Original Article

Effect of Coffee Intake on Blood Pressure in Male Habitual Alcohol Drinkers

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Many cross-sectional epidemiological studies have revealed that alcohol consumption is closely related to an increase in blood pressure, which is known to be associated with an elevated serum γ-glutamyltransferase (GGT) level, rather than to the volume of alcohol consumed. Since recent studies showed that coffee intake is inversely related to serum GGT, we investigated the effect of coffee on blood pressure in habitual alcohol drinkers. A total of 42 male hypertensive or prehypertensive volunteers who consumed alcohol and coffee daily completed this randomized controlled crossover trial. After a 2-week baseline period, these participants were randomly assigned to either a coffee-drinking group or a non-coffee-drinking group for the first 4 weeks. The situation was then reversed for the next 4 weeks. All participants continued their usual alcohol consumption. Blood pressure was measured once a week and compared between the two groups. After 1 week of coffee intake of more than 3 cups per day, the systolic and diastolic blood pressure began to fall slowly, and cessation of coffee intake raised the blood pressure. Systolic blood pressure was lowered by 7–10 mmHg, and diastolic pressure by 3–7 mmHg in 4 weeks. Alcohol consumption of more than 60 ml per day was maintained and there were no lifestyle changes in the participants of either group throughout the study period. Analyses of urine electrolytes and urea nitrogen indicated that there were no significant dietary changes. In conclusion, coffee intake of more than 3 cups per day in hypertensive and prehypertensive men who regularly consume alcohol lowers blood pressure. (*Hypertens Res* 2005; 28: 521–527)

***Key Words*: coffee, alcohol drinking, blood pressure, hypertension, randomized controlled crossover trial**

Introduction

Hypertension is one of the most common diseases in middle-aged and elderly people in Japan, as well as in Europe and the United States. Hypertension causes the progression of arteriosclerosis, sometimes in combination with lifestyle diseases such as obesity, hyperlipidemia and diabetes mellitus, which are often associated with hypertension. Thus, hypertension places people at higher risk for cardiovascular and cerebrovascular diseases. Since many cross-sectional epidemiological studies and randomized controlled trials have demonstrated that alcohol consumption is closely related to the increase of blood pressure, excessive alcohol intake is considered to be a risk factor of cardiovascular and cerebrovascular diseases. In epidemiological studies in Japan, the prevalence of hypertension in habitual heavy alcohol drinkers is three to four times higher than in abstainers (*1*). Development of hypertension by excessive intake of alcohol, which is considered to be an independent risk factor of hypertension, is not related to salt consumption, obesity or age (*2*).

High blood pressure in heavy alcohol drinkers is known to be associated with an alcohol-induced elevation of the serum γ-glutamyltransferase (GGT) level in the liver, rather than directly to the amount of alcohol consumed (*3*, *4*). Several epidemiological studies have shown that coffee protects against liver damage and coffee intake is inversely related to the serum GGT level, as well as to the levels of serum aminotransferases, independent of age, body-mass index (BMI), alcohol intake and cigarette smoking (*5*–*7*). These findings

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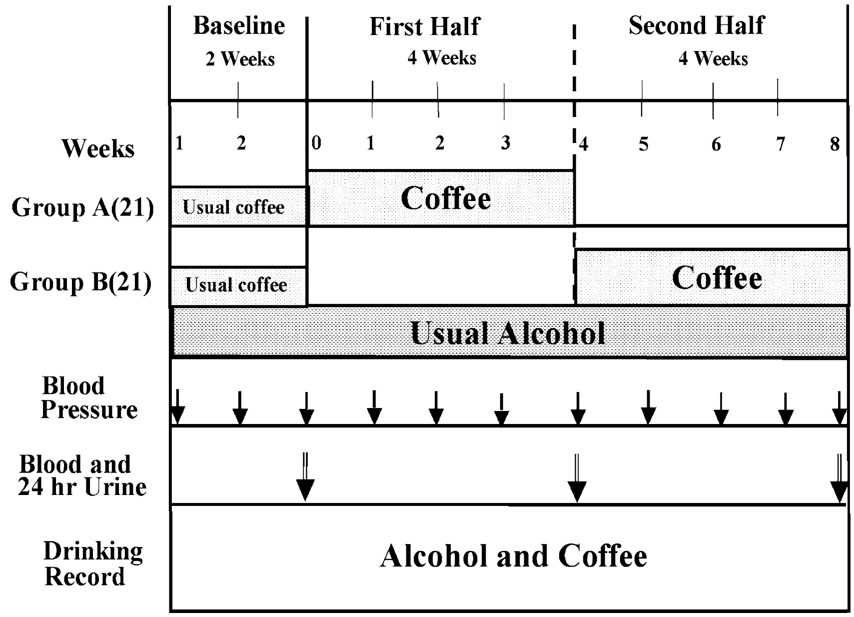

