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Blood pressure and chemistry: some correlations and apparent correlations

J B WHITFIELD* and N G MARTIN†‡
*From the *Department of Clinical Biochemistry, Royal Prince Alfred Hospital, Camperdown NSW 2050, Australia and the †Department of Population Biology, Research School of Biological Sciences, Australian National University, Canberra ACT 2600, Australia*

SUMMARY. The reported correlation between plasma calcium and blood pressure has been investigated in 412 young men and women. In this sample, it seemed to be due to a stronger correlation between blood pressure and plasma albumin. Blood pressures were also significantly correlated with plasma high-density lipoprotein in men and with plasma uric acid in women.

Several reports have recently appeared on the correlation between plasma calcium and blood pressure, and its probable cause and significance.[1–4] Correction of the total calcium results for albumin reduced but did not abolish this correlation, which suggests that albumin and blood pressure may be correlated. There have also been reports that other biochemical characteristics such as plasma lipids may be associated with blood pressure.[5, 6]

Correlations do not always reflect a causal relationship; they can also be due to common dependence of two variables on a third. We have therefore analysed data availlable from a previous study[7] to investigate correlation of blood pressure with certain biochemical variables and the possible causes of these correlations. Several such correlations have been found; some are easily explained in terms of known covariates but others may be new and of some importance.

Subjects and methods

Male and female subjects, aged 18–34 years (mean 23·1, SD 4·6) volunteered for a study of alcohol metabolism.[7] The 412 subjects comprised 206 pairs of twins, but in this paper each subject is considered as an individual rather than the results being used for pair-wise comparisons. Since twins are related, the observations are not genetically independent, but for the exploratory purposes of this paper we have regarded them as independent. To this extent our tests of significance are not conservative.

Subjects arrived for the study between 9 a.m. and 10 a.m. They answered a questionnaire on normal weekly alcohol consumption and were measured for height, weight and subscapular skinfold thickness. A venous blood sample was taken while they were stitting upright in a chair. After baseline studies of performance on various psychomotor tests and after lying quietly for at least 2 minutes they proceeded to have their blood pressure measured. All the results in this paper relate to the subjects before they ingested any alcohol.

Biochemical measurements on blood plasma were made using a Technicon SMAC analyser. Albumin was measured by the bromocresol green method with short incubation to reduce interference from globulins. High-density lipoprotein cholesterol (HDL) was measured after PEG-6000 precipitation of other lipoproteins.[8] Calcium was corrected for albumin using the formula:

$$\text{Corrected calcium} = \text{Calcium} - [0{\cdot}02 \times (\text{albumin} - 45)],$$

where calcium is measured in mmol/l and albumin in g/l.[4] Statistical analyses were carried out using SPSS.[9]

Results

The mean and standard deviations for the variables studied are shown in Table 1. It will

‡Present address: Department of Human Genetics, Medical College of Virgina, Box 33, Richmond, Va 23298, USA.

TABLE 1. Means and standard deviations, with tests for significant differences in means between men and women

	All subjects (410)	Men (198)	Women (212)
Age (years)	23·0 ± 4·6	23·3 ± 4·8	22·8 ± 4·4
Systolic b.p. (mm Hg)	113·9 ± 13·5	117·2 ± 14·8	110·7 ± 11·5***
Diastolic b.p. (mm Hg)	71·0 ± 11·4	72·8 ± 12·0	69·3 ± 10·5***
Total calcium (mmol/l)	2·414 ± 0·092	2·438 ± 0·092	2·391 ± 0·086***
Corrected calcium (mmol/l)	2·381 ± 0·087	2·388 ± 0·091	2·374 ± 0·083*
Albumin (g/l)	46·7 ± 3·2	47·5 ± 2·9	45·8 ± 3·2***
HDL cholesterol (mmol/l)	1·20 ± 0·32	1·08 ± 0·27	1·30 ± 0·33***
Uric acid (mmol/l)	0·323 ± 0·069	0·369 ± 0·053	0·280 ± 0·052***

***$P<0.001$, **$P<0.01$, *$P<0.05$.

be seen that the means for men and women are significantly different for almost all the measurements. Since the men had higher blood pressures (both systolic and diastolic) than the women, any other variable with a difference in means between the sexes will appear to be correlated with blood pressure if all subjects, male and female, are considered together. Therefore the correlations with blood pressures for the male and female subjects separately must be used, even though this reduces the numbers; these are shown in Table 2.

There were no significant correlations between systolic blood pressure and either total or corrected calcium; the significant correlations between diastolic blood pressure and calcium in both sexes disappear when correction of the total calcium results for albumin is performed. Correlations of the blood pressures with plasma albumin were significant except for diastolic blood pressure in the men. Correcting for albumin effects using data from these subjects rather than the formula given above, by calculating the partial correlations between calcium and diastolic blood pressure controlling for albumin, also reduced the correlation to non-significant levels.

