PAPERS

By how much does dietary salt reduction lower blood pressure?

I—Analysis of observational data among populations

M R Law, C D Frost, N J Wald

Abstract

***Objective*—To estimate the quantitative relation between blood pressure and sodium intake.**

***Design*—Data were analysed from published reports of blood pressure and sodium intake for 24 different communities (47 000 people) throughout the world.**

***Main outcome measure*—Difference in blood pressure for a 100 mmol/24 h difference in sodium intake. Allowance was made for differences in blood pressure between economically developed and undeveloped communities to minimise overestimation of the association through confounding with other determinants of blood pressure.**

***Results*—Blood pressure was higher on average in the developed communities, but the association with sodium intake was similar in both types of community. A difference in sodium intake of 100 mmol/24 h was associated with an average difference in systolic blood pressure that ranged from 5 mm Hg at age 15-19 years to 10 mm Hg at age 60-69. The differences in diastolic blood pressure were about half as great. The standard deviation of blood pressure increased with sodium intake implying that the association of blood pressure with sodium intake in individuals was related to the initial blood pressure—the higher the blood pressure the greater the expected reduction in blood pressure for the same reduction in sodium intake. For example, at age 60-69 the estimated systolic blood pressure reduction in response to a 100 mmol/24 h reduction in sodium intake was on average 10 mm Hg but varied from 6 mm Hg for those on the fifth blood pressure centile to 15 mm Hg for those on the 95th centile.**

***Conclusions*—The association of blood pressure with sodium intake is substantially larger than is generally appreciated and increases with age and initial blood pressure.**

Introduction

The importance of sodium intake as a determinant of blood pressure remains unresolved. In this and the next two papers (p 815 and p 819) we examine the published epidemiological data from observational studies and clinical trials.[1,2] Our aim was to clarify differences in effect suggested by different studies, to obtain a coherent quantitative estimate of the effect of sodium intake on blood pressure that is consistent with all the available data, and to estimate the effect of a reduction in dietary sodium on mortality from stroke and ischaemic heart disease.

In this paper we examined the average blood pressure and average sodium intake in separate geographically defined populations to obtain an estimate of the association between the two. Such an analysis faces at the outset the problem that the relation between blood pressure and sodium intake will be "confounded" by other determinants of blood pressure that are themselves associated among populations with sodium intake. Populations shown to have low sodium intakes (<100 mmol/24 h) are typically remote economically undeveloped communities, while those shown to have higher sodium intakes are generally urban economically developed communities. The lower average blood pressures found in the undeveloped communities must be due partly to differences between the two types of community in other factors that influence blood pressure (such as body weight, physical activity, alcohol consumption, dietary potassium and calcium, and mental stress). Some of these factors are difficult to measure, and many of the studies did not attempt to measure any of them. In estimating the association of blood pressure with sodium intake alone we reduced this problem of confounding by considering the two types of community separately and fitting two separate regression lines for blood pressure on sodium intake, one for each type of community.

Such an analysis estimates the average response of blood pressure to changing sodium intake, but the association is likely to vary among individual people. The finding that the standard deviation (or range) of blood pressure as well as the mean increases with sodium intake implies that those people with a higher initial blood pressure will show a greater response to increasing sodium intake than those with a lower blood pressure. (In the same way, as children grow the range of heights widens as their average height increases because taller children grow faster.) To estimate individual blood pressure response to a change in sodium intake we combined the results of the above regression analysis of average blood pressure on sodium intake with those of a similar analysis for standard deviation of blood pressure to estimate the slopes of specified centiles of blood pressure in relation to sodium intake.

Methods

We identified studies recording blood pressure and sodium intake for geographically defined populations.[3-26] We included in our analysis all studies that estimated 24 hour sodium intake from 24 hour urine collections (provided urinary creatinine concentrations suggested reasonably complete collection)[3,8,9,16-26] or from sodium analysis of replicate diets[10,11,14,15] and three studies with little variation in diet in which the authors estimated sodium intake from analysis of usual foodstuffs together with random urine samples or overnight collections.[7,12,13] We also included three studies of communities with no access to salt, for which sodium

Department of Environmental and Preventive Medicine, Medical College of St Bartholomew's Hospital, London EC1M 6BQ
M R Law, MRCP, *senior lecturer*
C D Frost, DIPSTAT, *lecturer*
N J Wald, FRCP, *professor*

Correspondence to: Dr Law.