Fig. 1. *Schematic design for a randomized, controlled crossover study testing the effect of coffee intake on blood pressure in 42 men who were not taking any medication and who regularly drank both alcohol and coffee.*

suggest that increases in blood pressure in alcohol drinkers may be lowered by coffee intake. The effects of drinking coffee on blood pressure in chronic alcohol drinkers remain to be elucidated. Accordingly, we investigated the relationship between coffee intake and blood pressure in habitual alcoholic drinkers using a randomized, crossover controlled study.

Methods

Study Subjects

Forty-four male volunteers, aged 30 to 65 years, were recruited from their workplaces, which consisted of several pharmaceutical companies and a metal foundry. All volunteers had a systolic blood pressure (SBP) ≥120 mmHg, diastolic blood pressure (DBP) ≥80 mmHg, or both, as measured during annual health check-ups. All of them drank both coffee and alcohol. None had ever received antihypertensive medication. The study was approved by the Mitsukoshi Health and Welfare Foundation Research Committee. All subjects provided written informed consent. Since 2 men dropped out in the course of the study because of transfer, a total of 42 men completed the study.

Investigations

After a 2-week baseline period, participants were randomly assigned to either group A or B. Twenty-one volunteers were enrolled in each group. Group A members were asked to drink more than 3 cups of filtered coffee per day for the first 4 weeks of the study period, and group B was told to stop coffee intake for the first 4 weeks. The situation was reversed for the next 4 weeks. Participants could drink filtered coffee with or without milk and were permitted to drink before, during, or after meals. They could also drink other beverages, such as black tea and green tea, freely. Changes of their lifestyle were checked every week at the time of blood pressure measurement. None of the participants made any changes in their daily lifestyle, such as changes with respect to work, sleep, eating, smoking, or drinking of green tea, soft drinks, or other beverages except for coffee, and all of them maintained their usual alcohol consumption throughout the period. Blood pressure was measured twice during the day (between 10 AM and 4 PM) using an oscillometric blood pressure monitor (Colin BP-103i II; Nippon Colin, Tokyo, Japan) with participants in the sitting position by a nurse who was blinded concerning the treatment phase of the participants. Before blood pressure measurement each participant was allowed a 5-min rest period. They refrained from smoking and strenuous exercise during the previous half hour. Blood was collected before lunch and more than 3 h after the meal. Figure 1 shows the detailed design for the randomized, crossover controlled study. Blood pressure was measured weekly; *i.e.*, 3 times during the 2-week baseline period and weekly during each 4-week study period. Blood chemical analyses and measurements of body weight were performed once at the starting point and once during each study period. The 24-h urine was collected during the baseline period and during each study period to measure sodium, potassium, phosphorus, and urea nitrogen (reflecting the intake of salt, fruits and vegetables, processed or instant foods, and protein, respectively) (*8*)

Table 1. A Comparison between the Baseline Data of Group A and Group B*

Characteristics	Coffee intake		p value†
	Group A First half (n=21)	Group B Second half (n=21)	
Age (years)	48.5±11.5	44.6±10.5	0.28
BMI (kg/m^2)‡	23.7±2.9	24.1±2.5	0.61
Weight (kg)	65.8±9.0	65.5±8.6	0.28
Cigarette smoking (No./day)	11.8±13.0	21.1±20.2	0.16
Smoking rate (%)	57.1	57.1	1.00
Alcohol (ethanol, ml/day)	71.9±35.0	61.6±16.6	0.42
Coffee (cups/day)	2.6±1.3	2.7±1.0	0.46
AST (U/l)	22.9±14.9	22.4±7.9	0.60
ALT (U/l)	28.9±32.1	28.6±17.5	0.83
GGT (U/l)	31.2±25.9	46.4±34.9	0.20
HDL-C (mg/dl)	59.3±16.8	57.9±18.6	0.81
Uric acid (mg/dl)	6.4±1.2	5.8±1.0	0.15
Creatinine	0.85±0.11	0.88±0.18	0.58
Urine volume (ml/day)	1,327±393	1,312±515	0.93
SBP (mmHg)	132.9±17.0	128.8±7.7	0.36
DBP (mmHg)	82.2±11.7	81.5±9.2	0.71

