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Coffee consumption and decreased serum gamma-glutamyltransferase and aminotransferase activities among male alcohol drinkers

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Background Attention has long been drawn to the potentially harmful effects of coffee on health, however recent epidemiological studies have suggested unexpected, possibly beneficial effects of coffee against the occurrence of alcoholic liver cirrhosis and upon serum liver enzyme levels.

Methods We examined the potential inverse association between coffee drinking and serum concentrations of gamma-glutamyltransferase (GGT) and aminotransferases, with special reference to interaction with alcohol consumption, in a cross-sectional study involving 12 687 health examinees (7398 men and 5289 women) aged 40–69 years from over 1000 workplaces in Nagano prefecture in central Japan. Those who had a history of liver disease and/or serum aminotransferases exceeding the normal range were excluded. Possible confounding effects of alcohol consumption, body mass index, cigarette smoking, and green tea consumption were controlled through multivariate analyses.

Results Increased coffee consumption was strongly and independently associated with decreased GGT activity among males (P trend < 0.0001); the inverse association between coffee and serum GGT was more evident among heavier alcohol consumers ($P < 0.0001$), and was absent among non-alcohol drinkers. Among females, however, coffee was only weakly related to lower GGT level. Similar inverse associations with coffee and interactions between coffee and alcohol intake were observed for serum asparate aminotransferase and alanine aminotransferase. Intake of green tea, another popular source of caffeine in Japan, did not materially influence the liver enzyme levels.

Conclusions Our results suggest that coffee may inhibit the induction of GGT in the liver by alcohol consumption, and may possibly protect against liver cell damage due to alcohol.

Keywords Coffee, gamma-glutamyltransferase, alanine aminotransferase, asparate aminotransferase, drinkers

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Attention has long been drawn to potentially harmful effects of coffee consumption on the development of coronary heart disease,[1] malignant neoplasms,[2] and reproductive adversities (e.g. low birthweight).[3] However, except for the link between risk of coronary heart disease and use of unfiltered coffee,[1] which contains cholesterol-raising substances,[4] the observed associations within usual consumption levels of coffee remain controversial and not so strong as expected.

On the other hand, recent epidemiological studies have suggested unexpected, possibly beneficial effects of coffee consumption on the occurrence of alcoholic cirrhosis,[5] and upon serum liver enzyme levels,[6,7] particularly gamma-glutamyltransferase (GGT) activity[6,8] which is closely related to alcohol

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consumption.[9] Interestingly, Kono *et al.* found that the inverse association of coffee, mostly instant or filtered, with serum GGT was more evident among heavier alcohol drinkers.[10]

To further explore the possible interaction between coffee and alcohol consumption on serum GGT and other liver enzymes, we have conducted a cross-sectional study of 12 687 Japanese health examinees, taking into account the effects of obesity, cigarette smoking, and green tea consumption, which are also implicated as potential determinants of serum liver enzyme levels.[10–13]

Subjects and Methods

The present study utilized data derived from the health screening carried out by the Chubu Institute of Public Health Medicine, which screened annually over 40 000 residents in a southern part of Nagano prefecture in central Japan. Although this institution provided both community- and workplace-based screenings, information on lifestyle variables was not available in the former setting where the staff of local municipalities independently obtained such information in a different format. An additional interview for lifestyle information was not feasible and so only the data through the workplace-based screening were used in this analysis.

Between April 1995 and March 1996, 33 976 workers from 1300 workplaces underwent the health screening. We excluded the following subjects: (1) those who were <40 or ⩾70 years old (n = 17 734) (this exclusion was done since most employees [63%] <40 years were not tested for liver enzyme levels, and there were only 369 people aged ⩾70 years); (2) those who did not have all measurements of serum GGT, asparate aminotransferase (AST) and alanine aminotransferase (ALT) (n = 1202); (3) those for whom survey data were not collected (n = 606), or whose questionnaire data in a computerized file could not be checked by the present authors due to loss of their questionnaires (n = 165) (since an optical reading system for data input had been designed to accept one digit numbers for coffee and green tea consumption, we had to reinput information from subjects who reported ⩾10 cups drunk); (4) those who were known to be mentally handicapped (n = 141); and (5) those who reported a history of liver disease (n = 177), or those whose serum levels of AST and/or ALT exceeded the normal upper limit (n = 1264). The last condition was applied so as to exclude subjects who might have reduced coffee consumption because of impaired caffeine clearance due to their liver disease or liver dysfunction.[5] As a result, a total of 12 687 subjects (7398 men and 5289 women) were included in this analysis. The median age at screening was 50 years in males and 49 years in females.

