Findings of the International Cooperative INTERSALT Study

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for the INTERSALT Cooperative Research Group

INTERSALT, an international cooperative study on electrolytes and other factors related to blood pressure, found, in within-population analyses involving 10,079 persons, a significant positive association between 24-hour urinary sodium excretion and systolic blood pressure and between the sodium/potassium ratio and systolic blood pressure. These significant findings were derived from analyses for individuals from all 52 centers and from the 48 centers remaining when persons from four low sodium centers were excluded. Potassium excretion of individuals was significantly and independently related inversely to their systolic blood pressure. For men and women, both separate and combined, the relation between sodium and systolic blood pressure was stronger for older than younger adults, perhaps reflecting the result of longer exposure with age or diminished capacity to handle a sodium load. Relations between electrolyte excretion and diastolic blood pressure in individuals were weaker than for systolic blood pressure. Body mass index and heavy alcohol consumption of individuals were strongly and independently related to blood pressure. In cross-population analyses with n=52 or n=48, sample median sodium excretion was significantly and independently related to the slope of systolic blood pressure and diastolic blood pressure with age. Other ecological analyses yielded inconsistent results. Four isolated populations showed low sodium excretion, low sodium/potassium excretion, low body mass index, and low alcohol consumption; sample median blood pressures were low, there was little or no upward slope of blood pressure with age, and high blood pressure was rare or nonexistent. (Hypertension 1991;17[suppl I]:I-9—I-15)

INTERSALT is an international, cooperative, cross-sectional, epidemiological study focusing on the relation of sodium and potassium intake to blood pressure. It was deliberately designed to explore these relations both within populations, that is, with individuals as the units of measurement and analysis, and across populations, in which whole-population samples serve in this capacity. It was also deliberately designed maximally to overcome the difficult methodological challenges confronting research in this area, particularly the ability validly to assess electrolyte intake, to account for possible confounders of their relation to blood pressure, and to achieve a standardized collection of high-quality, comparable data both within and across populations.1,2

Methods

To cope with these problems, INTERSALT conducted a standardized study of a large and varied total sample comprising 10,000 men and women ages 20–59 years identified in 52 populations from 32 countries from Africa, North and South America, Asia, and Europe (north, south, east, and west). Samples with expected low and high sodium intake were included. That is, INTERSALT conducted 52 identically designed, virtually concurrent, standardized epidemiological studies.

Each of the 52 centers was asked to recruit 200 men and women aged 20–59 years, with 25 in each of eight age–sex groups. Samples were randomly selected from population lists or by cluster sampling of defined populations. Local investigators were trained at one of five training meetings to implement a common, standardized protocol that was based on a
detailed operations manual prepared by the two co-
ordinating centers, located in Chicago and London.2

Blood pressure (sitting) was measured twice with a
Hawksley Random Zero sphygmomanometer (Hawks-
ley and Sons, Ltd., Lancing, England) after partici-
pants had emptied their bladders and were seated
quietly for 5 minutes. Systolic blood pressure was
recorded as the appearance of sound (phase I) and
diastolic as the disappearance of sound (phase V).

Both “spot” and 24-hour urine collections were
made to estimate electrolyte excretion. The begin-
ning and end of each 24-hour collection were super-
vised by clinic staff, and completeness was assessed
by a standardized interview.

Urine aliquots were stored locally at −20°C before
being shipped frozen to the Central Laboratory at St.
Raphael University in Leuven, Belgium, where all
urine analyses were performed with strict internal
and external quality control. Data forms were sent to
the London Coordinating Center for review, editing,
coding, data entry, and analysis. Repeat urine col-
cctions and blood pressure measurements were ob-
tained in a random 8% of participants to estimate
intraindividual variability.

Height and weight were each measured twice with
a stadiometer and beam balance scale where possi-
able. Sodium and potassium excretion were measured
by emission flame photometry. Daily consumption of
alcoholic drinks over the preceding 7 days was as-
sessed by questionnaire and converted into volume of
absolute alcohol, based on local information.

Blood pressure of individual participants was the
mean of the two readings. Individual 24-hour sodium
and potassium excretion values were the products of
concentrations in the urine and urinary volume cor-
tected to 24 hours. Body mass index (BMI) was calcu-
lated as weight divided by height squared (kg/m²).

Results and Discussion

Detailed findings accrued to date have been pub-
lished.3,4 The principal results are summarized here.