BMI, body-mass index; AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase; HDL-C, high-density lipoprotein cholesterol; SBP, systolic blood pressure; DBP, diastolic blood pressure. *Plus-minus values are means±SD. †Unpaired t-tests were used for a comparison of the baseline data for both groups, with the exception of the smoking rate for which the χ^2 test was used. ‡BMI is the weight in kg divided by the square of the height in m.

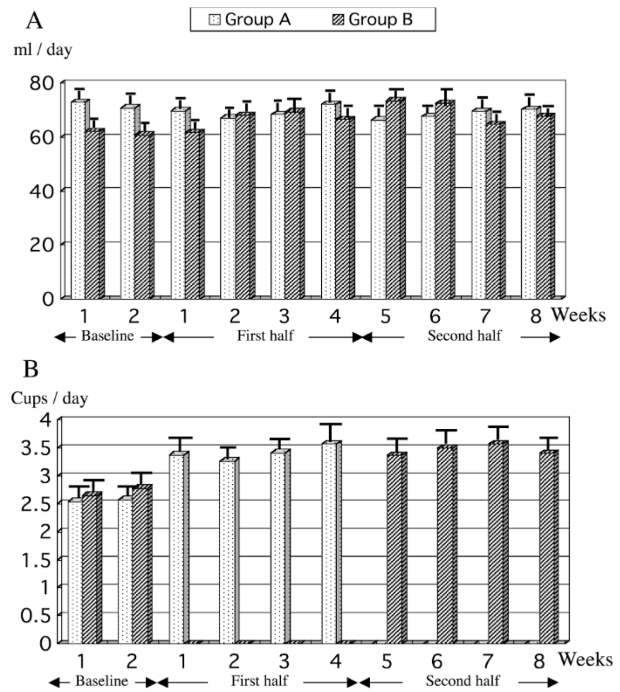

Fig. 2. *Bar graph with SEM showing average daily consumption of ethanol (panel A) and coffee (panel B) in groups A and B.*

using U-Mate, a 24-h urine measuring device based on a proportional sampling method (Akita Sumitomo Bakelite, Akita, Japan) (*9*).

The participants were asked to record their daily alcohol and coffee intake. Information on cigarette smoking, body weight, height, alcohol intake, and coffee intake was obtained at baseline.

Statistical Analysis

The sample size was calculated based on a preliminary study with 16 participants, to provide the study with 80% power to detect a 7 mmHg difference in SBP between the two groups at a two-sided α level of 0.05. Significance tests for blood pressure were conducted on the two groups during the first half and second half of the study. Two-way repeated-measures ANOVA was used to compare SBP or DBP for the two groups during each period. Changes of SBP or DBP of the subjects in either group A or B during the first half and second half were compared separately by one-way repeated-measures ANOVA. Changes of urine components, body weight and liver function in group A or group B were also compared with the use of one-way repeated-measures ANOVA. Basic data between the two groups were compared by the unpaired t-test, with the exception of the smoking rate, for which the χ^2 test was used. Statistical analyses were performed with StatView 5.0 software (Hulinks, Tokyo, Japan), and all tests of significance were 2-tailed with an α level of 0.05.