A self-administered questionnaire ascertained lifestyle characteristics, including alcohol consumption, cigarette smoking, and dietary habits. As for drinking habit, examinees were first asked about their current drinking frequency (none, 1–2 times/week, 3–4 times/week, or almost daily), and then those who drank at least once per week answered their usual consumption amount of each kind of alcoholic beverage (*sake* or wine, *shochu* [a distilled alcoholic beverage made in Japan], beer, and whisky). Daily alcohol consumption was calculated from the drinking frequency and the dose and alcoholic content of each beverage consumed. A close-ended question queried about smoking habit (never, past, or current smokers), with subsequent inquiry to past or current smokers about the number of cigarettes smoked per day and the duration of smoking in years. In this study, past and never smokers were combined, and the current amount of cigarettes smoked was used in the analysis. As regards coffee and green tea, examinees were asked their usual daily intake in cups. Information on the brewing method of coffee was not collected. Although nurses performed a supplementary interview regarding unanswered questions, some data were missing for the daily consumption of alcohol (n = 114), cigarettes (n = 52), coffee (n = 130), and green tea (n = 69).

Venous blood was taken for the determination of liver enzymes and other biochemical measurements. Serum GGT, AST, and ALT concentrations were assayed at the institution, based on the methods recommended by the Japan Society of Clinical Chemistry,[14] with an autoanalyzer (TBA-50M, Toshiba, Tokyo, Japan) using commercial reagents (GGT: International Reagents Corp., Kobe, Japan; AST and ALT: Nissui Pharmaceutical Co., Ltd., Tokyo, Japan); the normal ranges are 0–60 U/l for GGT, 5–40 U/l for AST, and 0–40 U/l for ALT. Height and weight were measured at screening, and body mass index (kg/m^2) was calculated as an indicator of obesity; because of missing information, body mass index was not computed for 35 subjects.

Throughout this paper, sex-specific analyses were conducted to examine the relationship of coffee and other factors with liver enzyme levels, using the PC/SAS statistical package (SAS Institute Inc., Cary, NC). Correlations between the factors under study were evaluated by computing the Spearman rank correlation coefficients (r), since most variables did not follow the normal distribution. To control for the effects of potential confounders, an analysis of covariance and a multiple regression analysis were performed with the GLM procedure.[15] The natural logarithm of serum GGT value was used as a dependent variable because of the right-skewed distribution of GGT, whereas no transformation was made for serum AST and ALT; the distributions of AST and ALT were not seriously skewed after elimination of the values exceeding the normal range. Age was always included in the model as two indicator variables representing 10-year interval class (50–59 and 60–69 years with 40–49 years as the reference). This was because the association of GGT with age was not monotonous (Results), although age was almost linearly related to AST (positive associations in both sexes) and ALT (a positive association among females but an inverse association among males). Adjusted means were derived from the GLM procedure as least-squares means, and a test for linear trend was based on statistical significance of the regression coefficient of a continuous variable for the factor under consideration. Interactions between covariates were examined based on a multiple regression model including main effect and interaction terms as continuous variables with no transformation. All the *P*-values quoted are two-sided, and those values <0.05 are regarded as statistically significant.