Within-Population Findings

For within-population analyses on relations of 24-
hour urinary sodium excretion to blood pressure of
individuals, multiple linear regression was used with
two models, one controlled for only age and sex and
the other for age, sex, BMI, alcohol consumption, and
24-hour urinary potassium excretion. The coefficients
of the multiple linear regression analysis for the
relation between sodium and systolic blood pressure
and between sodium and diastolic blood pressure
were first separately computed for each of the 52
population samples. On a probability basis (by chance
alone), if there was no relation between sodium and
blood pressure, about 26 of these coefficients should
have had a positive sign and about 26 a negative sign.
One or two should have been significantly positive
(\(p \leq 0.05\)) and one or two significantly negative. As
seen in Table 1, this was not the INTERSALT finding
in the sodium–systolic blood pressure analysis.3 With
adjustment for only age and sex, 39 of 52 coefficients
were positive, 15 significantly so. With adjustment for
five confounders, there were 33 positive coefficients,
with significantly positive coefficients numbering eight.
These results were significantly different from chance
expectation. The next analytical step involved pooling
of the 52 within-center regression coefficients, with-
etched by the inverse of their variance. This single
pooled coefficient was then corrected for reliability,
involving division of the pooled regression coefficient
by the pooled reliability coefficient obtained from
random, repeat 24-hour urine collections at all 52
centers. The result is a summary statistic on the
relation of 24-hour urinary sodium excretion to sys-
tolic blood pressure for the 10,079 individuals sur-
veyed by the INTERSALT field centers. Its value,
with adjustment for only age and sex, is 3.54 mm Hg
systolic blood pressure/100 mmol 24-hour sodium
excretion (Z score, 6.97); with adjustment for five
confounders, its value is 2.17 (Z score, 3.79). These
pooled coefficients are significantly different from zero
(\(p < 0.001\), two-tailed) with either adjustment.

These analyses were repeated, with the exclusion of
four centers from remote populations exhibiting low
and very low median sodium intake (see below), and
the pooled coefficients for the relation between indi-
vidual sodium excretion and systolic blood pressure
in the remaining 48 centers remained almost unchanged.
Their Z scores were 6.93 when adjusted for only age
and sex and 3.69 for age, sex, BMI, potassium, and
alcohol consumption (\(p < 0.001\), two-tailed).

With adjustment for only age and sex, similar
significant findings were recorded for the relation
between sodium and diastolic blood pressure, but the
regression coefficient was smaller.4 Significance was
lost when BMI, alcohol consumption, and potassium
excretion were added to the analysis, although the
association remained positive.

In similar analyses of the relation between the
urinary sodium/potassium ratio and systolic blood
pressure, the sign of the coefficient was positive for
37 of the 52 multivariate analyses, with \(p < 0.05\) for
four of these; no coefficient was significantly nega-
tive (Table 1).3 Again, these findings are significantly
different than those resulting from chance alone. The
combined-center coefficient corrected for reliability
was 2.10 mm Hg of systolic blood pressure per unit of
the sodium/potassium ratio with age–sex adjustment
only and 1.61 with adjustment for age, sex, BMI, and
alcohol consumption. Again, \(p\) values are less than
0.001 for the pooled coefficients.

Both coefficients were significant for the sodium/
potassium ratio and diastolic blood pressure but
smaller than for the sodium/potassium ratio and
systolic blood pressure.3

With five-factor adjustment, significant inverse rela-
tions were recorded for 24-hour urinary potassium
excretion and both systolic and diastolic blood pres-
sures (Table 1).3

Because the focus of this conference is on salt and
blood pressure, findings on BMI and alcohol con-
TABLE 1. Summary of Within-Center Associations Between 24-Hour Urinary Sodium Excretion, Sodium/Potassium Ratio, Potassium Excretion, and Blood Pressure (52 Centers, All Participants) *