Results

Baseline Characteristics

Table 1 shows a comparison of the baseline characteristics of the participants. Subjects in group A drank 2.6 cups of coffee and 71.9 ml of alcohol per day, and those in group B drank 2.7 cups of coffee and 61.6 ml of alcohol per day. Daily coffee and alcohol consumption did not differ between the two groups. The mean SBP and DBP of group A were 132.9 mmHg and 82.2 mmHg, respectively, and those of group B were 128.8 mmHg and 81.5 mmHg, respectively. SBP and DBP did not differ significantly between the two groups. Age, BMI, and weight were also not significantly different between the two groups. Although the number of cigarettes per day was slightly, but not significantly, higher in group B than group A, the smoking rate was the same between the two groups. Biochemical markers of alcohol consumption, such as high-density lipoprotein cholesterol (HDL-C), GGT, and uric acid, and serum aminotransferases were not significantly

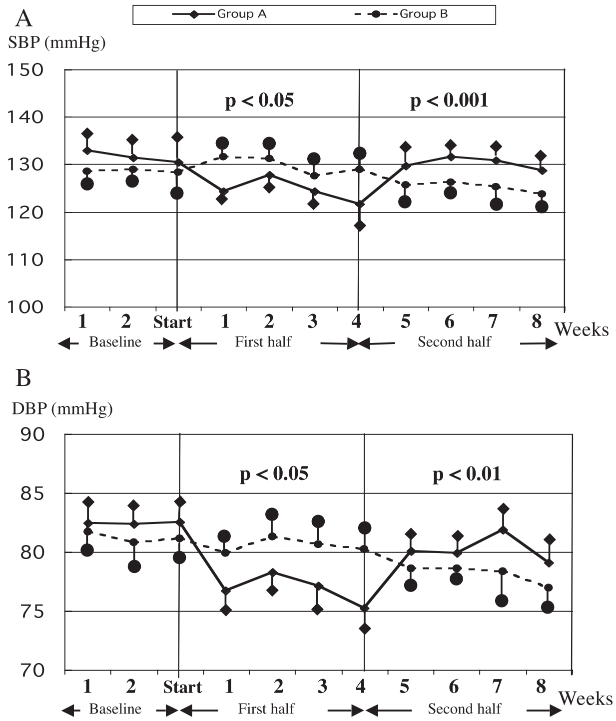

Fig. 3. *Line graph with SEM showing changes in systolic blood pressure (SBP) (panel A) and diastolic blood pressure (DBP) (panel B) in groups A and B.*

different between groups, and there were also no significant differences in creatinine or urine volume per day.

Coffee and Alcohol Intake

All participants complied with the study requirement of drinking no coffee for 4 weeks. Coffee and alcohol intake in the first half and second half of the study are shown in Fig. 2. The average daily alcohol consumption for groups A and B was between 61.8 and 73.5 ml (Fig. 2A), and the average daily coffee consumption was between 3.3 and 3.6 cups (Fig. 2B) during the study period. Average daily alcohol consumption for group A and group B during the study period and average daily coffee consumption for group A during the first half or for group B during the second half of the study did not change significantly. Further, the average daily alcohol consumption was not significantly different between the two groups in two-way repeated-measures ANOVA (p=0.383). Average daily coffee consumption for group A in the first half and for group B in the second half of the study was also not significantly different between the two groups in two-way repeated-measures ANOVA (p=0.096).

Measurement of Blood Pressure

In the first half of the study the SBP of the subjects in group A, who continued to drink more than 3 cups of coffee, showed a gradual decline compared with the SBP of those in group B, who drank no coffee (Fig. 3A). In the second half, the SBP of the subjects in group A, who stopped drinking coffee, increased from 1 week after cessation, whereas the SBP of those in group B, who returned to daily coffee intake of more than 3 cups per day, declined slowly from the level of the first half of the study. The SBP of group A declined by about 10 mmHg in the coffee-drinking period, but rose by about 8 mmHg in the non-coffee-drinking period. These changes in the SBP of participants in group A were significant during both the first and second half of the study by one-way repeated measures ANOVA (p=0.0015 and p=0.0003, respectively). On the other hand, the SBP of group B did not change significantly in the non-coffee-drinking period (p=0.2505), but declined by about 7 mmHg over the 4 weeks of the coffee-drinking period (p=0.1324). The differences in SBP between the two groups were significant during both the first and second half of the study by two-way repeated-measures ANOVA (first half $p<0.05$, second half $p<0.001$ between group A and group B).

The DBP of both groups A and B showed curves similar to those of the SBP (Fig. 3B). In the one-way repeated-measures ANOVA, the DBP of group A declined significantly by about 7 mmHg in the coffee-drinking period ($p<0.0001$), but increased by about 5 mmHg in the non-coffee-drinking period (p=0.0014), while the DBP of group B showed no significant changes in the non-coffee-drinking period (p=0.7098), but declined by about 3 mmHg in the coffee-drinking period (p=0.3290). The DBP differences between the two groups during the first half and second half of the study were significant based on two-way repeated-measures ANOVA (first half $p<0.05$, second half $p<0.01$ between group A and group B).

