largest estimated difference in mean tHcy was observed by age, followed by coffee consumption, smoking, and sex, whereas the inverse relation of tea to tHcy was much weaker. Moreover, restricting the analysis to the small group of tea drinkers who did not drink coffee, a weak positive tea-tHcy relation became apparent (data not shown). For cholesterol, the largest difference was observed with age, much less with tea, coffee, and smoking (Table 3). After multivariate adjustment, the increase in mean tHcy concentration between the lowest and highest coffee category (0 compared with  $\geq 9$  cups) was 13.7% for men and 17.7% for women. The corresponding adjusted increase in serum cholesterol was 4.8% and 7.3%.

To investigate whether the relations between tHcy concentration and the independent variables differed along the tHcy distribution, we performed a series of logistic regressions with high and low plasma tHcy as the outcome variable (Table 4). These analyses showed that smoking was associated with a

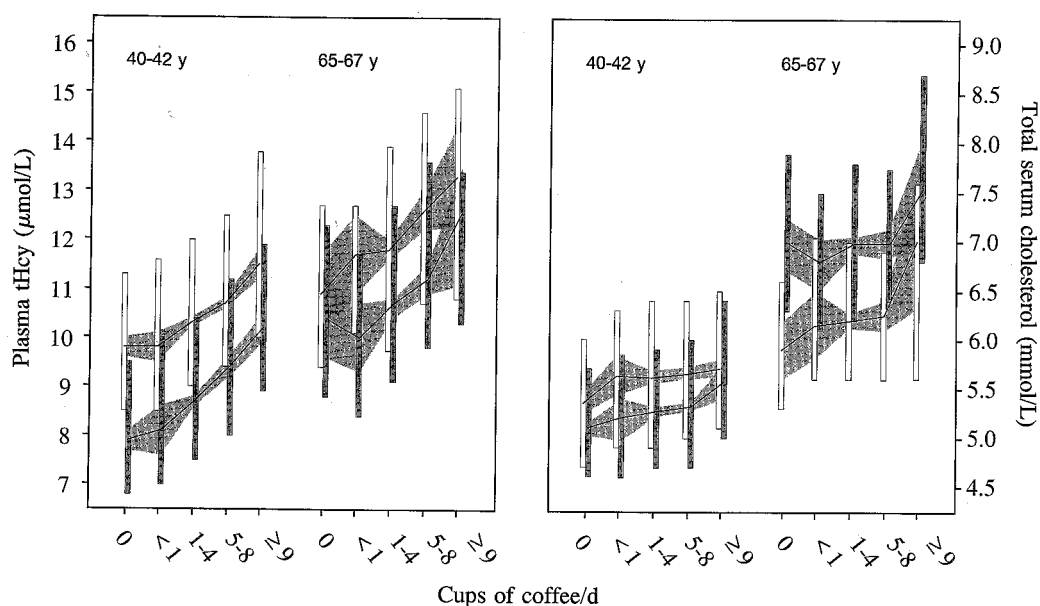
**TABLE 1**  
Plasma total homocysteine (tHcy) according to coffee consumption, by sex and age

Coffee consumption per day	Total study population <sup>1</sup>		Aged 40–42 y				Aged 65–67 y			
			Men		Women		Men		Women	
			<i>n</i>	%	<i>n</i>	$\mu\text{mol/L}$	<i>n</i>	$\mu\text{mol/L}$	<i>n</i>	$\mu\text{mol/L}$
0 cup	1285	7.9	476	10.1 (0.27) <sup>2</sup>	613	8.2 (0.18)	61	11.3 (0.71)	97	10.4 (0.65)
<1 cup	485	3.0	165	10.3 (0.43)	177	8.3 (0.33)	44	11.7 (0.94)	77	10.3 (0.63)
1–4 cups	8146	50.4	2352	10.6 (0.11)	3167	8.9 (0.09)	873	12.1 (0.22)	1430	11.0 (0.17)
5–8 cups	5285	32.7	2333	11.1 (0.12)	2118	9.7 (0.12)	360	12.9 (0.41)	303	11.6 (0.35)
$\geq 9$ cups	974	6.0	590	12.0 (0.29) <sup>3</sup>	274	10.5 (0.36) <sup>3</sup>	48	13.1 (1.07) <sup>3</sup>	25	12.0 (1.27) <sup>3</sup>
Total	16175		5916		6349		1386		1932	

<sup>1</sup> Included 592 subjects aged 43–64 y.