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intake was not estimated directly, but detailed description of the habitual diets established that the daily sodium intake could not have exceeded 10 mmol/24 h.[4-6] For studies reporting separate data for neighbouring communities we combined the data from communities with similar sodium intakes.[5 7 14 15 24]

We excluded studies that estimated 24 hour sodium intake by dietary recall or by random ("spot") urine samples alone, and studies in which the age range of the subjects was less than 30 years because of the importance of comparing the association between sodium and blood pressure in different 10 year age groups. We also excluded studies of African, American Caribbean, and other black populations because their blood pressure seems to be higher than that of other racial groups with the same sodium intake,[27-29] a difference that is likely to be genetically determined.[30] We confirmed that in four studies measuring blood pressure and sodium intake in urban black populations[17 31-33] blood pressure was indeed significantly higher than in other populations with similar sodium intake that were included in our analysis.

To deal with confounding (as described above) we considered economically undeveloped and economically developed communities separately. The undeveloped communities were food gatherers or subsistence farmers or fishermen, living in small, non-urban communities with a traditional diet, culture, and lifestyle. The developed communities were urban communities with a Western influence whose food was mostly bought. From the authors' descriptions the communities readily segregated into one or other category (table I) in all cases but two: a Korean[34] and a Chinese[35] community that were intermediate and showed features of both types of population. Members' blood pressures were closer to those expected for members of undeveloped rather than developed communities, but they were not included in our main analysis.

We included studies of 24 communities with data from 47 000 people. As the association of blood pressure with sodium intake varied with age we performed separate analyses for each 10 year age group. Most communities were large enough to yield precise estimates of their average blood pressure and sodium intake; the respective standard errors for each 10 year age group were generally less than 2 mm Hg and 5 mmol/24 h. We examined the data from the large Intersalt study[26] separately.

TABLE I—*Comparison of blood pressure and sodium intake in different populations for people aged 40-49 years*

Community	No of people*	Average blood pressure (mm Hg, systolic/diastolic)	Estimated sodium intake (mmol/24 h)
Economically undeveloped:			
Yanomano (Amazonian Indian tribe)[1]	46	103/65	1
Carajas (Amazonian Indian tribe)[4]	14	101/69	10
Szechwan (Chinese aboriginals)[5]	63	104/72	10
Bomai (New Guinea highlanders)[6]	18	113/72	10
Solomon Islanders: Baegu, Aita, and Kwaio[7]	148	114/74	20
Chimbu (New Guinea highlanders)[8]	104	116/75	26
Pukapukans (Cook Islanders)[9]	60	116/79	62
Solomon Islanders: Nasioi and Nagavisi[7]	77	113/72	90
Javan villagers[10 11]	320	120/73	153
Qashqai (Iranian nomads)[12]	55	123/84	169
Solomon Islanders: Lau[7]	39	129/84	190
Taiwanese fishing population[13]	1078	132/85	370
Economically developed:			
Newfoundland: inland town[14]	63	136/80	127
Japan: Osaka manual workers[15]	1896	124/77	136
Newfoundland: three coastal towns[14]	189	137/83	148
United States: Evans county[16 17]	345	133/88	148
New Zealand: Milton[18 19]	170	129/82	158
Belgian towns[20]	88	130/80	165
Belgian army[21]	3396	130/83	165
United States: Framingham[22 23]	772	137/88	184
Finland[24]	352	138/88	197
Japan: Osaka residents, physicians, and clerical workers[15]	2134	129/82	228
North eastern Japan[25]	1623	140/80	308
Japan: Akita residents[24]	465	143/86	340

*Numbers with blood pressure measurements given; numbers with measurements of 24 hour sodium intake were sometimes smaller but standard error of mean was generally less than 5 mmol/24 h.
†1 g of salt (NaCl)=17·1 mmol sodium; 100 mmol sodium=5·8 g salt.