Chemical Analyses of Blood and Urine and Changes of Body Weight

Urine excretion of sodium, potassium, phosphorus, and urea nitrogen did not change significantly, and urine volume per day and weight remained stable during the study period in groups A and B based on one-way repeated-measures ANOVA (Table 2).

Table 3 shows the changes of biochemical markers of liver function, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT) and GGT. These markers decreased slightly due to coffee consumption in both groups, but these changes were not significant in one-way repeated-measures ANOVA.

Discussion

In this study, coffee drinking was observed to significantly lower the SBP and DBP of prehypertensive and hypertensive men with an alcohol-drinking habit. This study was conducted under normal working conditions. While participants usually drank 2.6 to 2.7 cups of coffee per day, average daily

Table 2. Changes of Urinary Excretion, Urine Volume and Body Weight for Group A and Group B*

Variables	Coffee intake							
	Group A				Group B			
	Start	Middle	Last	*p* value†	Start	Middle	Last	*p* value†
Urine Na (mmol/day)	181±49	154±57	149±50	0.189	157±62	158±53	170±57	0.074
Urine K (mmol/day)	50±19	50±23	46±31	0.364	51±37	45±30	49±20	0.561
Urine P (mg/day)	804±305	816±371	772±312	0.908	842±326	804±354	778±315	0.783
Urine UN (g/day)	9.6±2.2	8.2±1.4	8.5±2.3	0.078	8.9±2.7	8.2±3.2	8.4±3.2	0.281
Urine volume (ml/day)	1,327±393	1,228±560	1,197±398	0.505	1,312±515	1,247±468	1,274±529	0.770
Weight (kg)	65.8±9.0	65.6±9.0	66.0±9.4	0.427	65.5±8.6	65.6±9.2	66.1±9.0	0.249

UN, urea nitrogen. *Plus-minus values are means±SD. †*p* values were calculated by one-way repeated-measures ANOVA for variables in either group A or group B.

Table 3. Changes of Serum Aminotransferases and γ-Glutamyltransferase for Group A and Group B*

Variables	Coffee intake							
	Group A				Group B			
	Start	Middle	Last	*p* value†	Start	Middle	Last	*p* value†
AST (U/l)	22.9±14.9	20.9±8.3	22.8±18.7	0.906	22.4±7.9	20.2±5.3	19.0±6.8	0.336
ALT (U/l)	28.9±32.1	24.9±24.6	29.4±39.4	0.837	28.6±17.5	29.9±17.9	27.3±16.1	0.786
GGT (U/l)	31.2±25.9	30.4±25.3	30.9±25.4	0.111	46.4±34.9	54.2±45.3	48.1±40.1	0.134

AST, aspartate aminotransferase; ALT, alanine aminotransferase; GGT, γ-glutamyltransferase. *Plus-minus values are means±SD. †*p* values were calculated by one-way repeated-measures ANOVA for variables in either group A or group B.

consumption of coffee was between 3.3 to 3.6 cups during the study period. Since participants did not change their lifestyle, including cigarette smoking, physical activity, and eating, during the study period, the results suggest that coffee intake may lower blood pressure significantly in drinkers and that an intake of 3 to 4 cups of coffee a day is feasible for such individuals.

Previous epidemiological studies have produced contradictory findings regarding the association between blood pressure and coffee consumption. A relationship between coffee intake and an increase in blood pressure was reported in a meta-analysis of 11 controlled clinical trials with a median duration of 56 weeks (*10*). Recently, after many years of follow-up, a study by Klag *et al*. reported that coffee drinking was associated with small increases in blood pressure, but appeared not to be closely involved in the development of hypertension (*11*). Other epidemiological studies found that habitual coffee drinkers had lower blood pressure than non-drinkers and that mean blood pressure levels decreased with increasing coffee consumption (*12*, *13*). In some of these epidemiological studies blood pressure could not be measured as precisely as in this study, which may have played a role in the contradictory findings. Although the caffeine in coffee can increase blood pressure, adaptation to this effect is known to occur rapidly, and thus caffeine is not considered to influence blood pressure in habitual coffee drinkers. In a study by Hartley *et al*., subjects with optimal or normotensive blood pressure were reported to remain normotensive by oral administration of caffeine (*14*). Recently, Roberto *et al*. reported that the blood pressure effects of acute coffee intake were not only due to caffeine but also to some unknown ingredients with sympathetic nerve stimulant function, since decaffeinated coffee had the same effects (*15*). However, since they could not find any increase in blood pressure in chronic coffee drinkers, they concluded that coffee is not likely to be a risk factor of hypertension. These conflicting findings have served to obscure the effects of coffee on blood pressure.

