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II—Analysis of observational data within populations

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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.

Blood pressure is likely to respond not to day to day

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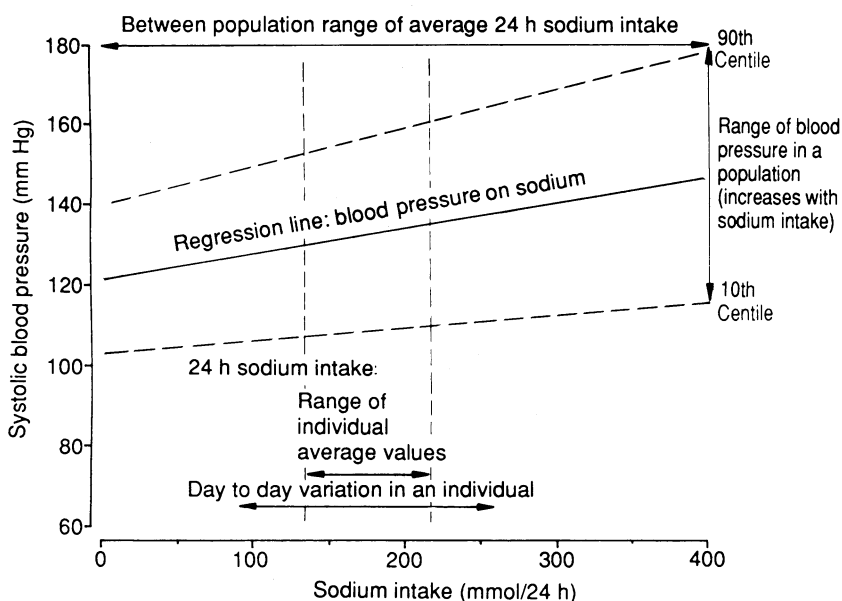


FIG 1—The relation between blood pressure and sodium intake in a typical Western population showing between person variation in average sodium intake within person day to day variation in sodium intake and variation in blood pressure at any given sodium intake (ranges are 10th to 90th centile)

fluctuations in sodium intake but to the average sodium intake over a period (a view reinforced by the results of our analysis of the trials of dietary salt reduction (p 819),⁴ which show that the full response of blood pressure to salt reduction is seen only after a few weeks). Figure 2 shows hypothetical but typical data illustrating how using a single measurement of individual sodium intake (rather than the average of several measures) will greatly underestimate the association of blood pressure with sodium intake. Average blood pressure is plotted against sodium intake (the variation among individuals in average blood pressure at any given sodium intake is ignored for simplicity). In figure 2 (top) blood pressure is plotted against each person's average sodium intake, and the slope of the regression line corresponds to that of the between population regression line in figure 1. Figure 2 (middle) shows the effect of measuring the sodium intake of each individual only once based on the American estimates of within person standard deviation.^{2,3} The slope of the regression line with single sodium measurements (fig 2 (bottom)) is reduced to about one quarter of the true value. Also, the shallow observed regression line is less likely to be significant and thus within population studies are more likely to miss any effect.

Within population regression slopes (blood pressure differences per 100 mmol/24 h difference in sodium