TABLE II—*Mean (standard error) differences in mean and standard deviation of systolic and diastolic blood pressure (mm Hg) for a 100 mmol/24 h difference in sodium intake according to age among different studies*

Age (years)	Systolic: Mean	Systolic: Standard deviation	Diastolic: Mean	Diastolic: Standard deviation
15-19	5·0 (1·1)	1·3 (0·8)	1·8 (1·0)	0·5 (0·6)
20-29	4·9 (0·8)	1·7 (0·3)	2·6 (0·7)	1·0 (0·3)
30-39	5·5 (0·9)	2·0 (0·5)	3·0 (0·8)	1·3 (0·5)
40-49	6·6 (1·0)	2·6 (0·6)	3·6 (0·8)	0·9 (0·3)
50-59	9·2 (1·2)	3·3 (0·7)	4·7 (0·8)	1·5 (0·4)
60-69	10·3 (1·3)	2·9 (0·9)	4·3 (0·7)	1·6 (0·4)

We carried out separate linear regression analyses of average systolic and diastolic blood pressure on sodium intake in 10 year age groups. (The association between blood pressure and sodium intake may be better described by a quadratic curve, becoming less steep with increasing sodium, but the difference from a linear regression was small and significant in only one age group.) We used an unweighted regression analysis because most of the residual variation was likely to be due not to random error but to variation in other determinants of blood pressure. We combined data from men and women in each study as separate analyses showed age specific regression slopes to be similar for the two sexes.

We first fitted separate regression lines for each age category in the two types of community. We found no significant difference between the slopes of the two regression lines (only in their intercepts) for any age group and therefore used a weighted average of the two slopes (calculated by fitting two parallel regression lines for each age group). In the undeveloped communities with very low sodium intake blood pressure did not rise with age, and we therefore constrained the regression lines for undeveloped communities through the same intercept for all six age groups. This intercept, the average blood pressure at zero sodium intake for all ages weighted by residual variation, was 110 mm Hg for systolic blood pressure and 72 mm Hg for diastolic.

We similarly regressed the standard deviation of blood pressure on average sodium intake with two parallel regression lines for each age group. We combined the analyses of mean and standard deviation of blood pressure to estimate the slopes of specified centiles of blood pressure in relation to sodium intake. The regression line for mean blood pressure represents the 50th centile; a line for any given sodium intake 1·28 standard deviations above this line will describe the change in blood pressure with change in sodium intake corresponding to the 90th centile of blood pressure. We calculated the slopes of all the blood pressure centiles in the same way. The data were inconsistent with the simple model of direct proportionality, whereby for all blood pressure centiles the percentage change in blood pressure for a given change in sodium intake would be constant; the proportional change, like the absolute change, in fact increased with blood pressure centile.

Results

Table II shows the differences in the mean and standard deviation of blood pressure for a 100 mmol/24 h difference in sodium intake for all six age groups. The associations were significant ($p<0·001$) in nearly all 10 year age groups and were more than twice as great for the oldest age group (60-69 years) as for the youngest (15-19 years)—respectively 10·3 and 5·0 mm Hg (systolic) for each 100 mmol sodium/24 h for mean blood pressure and 2·9 and

TABLE III—*Estimated mean blood pressure (SD) at zero sodium intake for economically developed communities* according to age*

Age (years)	Systolic	Diastolic
15-19	113·4 (9·9)	67·3 (9·9)
20-29	117·0 (9·8)	69·4 (9·3)
30-39	119·0 (12·0)	73·8 (9·3)
40-49	121·3 (14·1)	76·1 (10·7)
50-59	125·3 (16·9)	77·0 (10·2)
60-69	133·9 (19·5)	78·9 (10·4)

*For economically undeveloped communities mean blood pressure = 109·9 (systolic) and 71·8 (diastolic) at all ages; SD=9·9, 9·7, 10·5, 12·1, 14·6, and 15·9 (systolic) and 8·0, 7·5, 7·6, 8·5, 9·2, and 9·2 (diastolic) for the six age groups (youngest to oldest).