In contrast to coffee, many cross-sectional epidemiological studies and controlled studies have demonstrated a link between habitual alcohol consumption and increased blood pressure (*2*, *16–22*). Recently, a correlation was reported between blood pressure in alcohol drinkers and the GGT level induced by alcohol in the liver, rather than alcohol intake *per* *se* (*3*, *4*). Since GGT is considered to be one of the markers of insulin resistance and is correlated with the level of visceral fat, blood pressure may correlate with GGT in alcohol drinkers (*23*). There have been several reports of potential inverse association between coffee intake and serum transaminases or GGT (*5–7*), which indicates that coffee may protect against liver injury and also suggests that coffee may decrease blood pressure. In this study, transaminases and GGT in chronic alcohol drinkers were slightly, but not significantly, decreased by coffee intake. Since the GGT changes were too small to elucidate the blood pressure effects of coffee in this study, other coffee-induced mechanisms distinct from GGT effects should also be investigated. It has been reported recently that flavonoid-rich foods, such as tea, cocoa, chocolate, coffee or red wine, have antioxidant properties and may reduce cardiovascular disease risk (*24–33*). The antioxidant effects of flavonoids in foods are among the potential mechanisms that might underlie the protective effects, which include attenuating the inflammatory process in atherosclerosis, reducing thrombosis, promoting normal endothelial function, and blocking expression of cellular adhesion molecules. The reduction of risk for type 2 diabetes mellitus associated with coffee drinking may also be due to the antioxidative activities of coffee (*34–36*). However, the blood pressure effects of dietary antioxidants are not well known. Recently, the water-soluble components of coffee bean extract were reported to induce hypotensive activity in rats (*37*). Further, the chlorogenic acid contained in coffee beans, which has been known to act on nitric oxide derived from the vascular endothelium, might reduce blood pressure by the improvement in vasoreactivity (*38*). Although it might be speculated based on these reports that the antioxidant components of coffee decreased the blood pressure of alcohol drinkers in the present study, the blood pressure effects of these flavonoid-rich foods remain to be demonstrated.

Sodium is widely prevalent in the food supply and an increase in dietary sodium induces a rise in blood pressure (*8*). In this study, salt consumption was stable during the study period, which indicates that the depressive effect of coffee intake on blood pressure was independent of changes in sodium intake. Furthermore, since the urinary excretion of potassium, phosphorus, and urea nitrogen did not change in either group, we concluded that participants did not change their dietary lifestyle during the study period. And the reductions in SBP and DBP were not related to weight change, since the body weight of all subjects remained stable during the study period.

The present results suggest that, first, alcohol drinkers with hypertension should reduce their intake of alcohol to no more than 30 ml of ethanol per day. In addition, the hypotensive effects of coffee may reduce the prevalence of hypertension in alcohol drinkers, in addition to possibly decreasing the risk of cardiovascular and cerebrovascular disease in alcohol drinkers. However, because coffee might increase blood pressure (*39*), inflammation processes (*40*), or the risk of thromboembolic stroke in older hypertensive patients (*41*), coffee consumption should be recommended for younger and middle-aged alcohol drinkers with hypertension rather than for older hypertensives.

