2 Barton JR, Ferguson A. Clinical features, morbidity and mortality of Scottish children with inflammatory bowel disease. *Q J Med* 1990;75:423-39.
3 Sedgwick DM, Barton JR, Hamer-Hodges DW, Nixon SJ, Ferguson A. Population based study of surgery in juvenile onset Crohn's disease. *Br J Surg* 1991;78:171-5.
4 Sedgwick DM, Barton JR, Hamer Hodges DW, Nixon SJ, Ferguson A. Population based study of surgery in juvenile onset ulcerative colitis. *Br J Surg* 1991;78:176-8.
5 Barton JR, Ferguson A. Failure to record variables of growth and development in children with inflammatory bowel disease. *BMJ* 1989;298:865-6.
6 Ferguson A, Sedgwick DM. Juvenile-onset inflammatory bowel disease: predictors of morbidity and health status in early adult life. *J R Coll Physicians, Lond* (in press).
7 Ferguson A, Sedgwick DM, Drummond J. Morbidity of juvenile-onset inflammatory bowel disease: effects on education and employment in early adult life. *Gut* (in press).
8 Best WR, Becktel JM, Singleton JW, Kern F. Development of a Crohn's disease activity index: National cooperative Crohn's disease study. *Gastroenterology* 1976;70:439-44.
9 Knight I. *The heights and weights of adults in Great Britain.* London: HMSO, 1984.
10 Gregory J, Foster K, Tyler H, Wiseman H. *Diet and nutritional survey: British adults.* London: HMSO, 1990.
11 Kirschner BS. Growth and development in chronic inflammatory bowel disease. *Acta Paediatr Scand* (suppl) 1990;366:98-104.
12 Kanof ME, Lake AM, Bayless TM. Decreased height velocity in children and adolescents before the diagnosis of Crohn's disease. *Gastroenterology* 1988; 95:1523-37.
13 Homer DR, Grand RJ, Colodny AH. Growth, course, and prognosis after surgery for Crohn's disease in children and adolescents. *Pediatrics* 1977;59: 717-25.
14 Castile RG, Telander RL, Cooney DR, Ilstrup DM, Perrault J, Van Heerden J, *et al.* Crohn's disease in children: Assessment of the progression of disease, growth and prognosis. *J Pediatr Surg* 1980;15:462-9.
15 McLain BI, Davidson PM, Stokes KB, Beasley SW. Growth after gut resection for Crohn's disease. *Arch Dis Child* 1990;65:760-2.
16 Lipson AB, Savage MO, Davies PSW, Bassett K, Shand WS, Walker-Smith JA. Acceleration of linear growth following intestinal resection for Crohn disease. *Eur J Pediatr* 1990;149:687-90.
17 Griffiths AM, Nguyen P, Smith C, MacMillan JH, Sherman PM. Growth and clinical course of children with Crohn's disease. *Gut* 1993;34:939-43.
18 Motil KJ, Grand RJ, Davis-Kraft L, Ferlic LL, O'Brian Smith E. Growth failure in children with inflammatory bowel disease: a prospective study. *Gastroenterology* 1993;105:681-91.
19 Markowitz J, Grancher K, Rosa J, Aiges H, Daum F. Growth failure in pediatric inflammatory bowel disease. *J Pediatr Gastroenterol Nutr* 1993;16: 373-80.
20 Kushner RF, Schoeller DA. Resting and total energy expenditure in patients with inflammatory bowel disease. *Am J Clin Nutr* 1991;53:161-5.
21 Farthing MJG, Campbell CA, Walker-Smith J, Edwards CRW, Rees LH, Dawson AM. Nocturnal growth hormone and gonadotrophin secretion in growth retarded children with Crohn's disease. *Gut* 1981;22:933-8.
22 Kirschner BS, Sutton MM. Somatomedin-C levels in growth-impaired children and adolescents with chronic inflammatory bowel disease. *Gastroenterology* 1986;91:830-6.
23 Clemmons DR, Underwood LE, Dickerson RN, Brown RO, Hak LJ, MacPhee D, *et al.* Use of plasma somatomedin-C/insulin-like growth factor I measurements to monitor the response to nutritional repletion in malnourished patients. *Am J Clin Nutr* 1985;41:191-8.
24 Seidman EG, Roy CC, Weber AM, Morin CL. Nutritional therapy of Crohn's disease in childhood. *Dig Dis Sci* 1987;32:82-8S.