Results

Age-adjusted analyses of gamma-glutamyltransferase

Serum GGT activity (U/l) range was 4–569 in males and 1–207 in females, with the geometric mean (and 95%CI) being 30.1 (95% CI : 29.6–30.5) and 15.3 (95% CI : 15.0–15.5), respectively; the difference between both mean estimates was statistically significant ($P < 0.0001$). Male subjects in their 40s, 50s, and 60s

Table 1 Age-adjusted geometric means of serum gamma-glutamyltransferase (U/l) by selected factors among 12 687 health examinees

Factor	Males		Females	
	No.[a]	Mean	No.[a]	Mean
Body mass index (kg/m^2)[b]				
13.60–20.68	1681	24.3	1478	14.3
20.69–22 47	1787	27.6	1384	15.2
22.48–24.38	1996	31.1	1173	15.6
24.39–38.87	1920	35.2	1233	18.3
P trend[c]		<0.0001		<0.0001
Alcohol (ml/day)				
None	1602	21.1	3976	15.2
1–29	3861	28 7	1231	17.2
30–59	1357	41.2	24	25.4
60+	517	44.9	5	22.8
P trend		<0.0001		<0.0001
Cigarettes (no./day)				
None	3445	28.3	4973	15.6
1–14	676	28 3	184	18.1
15–29	2550	30.7	109	16.9
30+	691	34.2	7	18 6
P trend		<0.0001		0.0009
Coffee (cups/day)				
None	2264	31.1	1993	15.9
1–2	3381	29.4	2741	15.6
3–4	1394	26.5	420	15.7
5+	293	25 4	71	14.7
P trend		<0.0001		0.20
Green tea (cups/day)				
None	1124	29 1	533	16.0
1–3	4388	29.8	2818	15.8
4–9	1565	29.1	1677	15 4
10+	277	28 7	236	16.0
P trend		0.18		0.48

[a] The presented figures do not add up to 7398 in males or 5289 in females because of missing information.

[b] Quartile classification for both sexes combined.

[c] Based on a multiple regression model including, as independent variables, a continuous variable for each of the five factors (body mass index, alcohol, cigarettes, coffee, and green tea) and indicators for age category (50–59 and 60–69 years with 40–49 years as the reference).

had average GGT levels of 29.9, 31.3, and 27.4 U/l, respectively, and the corresponding figures for females were 13.9, 16.8 and 16.6 U/l, respectively.

Table 1 shows the age-adjusted geometric means of serum GGT according to coffee consumption and other factors. There was a significant inverse association between coffee drinking and serum GGT among males, but such an association was not clear among females. Body mass index and alcohol consumption were strongly positively associated with serum GGT. Cigarette smoking was also positively related to serum GGT, whereas green tea consumption did not materially influence the enzyme level.

Table 2 Adjusted average difference (%) in serum gamma-glutamyltransferase (GGT) by selected factors and by sex

Factor (unit)	% Average difference in serum GGT[a]			
	Males		Females	
Body mass index (kg/m^2)	5.2	(4.6, 5.7)[b]	3.1	(2.7, 3.6)
Alcohol (10 ml/day)	9.1	(8.5, 9 7)	9.1	(6.9, 11.4)
Cigarettes (no./day)	0.4	(0.3, 0.6)	0.6	(0.2, 1.0)
Coffee (cups/day)	–4.5	(–5 5, –3.5)	–1.6	(–2.9, –0.3)
Green tea (cups/day)	–0.9	(–1.5, –0.3)	–0.2	(–0.8, 0.3)

[a] Based on a multiple regression model including, as independent variables, all the continuous variables listed and indicators for age category (50–59 and 60–69 years with 40–49 years as the reference)

[b] % difference by one unit increase of each variable with its 95% CI in parentheses.

Multivariate analyses of gamma-glutamyltransferase

The correlation with coffee drinking (cups/day) was negligible or very weak for body mass index (kg/m^2) (r = –0.03 for males, –0.03 for females) and alcohol use (ml/day) (r = –0.07 for male, 0.12 for females). Coffee was positively correlated with cigarette smoking (number/day) (r = 0.35 for males, 0.18 for females) and inversely correlated with green tea consumption (cups/day) (r = –0.19 for males, –0.25 for females).