References

1. Ueshima H, Shimamoto T, Iida M, *et al*: Alcohol intake and hypertension among urban and rural Japanese populations. *J Chron Dis* 1984; **37**: 585–592.
2. INTERSALT Study Group: INTERSALT: an international study of electrolyte excretion and blood pressure: results for 24 hour urinary sodium and potassium excretion. *BMJ* 1988; **297**: 319–328.
3. Yamada Y, Tsuritani I, Ishizaki M, *et al*: Serum gamma-glutamyl transferase levels and blood pressure falls after alcohol moderation. *Clin Exp Hypertens* 1997; **19**: 249–268.
4. Lee DH, Ha MH, Kim JR, Gross M, Jacobs DR Jr: Gammma-glutamyltransferase, alcohol, and blood pressure. A four year follow-up study. *Ann Epidemiol* 2002; **12**: 90–96.
5. Nakanishi N, Nakamura K, Nakajima K, Suzuki K, Tatara K: Coffee consumption and decreased serum gamma-glutamyltransferase: a study of middle-aged Japanese men. *Eur J Epidemiol* 2000; **16**: 419–423.
6. Honjo S, Kono S, Coleman MP, *et al*: Coffee consumption and serum aminotransferases in middle-aged Japanese men. *J Clin Epidemiol* 2001; **54**: 823–829.
7. Poikolainen K, Vartiainen E: Determinants of gamma-glutamyltransferase: positive interaction with alcohol and body mass index, negative association with coffee. *Am J Epidemiol* 1997; **146**: 1019–1024.
8. Sacks FM, Svetkey LP, Vollmer WM, *et al*: Effects on blood pressure of reduced dietary sodium and the dietary approaches to stop hypertension (DASH) diet. *N Engl J Med* 2001; **344**: 3–10.
9. Tochikubo O, Uneda S, Kaneko Y: Simple portable device for sampling a whole day's urine and its application to hypertensive outpatients. *Hypertension* 1983; **5**: 270–274.
10. Jee SH, He J, Whelton PK, Suh I, Klag MJ: The effect of chronic coffee drinking on blood pressure: a meta-analysis of controlled clinical trials. *Hypertension* 1999; **33**: 647–652.
11. Klag MJ, Wang NY, Meoni LA, *et al*: Coffee intake and risk of hypertension: the Johns Hopkins Precursors Study. *Arch Intern Med* 2002; **162**: 657–662.
12. Wakabayashi K, Kono S, Shinchi K, *et al*: Habitual coffee consumption and blood pressure: a study of self-defense officials in Japan. *Eur J Epidemiol* 1998; **14**: 669–673.
13. Salvaggio A, Periti M, Miano L, Zambelli C: Association between habitual coffee consumption and blood pressure levels. *J Hypertens* 1990; **8**: 585–590.
14. Hartley TR, Sung BH, Pincomb GA, Whitsett TL, Wilson MF, Lovallo WR: Hypertension risk status and effect of caffeine on blood pressure. *Hypertension* 2000; **36**: 137–141.
15. Roberto C, Christian B, Isabella S, *et al*: Coffee acutely increase sympathetic nerve activities and blood pressure