<table>
<thead>
<tr>
<th>Variables</th>
<th>Systolic blood pressure</th>
<th>Diastolic blood pressure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for age and sex</td>
<td>Adjusted for age, sex, and other confounders*</td>
</tr>
<tr>
<td>Sodium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of positive coefficients</td>
<td>39</td>
<td>33</td>
</tr>
<tr>
<td>Not significant (p &lt; 0.05)</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>Number of negative coefficients</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Not significant (p &lt; 0.05)</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Pooled regression coefficient (mm Hg/mmol)</td>
<td>0.0163</td>
<td>0.0100</td>
</tr>
<tr>
<td>SEM</td>
<td>0.0023</td>
<td>0.0026</td>
</tr>
<tr>
<td>Z score</td>
<td>6.97†</td>
<td>3.79†</td>
</tr>
<tr>
<td>Pooled regression coefficient corrected for reliability§</td>
<td>0.0354</td>
<td>0.0217</td>
</tr>
<tr>
<td>Sodium/potassium ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of positive coefficients</td>
<td>40</td>
<td>37</td>
</tr>
<tr>
<td>Not significant (p &lt; 0.05)</td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>Number of negative coefficients</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Not significant (p &lt; 0.05)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pooled regression coefficient (mm Hg/mmol)</td>
<td>0.8097</td>
<td>0.6209</td>
</tr>
<tr>
<td>SEM</td>
<td>0.1062</td>
<td>0.1045</td>
</tr>
<tr>
<td>Z score</td>
<td>7.62†</td>
<td>5.94†</td>
</tr>
<tr>
<td>Pooled regression coefficient corrected for reliability§</td>
<td>2.0977</td>
<td>1.6085</td>
</tr>
<tr>
<td>Potassium</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of positive coefficients</td>
<td>24</td>
<td>13</td>
</tr>
<tr>
<td>Not significant (p &lt; 0.05)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Number of negative coefficients</td>
<td>28</td>
<td>39</td>
</tr>
<tr>
<td>Not significant (p &lt; 0.05)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Pooled regression coefficient (mm Hg/mmol)</td>
<td>0.0012</td>
<td>-0.0254</td>
</tr>
<tr>
<td>SEM</td>
<td>0.0065</td>
<td>0.0070</td>
</tr>
<tr>
<td>Z score</td>
<td>0.19</td>
<td>-3.63†</td>
</tr>
<tr>
<td>Pooled regression coefficient corrected for reliability§</td>
<td>0.0021</td>
<td>-0.0446</td>
</tr>
</tbody>
</table>

*Other confounders were (for sodium model) body mass index, alcohol consumption, and urinary potassium; (for sodium/potassium ratio model) body mass index and alcohol consumption; and (for potassium model) body mass index, alcohol consumption, and urinary sodium.  
†p<0.001.  
‡p<0.05.  
§Coefficient of reliability calculated from data on repeat urine measurements (see text).  
¶p<0.01.  

Summary: The associations between 24-hour urinary sodium excretion and blood pressure were significant for older but not younger subgroups. The reliability coefficients used to correct for this error probably underestimated the bias.
### TABLE 2. Relation of 24-Hour Urinary Sodium, Potassium, and Sodium/Potassium Excretion to Systolic Blood Pressure: Within-Center Linear Regression Analyses, Pooled Men and Women by Age, All 52 Centers; INTERSALT

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>SBP on sodium (mm Hg/10 mmol)</th>
<th>SBP on potassium (mm Hg/10 mmol)</th>
<th>SBP on sodium/potassium (mm Hg/unit)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All men</td>
<td>5,045</td>
<td>0.056</td>
<td>-0.214*</td>
<td>0.508$</td>
</tr>
<tr>
<td>20-39</td>
<td>2,525</td>
<td>-0.008</td>
<td>-0.022</td>
<td>0.131</td>
</tr>
<tr>
<td>40-59</td>
<td>2,520</td>
<td>0.110*</td>
<td>-0.386†</td>
<td>0.948‡</td>
</tr>
<tr>
<td>All women</td>
<td>5,034</td>
<td>0.131†</td>
<td>-0.266*</td>
<td>0.636‡</td>
</tr>
<tr>
<td>20-39</td>
<td>2,521</td>
<td>0.083</td>
<td>0.016</td>
<td>0.241</td>
</tr>
<tr>
<td>40-59</td>
<td>2,513</td>
<td>0.155*</td>
<td>-0.561†</td>
<td>0.963‡</td>
</tr>
</tbody>
</table>

Multiple linear regression coefficient adjusted for age and other confounders, including body mass index and alcohol consumption, but not for reliability. SBP, systolic blood pressure.

*p<0.05; †p<0.01; ‡p<0.001.

3) Despite efforts to minimize the problem, it is probable that there were varying degrees of incompleteness of 24-hour urine collection in some or all centers. This shortcoming also tended to produce underestimates of the true associations.