In sex-specific multivariate analyses (Table 2), the inverse association between coffee and serum GGT was found to be significant in both males (*P* trend <0.0001) and females (*P* trend = 0.02), although the relation was much weaker among females than among males. Strong positive associations with serum GGT were evident for body mass index and alcohol consumption. After adjustment for other covariates, green tea consumption was significantly, weakly associated with decreased serum GGT among males (*P* trend = 0.002), but not among females (*P* trend = 0.39).

Cigarette smoking also appeared to be an independent predictor (Table 2). However, since cigarette smoking was positively correlated with alcohol consumption (r = 0.14 for males, 0.12 for females), the observed association between smoking and GGT may be ascribed to residual uncontrolled confounding by alcohol drinking. We thus performed an additional analysis of non-alcohol drinkers (1602 male and 3976 female subjects, including 841 male and 179 female current smokers). Among these subjects, the per cent average difference in serum GGT by one cigarette increase was estimated to be 0.06% (*P* trend = 0.64) for males and 0.09% (*P* trend = 0.74) for females after controlling for age category, body mass index, coffee, and green tea.

Interactions between coffee and other factors on gamma-glutamyltransferase

The interactions between coffee and each of four covariates (body mass index, alcohol, cigarettes, and green tea) on serum GGT were evaluated by adding each interaction term to the multiple regression model described in Table 2. Significant interactions were observed for coffee and alcohol among males ($P < 0.0001$ for the negative regression coefficient), and for coffee and smoking among males ($P = 0.0003$ for the negative regression coefficient); no other combinations were statistically significant in either sex ($P > 0.1$). While the interaction between

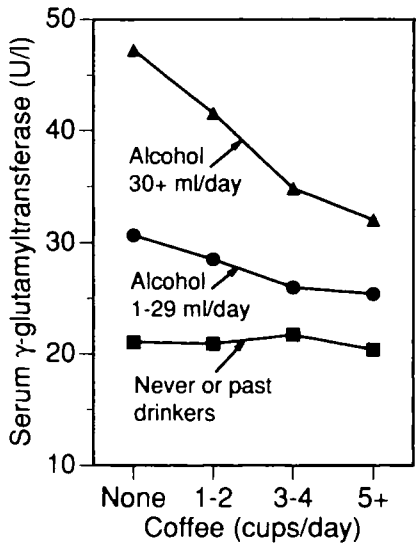

Figure 1 Geometric means of serum gamma-glutamyltransferase activity among males by coffee and alcohol consumption, after controlling for age category, body mass index, cigarette smoking, and green tea consumption

coffee and alcohol was significant among 3445 non-smoking men ($P = 0.01$), that between coffee and smoking was found to be insignificant among 1602 non-alcohol drinking men ($P = 0.15$).

Figure 1 illustrates the adjusted geometric means of serum GGT among males according to coffee and alcohol consumption. It is evident that the downward slope of serum GGT activity with increasing coffee is progressively steeper with increasing alcohol consumption, and that coffee use is not associated with decreased serum GGT among non-alcohol drinkers.

Analyses of alanine aminotransferase and aspartate aminotransferase

Table 3 demonstrates the sex-specific associations of coffee and other factors with serum AST and ALT. Coffee intake was significantly related to decreased serum concentrations of both enzymes among males, whereas the corresponding relations among females were found to be weak and insignificant. Among males, the interaction between coffee and alcohol consumption was significant for both AST ($P = 0.0005$ for the negative regression coefficient) and ALT ($P = 0.003$ for the negative regression coefficient), but such was not the case among females ($P = 0.49$ and $P = 0.12$, respectively). No significant interaction between coffee and cigarette smoking was observed for either enzyme level or sex ($P > 0.1$).

Discussion

Our study provides further evidence that coffee drinking is associated with decreased serum GGT activity, particularly among males. In a cross-sectional analysis of the Tromso Heart Study, Arnesen *et al.* first discovered an inverse association between coffee consumption and serum GGT,[6] and subsequently four cross-sectional studies[7,8,10,16] and one longitudinal[17] study consistently observed the same association in different populations. All of these studies took into account potential confounding effects of major determinants such as alcohol consumption and obesity in data analyses.