(Accepted 22 February 1994)

Alcohol and blood pressure: the INTERSALT study

M G Marmot, P Elliott, M J Shipley, A R Dyer, H Ueshima, D G Beevers, R Stamler, H Kesteloot, G Rose, J Stamler

Department of Epidemiology and Public Health, University College London Medical School, London WC1E 6EA
M G Marmot, *professor*
M J Shipley, *senior lecturer in medical statistics*

Environmental Epidemiology Unit, Department of Public Health and Policy, London School of Hygiene and Tropical Medicine, London WC1E 7HT
P Elliott, *reader in environmental epidemiology*

Department of Preventive Medicine, Northwestern University Medical School, Chicago, IL 60611, USA
A R Dyer, *professor*
R Stamler, *professor*
J Stamler, *professor*

Department of Health Science, Shiga University of Medical Science, Otsu, Japan
H Ueshima, *professor*

Department of Medicine, Dudley Road Hospital, Birmingham B18 7QH
D G Beevers, *reader*

Department of Epidemiology, St Raphael University Hospital, B-3000 Leuven, Belgium
H Kesteloot, *professor*

Department of Epidemiology and Population Sciences, London School of Hygiene and Tropical Medicine, London WC1E 7HT
G Rose, *professor* (deceased)

Correspondence to:
Professor Marmot.

BMJ 1994;308:1263-7

Abstract

***Objectives*—To assess the relation between alcohol intake and blood pressure in men and women and in men at younger and older ages; to examine the influence of amount and pattern of alcohol consumption, as well as of acute effects, taking into account body mass index, smoking, and urinary sodium and potassium excretion.**

***Design*—Subjects reported alcohol consumption for each of seven days before standardised blood pressure measurement, and whether they had consumed any alcohol in the 24 hours before measurement.**

***Setting*—50 centres worldwide.**

***Subjects*—4844 men and 4837 women aged 20-59.**

***Main outcome measures*—Effect of alcohol on blood pressure estimated by taking a weighted average of regression coefficients from centres. Acute effect assessed by examining mean differences in blood pressure of non-drinkers and of heavy drinkers who had and had not consumed alcohol in the 24 hours before measurement. Effect of pattern of consumption assessed by examining mean differences in blood pressure of non-drinkers compared with drinkers (*i*) whose intake was concentrated in fewer days or who were drinking more frequently, and (*ii*) whose alcohol intake varied little over the seven days or varied more substantially, as indicated by the standard deviation of daily consumption.**

***Results*—Of the 48 centres in which some people reported consuming at least 300 ml/week of alcohol, 35 had positive regression coefficients linking heavy alcohol consumption to blood pressure. Overall, alcohol consumption was associated with blood pressure, significantly at the highest intake. After account was taken of key confounders, men who drank 300-499 ml alcohol/week had systolic/diastolic blood pressure on average 2·7/1·6 mm Hg higher than non-drinkers, and men who drank ⩾500 ml alcohol/week had pressures of 4·6/3·0 mm Hg higher. For women, heavy drinkers (⩾300 ml/week) had blood pressures higher by 3·9/3·1 mm Hg than non-drinkers. Heavy drinking and blood pressure were strongly associated in both sexes, and in men at both younger (20-39 years) and older (40-59 years) ages. In men who were heavy drinkers, episodic drinkers (those with great variation in daily alcohol consumption) had greater differences in blood pressure compared with non-drinkers than did regular drinkers of relatively constant amounts.**

***Conclusion*—The significant relation of heavy drinking (3-4 or more drinks/day) to blood pressure, observed in both men and women, and in younger and older men, was independent of and added to the effect on blood pressure of body mass index and urinary excretion of sodium and potassium. The findings indicate the usefulness of targeting those at high risk as well as the general population to reduce the adverse effects of alcohol on blood pressure.**

Introduction

INTERSALT, an international multicentre epidemiological study,[1,2] earlier reported significant associations of urinary sodium excretion and body mass index (direct), and urinary potassium excretion (inverse) with blood pressure.[3,4] The study showed, in addition, that consumption of 300 ml of alcohol per week (three or four drinks a day) or more was directly related to higher blood pressure of individuals. In two of the 52 centres in the study, the Yanomamo and Xingu Indians of Brazil, no alcohol was consumed. This report uses data on 9681 men and women from the remaining 50 centres to examine the relation between amount of alcohol consumed and blood pressure in men and women separately, and in younger and older men, independent of the effects of body mass index, smoking, and urinary excretion of sodium and potassium.

Although many studies have shown a positive relation between alcohol consumption and blood pressure,[5-14] it has not been clear whether the higher blood pressure in drinkers represents only an acute pharmacological effect of alcohol. We examined this question in heavy drinkers. We also assessed whether, in addition to the amount of alcohol consumed, there is an effect on blood pressure of the pattern of alcohol consumption—whether regular drinkers of relatively constant amounts have different blood pressure levels from those with a more episodic pattern of alcohol consumption.

Methods

INTERSALT originated as a project of the First Advanced Seminar of the International Society and Federation of Cardiology's Council on Epidemiology and Prevention (Finland, 1982). Details of study design and field methods have been published.[1,2] Briefly, INTERSALT followed a standardised protocol, using field methods common to all centres, with investigators from each centre required to take part in one of the five training and testing sessions conducted by the study's two coordinating centres, in London and Chicago. Each centre was asked to recruit 200 men and women, aged 20-59, stratified by age and sex into eight groups of 10 years. The samples were selected randomly from population lists or by chunk sampling of defined populations. Blood pressure was measured twice in the sitting position with a Hawksley random zero sphygmomanometer, after participants had emptied their bladders and sat quietly for five minutes. Height and weight were measured twice, a stadiometer and beam balance scale being used wherever possible.

Timed 24 hour urine collections were obtained for the estimation of electrolyte excretion. Urine aliquots were stored locally at −20°C before being shipped frozen to the central laboratory in Leuven, Belgium, where all urine analyses were performed with strict internal and external quality control. Data forms were sent to London for review, editing, coding, data entry, and analysis.

Alcohol intake in the seven days immediately before interview was assessed by questionnaire, followed by an interview to assist recall. Respondents were asked to list, for each of the seven days, the types and amount of alcoholic beverage consumed, and were asked separately whether they had taken an alcoholic drink in the 24 hours before interview. Local investigators provided the London centre with data on the alcoholic content of locally available drinks. In centres where this was not routinely available, chemical analysis was carried out locally. Individual daily alcohol consumption was then converted by computer into millilitres absolute alcohol.

As a definition of heavy drinking we used ⩾300 ml absolute alcohol per week, corresponding approximately to ⩾34 g alcohol per day. A unit of alcohol, a standard drink, is considered to contain 8-10 g of alcohol in Britain and 13 g in the United States. Hence 34 g alcohol is the equivalent of three or four drinks.

Statistical methods used in the main analyses have been described in detail.[3] Alcohol consumption was treated as a series of discrete (dummy) variables: each level of alcohol intake (for example, 1-49 ml/week) was treated as a separate variable and each individual was assigned a score of 0 or 1 on each variable. For each centre and sex, mean difference in blood pressure between each drinking category and non-drinkers was estimated by using the coefficients from multiple linear regression analyses, adjusted for age. For men, drinking categories up to ⩾500 ml/week were defined; for women, because of the small number of heavy drinkers, the highest drinking category used was ⩾300 ml/week. Further regression analyses controlled also for confounding effects of body mass index and 24 hour urinary sodium and potassium excretion, all entered as continuous variables, and smoking (smokers versus non-smokers), by entering these four terms together into the regression.

The statistical method, in which each centre is treated as a separate stratum in the analysis, is directly analogous to a meta-analysis of clinical trials assuming a "fixed effects" model[15,16]—except that in this study all the data were collected as part of one large study, with standardised methods of data collection and high levels of quality control.[16] Thus for each alcohol category, separately for men and women, each centre provided an independent estimate of the mean blood pressure difference in individuals between non-drinkers and drinkers. For study-wide estimates, these within centre comparisons (mean blood pressure differences, estimated from the within centre multiple regression coefficients relating alcohol to blood pressure) were averaged across centres, each centre coefficient being weighted by the inverse of its variance. This fixed effects approach has the advantage that any cross centre (ecological) differences in mean blood pressure levels do not influence estimation of the relation of alcohol and blood pressure among individuals (within centres). To assess the adequacy of the fixed effects model, the alcohol-blood pressure coefficients specific for each centre, for each alcohol category, were tested for heterogeneity across the centres by using the standard χ^2 statistic.[15]

Within centres the numbers of participants in some alcohol categories were small, and therefore each weighted average was based only on those centres where there were five or more subjects in both the non-drinking group and the alcohol category being compared. Numbers of participants and centres contributing to these averages are given in the tables. Standard errors for age adjusted and fully adjusted mean differences were virtually identical and are given only for the fully adjusted results in the tables.