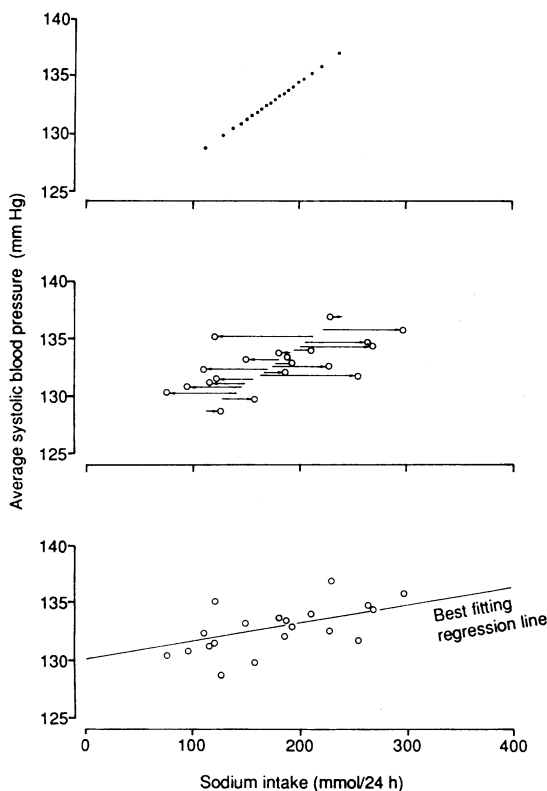


FIG 2—Effect of random error on within population studies: (top) blood pressure plotted against average 24 hour sodium intake for 20 people; (middle) typical deviation from average values when single measurements of 24 hour sodium intake are taken; (bottom) shallow regression slope obtained with single measurements of 24 hour sodium intake

TABLE 1—Estimates of within person and between person standard deviations of 24 hour sodium intake (mmol)

	No of subjects	Within person (w)	Between person (b)	Total (t) ($\sqrt{w^2+b^2}$)	Ratio of between person variance to total variance (b^2/t^2)
Northern United States weighted average (Liu <i>et al</i> , ² Luft <i>et al</i> ³)	151 (142, 9)	58 (58, 61)	33 (32, 38)	67 (66, 72)	0.24 (0.23, 0.28)
Belgium (Joossens <i>et al</i> ⁵) (men, women)	133, 167	54, 43	45, 44	70, 62	0.40, 0.50
Beijing, China (Lisheng <i>et al</i> ⁶)	50	77	63	99	0.40
Naples, Italy (Siani <i>et al</i> ⁷)	22	43	41	59	0.47
London, United Kingdom (Elliott <i>et al</i> ⁸)*	11	30	74	80	0.86

*Study in retired community.

intake) can be shown algebraically to be shallower than the true regression slope by the ratio of the between person variance to the total variance (between person plus within person) of 24 hour sodium intake.⁵ The estimate of Liu *et al* for an American population therefore suggests that the within population regression slope would be 23% of the true value ($32^2/(32^2+58^2)$).² Table I lists estimates of between person and total standard deviations in sodium intake (obtained from multiple non-consecutive 24 hour urinary collections) from the two American studies and from studies in four other communities. These estimates suggest that in different communities the within population regression slope would generally be between 23% and 50% of the true value. The underestimation was less for the London community; within person variance in sodium intake was smaller, perhaps because this study recruited mostly retired people who ate away from home infrequently and so had less variation in their diet,⁹ whereas the other studies recruited working people.

STUDIES INCLUDED

We included 14 within population studies in the analysis (see table II). As a criterion of reliability of estimation of 24 hour sodium intake we included only studies that collected 24 hour urine samples and excluded those that estimated sodium intake from a random (spot) or overnight urine collection or by dietary recall. We excluded studies of black populations because of likely differences in the association of blood pressure with sodium intake, as discussed in our first paper.¹

STATISTICAL ANALYSIS

To determine whether the results of the within population studies were consistent with our between population analysis we first calculated a predicted value for the regression slope (the difference in blood pressure per 100 mmol/24 h difference in sodium intake) in each within population study. We did this by taking the between population regression slope (from table II in our first paper¹) appropriate to the mean age of the subjects in the study as the "true" value and multiplying this value by the ratio of between person to total variance of 24 hour urinary sodium concentration. For 10 of the within population studies this ratio could be estimated from a study conducted in the same locality, and for the other four studies we used the most appropriate of the available estimates of the ratio from table I. We then compared the predicted attenuated regression slope with that actually observed in each within population study. Observed regression slopes of blood pressure on sodium intake, if not published,^{10 12 13 15 16} were calculated from published correlation coefficients (r) and standard deviations (SD) of blood pressure (BP) and sodium intake (Na) as regression slope of BP on Na= $r \times SD(BP)/SD(Na)$. The differences between observed and predicted regression slopes for individual studies were summed, weighting each study inversely by the square of the standard error of its observed regression slope, to give an overall average difference with standard error for all studies.