4) Public health and medical care campaigns in several countries (e.g., the United States and Japan) have recommended a reduction in salt intake. If individuals with higher blood pressures were taking action consistent with this advice (the actual findings of INTERSALT), it would tend to bias sodium–blood pressure associations downward or even convert positive relations to negative ones. When INTERSALT analyses were done to correct

![Figure 1](http://hyper.ahajournals.org/DownloadedFrom)
for this bias, the sodium–blood pressure coefficients became larger.

5) Some persons in most centers were on antihypertensive drugs (a majority at older ages in some centers). Their blood pressures were artificially low, tending to reduce sodium–blood pressure relations.

6) Adjustment for body mass index and other confounders, which are more accurately measured than sodium excretion and positively correlated with it, may have underestimated the independent effect of sodium on blood pressure.

This judgment is concordant with the findings of the North London Study. In that study, with an older population sample manifesting little day-to-day variation in urinary sodium excretion and with ability (by means of a PABA marker) objectively to identify people whose 24-hour urine collections were incomplete, the adjusted coefficient for the sodium–systolic blood pressure relation was 17 mm Hg/100 mmol sodium, more than four times higher than the pooled adjusted INTERSALT coefficient for men and women aged 50–59 years.

Cross-Population Findings

The following is a summary of the INTERSALT cross-population (ecological) analyses and their results. These analyses involved not a sample size of 10,000+ but one of only 52 (or 48 in some analyses, for reasons noted below). This sample size limited statistical power. In accordance with INTERSALT design and implementation, sample median values of BMI, body mass index. 24-hour sodium excretion ranged widely from 0.2 mmol/24 hr for the Yanomamo Indians of Brazil to 242.1 mmol/24 hr for the sample from Tianjin, North China. But none came close to the level reported for the northern Japanese in Dahl’s famous figure—about 435 mmol sodium/24 hr. Furthermore, 36 of the 52 centers (69%) had median 24-hour sodium excretions
clustered in the range of 130–179 mmol/24 hr, further attenuating statistical power to detect significant relations between population median electrolyte excretion and blood pressure.

In the cross-population analyses, five blood pressure end points were used: slope of systolic and diastolic blood pressures with age, sample median systolic and diastolic blood pressures, and prevalence of high blood pressure. With adjustment for age, sex, BMI, and alcohol consumption, the regression of sample slope for systolic or diastolic blood pressures with age on sample median 24-hour sodium excretion for 52 samples was significant (p<0.001) (Figures 1 and 2). The value for the slope of systolic blood pressure with age is 0.34 mm Hg/100 mmol sodium/yr. That is, for a person who habitually eats 70 mmol sodium/day compared with one who eats 170 mmol sodium/day, a slope upward in systolic blood pressure from age 25 to age 55 is estimated to be less by 10.2 mm Hg.

Because four centers with low median sodium intake (Yanomamo and Xingu Indians of Brazil, Papua New Guinea highlanders, and rural Kenyans) seemed to exert an important influence on these analyses, they were repeated with the exclusion of these four samples; the distributions were truncated in analyses of the remaining 48 centers. The relations of sodium to the slopes of both systolic and diastolic blood pressures with age remained significant for the remaining 48 centers with four-factor adjustment (p<0.001) (Figures 1 and 2).

Findings for the four low sodium samples merit separate attention (Table 3). With reference to sodium excretion, urinary sodium/potassium ratio, BMI, and alcohol consumption, they markedly differed from the other 48 samples. Their median systolic and diastolic blood pressure values were low, the slope of systolic and diastolic blood pressures with age varied little or not at all from zero, and prevalence of high blood pressure was very low, again in contrast to the other 48 centers. (In all these traits, the rural Kenyans [median urinary sodium excretion of 51 mmol, sodium/potassium ratio of 1.8, and 31% reporting alcohol consumption] may be transitional.) Other ecological analyses done in INTERSALT yielded inconsistent findings. With median systolic blood pressure or prevalence of high blood pressure as the dependent variable and 52 centers in the analyses, the relation of sodium and sodium/potassium ratio was significant (i.e., findings were concordant with those reported by Dahl, Gleibermann, and Froment). However, findings were not significant with diastolic blood pressure as the dependent variable or in those analyses truncated by exclusion of the four low sodium centers.

In conclusion, the significant, positive, independent findings of INTERSALT on sodium and blood pressure are concordant with a vast array of data from all major research disciplines. