Session I: Epidemiological Overview

Observational Studies of Salt and Blood Pressure

Paul Elliott

The observational data relating salt and blood pressure (excluding INTERSALT) are reviewed. Important methodological difficulties and biases are inherent to both across- and within-population studies and confuse their interpretation. Across-population studies are positive but rely on data drawn from the international literature based on a variety of unstandardized field methods; they are prone to unmeasured (ecological) confounding. Within-population studies generally lack statistical power and are subject to major regression-dilution bias (because of considerable day-to-day variation in sodium intake), which could conceal true correlations between sodium and blood pressure. Nevertheless, an overview of reported studies that used 24-hour urine excretion to quantify intake shows positive and highly significant correlations between sodium and blood pressure for both men and women and for systolic and diastolic blood pressures. These results are consistent with the INTERSALT findings and those from trials of sodium restriction. (Hypertension 1991;17[suppl I]:I-3-I-8)

Evidence relating salt and blood pressure (BP) comes from a variety of sources: animal and clinical studies, trials of sodium restriction and supplementation, and epidemiological studies, both across and within populations. In reviewing the observational evidence, my objectives were, first, to discuss some of the complex methodological issues that have confused much of the research in this area, and second, to briefly summarize the contribution of this large body of work to our understanding of the epidemiology of salt and BP. I have excluded consideration of the INTERSALT findings, which are discussed elsewhere in this issue.1-2

Across-Population Studies

A positive across-population association between salt and BP was first described by Dahl in 1960,3 who found, over five population groups, a remarkable straight-line relation between the average sodium intake of a population and the prevalence of hypertension. Dahl also noted that hypertension was uncommon in populations whose members consumed less than 4 or 5 g salt/day (i.e., about 70-80 mmol sodium) and hypothesized that salt intake increased the probability of elevated BP in a group although not necessarily in an individual.

Publication of Dahl's straight-line graph stimulated others to review the international literature for data on mean sodium intake and mean BP of populations.4-8 These studies generally confirmed the Dahl correlation but to a greater or lesser extent suffered from a number of uncertainties and biases. One major concern is that the data were not derived from one standardized source but from a variety of studies in the published literature, in which unstandardized and often unspecified methods were used. Frequently, data on sodium intake and BP for a particular population were derived from different sources, and even the author's own estimates of sodium intake were used (in the well-known paper by Gleibermann in 19734). Systematic error of measurement in a population (e.g., of BP) is another perennial source of bias in across-population (ecological) comparisons. Additionally, few data on confounding variables were available. Because of multiple social, geographic, and environmental differences among populations around the world, which may also relate to differences in BP, correlations in ecological studies are particularly susceptible to major, unmeasured confounding. Under these circumstances, there is the danger of committing an ecological fallacy9 if inappropriate inferences concerning correlations among individuals are made from those among groups.

One of the most comprehensive across-population studies of sodium and BP was published by Froment et al in 19799 and used literature-derived data from 28 populations around the world. The data were presented separately by sex and at approximate ages of 20 and 50 years; values of sodium intake were

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FIGURE 1. Scatterplot showing across-population association between mean systolic blood pressure and mean 24-hour sodium excretion for 28 populations (continuous line) and 19 populations (interrupted line) in men aged 50 years (adapted from data provided by Froment et al). Continuous line, $b=9.97$ mmHg/100 mmol sodium ($p<0.001$) (SE, 1.99); interrupted line, $b=5.30$ mmHg/100 mmol sodium (SE, 2.96).

FIGURE 2. Scatterplot showing across-population association between systolic blood pressure (SBP) slope with age and mean 24-hour sodium excretion for 28 populations (continuous line) and 19 populations (interrupted line) in men (adapted from data provided by Froment et al). Continuous line, $b=0.26$ mmHg/yr/100 mmol sodium ($p<0.001$) (SE, 0.05); interrupted line, $b=0.15$ mmHg/yr/100 mmol sodium (SE, 0.08).

derived mostly from 24-hour urine collections although not necessarily from the same studies as the BP data. An example is shown in Figure 1; this gives the correlation between mean systolic blood pressure (SBP) and mean sodium intake for 50-year-old men. The continuous line shows the regression across all 28 populations and is significantly positive, with a slope of 10 mmHg/100 mmol sodium. However, as discussed elsewhere, the regression analyses are strongly influenced by the nine populations with low average sodium intakes (less than 2 g salt/day). These isolated populations probably had the least adequate data for both sodium intake and BP and likewise probably differed from the remainder in many ways other than sodium intake. When the nine populations are excluded from the analysis, as shown by the interrupted line, the regression slope correlating sodium and BP is reduced and is no longer significant. (This may reflect to some extent the smaller number of populations and the more limited range of sodium intakes in the latter analysis.)