For HDL there was a significant correlation but only in men and only for systolic blood pressure; the correlation was increased and became significant also for diastolic blood pressure when allowance was made for skinfold thickness.

Uric acid was significantly correlated with both systolic and diastolic blood pressures in women but not in men, and this correlation

TABLE 2. Correlations with blood pressures by sex and partial correlations after controlling for relevant covariates

	Systolic		Diastolic	
	Men	Women	Men	Women
Total calcium	0·108	0·101	0·144*	0·173*
Corrected calcium	−0·012	−0·059	0·082	−0·010
Albumin	0·191**	0·213**	0·094	0·247***
Controlling for:				
Haematocrit	0·190**	0·214**	0·090	0·235**
HDL	0·200**	0·038	0·127	0·127
Controlling for:				
Age	0·182*	0·035	0·104	0·199
Alcohol intake	0·181*	0·037	0·121	0·119
Skinfold thickness	0·227**	0·050	0·164*	0·134
Uric acid	0·061	0·137*	0·062	0·155*

***$P<0.001$, **$P<0.01$, *$P<0.05$ (2-tailed).

remained significant after allowing for the effects of age, alcohol consumption or skinfold thickness.

Discussion

Reports on the association between blood pressure and calcium have tended to ignore the effect of albumin levels on total plasma calcium, although Robinson, Bailey and Williams found a decrease in correlation when total calcium was corrected for albumin.[4] With our comparatively small number of subjects, especially after division into male and female groups because of sex differences in means for most variables, we cannot rule out an association between blood pressure and ionised (or 'corrected') calcium, but it certainly seems that albumin is a more important factor.

This correlation between plasma albumin and blood pressure may reflect a cause and effect relationship or it may be due to the dependence of each on some third factor. One such factor which could affect both albumin and blood pressure is posture, but there are two reasons why this is probably not the explanation. Firstly, the blood pressure measurement was taken about half an hour after the blood sample, in a different position and with several different activities in the intervening period; and secondly if postural haemodilution and concentration were the explanation the haematocrit would also be affected. We found that partial correlation of albumin with systolic or diastolic blood pressure controlling for haematocrit did not abolish the original correlation.

If there is a direct correlation between albumin and blood pressure it could be due to the effect of albumin on colloid osmotic pressure. It appears[10] that a difference of 10 g/l in albumin concentration will lead to about 5 mm Hg difference in plasma oncotic pressure, which would need to be matched by a change in the hydrostatic pressure at the arteriolar end of the capillaries to maintain a balance between fluid flows across the capillary wall. Alternatively, an increased hydrostatic pressure would move water from the blood to the extravascular compartment until the plasma protein concentration rose to a new equilibrium.

Plasma uric acid is higher in men than in women, as are the blood pressures, and so an apparent correlation would be found if the entire group was considered. Consideration of the male and female results separately shows that uric acid is significantly correlated with both systolic and diastolic blood pressures in women. Controlling for age, alcohol consumption or skinfold thickness made no difference, and no explanation for this correlation can be offered. One previous study found no correlation between blood pressures and uric acid.[1]

For HDL, there is a significant correlation in men. Since age, alcohol intake, and obesity are related to blood pressure and blood lipids, partial correlation controlling for each of these in turn was performed. A slight decrease in correlation was found after allowing for the effects of age or alcohol, but significance remained; when the skinfold thickness was included the correlation was enhanced, presumably because obesity is associated with both an increase in blood pressure and a decrease in HDL.

Other authors have also examined the relationship between HDL and blood pressure. In 40-year-old men a significant correlation was found with systolic but not diastolic blood pressure;[5] it is notable that in our subjects the correlation with diastolic blood pressure was not significant until skinfold thickness was considered. Other studies have found associations with plasma total cholesterol, which we did not. In one study the total cholesterol correlation was thought to be due to common association with weight and age,[6] and no association was found with HDL.

The biochemical and blood pressure status of the subjects is probably not affected by their being twins; the data in Table 1 suggest that they are similar to the non-twin population of their age and sex. However, it should be acknowledged that correlations observed in 206 pairs of twins do not reach the same level of statistical significance as in 412 unrelated individuals, if the measurements in the two members of a pair are not independent. In the most extreme case, of complete heritability and a study involving only monozygotic twins, the effective number of observations is halved and the standard error of the correlation is increased by $\sqrt{2}$ (1·414). In practice, the heritability of these variables is less than absolute and 60% of the twin pairs were dizygotic. Therefore the reduction in significance levels should not be as great as this and the correlations discussed are unlikely to have arisen by chance.

In conclusion, we have shown (as others have before) that there are several biochemical correlates of blood pressure. Some of the correlations, however, can be demonstrated to be spurious by considering the sexes separately

or making corrections for obvious covariates. Others, notably those with plasma albumin and high-density lipoprotein may be of some significance. The associations with albumin and high-density lipoprotein raise questions of the mechanisms involved, while the higher high-density lipoprotein levels found in men with higher blood pressures may affect the balance of risks for coronary artery disease.

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