<sup>2</sup> Geometric mean of tHcy and  $(100 \times \text{SE of log tHcy})$ .

<sup>3</sup>  $P$  value for linear trend (coffee consumption)  $< 0.001$ .



**FIGURE 1.** Total homocysteine (tHcy) in plasma and total cholesterol in serum according to the number of cups of coffee consumed per day by 40–42- and 65–67-y-old men and women. The solid lines are median values, the shaded area indicates 95% CIs; the boxes show the 25th to 75th percentile intervals and are open for men and shaded for women.

complete shift of the tHcy distribution to higher values but tended to be more strongly associated with high tHcy. In contrast, coffee consumption was strongly related with tHcy at low and intermediate tHcy concentrations, and there was no significant coffee-tHcy association above the 95th percentile of tHcy concentration (16.7  $\mu\text{mol/L}$ ). The analyses further showed that sex and age also had their major influence on plasma tHcy concentration in the lower part of tHcy distribution. Separate analyses for men and women showed essentially

the same pattern, except that smoking and age were more strongly associated with tHcy concentration in women.

The difference in the coffee-tHcy and smoking-tHcy relations was also shown by using cumulative-frequency distribution curves of tHcy according to extreme categories of coffee and/or smoking habits, as shown for 40–42-y-old women in **Figure 3**. Further stratification by intake of vitamin supplements, fruit, and vegetables shifted, but did not change the shape of these distribution functions.

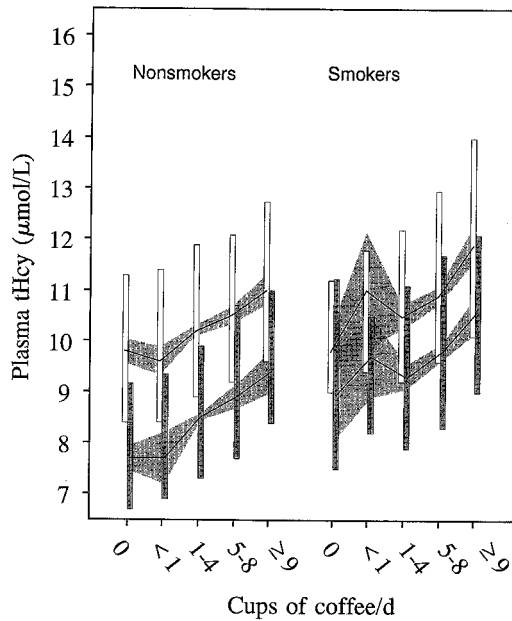
**TABLE 2**

Percentage of the study population group aged 40–42 y with selected characteristics according to consumption of coffee

Sex and characteristic	Coffee consumption (cups/d)					Linear trend
	0	<1	1–4	5–8	$\geq 9$	
	% with characteristic					P
<b>Men</b>						
No intake of vitamin supplements	42.5	35.0	42.1	46.4	53.8	<0.001
Low intake of fruit and vegetables <sup>1</sup>	15.4	11.1	14.9	16.6	26.3	<0.001
Current smoking	15.6	21.8	30.4	49.5	71.3	<0.001
No exercise	15.6	16.4	15.7	17.7	25.3	<0.001
BMI (in $\text{kg/m}^2$ ) in lowest quintile (<22.8)	23.4	23.2	18.9	20.2	21.5	0.54
Alcohol intake <1 unit/wk <sup>2</sup>	40.2	24.6	22.2	17.8	18.3	<0.001
Daily tea consumption	59.6	56.0	31.6	16.0	7.7	<0.001
<b>Women</b>						
No intake of vitamin supplements	24.1	23.4	24.0	25.6	34.1	0.04
Low intake of fruit and vegetables	24.6	23.4	21.5	27.5	38.7	<0.001
Current smoking	18.3	20.9	30.8	52.9	69.7	<0.001
No exercise	18.8	19.2	15.0	17.9	23.0	0.30
BMI (in $\text{kg/m}^2$ ) in lowest quintile (<21.1)	20.0	19.8	18.9	21.1	18.7	0.50
Alcohol intake <1 unit/wk	56.0	38.7	41.6	43.1	52.7	0.02
Daily tea consumption	74.9	65.1	41.7	23.8	14.8	<0.001