Other confounders that were not evaluated or are unmeasured in this study could be physical activity level,[8,11,12,16,17] dietary factors,[6] and, for women, use of oral contraceptives[6,8,17] and menopausal status.[8,17] In the current study, increased physical activity at work, but not in leisure time, was significantly related to decreased serum GGT (data not shown). However, an additional adjustment for this variable did not alter the inverse association between coffee and GGT. To our knowledge, no specific food has been implicated as being so strongly associated with serum GGT as to account for the coffee and GGT relation. Oral contraceptive use remains rare in Japan, since the Japanese government has not officially permitted the use of steroidal hormones for contraception. An analysis of women >50 years (n = 2384), most of whom were likely to be post-menopausal, revealed virtually the same association between coffee and serum GGT (data not shown).

Because of the cross-sectional design of this study, it is possible that the inverse association between coffee and serum GGT could be attributable to a reduction of coffee use among individuals who had elevated serum GGT as a manifestation of their liver disease or liver dysfunction; such individuals could involuntarily have avoided coffee due to their impaired caffeine clearance.[5] However, we excluded subjects who had a history of liver disease or elevated aminotransferase levels, and it is unlikely that increased serum GGT could solely induce a reduction in coffee consumption. Non-differential measurement errors of both serum GGT and coffee consumption may have caused some underestimation of relevant estimates on the associations, but this issue does not appear to seriously jeopardize our interpretations.

Table 3 Adjusted average difference (U/l) in serum asparate aminotransferase (AST) and alanine aminotransferase (ALT) by selected factors[a]

	AST		ALT	
Factor (unit)	Males	Females	Males	Females
Body mass index (kg/m^2)	0.07 (0.03, 0.12)[b]	0.04 (0.001, 0.09)	0.92 (0.86, 0.99)	0.54 (0.48, 0.60)
Alcohol (10 ml/day)	0.47 (0.42, 0.52)	0.30 (0.11, 0.49)	0.09 (0.02, 0.16)	0.07 (−0.19, 0.32)
Cigarettes (no./day)	−0.01 (−0.02, 0.003)	−0.01 (−0.05, 0.03)	−0.01 (−0.03, 0.001)	−0.01 (−0.06, 0.05)
Coffee (cups/day)	−0.48 (−0.58, −0.39)	−0.12 (−0.24, 0.0001)	−0.42 (−0.55, −0.30)	−0.14 (−0.30, 0.03)
Green tea (cups/day)	0.03 (−0.02, 0.08)	0.03 (−0.02, 0.08)	−0.03 (−0.11, 0.04)	0.03 (−0.03, 0.10)

[a] Based on a multiple regression model including, as independent variables, all the continuous variables listed and indicators for age category (50–59 and 60–69 years with 40–49 years as the reference).

[b] Absolute difference (U/l) by one unit increase of each variable with its 95% confidence interval in parentheses.

This study also showed a significant inverse relation between coffee use and serum levels of AST and ALT among males. Since we eliminated 1264 subjects who had raised aminotransferase levels, the magnitude of the observed associations between coffee and the enzymes may have been biased. These data should be viewed as reflecting the directions of the associations and the relative importance of the factors under investigation. Casiglia *et al.* previously reported similar findings on coffee and various liver enzymes,[7] but without any consideration of the possibility that people with liver dysfunction may have reduced coffee consumption.

Our key finding is the strong interaction between coffee and alcohol consumption on serum GGT among males; the inverse association of coffee with serum GGT was progressively stronger with increasing alcohol consumption and was absent among non-alcohol drinkers. This finding is very consistent with the previous observation by Kono *et al.*[10] Furthermore, a similar interaction was observed for serum AST and ALT. Although it is difficult to infer the clinical significance of the observed differences in liver enzyme levels associated with coffee and alcohol consumption, our results suggest that coffee may inhibit the elevation of GGT levels induced by alcohol consumption,[9] and may possibly protect against liver cell damage due to alcohol.