For each alcohol group, each mean difference in blood pressure in comparison with non-drinkers is a weighted average of effects from a different number of centres, so it is not possible to compare them directly (in a formal statistical sense). A direct comparison of these mean blood pressure differences in the various alcohol categories largely is precluded since the number of centres with sufficient numbers of participants in the alcohol drinking groups of interest was too few to allow meaningful inference.

To examine possible acute effects of alcohol, non-drinkers were compared with drinkers who did and did not report any alcohol consumption within the 24 hours before interview. As drinkers who reported no consumption of alcohol within the previous 24 hours were unlikely to have drunk alcohol on the day before examination, two sets of analyses were done. Firstly, an analysis that included all men was carried out; secondly, to maintain comparability between the groups, the analysis was restricted to men who did not drink alcohol on all seven days. In this manner, both the recent (within the previous 24 hours) and non-recent drinkers would not have consumed alcohol on more than six days.

To explore the effects on blood pressure of patterns of drinking in men, two analyses were carried out. Firstly, men were characterised by whether they drank on 1-3 days/week, 4-5 days/week, or 6-7 days/week. For each group, mean differences in blood pressure were estimated for drinkers of 1-299 ml/week and ⩾300 ml/week in comparison with non-drinkers. Secondly, men were characterised by the standard deviation of daily alcohol consumption. Three groups

were created to contrast relatively constant drinkers (low variability) with more episodic drinkers (medium and high variability) as follows: low (SD ≤15 ml/day—one drink or less per day), medium (15<SD ≤40), and high (SD >40). Again, for each group, mean differences in blood pressure were estimated for drinkers of 1-299 ml/week and ≥300 ml/week in comparison with non-drinkers. These two analyses are not independent. Thus a heavy drinker with low day to day variability is also a daily drinker of alcohol, as zero consumption on any one day would contribute to a SD >15 ml/day; and for heavy drinkers with high variability in intake, alcohol consumption was very high on some days. These analyses were not carried out in women because of insufficient numbers who consumed ≥300 ml/week.

Overall, INTERSALT collected data on 10 079 men and women, but 393 Yanomamo and Xingu were excluded from the analyses reported here as none drank alcohol. From the remaining centres the amount of alcohol consumed could not be ascertained for five alcohol drinkers, three men and two women; they were also excluded. The analyses given here therefore relate to 9681 people—4844 men and 4837 women.

Results

DOSE-RESPONSE BY SEX AND AGE

Table I (men) and table II (women), based on pooled regressions, show for each level of alcohol intake the mean difference in blood pressure of drinkers compared with non-drinkers. These differences were greatest in both men and women who reported an alcohol intake of ≥300 ml in the week before blood pressure measurement. For men, the largest blood pressure difference in comparison with non-drinkers was found in those in the highest alcohol consumption category (≥500 ml/week). For women, the small number of heavy drinkers precluded subdividing intakes above 300 ml. In the analysis adjusted only for age, there was little evidence for either sex of a dose-response below 300 ml.

With control for smoking and major factors related to blood pressure—body mass index and 24 hour urinary sodium and potassium excretion—the association of heavy alcohol intake with blood pressure became stronger. After such adjustment, blood pressures were considerably higher in heavy drinkers than in non-drinkers both for men (4·6/3·0 mm Hg (systolic/diastolic) higher in men consuming ≥500 ml), and women (3·9/3·1 mm Hg in women consuming ≥300 ml). At levels of alcohol intake below 300 ml/week both systolic and diastolic pressures in men and systolic pressures in women tended to be higher than in non-drinkers, although the differences were not significant at the 5% level.

The mean differences in blood pressure, in comparison with non-drinkers, contributed by each centre for the various alcohol categories shown in tables I and II were tested for heterogeneity across the centres. No significant heterogeneity was found for women, nor for men in most analyses, except for weak evidence ($p<0·05$) for intakes of 1-49 ml/week and of 300-499 ml/week (fully adjusted model only), although in these analyses much of the heterogeneity was contributed by only two or three centres.

The analysis by age was confined to men because of the small number of women at the higher levels of consumption. For both younger (age 20-39) and older men (age 40-59), effects on blood pressure of heavy drinking (≥300 ml alcohol/week) were similar and statistically significant (not shown in the tables). Thus in comparison with non-drinkers, mean blood pressure differences for heavy drinkers were 3·43 (SE 0·99) mm Hg (systolic) and 2·43 (0·92) mm Hg (diastolic) at ages 20-39, and 3·22 (1·30)/2·05 (0·90) mm Hg at ages 40-59.

PATTERNS OF CONSUMPTION

The possible relation between recency of drinking and blood pressure was examined in heavy drinking men (≥300 ml/week). Data are shown in table III for those who did and did not consume alcohol during the 24 hours before blood pressure measurement; results for all men (table III) were similar to results when men who drank on all seven days were excluded (see methods: results not shown). Blood pressures were significantly higher for heavy drinking men than for non-drinkers, irrespective of whether they drank in the previous 24 hours. As indicated by the regression coefficients, the difference in blood pressure between heavy drinkers and non-drinkers tended to be larger for those heavy drinkers who reported no alcohol intake in the previous 24 hours than for those reporting such recent drinking, although it is difficult to compare these two sets of mean differences directly since different centres contributed to each estimate. Further analyses were done to compare directly the blood

TABLE I—*Mean differences in blood pressure in 4626 men between drinkers and non-drinkers based on weighted averages of the regression coefficients, derived from each centre, linking alcohol to blood pressure*

	Alcohol intake (ml/week)					
	1-49	50-99	100-199	200-299	300-499	≥500
No of centres†	43	46	43	40	39	32
No of drinkers‡	585	485	634	478	568	428
No of non-drinkers‡	1218	1352	1104	955	900	686
Systolic blood pressure:						
Adjusted for age	−0·13	1·04	1·18	0·63	2·29**	4·13**
Fully adjusted (SE)§	0·00 (0·76)	1·17 (0·79)	1·47 (0·78)	0·69 (0·85)	2·70 (0·84)**	4·59 (0·98)**
Diastolic blood pressure:						
Adjusted for age	0·13	0·57	0·47	0·17	0·97	2·45***
Fully adjusted (SE)§	0·55 (0·56)	1·01 (0·59)	1·07 (0·58)	0·58 (0·63)	1·56 (0·76)*	3·04 (0·76)***

*P<0·05; **P<0·01; ***P<0·001.
†Number of centres with at least five people in each of the alcohol categories being compared.
‡For centres with some drinkers in the given alcohol category, the numbers of drinkers and non-drinkers being compared in each analysis.
§Adjusted for age, body mass index, smoking, and 24 hour urinary sodium and potassium excretion.

TABLE II—*Mean differences in blood pressure in 4647 women between drinkers and non-drinkers based on weighted averages of the regression coefficients, derived from each centre, linking alcohol to blood pressure*

	Alcohol intake (ml/week)				
	1-49	50-99	100-199	200-299	≥300
No of centres†	43	32	27	14	11
No of drinkers‡	994	416	380	122	114
No of non-drinkers‡	2135	1303	929	351	378
Systolic blood pressure:					
Adjusted for age	−0·44	−0·04	0·39	1·62	2·46
Fully adjusted (SE)§	−0·03 (0·58)	1·16 (0·84)	1·38 (0·92)	2·14 (1·54)	3·89 (1·70)*
Diastolic blood pressure:					
Adjusted for age	−0·60	−0·74	−0·51	−0·19	2·23
Fully adjusted (SE)§	−0·32 (0·39)	−0·05 (0·57)	0·28 (0·63)	−0·11 (1·08)	3·06 (1·18)**

*P<0·05; **P<0·01,
†Number of centres with at least five people in each of the alcohol categories being compared.
‡For centres with some drinkers in the given alcohol category, the numbers of drinkers and non-drinkers being compared in each analysis.
§Adjusted for age, body mass index, smoking, and 24 hour urinary sodium and potassium excretion.

TABLE III—*Mean difference in blood pressure in men between high alcohol consumers (≥300 ml/week) and non-drinkers by time of last drink*

	Drinking within past 24 hours	
	Yes	No
No of centres	41	15
No of heavy drinkers	837	142
No of non-drinkers	1007	383
Systolic blood pressure:		
Adjusted for age	2·60***	4·37**
Fully adjusted (SE)†	3·02 (0·81)***	5·05 (1·41)***
Diastolic blood pressure:		
Adjusted for age	1·70**	2·91**
Fully adjusted (SE)†	2·19 (0·61)***	3·43 (1·05)**

*P<0·05; **P<0·01; ***P<0·001.
†Adjusted for age, body mass index, smoking, and 24 hour urinary sodium and potassium excretion.