<sup>1</sup> The level closest to the 20th percentile was chosen as the cutoff for low intake. For men and women this corresponded to percentile 16.6 and 24.6 of the fruit-vegetable score (levels 5 and 7), respectively.

<sup>2</sup> 1 unit of alcohol equals 1 bottle of beer, 1 glass of wine, or 1 mixed drink with spirits.



**FIGURE 2.** Total homocysteine (tHcy) in plasma of nonsmokers and current smokers according to the number of cups of coffee consumed per day at age 40–42 y. The solid lines are median values, the shaded area indicates 95% CIs; the boxes show the 25th to 75th percentile intervals and are open for men and shaded for women.

## DISCUSSION

We showed a clear dose-response relation between coffee and plasma tHcy concentration in the Hordaland Homocysteine Study population. In multivariate analyses, coffee consumption was among the strongest lifestyle determinants of plasma tHcy. The size of the population, the large variation in coffee intake, combined with a high proportion of heavy coffee consumers, provided an ideal setting in which to estimate relations between coffee use and plasma tHcy.

In univariate analyses the difference in geometric mean plasma tHcy was 1.6–2.3  $\mu\text{mol/L}$  between the extreme groups of coffee intake. Confounding with diet and lifestyle habits was expected to contribute to this strong association. Smoking and lower intake of vitamin supplements and fruit and vegetables were associated with coffee consumption in earlier studies (43, 44) and we reported recently that these lifestyle factors are associated with plasma tHcy in the Hordaland population (9). In the present study, we observed a strong correlation between coffee and smoking with a three- to fivefold change in smoking prevalence between extreme groups of coffee use. However, adjustment for smoking only moderately attenuated the association between coffee and tHcy. Further adjustment for intake of vitamin supplements, fruit, and vegetables had a minor influence on the results.

**TABLE 3**

Estimated differences in plasma total homocysteine (tHcy) and serum total cholesterol concentrations according to consumption of coffee and tea and smoking habits<sup>1</sup>

Variables	Estimated differences in plasma tHcy		Estimated differences in serum total cholesterol	
	Adjusted for age and sex (n = 12 388)	Adjusted for multiple variables (n = 10 613)	Adjusted for age and sex (n = 12 388)	Adjusted for multiple variables (n = 10 613)
	$\mu\text{mol/L}$		$\text{mmol/L}$	
Sex				
Female (compared with male)	-1.78 <sup>2</sup>	-1.37 <sup>2</sup>	-0.13 <sup>2</sup>	-0.10 <sup>2</sup>
Age (compared with 40–42 y)				
43–64	0.74 <sup>2,3</sup>	0.62 <sup>2,3</sup>	0.64 <sup>2,3</sup>	0.65 <sup>2,3</sup>
65–67	2.10 <sup>2,3</sup>	2.48 <sup>2,3</sup>	1.22 <sup>2,3</sup>	1.27 <sup>2,3</sup>
Coffee consumption (cups/d) (compared with coffee abstainers)				
<1	0.34 <sup>2,3</sup>	0.42 <sup>2,3</sup>	0.14 <sup>2,3</sup>	0.11 <sup>2,3</sup>
1–4	0.83 <sup>2,3</sup>	0.72 <sup>2,3</sup>	0.22 <sup>2,3</sup>	0.16 <sup>2,3</sup>
5–8	1.56 <sup>2,3</sup>	1.09 <sup>2,3</sup>	0.26 <sup>2,3</sup>	0.15 <sup>2,3</sup>
$\geq 9$	2.52 <sup>2,3</sup>	1.66 <sup>2,3</sup>	0.48 <sup>2,3</sup>	0.27 <sup>2,3</sup>
Tea consumption (cups/d) (compared with tea abstainers)				
<1	-0.40 <sup>2,3</sup>	-0.06 <sup>4,5</sup>	-0.11 <sup>2,3</sup>	-0.06 <sup>2,3</sup>
1–2	-0.84 <sup>2,3</sup>	-0.20 <sup>4,5</sup>	-0.22 <sup>2,3</sup>	-0.12 <sup>2,3</sup>
3–7	-1.29 <sup>2,3</sup>	-0.31 <sup>4,5</sup>	-0.32 <sup>2,3</sup>	-0.19 <sup>2,3</sup>
$\geq 8$	-0.84 <sup>2,3</sup>	0.09 <sup>4,5</sup>	-0.42 <sup>2,3</sup>	-0.28 <sup>2,3</sup>
Smoking habits (cigarettes/d) (compared with never smokers)				
Exsmoker	0.15 <sup>2,3</sup>	-0.02 <sup>2,3</sup>	0.04 <sup>2,3</sup>	-0.00 <sup>2,3</sup>
Light smoker (1–9)	0.95 <sup>2,3</sup>	0.78 <sup>2,3</sup>	-0.01 <sup>2,3</sup>	-0.03 <sup>2,3</sup>
Moderate smoker (10–19)	1.43 <sup>2,3</sup>	1.03 <sup>2,3</sup>	0.19 <sup>2,3</sup>	0.14 <sup>2,3</sup>
Heavy smoker ( $\geq 20$ )	2.01 <sup>2,3</sup>	1.39 <sup>2,3</sup>	0.32 <sup>2,3</sup>	0.20 <sup>2,3</sup>

<sup>1</sup> The models estimated the differences in geometric mean tHcy and mean serum total cholesterol concentrations between each specified value and the reference value of the variables. Adjustment for multiple variables denotes all variables in this table and intake of vitamin supplements, fruit, and vegetables.

<sup>2</sup>  $P < 0.001$ ; test for homogeneity.

<sup>3</sup>  $P < 0.005$ ; test for linear trend.

<sup>4</sup>  $P = 0.10$ ; test for homogeneity.

<sup>5</sup>  $P = 0.02$ ; test for linear trend.

**TABLE 4**

Odds ratio (OR) for low and high concentrations of plasma total homocysteine (tHcy) according to consumption of coffee and smoking habits in 5160 men and 6355 women aged 40–67 y<sup>1</sup>

Variables	Percentile cutpoints for tHcy ( $\mu\text{mol/L}$ )				Percentile cutpoints for tHcy ( $\mu\text{mol/L}$ )			
	1.0 (5.5)	2.5 (6.1)	5.0 (6.6)	10.0 (7.2)	90.0 (14.5)	95.0 (16.7)	97.5 (19.9)	99.0 (28.3)
	<i>OR for low tHcy</i>				<i>OR for high tHcy</i>			
Sex								
Female (compared with male)	13.9 <sup>2</sup>	13.8 <sup>2</sup>	6.86 <sup>2</sup>	5.16 <sup>2</sup>	0.73	0.85	0.97	1.07
Age (y) (compared with 40–42)								
43–64	0.61	0.54	0.48 <sup>2</sup>	0.48 <sup>2</sup>	1.20	1.36	1.35	1.35
65–67	0.09 <sup>2</sup>	0.09 <sup>2</sup>	0.13 <sup>2</sup>	0.13 <sup>2</sup>	3.26 <sup>2</sup>	2.95 <sup>2</sup>	2.07 <sup>2</sup>	1.45
Coffee consumption (cups/d) (compared with coffee abstainers)								
<1	0.71	0.68	0.62 <sup>2</sup>	0.71	0.68	0.87	0.79	1.71
1–4	0.38 <sup>2</sup>	0.41 <sup>2</sup>	0.47 <sup>2</sup>	0.50 <sup>2</sup>	1.12	0.96	0.76	1.11
5–8	0.18 <sup>2</sup>	0.25 <sup>2</sup>	0.32 <sup>2</sup>	0.34 <sup>2</sup>	1.27	1.09	0.77	0.65
$\geq 9$		0.14 <sup>2</sup>	0.19 <sup>2</sup>	0.23 <sup>2</sup>	1.76 <sup>2</sup>	1.34	0.85	1.04
Smoking habits (cigarettes/d) (compared with never smokers)								
Exsmoker	1.27	1.20	1.17	1.07	1.21	1.21	1.19	1.30
Light smoker (1–9)	0.86	0.82	0.63 <sup>2</sup>	0.64 <sup>2</sup>	1.85 <sup>2</sup>	1.90 <sup>2</sup>	2.19 <sup>2</sup>	3.48 <sup>2</sup>
Moderate smoker (10–19)	0.38 <sup>2</sup>	0.54 <sup>2</sup>	0.57 <sup>2</sup>	0.60 <sup>2</sup>	2.28 <sup>2</sup>	2.30 <sup>2</sup>	3.05 <sup>2</sup>	3.38 <sup>2</sup>
Heavy smoker ( $\geq 20$ )	0.47	0.74	0.60 <sup>2</sup>	0.42 <sup>2</sup>	2.58 <sup>2</sup>	3.16 <sup>2</sup>	3.45 <sup>2</sup>	3.86 <sup>2</sup>