In this study, we employed the current consumption for both coffee and alcohol, and the lifetime dose was not ascertained for either variable. However, among our study subjects who did not suffer from definite liver disease, serum liver enzyme levels, particularly GGT activity, were more likely to be affected by the recent exposure than by the exposure in the distant past. Alcohol drinking pattern (i.e. binging versus steady drinking) may be of interest in considering the interaction between coffee and alcohol, although we had no relevant data.

We found a much weaker association of coffee with serum GGT among females than among males. Women may be less sensitive to coffee, or may have reported coffee or alcohol consumption less precisely, which could have led to a weaker association. However, the lower alcohol consumption among the female subjects appeared more relevant. In the present study, current drinkers represented only 24% of the female subjects, as compared with 78% of the male subjects. Even within an identical alcohol consumption category of 1–29 ml/day, which included most current drinkers (3861 males and 1231 females), women tended to consume much less alcohol (median 3.1 ml/day) than did men (median 14.2 ml/day). This may account for the above sex difference if a similar interaction between coffee and alcohol on serum GGT was occurring in both sexes. Further studies involving more women with moderate to heavy alcohol use are needed to address this issue.

A positive association of smoking with serum GGT was observed even after statistical adjustment for other covariates. However, it is uncertain whether such an association was truly independent of the confounding effect of alcohol consumption which correlated positively with cigarette smoking. The interaction between smoking and coffee on serum GGT can be questioned as well, since heavier smokers tended to drink more alcohol and thus may have revealed a somewhat larger inverse association between coffee and serum GGT. In this study, analyses of non-alcohol drinking subjects that included a substantial number of current smokers did not show any significant association with smoking or interaction between coffee and smoking. In addition, cigarette smoking was not related to serum aminotransferase levels. Thus, caution must be exercised in interpreting the above findings on smoking.

We did not obtain information regarding brewing methods of coffee. In Japan, instant coffee is most popular, followed by brewed (mostly filtered) coffee, whereas use of unfiltered coffee is virtually absent.[18] To our knowledge, there is no *a priori* reason for assuming a different effect of instant and filtered coffee, although the effect of unfiltered coffee brews, such as boiled coffee, is likely to differ from that of other types of coffee as described below.

In the Tromso Heart Study, Nilssen *et al.* noticed that the inverse association between coffee and serum GGT was more remarkable for boiled coffee than for filtered coffee.[8] A subsequent intervention study, which primarily aimed at identifying the cholesterol-raising factors in boiled coffee, has shown that the coffee diterpenes cafestol and, possibly, kahweol are responsible for raised cholesterol levels, and that at least cafestol substantially depresses serum GGT and raises serum ALT.[4] Since cafestol and kahweol are rich in unfiltered coffee but negligible in filtered and instant coffee,[19] the above finding by Nilssen *et al.* is likely to be attributable to the presence of such diterpenes in boiled coffee. However, the association between coffee and serum GGT in this study does not appear to originate from the diterpenes, since the great majority of our study subjects perhaps do not drink unfiltered coffee, and, most importantly, coffee use was related to decreased levels of serum AST and ALT.

One may consider that caffeine, one of the major ingredients contained in coffee with various biological actions, possibly plays a crucial role in the observed associations of coffee. Sharp and Benowitz showed that estimated caffeine intake and serum caffeine level were associated with decreased serum GGT.[20] In our study, however, intake of green tea, another popular source of caffeine in Japan, was not or only weakly associated with serum GGT, and it did not affect serum aminotransferase levels at all. Although Imai and Nakachi reported an inverse relation of borderline significance between heavy green tea intake (≥10 cups per day) and serum AST or ALT,[13] we could not detect such a relation. Further studies are warranted to elucidate what substances in instant and filtered coffee are responsible for decreased liver enzyme levels.

In connection with our findings, it is interesting to note that, in a large-scale prospective study in the US, Klatsky and Armstrong observed a decreased risk of alcoholic, but not non-alcoholic, cirrhosis among coffee drinkers.[5] Another case-control study also demonstrated a protective association of coffee with the risk of cirrhosis among alcohol users.[21] The potential beneficial effect of coffee on the liver among alcohol drinkers deserves further investigation.

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