TABLE IV—*Differences in blood pressure in men between drinkers and non-drinkers by weekly amount of alcohol consumption and daily variability of alcohol intake*

Total amount of alcohol consumed (ml/week)	Low variability (SD ≤ 15)			Medium variability (15 < SD ≤ 40)			High variability (SD > 40)		
	No of centres	No of drinkers	No of non-drinkers	No of centres	No of drinkers	No of non-drinkers	No of centres	No of drinkers	No of non-drinkers
1-299	45	979	1253	47	928	1351	28	293	792
≥300	15	249	226	22	314	202	34	525	785
Mean (SE) differences† (mm Hg) in comparison with non-drinkers									
Systolic blood pressure:									
1-299		−0·38 (0·71)			1·32 (0·69)			2·18 (1·11)*	
≥300		1·02 (1·46)			4·27 (1·37)**			4·50 (0·95)***	
Diastolic blood pressure:									
1-299		−0·28 (0·52)			1·03 (0·50)*			1·82 (0·71)*	
≥300		−0·83 (1·11)			2·32 (1·03)*			3·09 (0·71)***	
Mean weekly alcohol consumption (ml):									
1-299		29			86			152	
≥300		490			441			511	

*P < 0·05; **P < 0·01; ***P < 0·001.
†Adjusted for age, body mass index, smoking, and 24 hour urinary sodium and potassium excretion.

pressure differences for the two groups of men consuming high amounts of alcohol, for those centres with sufficient numbers. As a result, the fully adjusted mean differences between the two groups were reduced from the 2·03 mm Hg (that is, 5·05 − 3·02 mm Hg) shown in table III to 1·06 (SE 1·37) mm Hg for systolic pressure, and from 1·24 (3·43 − 2·19 mm Hg) to 0·77 (SE 1·11) mm Hg for diastolic pressure, based on data for a total of 424 heavy drinkers in 15 centres.

The relation of pattern of daily drinking (number of days that alcohol was consumed) to blood pressure in men is not shown in tables. With adjustment for confounders, among both heavy (≥300 ml/week) and moderate drinkers (1-299 ml/week), no consistent effect of pattern on differences in blood pressure in comparison with non-drinkers was observed. Thus for heavy drinkers, mean differences in systolic pressure in comparison with non-drinkers were 3·81 (SE 1·50) mm Hg, 4·83 (1·66) mm Hg, and 3·63 (0·96) mm Hg for drinking on 1-3 days, 4-5 days, and 6-7 days respectively. For diastolic pressure, corresponding figures were 2·87 (1·10), 2·22 (1·25), and 2·27 (0·72) mm Hg.

Table IV shows the relation in men of blood pressure to variability in daily alcohol consumption after adjustment for confounders. In all analyses, among both heavy and moderate drinkers, the largest mean difference in blood pressure between drinkers and non-drinkers was found in the group with high variability and the lowest mean difference in the group with low variability. For the moderate drinkers this pattern reflected considerable differences in mean alcohol consumption among the groups, but this was not the case for heavy drinkers. For systolic blood pressure in heavy drinkers, mean differences in blood pressure in comparison with non-drinkers were 4·50 (SE 0·95) mm Hg in the group with high variability and 1·02 (1·46) mm Hg in the group with low variability. For diastolic pressure the corresponding figures were 3·09 (0·71) and −0·83 (1·11) mm Hg.

Mean blood pressure differences were also examined in male smokers and non-smokers. For heavy drinkers, in the fully adjusted analysis, similar differences in blood pressures, compared with non-drinkers, were observed in the two groups. Thus, for systolic pressure, mean differences were 4·06 (1·11) mm Hg in smokers and 4·04 (1·34) in non-smokers; for diastolic pressure they were 2·53 (0·87) mm Hg and 2·43 (1·03) mm Hg.

Discussion

The main finding of these analyses is that the significant and independent relation of heavy alcohol intake (≥300 ml/week) to blood pressure is seen in both men and women and for younger and older men. The INTERSALT study can be regarded as 52 separate epidemiological studies using a common protocol and methods.[16] As noted in the initial study report,[3] of the 48 centres in which some people reported consuming at least 300 ml/week of alcohol, 35 had positive regression coefficients linking heavy consumption to blood pressure. The present analyses add quantitative data, by sex and age, to this finding and also investigate the impact on blood pressure of patterns of alcohol consumption. After body mass index, smoking, and urinary excretion of sodium and potassium were taken into account, systolic/diastolic blood pressure was on average 2·7/1·6 mm Hg higher for men consuming 300-499 ml alcohol per week than for non-drinkers, and 4·6/3·0 mm Hg higher for men consuming ≥500 ml/week; for women consuming ≥300 ml/week, pressures were 3·9/3·1 mm Hg higher than for non-drinkers.

There is understandable concern over the accuracy of alcohol histories. In INTERSALT, considerable effort went into collecting good quality data that would be comparable across centres. A day by day, seven day recall method was used, with collection of detailed information on glass size and beverage type. Local beverages and quantities were converted into ml absolute alcohol. There is still a possibility for error in a study spanning so many cultures and patterns of

Public health implications

- Previous studies have indicated a positive association of alcohol to blood pressure, though the nature and shape of that association have been unclear
- Questions have remained as to what extent the alcohol-blood pressure relation reflects either acute effects or the effects of withdrawal in heavy drinkers
- In this study, alcohol intake was positively associated with blood pressure in both men and women, and in younger and older men, significantly so at higher intakes (more than three or four drinks a day)
- Heavy drinkers had higher blood pressures whether they had consumed alcohol over the previous 24 hours (possible acute effect) or had not (withdrawal effect), implying a sustained effect on blood pressure of chronic alcohol consumption
- Overall, INTERSALT study findings indicate the usefulness of targeting those at high risk as well as the general population with regard to the problem of alcohol drinking and its effects on blood pressure

drinking; consequent misclassification of alcohol intake would probably reduce the size of the blood pressure-alcohol regression coefficients and underestimate the size of the association.

There is evidence that alcohol may have an acute pressor effect.[5] It is therefore possible that the relation between alcohol and blood pressure observed in epidemiological studies represents not only chronic effects of alcohol intake but an acute transient effect on blood pressure.[6,7] It has also been suggested that high blood pressure in heavy drinkers may reflect the effect of alcohol withdrawal before blood pressure measurement.[8] Our data suggest that neither of these is the dominant explanation, even though they may play some part in the observed association of alcohol and blood pressure. Heavy drinkers had higher blood pressure than non-drinkers whether they had consumed alcohol over the previous 24 hours (possible acute effect) or had not (withdrawal effect). While those who had not tended to have somewhat higher pressures than those who had, the difference was within chance limits.

The effect of alcohol on blood pressure may be a function not only of average amount consumed weekly but also of pattern of ingestion—that is, "doses" of intake.[9] Among heavy drinkers, men with low variability of alcohol intake (SD $\leq$15 ml/day) had small non-significant mean blood pressure differences in comparison with non-drinkers, in contrast with the findings for men with a more episodic pattern of intake. To our knowledge, this is the first time that such a finding has been reported. Klatsky *et al* found, if anything, higher blood pressure differences among a low variability group defined on the basis of questionnaires.[7] Our own results need to be viewed with caution. Firstly, they must be seen in relation to the size of the whole dataset: they are based on relatively small numbers of drinkers and non-drinkers in only 15 of the centres. Secondly, even though the analysis was carried out according to an a priori hypothesis, it is in effect a subgroup analysis (among daily heavy drinkers) with the concomitant problems of multiple testing and difficulties of interpretation. None the less, this finding needs further investigation in other datasets.

With observations on 9681 people, these data may also add to knowledge on the shape of the relation of alcohol to blood pressure. Is it continuous or is there a threshold effect, such that the relation is only seen at higher intakes? Some studies have suggested a threshold,[10-12] others not.[13,14] One of the largest, from Kaiser Permanente in California,[10] found a continuous relation in men and some evidence of a threshold, or J shaped relation, in women. The analyses presented here are consistent with a weak but positive relation at levels of alcohol below 300 ml/week and a strong relation at higher intake.

Public health implications

These findings have public health implications. They suggest a potential benefit both from reducing average population intake and reducing heavy drinking. If the effect is indeed continuous, and causal, reducing even a low order excess risk by shifting alcohol intake and blood pressure downward in the general population could have an important impact on morbidity and mortality.[17-20] Further, as reported elsewhere,[18] data from the INTERSALT study show a strong relation between mean level of alcohol consumption and prevalence of heavy drinkers among the 52 populations that make up the study. Therefore a reduction in mean alcohol consumption may reduce the prevalence of heavy consumption, with consequent favourable effects on blood pressure. Overall, the data indicate the usefulness of an approach targeting those at high risk as well as the general population to reduce the adverse effects of alcohol on blood pressure.