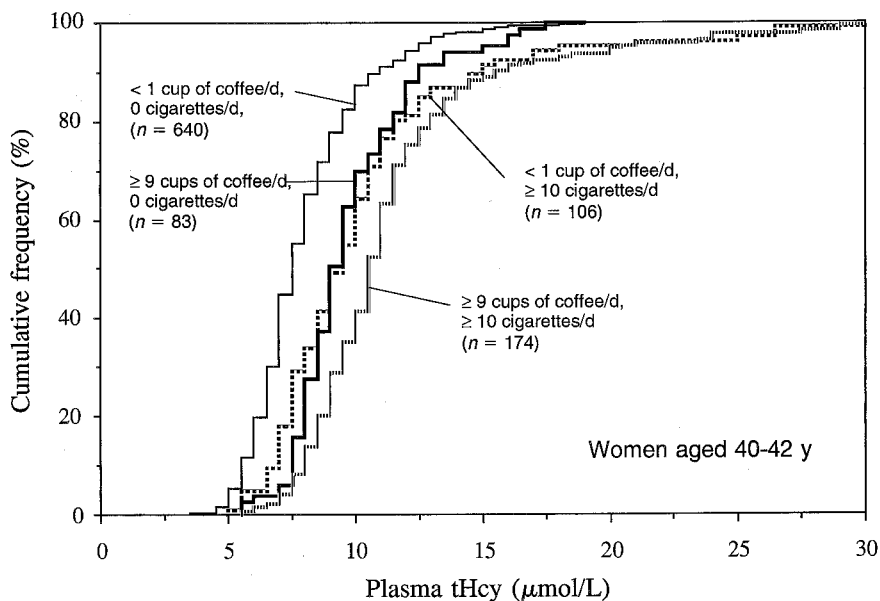
<sup>1</sup> The models estimated the OR associated with each specified concentration compared with the reference value of the variable for having tHcy below or above the specified percentiles. In the first model, the coffee consumption categories 5–8 cups and  $\geq 9$  cups were combined because of small numbers. All variables in this table plus intake of vitamin supplements, fruit, and vegetables were included in the models.

<sup>2</sup>  $P < 0.05$  (test of OR = 1).

It is not possible to entirely rule out residual confounding with folate status as an explanation of our finding. The reason we believe that the association between coffee consumption and tHcy is causal is twofold. First, there was a clear dose-response relation, and, second, adjustment with a combined dietary and supplemental folate score that showed a correlation of  $r = 0.45$  with plasma folate in the subsample did not further weaken the relation.

Coffee consumption and smoking were associated with approximately the same increase in mean tHcy concentration.

Still, the relations of the two factors with tHcy were quite different. Whereas smoking was associated with a complete shift of tHcy distribution toward higher values, coffee consumption was not related to plasma tHcy above its 95th percentile. We showed recently that intake of vitamin supplements was associated with a complete shift of the distribution to the left (45), thus resembling the smoking-tHcy relation. These differences may suggest that smoking and vitamin intake are related to tHcy concentration through different mechanisms than is coffee. It has been suggested that the adverse cardio-



**FIGURE 3.** Cumulative frequency distribution curves of total homocysteine (tHcy) in plasma according to extreme categories of coffee and/or smoking habits in 40–42-y-old women.

vascular effects of tHcy only become apparent at high concentrations (2). If such a threshold effect exists, the coffee-induced increase in mean tHcy concentration should represent a smaller increase in risk than the change induced by smoking.


The mechanism behind the observed coffee-tHcy relation is unknown. In our study, almost 95% of the coffee consumers used filtered coffee. Despite limited data, we also showed significant dose-response relations between boiled or instant coffee and tHcy concentration but not for decaffeinated coffee. This may point to a possible influence of caffeine on tHcy concentration. Tea also contains caffeine, but less than coffee (46). However, tea also contains moderate amounts of folates (47). This may explain the weak and conflicting results we observed between tea consumption and tHcy concentration in multivariate analyses of the total study population and confined to coffee abstainers.

The cholesterol-raising effect of coffee is linked to the concentration of cafestol and kahweol (48, 49) rather than caffeine. In our study, the increase in total cholesterol with coffee was of a magnitude similar to that in a previous trial with filtered coffee (50). This is less than the 8–12% change in cholesterol observed in other Norwegian counties (51, 52) and may be due to infrequent use of boiled coffee, which has high concentrations of cafestol and kahweol (48, 49). In multivariate analyses, heavy coffee consumption showed a stronger association with tHcy than with cholesterol concentration. Our results therefore indicate that tHcy as well as cholesterol should be considered when evaluating the effect of coffee on disease.

We found that heavy coffee consumption was associated with increases in total cholesterol and tHcy concentrations of  $\approx 0.5$  mmol/L and  $2 \mu\text{mol/L}$ , respectively. Previous studies have shown that an increase in total cholesterol of  $0.5$  mmol/L resulted in a relative risk of heart disease of 1.1–1.3 (53, 54). In a recent meta-analysis, a difference in plasma tHcy concentration of  $2 \mu\text{mol/L}$  was associated with a relative risk of heart disease of 1.14–1.2 (7), which is similar to the observed relative risk of 1.15 shown in a Norwegian cohort-based case-control study on heart disease and tHcy (3). Based on these estimates, the observed differences in tHcy and total serum cholesterol concentrations with coffee use may be associated with changes in risk of heart disease of the same magnitude. Higher tHcy concentrations in coffee drinkers may therefore partly account for the increased risk of heart disease beyond that explained by cholesterol (12, 14, 15, 24). However, several studies have not found an association between coffee and heart disease (18–20). If there is an adverse clinical effect of coffee that is partly mediated through tHcy, one characteristic of the population that may contribute to the heterogeneity among studies of the coffee-heart disease association is folate intake. Populations with a high folate intake, either from supplements or diet, may be protected from this adverse effect of coffee.

The fact that coffee consumption and smoking induced an additive increase in mean tHcy concentration in our study may have clinical implications. The combination of cigarette smoking and high coffee intake has been shown to have a particularly unfavorable effect on risk of acute myocardial infarction (15). Moreover, several studies have shown that women who smoked and had a high caffeine intake were at higher risk of delivering children with low birth weight (28, 29, 31). The current knowledge of the possible role of tHcy in cardiovascular disease (1–8) and in pregnancy (35–38), combined with

our findings of associations of plasma tHcy with smoking and coffee intake, should promote future studies on interactions among these factors.

In conclusion, we found a strong dose-response relation between coffee intake and plasma tHcy concentration. Heavy smokers with a high coffee consumption had particularly high tHcy concentrations. Given the widespread use of coffee, even small adverse consequences will have important health implications. This association between tHcy and coffee should be considered in the design and interpretation of future studies on either factor and disease. 

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