independently of caffeine content: role of habitual *versus* nonhabitual drinking. *Circulation* 2002; **106**: 2935–2940.
16. Ueshima H, Mikawa K, Baba S, *et al*: Effect of reduced alcohol consumption on blood pressure in untreated hypertensive men. *Hypertension* 1993; **21**: 248–252.
17. Fucks FD, Chambless LE, Whelton PK, Nieto FJ, Heiss G: Alcohol consumption and the incidence of hypertension; the Atherosclerosis Risk in Communities Study. *Hypertension* 2001; **37**: 1242–1250.
18. Okubo Y, Miyamoto T, Suwazono Y, Kobayashi E, Nogawa K: Alcohol consumption and blood pressure in Japanese men. *Alcohol* 2001; **23**: 149–156.
19. Rakic V, Puddey IB, Burke V, Dimmitt SB, Beilin LJ: Influence of pattern of alcohol intake on blood pressure in regular drinkers: a controlled trial. *J Hypertens* 1998; **16**: 165–174.
20. Kawano Y, Abe H, Kojima S, Takishita S, Matsuoka H: Effects of repeated alcohol intake on blood pressure and sodium balance in Japanese males with hypertension. *Hypertens Res* 2004; **27**: 167–172.
21. Iso H, Kitamura A, Shimamoto T, *et al*: Alcohol intake and the risk of cardiovascular disease in middle-aged Japanese men. *Stroke* 1995; **26**: 767–773.
22. Tsuruta M, Adachi H, Hirai Y, Fujiura Y, Imaizumi T: Association between alcohol intake and development of hypertension in Japanese normotensive men: 12-year follow-up study. *Am J Hypertens* 2000; **13**: 482–487.
23. Rantala AO, Lilja M, Kauma H, Savolainen MJ, Reunanen A, Kesaniemi YA: Gamma-glutamyl transpeptidase and the metabolic syndrome. *J Intern Med* 2000; **248**: 230–238.
24. Svilaas A, Sakhi AK, Andersen LF, *et al*: Intakes of antioxidants in coffee, wine, and vegetables are correlated with plasma carotinoids in humans. *J Nutr* 2004; **134**: 562–567.
25. Lee KW, Kim YJ, Lee HJ, Lee CY: Cocoa has more phenolic phytochemicals and a higher antioxidant capacity than teas and red wine. *J Agric Food Chem* 2003; **51**: 7292–7295.
26. Steinberg FM, Bearden MM, Keen CL: Cocoa and chocolate flavonoids: implications for cardiovascular health. *J Am Diet Assoc* 2003; **103**: 215–223.
27. Kris-Etherton PM, Keen CL: Evidence that the antioxidant flavonoids in tea and cocoa are beneficial for cardiovascular health. *Curr Opin Lipiodol* 2002; **13**: 41–49.
28. Natella F, Nardini M, Giannetti I, Dattilo C, Scaccini C: Coffee drinking influences plasma antioxidant capacity in humans. *J Agric Food Chem* 2002; **50**: 6211–6216.
29. Richelle M, Tavazzi I, Offord E: Comparison of the antioxidant activities of commonly consumed polyphenolic beverages (coffee, cocoa, and tea) prepared per cup serving. *J Agric Food Chem* 2001; **49**: 3438–3442.
30. Del Castillo, Ames JM, Gordon MH: Effect of roasting on the antioxidant activities of coffee brews. *J Agric Food Chem* 2002; **50**: 3698–3703.
31. Daglia M, Papetti A, Gregotti C, Berte F, Gazzani G: *In vitro* antioxidant and *ex vivo* protective activities of green and roasted coffee. *J Agric Food Chem* 2000; **48**: 1449–1454.
32. Yanagimoto K, Ochi H, Lee KG, Shibamoto T: Antioxidative activities of fractions obtained from brewed coffee. *J Agric Food Chem* 2004; **52**: 592–596.
33. Xu JW, Ikeda K, Yamori Y: Genistein inhibits expressions of NADPH oxidase p22phox and angiotensin II type 1 receptor in aortic endothelial cells from stroke-prone spontaneously hypertensive rats. *Hypertens Res* 2004; **27**: 675–683.
34. Rosengren A, Dotevall A, Wilhelmsen L, Thelle D, Johansson S: Coffee and incidence of diabetes in Swedish women: a prospective 18-year follow-up study. *J Intern Med* 2004; **255**: 89–95.
35. Salazar-Martinez E, Willett WC, Ascherio A, *et al*: Coffee consumption and risk for type 2 diabetes mellitus. *Ann Intern Med* 2004; **140**: 1–8.
36. Tuomilehto J, Hu G, Bidel S, Lindstrom J, Jousilahti P: Coffee consumption and risk of type 2 diabetes mellitus among middle-aged Finnish men and women. *JAMA* 2004; **291**: 1213–1219.
37. Suzuki A, Kagawa D, Ochiai R, Tokimitsu I, Saito I: Green coffee bean extract and its metabolites have a hypotensive effect in spontaneously hypertensive rats. *Hypertens Res* 2002; **25**: 99–107.
38. Ochiai R, Jokura H, Suzuki A, *et al*: Green coffee bean extract improves human vasoreactivity. *Hypertens Res* 2004; **27**: 731–737.
39. Rakic V, Burke V, Beilin LJ: Effect of coffee on ambulatory blood pressure in older men and women: a randomized controlled trial. *Hypertension* 1999; **33**: 869–873.
40. Zampelas A, Panagiotakos DB, Pitsavos C, Chrysohoou C, Stefanadis C: Associations between coffee consumption and inflammatory markers in healthy persons: the ATTICA study. *Am J Clin Nutr* 2004; **80**: 862–867.
41. Hakim AA, Ross GW, Curb JD, *et al*: Coffee consumption in hypertensive men in older middle-age and the risk of stroke: the Honolulu Heart Program. *J Clin Epidemiol* 1998; **51**: 487–494.