In conclusion, alcohol has an association with blood pressure independent of sodium, potassium, body mass index, and smoking. Similarly, sodium, potassium (inversely), and body mass index are associated with blood pressure independent of each other and of alcohol intake. Data from the INTERSALT study allow quantitative estimates of the reductions in morbidity and mortality that could be predicted if the associations observed could be translated into favourable lifestyle changes with consequent reductions in population blood pressure—for example, coronary mortality would be reduced by 9% and stroke mortality by 14% for an averge reduction in population systolic blood pressure of 5 mm Hg.[19,20]

The work was supported by the Council on Epidemiology and Prevention of the International Society and Federation of Cardiology; World Health Organisation; International Society of Hypertension; Wellcome Trust (UK); National Heart, Lung, and Blood Institute (USA); Heart Foundations of Canada, Great Britain, Japan, and the Netherlands; Chicago Health Research Foundation; Belgian National Research Foundation; Parastatal Insurance Company, Brussels; and by many national agencies supporting local studies.

A full list of members of the Executive Committee and the Steering and Editorial Committee, local centres and investigators, and members of the central laboratory and coordinating centres was published in the *BMJ* in 1988 (vol 297, pp 327-8).

This is the last paper coauthored by Geoffrey Rose in his long and distinguished career before his untimely death in November 1993. We dedicate this paper to his memory.

1 INTERSALT Co-operative Research Group. INTERSALT study. An international co-operative study on the relation of blood pressure to electrolyte excretion in populations. 1: Design and methods. *J Hypertens* 1986;4:781-7.
2 Elliott P, Stamler R, on behalf of the INTERSALT Co-operative Group. Manual of operations for "INTERSALT," an international co-operative study of the relation of sodium and potassium to blood pressure. *Controlled Clin Trials* 1988;9(suppl):1-118S.
3 INTERSALT Co-operative Research Group. "INTERSALT": an international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium. *BMJ* 1988;297:319-28.
4 INTERSALT Co-operative Research Group. INTERSALT special issue. *J Hum Hypertens* 1989;3:279-407.
5 Potter JF, Beevers DG. Pressor effect of alcohol in hypertension. *Lancet* 1984;i:119-22.
6 Maheswaran R, Gill JS, Davies P, Beevers DG. High blood pressure due to alcohol. A rapidly reversible effect. *Hypertension* 1991;17:787-92.
7 Klatsky AL, Friedman GD, Armstrong MA. The relationships between alcoholic beverage use and other traits to blood pressure: a new Kaiser Permanente study. *Circulation* 1986;73:628-36.
8 Saunders JB, Beevers DG, Paton A. Alcohol-induced hypertension. *Lancet* 1981;ii:653-6.
9 Wannamethee G, Shaper AG. Alcohol intake and variations in blood pressure by day of examination. *J Hum Hypertens* 1991;5:59-67.
10 Klatsky AL, Friedman GD, Abraham BS, Gerard MJ. Alcohol consumption and blood pressure: Kaiser Permanente multiphasic health examination data. *N Engl J Med* 1977;296:1194-2000.
11 Klatsky AL. Blood pressure and alcohol consumption. In: Bulpitt CJ, ed. *Handbook of hypertension.* Vol 6. *Epidemiology of hypertension.* Amsterdam: Elsevier Science, 1985:159-74.
12 Elliott P, Fehily AM, Sweetnam P, Yarnell JWG. Diet, alcohol, body mass, and social factors in relation to blood pressure: the Caerphilly heart study. *J Epidemiol Community Health* 1987;41:37-43.
13 Dyer AR, Stamler J, Paul O, Berkson DM, Lepper H, McKean RB, *et al.* Alcohol consumption, cardiovascular risk factors and mortality in two Chicago epidemiologic studies. *Circulation* 1977;56:1067-74.
14 Criqui MH, Wallace RB, Mishkel M, Barrett-Connor E, Heiss G. Alcohol consumption and blood pressure—the lipid research clinics prevalence study. *Hypertension* 1981;3:557-65.
15 Fleiss JL. The statistical basis of meta-analysis. *Stat Methods Med Res* 1993;2:121-45.
16 Elliott P. Design and analysis of multicentre epidemiological studies: the INTERSALT study. In: Marmot M, Elliott P, eds. *Coronary heart disease epidemiology: from aetiology to public health.* Oxford: Oxford University Press, 1992:166-78.
17 Rose G. Strategy of prevention: lessons from cardiovascular disease. *BMJ* 1981;282:1847-51.
18 Rose G, Day S. The population mean predicts the number of deviant individuals. *BMJ* 1990;301:1031-4.
19 Stamler J, Rose G, Stamler R, Elliott P, Dyer A, Marmot M. INTERSALT study findings: public health and medical care implications. *Hypertension* 1989;14:570-7.
20 Stamler R. Implications of the INTERSALT study. *Hypertension* 1991; 17(suppl 1):16-20.

(Accepted 3 March 1994)