TABLE IV—*Predicted change in systolic and diastolic blood pressure (mm Hg) for each 100 mmol/24 h change in sodium intake for various centiles of blood pressure distribution*

Age (years)	Centile 5th	20th	50th	80th	95th
			Systolic		
15-19	3	4	5	6	7
20-29	2	4	5	6	8
30-39	2	4	6	7	9
40-49	2	4	7	9	11
50-59	4	6	9	12	15
60-69	6	8	10	13	15
			Diastolic		
15-19	1	1	2	2	3
20-29	1	2	3	3	4
30-39	1	2	3	4	5
40-49	2	3	4	4	5
50-59	2	3	5	6	7
60-69	2	3	4	6	7

1·3 mm Hg for standard deviation of blood pressure. Figure 1 shows the regression of average systolic blood pressure according to sodium intake for three of the six age groups examined.

Table III shows the estimated mean and standard deviation of blood pressure at zero sodium intake from the regression equations. The differences in mean blood pressure between the economically undeveloped and developed communities are apparent from table III; they were significant in most age groups and increased with age from 3·5 mm Hg (systolic) at age 15-19 to 24·0 mm Hg at age 60-69. The two parallel regression lines fitted the data significantly better than a single line for both types of community, indicating that the steeper slope of such a regression line is likely to be an exaggeration of the true association. The appendix gives the equations for the regression of mean and standard deviation of systolic and diastolic blood pressure on sodium intake for all six age groups.

The Intersalt study,[26 36] though large (10 000 subjects compared with a total of 47 000 in the 24 studies listed in table I), was not included in our between population analysis. Of the 52 communities in the Intersalt study, 36 could be clearly classified as economically developed (33) or undeveloped (3) and so might, in principle, be included in our analysis. However, the age specific blood pressure recordings were strikingly low—in the age group 40-49 years—for example, recordings of systolic blood pressure were about 15 mm Hg lower than recordings in other studies of the same communities[14 24 27 36]; too large a difference, in our judgment, to combine the data with all the other published studies. Analysed separately, the Intersalt data yielded regression slopes of blood pressure on sodium intake that were slightly lower than our age specific estimates (although with wide confidence limits that included our estimates). Combining the Intersalt data with the studies listed in table I had the opposite effect, yielding higher regression slopes. It is clear that there are sources of heterogeneity between the Intersalt data and the other published data which invalidate combining them.

Figure 2 shows centiles of systolic blood pressure according to sodium intake in people aged 60-69 years. The mathematical details of their derivation are given in the appendix. The 50th centile line corresponds to the regression of mean blood pressure on sodium intake, and the other centiles are a specified number of

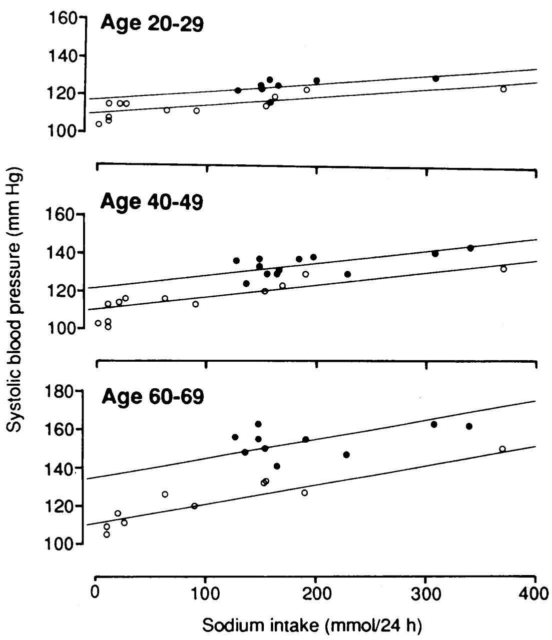

FIG 1—*Systolic blood pressure according to sodium intake for three age groups in economically developed (●) and undeveloped (○) communities*

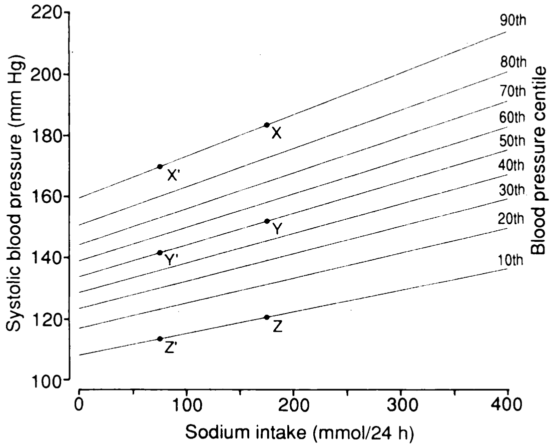

FIG 2—*Centiles of systolic blood pressure according to sodium intake for people aged 60-69 years. A person lies on a blood pressure centile line at a position determined by his or her sodium intake. The change in blood pressure after a change in sodium intake can then be predicted—for example, X to X', Y to Y', Z to Z'. (Centile lines are based on distribution of true blood pressure (that is, after eliminating variation due to within person fluctuations) but labelled according to distribution of single measurements)*

standard deviations above and below the 50th centile—for example, the 90th and 10th centile lines are 1·28 standard deviations above and below the 50th. The centile lines diverge because the standard deviation of blood pressure increases with sodium intake.

A person aged 60-69 years in an economically developed population who is on the 90th centile of the systolic blood pressure distribution with average sodium intake of 175 mmol/24 h would correspond to position X in figure 2. According to our model, with a 100 mmol/24 h reduction in sodium intake the person's systolic blood pressure would be expected to move down the 90th centile line from position X to position X' and fall by 14 mm Hg (the vertical distance between X and X'). A person on the 50th centile moves from Y to Y' and has a smaller blood pressure fall of 10 mm Hg, and a person on the 10th centile moves from Z to Z' with an even smaller reduction in blood pressure of 7 mm Hg. People with a high blood pressure thus experience a greater fall in blood pressure for a given reduction in sodium intake than people with lower blood pressures. The centile lines, as labelled, relate to single blood pressure measurements. Although the centile line to which X is assigned is the 90th based on a single blood pressure measurement, if many measurements were performed, for practical purposes abolishing within person fluctuations, the same line would correspond to a more extreme (true) centile (in our data the 96th).

Table IV summarises our estimates of the association between systolic and diastolic blood pressure and sodium intake, presenting for each of the six 10 year age groups the predicted difference in blood pressure for each 100 mmol/24 h difference in sodium intake for various centiles of the blood pressure distribution.

Discussion

We have shown that blood pressure varies according to sodium intake, the change in blood pressure for a given change in sodium intake depending on a person's age and existing blood pressure. There is no evidence of a threshold below which there is no further effect. The older people are, and the higher their blood pressure, the greater is the difference in blood pressure associated with a given difference in sodium intake. For example, at age 20-29 years the average difference in systolic blood pressure associated with a 100 mmol/24 h difference in sodium intake was 5 mm Hg (2 mm Hg at the fifth and 8 mm Hg at the 95th blood pressure centile); at 60-69 years the average blood pressure difference was 10 mm Hg (6 mm Hg at the fifth and 15 mm Hg at the 95th centile).

Our estimates of the change in blood pressure in response to changes in sodium intake are smaller than estimates from other studies that have compared geographically different populations,[37 38] but these did not consider the confounding effects of determinants of blood pressure other than sodium intake. Our separate analyses for economically developed and undeveloped communities are likely to have largely resolved this problem. Potassium intake (measured in 49 communities) and body mass index and alcohol intake (33 communities) differ on average between developed and undeveloped communities, as does sodium intake (so that confounding is introduced), but among different developed communities or among different undeveloped communities variations in these determinants of blood pressure show no correlation with variation in sodium intake.[3 12 14 17-26] Unless other unmeasured blood pressure determinants or errors in blood pressure measurements change systematically with sodium intake for each type of community our regression slopes should be unbiased estimates of the causal association between blood pressure and sodium and so permit the prediction of the expected change in blood pressure resulting from a given change in sodium intake in individuals.