Figure 2, again derived from Froment et al, shows the relation in men between mean sodium intake and population SBP slope with age (estimated from data at approximate ages of 20 and 50 years). The correlation across all 28 populations is positive and significant, as shown by the continuous line. The regression slope indicates an SBP lower by 7.7 mmHg over a 30-year period for sodium intake lower by 100 mmol. As can be seen, seven of the nine low salt populations (and two others) recorded lower mean BPs with increasing age. When the nine low salt populations are excluded, the size of the regression coefficient relating sodium and BP slope with age is reduced, as shown by the interrupted line.

To summarize, across-population (ecological) studies of sodium and BP generally support Dahl's salt hypothesis, but they rely on a variety of unstandardized field methods and are subject to varying degrees of bias and confounding. Regression analyses across populations appear to be particularly influenced by a number of remote and isolated populations with low sodium intakes and low BPs.

Within-Population Studies

A different set of problems befall studies of salt and BP within populations. As elucidated by Watt and Foy in 1982, as many as 5,700 participants, each collecting a single 24-hour urine specimen, may be required to significantly demonstrate a true regression slope between SBP and sodium of 10 mmHg/100 mmol sodium (the value of the across-population slope observed by both Gleibermann and Froment et al), resulting in deficient statistical power in all but the largest studies. This is because (at least in most Western populations) true differences in sodium intake and urinary excretion between persons are swamped by the large day-to-day variation within persons, so that individuals are grossly misclassified with respect to their true (habitual) sodium intake. The result is a major bias toward a zero regression-correlation ("regression-dilution") between sodium and BP.

This problem of measurement should be contrasted to the situation with other variables, such as body weight and serum cholesterol, where within-person variability is relatively small compared with between-person variability; individuals can be appropriately classified into groups (e.g., based on high and low values) using a single (casual) measure. Disease associations (e.g., between serum cholesterol and coronary heart disease) are thus more readily demonstrated for these variables than is the case for sodium and BP.

In addition to regression dilution, another major potential source of bias in within-population studies of sodium and BP is the difficulty in obtaining...
TABLE 1. Age-, Sex-, and Body Mass Index-Adjusted Regression Coefficients Relating Blood Pressure and Sodium Excretion in a North London Population, With Consideration of the Effects of Within-Person Variability of Sodium Excretion and Incompleteness of Urine Collections

<table>
<thead>
<tr>
<th>Sample</th>
<th>Regression coefficients (SE) (mm Hg/100 mmol sodium)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All persons (n=58)</td>
<td>9.1* (3.7) 2.5 (2.0)</td>
</tr>
<tr>
<td>All persons, corrected for reliability (point estimate)</td>
<td>10.6 2.9</td>
</tr>
<tr>
<td>Complete collectors by PABA excretion (n=28)</td>
<td>14.5* (5.9) 5.9 (3.0)</td>
</tr>
</tbody>
</table>

Data used is from Reference 16. Correction for reliability is based on repeated measures. BP, blood pressure; PABA, para-aminobenzoic acid.

*p<0.05.

complete 24-hour urine specimens in general population samples. The effect of these two biases in deriving quantitative estimates of the sodium-BP relation is illustrated by the results of a small methodological study conducted in a random sample from a general practice in North London. In this middle-aged and elderly population with a broad spread of sodium intakes, the day-to-day variation in individual sodium excretion was small compared with other studies. Analysis of repeated urine collections in a subsample indicated that day-to-day, within-individual variation in sodium intake biased regression slopes by only 14% (based on a single 24-hour urine collection) compared with a downward bias of over 75% in some other studies. Under these circumstances, whereby individual sodium excretion was apparently well characterized by a single 24-hour urine collection, the within-population regression estimates relating sodium with SBP were similar to the aforementioned across-population estimates of Gleibermann and Froment et al, and the results were statistically significant even though the sample size was relatively small.