Results

The observed regression slopes of differences in (systolic blood pressure per 100 mmol/24 h difference in sodium intake) were significant ($p < 0.05$) in only six of the 14 within population studies (table II), but collectively they were highly significant ($p < 0.001$), establishing that when considered together the within population studies confirm an association of blood pressure with sodium intake.

The observed regression slopes were similar to the predicted values for each study obtained from the age specific between population analysis (table II). Collectively, the differences between the observed and predicted slopes were not significantly heterogeneous, and the summed difference of -0.1 (SE 0.2) mm Hg/100 mmol/24 h was not significantly different from zero. The results for diastolic blood pressure were similar; the observed regression slopes were collectively highly significant ($p < 0.001$), and the summed difference of 0.04 (0.1) mm Hg/100 mmol/24 h between the observed and predicted slopes was not significantly different from zero. Therefore, within the bounds of random error, the individual within population studies were consistent with the results of our between population analysis.¹

The Intersalt study gave inconsistent results.¹¹ Duplicated measurements of 24 hour urinary sodium excretion in 8% of the subjects from each centre produced an estimate of 0.46 for the ratio of between person to total variance in 24 hour sodium intake.¹¹ The age specific between population regression slope multiplied by this estimate gave a predicted within population slope of systolic blood pressure regressed on sodium intake of 2.8 (6.0 × 0.46) mm Hg/100 mmol/24 h, which is significantly greater than the overall average observed slope of 1.7 (SE 0.2) mm Hg/100 mmol/24 h. The coordinators of the Intersalt study considered that 0.46 was an overestimate of the ratio,¹⁸ probably because the within person variance of sodium intake was underestimated. As a result the between population estimate was not attenuated enough. As shown in table II the observed regression slopes for certain communities in the Intersalt study were similar to predicted values based on other estimates of the ratio of between person to total variance in 24 hour sodium intake carried out in those communities. If, as an approximation, the average value 0.34 for the ratio of between person to total variance in 24 hour sodium

intake from the American and Belgian studies listed in table I is applied to the entire Intersalt study the resulting predicted regression slope is 2.0 (6.0 × 0.34) mm Hg/100 mmol/24 h—similar to the mean observed value of 1.7.

Discussion

The within population studies collectively showed a highly significant association between blood pressure and sodium intake ($p < 0.001$). Random error in the measurement of a person's average sodium intake reduced the slopes of the regression lines, but when allowance was made for this underestimation bias, the results of the within population studies were consistent with the results of our between population analysis. There is, therefore, no unexplained discrepancy between the estimates of the association of blood pressure with sodium intake from within population and between population studies.

The low values for the correlation coefficient (r) between blood pressure and sodium intake that have generally been observed in within population studies are also to be expected and should not be misinterpreted as evidence against an association. The wide range of blood pressure at any given true sodium intake (fig 1) and the random error in measuring sodium intake both reduce the correlation coefficient, as can be seen from a derivation of the equation given in the section on statistical analysis:

$$r = \text{regression slope} \times \text{SD}(\text{Na}) / \text{SD}(\text{BP}).$$

For a typical American population aged 20-59 the predicted regression slope is 1.4 mm Hg/100 mmol/24 h (table II), the estimated standard deviation for sodium intake is 67 mmol/24 h (table I) and standard deviation for blood pressure is about 18 mm Hg (calculated from the regression equations in our first paper,¹ taking the mean sodium intake as 175 mmol/24 h). Therefore $r = 1.4/100 \times 67/18 = 0.05$.