The variation among individuals in the response or susceptibility of blood pressure to sodium intake found in these results is similar in nature to that shown in Dahl's experiments on rats.[39] Dahl showed that the variation in response was normally distributed and genetically determined, and human evidence also suggests this.[40] The association of blood pressure with sodium intake may be with sodium chloride (salt) intake only,[41] but this is of little public health importance as variation in sodium intake closely reflects variation in sodium chloride intake.

In this paper we have produced a quantitative model from a between population analysis for the relation between blood pressure and sodium intake, which is summarised in table IV. In the next two papers we test these estimates by using them to predict the magnitude of the association between blood pressure and sodium intake in observational studies within populations and trials of salt restriction: in each case we compare the predicted values with those that were actually found, and so test the accuracy of our model and our predictions.

Appendix

AGE SPECIFIC LINEAR REGRESSION EQUATIONS OF BLOOD PRESSURE ON SODIUM INTAKE

Mean blood pressure=a+bx where: a is the intercept or mean blood pressure (mm Hg) at zero sodium intake (table III); b is the regression coefficient or change in mean blood pressure (mm Hg) for each 100 mmol/24 h change in sodium intake (table II); x is the sodium intake (100 mmol/24 h).

Standard deviation of blood pressure = c+dx where: c is the intercept or standard deviation of blood pressure (mm Hg) at zero sodium intake (table III); d is the regression coefficient or change in standard deviation of blood pressure (mm Hg) for each 100 mmol/24 h change in sodium intake (table II).

CALCULATION OF CENTILE OF GIVEN BLOOD PRESSURE ACCORDING TO SODIUM INTAKE

For a given age group the number (z) of standard deviations from the mean for a given blood pressure (BP) is:

$$z=\frac{BP-(a+bx)}{(c+dx)}$$

z can be converted to a centile by consulting a table of the standard normal distribution.

CALCULATION OF PREDICTED CHANGE IN BLOOD PRESSURE RESULTING FROM SPECIFIED CHANGE IN SODIUM INTAKE

Assuming that with change in sodium intake a person remains on the same blood pressure centile then for a given age group the change in blood pressure, ΔBP, is:

$$\Delta BP=[(a+bx_2)+z(c+dx_2)] -[(a+bx_1)+z(c+dx_1)] =(b+zd)\ (x_2-x_1)$$

where x_1 and x_2 are respectively the original and new sodium intake (100 mmol/24 h).

EXAMPLE

What is the predicted change in systolic blood pressure after a 100 mmol/24 h reduction in sodium intake for people aged 60-69 years in an economically developed community with systolic blood pressure 183 mm Hg and sodium intake 175 mmol/24 h (position X in fig 2)?

The number of standard deviations from the mean of the blood pressure 183 mm Hg is:

$$z=\frac{183-[133\cdot9+(1\cdot75\times10\cdot3)]}{19\cdot5+(1\cdot75\times2\cdot9)}$$

$$=1\cdot3 \text{ (this corresponds to the 90th centile)}$$

The predicted change in blood pressure is then

$$(10\cdot3+1\cdot3\times2\cdot9)\ (0\cdot75\text{-}1\cdot75)$$
$$=-14 \text{ mm Hg.}$$

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II—Analysis of observational data within populations

C D Frost, M R Law, N J Wald

Department of Environmental and Preventive Medicine, St Bartholomew's Hospital Medical College, London EC1M 6BQ
C D Frost, DIPSTAT, *lecturer*
M R Law, MRCP, *senior lecturer*
N J Wald, FRCP, *professor*

Correspondence to: Dr Law.