The results are summarized in Table 1. The regression slope relating sodium with SBP was 9.1 mm Hg/100 mmol sodium after adjustment for age, sex, and body mass index; with correction for reliability, which statistically adjusts for the regression-dilution bias introduced by physiological within-person variability in sodium excretion, the SBP-sodium regression slope was 10.6 mm Hg/100 mmol sodium. However, because of the incompleteness of urine collections, it is probable that this reliability-corrected estimate was still too low. Although all 58 participants reported complete collections, only 28 of the collections were found to be complete by excretion of para-aminobenzoic acid (PABA), a biological marker orally ingested (as capsules) during the day of the urine collection. Among the 28 people with complete urine collections, the regression estimate of the SBP-sodium relation, after adjustment for confounding variables, was 14.5 mm Hg/100 mmol sodium. A similar progression in the size of regression slopes was found for sodium and diastolic BP (DBP) (Table 1).

Further methodological problems of within-population studies include statistical overadjustment of the BP-sodium relation for covariates (such as body weight) that are much more precisely measured than sodium (giving estimates of the sodium effect that are biased down toward zero in multiple regression analyses) and other biases caused by the effects of antihypertensive drug treatment on BP and by hypertensive persons selectively reducing their sodium intakes as a consequence of the diagnosis of high BP.

Within-population studies of salt and BP have used a variety of dietary methods to estimate sodium intake, from a salt frequency questionnaire to multiple 24-hour urine collections. Early reports by Dahl and Love that the frequency of adding salt to food at table was related to prevalence of high BP were supported by the findings of one study but could not be confirmed by others. Recent data from the United Kingdom suggest that the proportion of non-discretionary sodium in the diet of Western industrialized populations is as high as 85% of intake, so that, given the variation in sodium content of many processed foods, methods using diet history are unlikely to yield reliable estimates of the sodium intake of individuals. Nevertheless, significantly positive correlations of dietary sodium with BP have been described in studies from Belgium, Northern Kashmir, and Southern California and significantly negative correlations in one study from the Netherlands. In analyses of the National Health and Nutrition Examination Survey (NHANES) study, in which the same data set was used but with different analytical methods, both positive and negative correlations of sodium with BP have been described.

Most studies have measured the urinary excretion of sodium as a proxy for intake. Although the use of casual (spot) urine samples has been criticized, six of eight population studies that used this method, which were identified in the literature, reported significantly positive sodium-BP correlations. Similarly, with the use of overnight rather than spot urine collections to characterize sodium intake, six of seven population studies (including four with Chinese populations) reported significantly positive correlations with BP. No significantly negative associations were reported, perhaps reflecting a degree of publication bias toward positive results.

Studies of 24-Hour Urinary Sodium Excretion and Blood Pressure: Overview Analysis

Most within-population studies have used 24-hour urine collections to estimate sodium intake. Both positive and negative correlations with BP have been described, although many studies have been too small to show significant associations. The literature was scanned to identify those studies of 24-hour urinary sodium and BP that could be incorporated into an overview analysis. The aim was to include all studies that published a quantitative
### Table 2. Overview of Studies of 24-Hour Urinary Sodium Excretion and Blood Pressure: Summary of Abstracted Data