Published within population studies of blood pressure and sodium intake have typically reported correlation coefficients of this order. Because of this low correlation coefficient the statistical power of within population studies is low, and large numbers are needed to show the associations. A study of 200 subjects, for example, would be unlikely to give a significant result (12% probability), and even with

TABLE II—Comparison of observed differences in systolic blood pressure for a 100 mmol/24h difference in sodium intake in within population studies with values predicted from between population analysis¹ and adjusted for the underestimation bias in measuring 24 hour urinary sodium excretion only once. Values are mm Hg/100 mmol sodium 24 h

Study	No of subjects	Between population value*	Predicted within population value (adjusted for error in measuring sodium intake, from table I)	Observed within population value	Difference: observed—predicted value (SE)
Northern United States (Connor <i>et al</i>) ¹⁰	352	5.5	5.5 × 0.24 = 1.3	1.7	0.4 (1.1)
Northern United States (Intersalt (Chicago, Goodman and Jackson ¹¹))	593	6.0	6.0 × 0.24 = 1.4	1.4	0 (0.9)
Belgium (Staessen <i>et al</i>) ¹² :					
Adults	528	6.0	6.0 × 0.45 = 2.7	1.4	-1.3 (1.0)
Teenagers	160	5.0	5.0 × 0.45 = 2.3	2.7	0.4 (1.8)
Belgium (Intersalt (Charleroi, Ghent) ¹¹)	357	6.0	6.0 × 0.40 = 2.4	1.9	-0.5 (1.4)
Beijing and environs (Kesteloot <i>et al</i>) ¹³	1 003	6.0	6.0 × 0.40 = 2.4	3.8†	1.4 (0.6)
Beijing and environs (Intersalt (Beijing, Tianjin) ¹¹)	400	6.0	6.0 × 0.40 = 2.4	3.2†	0.8 (1.1)
Naples (Strazzullo <i>et al</i>) ¹⁴	188	6.0	6.0 × 0.47 = 2.8	4.0	1.2 (2.1)
Naples (Intersalt ¹¹)	200	6.0	6.0 × 0.47 = 2.8	1.5	-1.3 (1.9)
London (retired community) (Elliott <i>et al</i>) ¹⁵	58	9.2	9.2 × 0.86 = 7.9	9.1†	1.2 (3.6)
Other communities‡:					
Scotland (Smith <i>et al</i>) ¹⁶	7 354	7.9	7.9 × 0.24 = 1.9	1.3†	-0.6 (0.3)
London civil servants (Bulpitt <i>et al</i>) ¹⁷	618	6.6	6.6 × 0.24 = 1.6	0.8	-0.8 (1.2)
South China (Kesteloot <i>et al</i>) ¹³	504	6.0	6.0 × 0.40 = 2.4	2.8†	0.4 (0.8)
Korea (Kesteloot <i>et al</i>) ¹³	458	6.0	6.0 × 0.67 = 4.0§	4.1†	0.1 (0.6)
All studies	12 773				-0.1 (0.2)

*From table II in our first paper,¹ for the age group that includes the mean age of the subjects in the study. (The value of 6.0, for subjects with mean age 40 years, is the average value of the two age groups 30-39 and 40-49.)

†Statistically significant value in individual study ($p < 0.05$).

‡No direct measure of between person variance in sodium intake has been reported for these four communities: the most appropriate of the available estimates (table I) was used.

§In this study each person provided three 24 hour urine collections; $0.67 = (63 / (63 + 77 / 3))$.