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Abstract

***Objective*—To determine whether the estimates of the size of the association between blood pressure and sodium intake derived from studies of individuals within populations can be quantitatively reconciled with our estimates derived from comparisons of the average blood pressure and sodium intake between different populations.**

***Design*—Examination of data from 14 published studies that correlated blood pressure recordings in individuals against measurements of their 24 hour sodium intake (within population studies).**

***Main outcome measure*—Comparison of observed differences in blood pressure per 100 mmol/24 h difference in sodium intake in each within population study with predicted differences calculated from the between population data, after allowing for the underestimation of the true association of blood pressure with sodium intake caused by the large day to day variation in 24 hour sodium intake within individuals.**

***Results*—The underestimation bias inherent in the within population studies reduced the regression slope of blood pressure on single measures of 24 hour sodium intake to between a half and a quarter of the true value (for example, in one study from 6·0 to 2·4 mm Hg/100 mmol/24 h). Estimates from between population comparisons of the regression slope of blood pressure on sodium intake, after adjustment to take this underestimation bias into account, were similar to the values actually observed in the within population studies.**

***Conclusion*—The within population studies confirm our estimates from between population comparisons of the magnitude of the association between blood pressure and sodium intake.**

Introduction

Studies correlating individuals' blood pressure and sodium intake (so called within population studies) have generally failed to confirm the association between blood pressure and sodium intake that can readily be shown by studies correlating the average blood pressure and sodium intake of different populations (between population studies). In our previous paper (p 811)[1] we showed that between population comparisons exaggerate the association if allowance is not made for the effect of confounding (factors associated with both blood pressure and sodium intake). But, as we discuss below, within population studies underestimate the true association.[2] In this paper we examine whether this underestimation bias explains the difference between the results of within population and between population studies.

Methods

UNDERESTIMATION BIAS IN WITHIN POPULATION STUDIES

In studies of individuals in a defined population estimates of the association between blood pressure and sodium intake are subject to a systematic underestimation (sometimes called regression dilution bias). This arises from the random error involved in taking a single measurement of 24 hour sodium intake on a person as adequately representing the average daily sodium intake of that person.[2] Sodium intake (as estimated by 24 hour urinary sodium excretion) can vary substantially from day to day. In a group of American men Liu *et al* estimated the typical within person standard deviation of 24 hour sodium intake (a measure of the average random deviation from an individual's long term mean 24 hour sodium intake occurring in one particular 24 hour period) to be 58 mmol/24 h, about one third of the mean.[2] The between person standard deviation was only 32 mmol/24 h. A second American study obtained similar estimates.[3] Figure 1 shows the day to day variation in sodium intake for a typical man and the relatively narrow variation in long term average sodium intake among individuals, as reflected by the 10th to 90th centile ranges.

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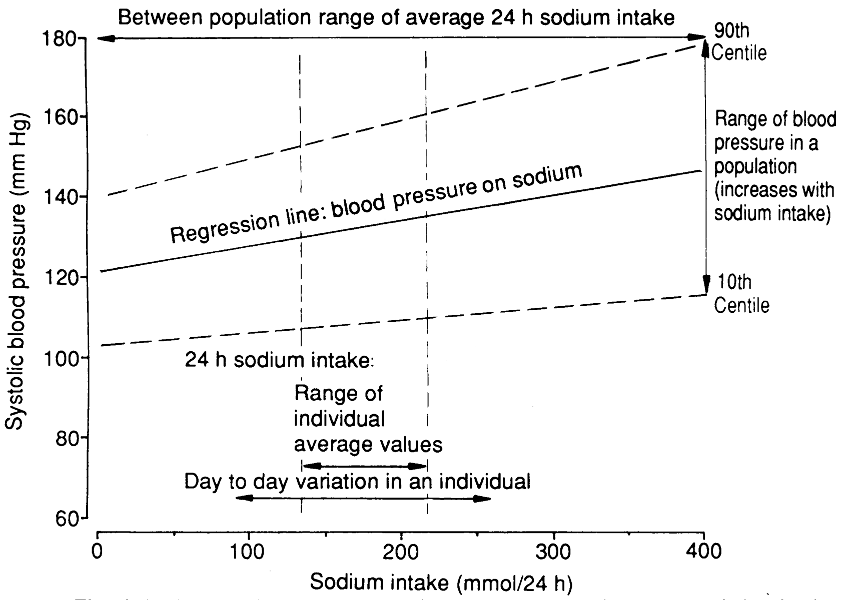

FIG 1—*The relation between blood pressure and sodium intake in a typical Western population showing between person variation in average sodium intake within person day to day variation in sodium intake and variation in blood pressure at any given sodium intake (ranges are 10th to 90th centile)*