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>n</th>
<th>Mean age</th>
<th>Regression coefficients (mm Hg/100 mmol sodium)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Systolic BP</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b(SE)</td>
</tr>
<tr>
<td>1. Joossens et al, 1971⁵¹</td>
<td>M</td>
<td>1,314</td>
<td>44.7</td>
<td>3.35* (0.91)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>713</td>
<td>46.6</td>
<td>4.88† (1.82)</td>
</tr>
<tr>
<td>2. Sinnett et al, 1973³²</td>
<td>M</td>
<td>138</td>
<td>30-39†</td>
<td>-10.24 (10.29)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>135</td>
<td>30-39†</td>
<td>-3.45 (7.47)</td>
</tr>
<tr>
<td>3. Karvonen et al, 1977⁵³</td>
<td>West Finns</td>
<td>M</td>
<td>98</td>
<td>63.7</td>
</tr>
<tr>
<td></td>
<td>East Finns</td>
<td>M</td>
<td>94</td>
<td>62.9</td>
</tr>
<tr>
<td>4. Watson et al, 1980⁵⁴</td>
<td>Blacks</td>
<td>F</td>
<td>356</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Whites</td>
<td>F</td>
<td>104</td>
<td>6</td>
</tr>
<tr>
<td>5. Prior et al, 1980⁵⁵</td>
<td>M</td>
<td>234</td>
<td>35-44‡</td>
<td>3.06 (3.85)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>261</td>
<td>35-44‡</td>
<td>2.25 (6.07)</td>
</tr>
<tr>
<td>6. Staessen et al, 1981⁵⁶</td>
<td>M</td>
<td>233</td>
<td>41.0</td>
<td>-0.95 (1.25)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>202</td>
<td>40.4</td>
<td>2.01 (2.03)</td>
</tr>
<tr>
<td>7. Staessen et al, 1983⁵⁷</td>
<td>M</td>
<td>273</td>
<td>41.6</td>
<td>-0.59 (1.19)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>255</td>
<td>39.3</td>
<td>2.07 (1.85)</td>
</tr>
<tr>
<td>8. Strazzullo et al, 1983⁵⁸</td>
<td>M</td>
<td>188</td>
<td>40.6</td>
<td>3.99 (2.07)</td>
</tr>
<tr>
<td>9. Connor et al, 1984⁵⁹</td>
<td>M</td>
<td>170</td>
<td>36</td>
<td>1.79 (1.14)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>182</td>
<td>36</td>
<td>3.77 (1.99)</td>
</tr>
<tr>
<td>10. M’Buyamba-Kabangui et al, 1986⁶⁰</td>
<td>M</td>
<td>144</td>
<td>32</td>
<td>1.85 (3.88)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>169</td>
<td>32</td>
<td>5.27 (3.11)</td>
</tr>
<tr>
<td>11. Bulpitt et al, 1986⁶¹</td>
<td>M</td>
<td>459</td>
<td>45</td>
<td>0.29 (1.37)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>159</td>
<td>46</td>
<td>2.77 (2.76)</td>
</tr>
<tr>
<td>12. Smith et al, 1988⁶²</td>
<td>M</td>
<td>3,754</td>
<td>40-59‡</td>
<td>0.61 (0.40)</td>
</tr>
<tr>
<td></td>
<td>F</td>
<td>3,600</td>
<td>40-59‡</td>
<td>1.94† (0.59)</td>
</tr>
<tr>
<td>13. Pietinen et al, 1979⁶³</td>
<td>M and F</td>
<td>50</td>
<td>26.4</td>
<td>7.01† (2.06)</td>
</tr>
<tr>
<td>14. Elliott et al, 1988⁶⁴</td>
<td>M and F</td>
<td>58</td>
<td>57.9</td>
<td>9.50 (3.60)</td>
</tr>
</tbody>
</table>

BP, blood pressure; M, male; F, female.

*<p>0.0001.
†<p>0.01.
‡Age group, including median age.
§Young persons (originally screened at high school).
ί<p>0.05.
†Range.

Regression or correlation estimate, either positive or negative, of the relation of sodium to both SBP and DBP in populations. Excluded were studies that compared hypertensive with normotensive persons (e.g., studies in Scotland, Finland, and Australia) or that reported only significant findings (e.g., studies in China, Korea, and Sweden). Because nearly all of these significant findings were positive, inclusion of the latter studies could have introduced a bias toward a positive relation if significantly negative findings were being underreported. Additionally, selective inclusion of significant results (either positive or negative) would tend to enter more extreme values into the overview analysis.

Fourteen studies (of 16 populations) fulfilled the entry criteria and are listed in Table 2, together with their sample sizes, regression coefficients, and standard errors. From each population, the regression estimates were either directly obtained or algebraically derived from the Pearson $r$ correlation coefficient and the standard deviations of both sodium and BP. Data were available only for simple (unadjusted) regression; where data (e.g., standard deviations) were given stratified by some other variable (e.g., age), the appropriate unbiased (whole-sample) estimate was obtained by analysis of variance. Where possible, regression coefficients were separately obtained for men and women in each population and then averaged to yield an overall estimate of association. Two studies reported only data for men and women combined. Regression slopes were pooled by weighting with the inverse of the variance; total sample sizes for the three analyses were 7,099 men, 6,136 women, and 12,503 men and women combined.
The results are shown in Table 3, after correction for reliability using the INTERSALT estimate of 0.46. Statistical analysis reveals significant positive correlations between sodium and blood pressure. Across-population studies generally show positive results; however, within-population studies often lack statistical power. The analysis uses 24-hour urinary sodium excretion to quantify intake and has demonstrated positive and highly significant correlations between sodium and blood pressure.

In conclusion, important methodological problems and biases are inherent to both across- and within-population studies of sodium and BP. Across-population studies are generally positive but rely on standardized data and are prone to major ecological confounding. The within-population studies generally lack statistical power, but for the first time a pooling analysis that uses 24-hour urinary sodium excretion to quantify intake has demonstrated positive and highly significant correlations between sodium and BP. These results are consistent with the INTERSALT findings and those from trials of sodium restriction.

**Acknowledgment**

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