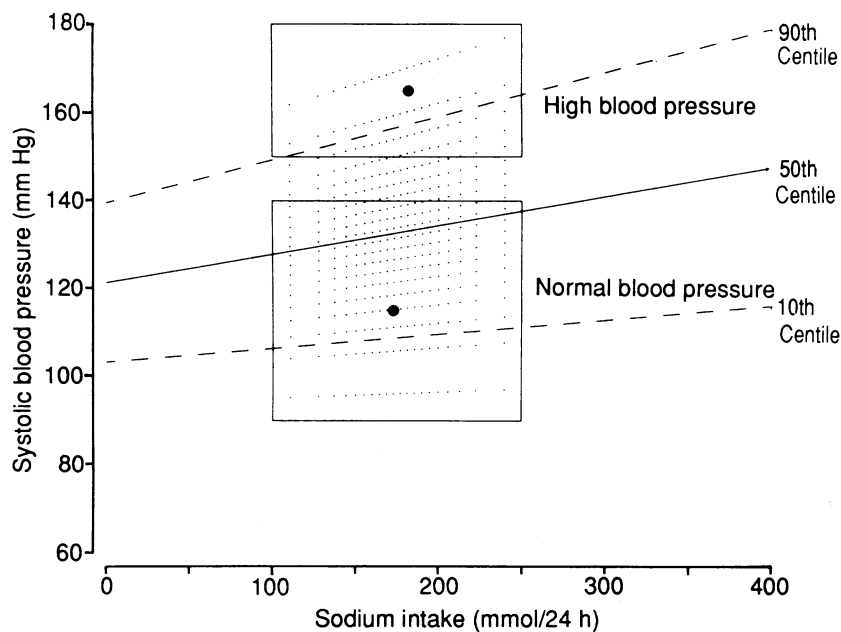


FIG 3—Simulation of study comparing the 24 hour sodium intake in people with high blood pressure and people with normal blood pressure. The solid circles show the mean 24 hour sodium intake for each group

2000 subjects the probability is only 68%. It is therefore not surprising that only six of the 14 individual within population studies (median size 500 subjects) and only seven out of 52 Intersalt centres (each with 200 subjects)¹¹ recorded a significant positive result.¹¹

Some published within population studies have been designed differently but have also misleadingly suggested little or no association between blood pressure and sodium intake. These studies have identified people with high blood pressure (usually on a single reading) and compared their 24 hour sodium excretion (single measurement) with that of controls with "normal" blood pressure. Such studies have usually found little or no difference.¹⁹ Figure 3 shows a simulation of such a study. From the Western population in figure 1 we plotted typical values of blood pressure and 24 hour sodium intake for 400 people. From these 400 people, those with high and normal blood pressure (systolic pressure >150 and <140 mm Hg respectively) were selected. The average sodium intake in subjects with normal blood pressure was 173 mmol/24 h and that in subjects with high blood pressure was 182 mmol/24 h; the mean difference in sodium intake between the two groups was only 9 mmol/24 h. The difference is small because the between person range of 24 hour sodium intake across Western populations is narrow, whereas the range of blood pressure values at any given sodium intake is wide (reflecting mainly genetic differences). In selecting people with high and normal blood pressure within a population, we are predominantly selecting for genetic differences among people with similar average sodium intake.

For a 50% probability of showing the small difference in sodium intake to be significant a study of this design would need to recruit 400 subjects with high blood pressure and 400 with normal blood pressure, and for an 80% probability 800 of each. Studies conducted to date have been much smaller than this,¹⁹ and it is therefore not surprising that their results have mostly been negative.

The two types of within population study, those yielding regressions of blood pressure on sodium

intake in a defined group of people and those estimating the average difference in sodium intake in people with high and normal blood pressure, are both consistent with the estimates of the association of blood pressure with sodium intake derived from our between population analysis. There is no discrepancy between the estimates of the association between blood pressure and sodium intake from within population and between population data.

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Corrections

Clinical trials of homoeopathy

An editorial error occurred in the second paragraph of the introduction of this paper by Dr Jos Kleijnen and others (9 February, p 316). Hahnemann's *similia* concept is "*similia similibus curentur*," which is a recommendation, not "*similia similibus curantur*" as published, which is an order.

Case-control study of leukaemia and non-Hodgkin's lymphoma in children in Caithness near the Dounreay nuclear installation

There was an authors' error in this paper by Mr James D Urquhart and others (23 March, p 687). In the last line of table IV (father's radiation dose six months before conception ≥ 10 v < 10 mSv, resident anywhere in Caithness at diagnosis) of a total of 45 controls, one was positive. This gives a Fisher's exact p value of 0.38. The conclusions remain unchanged.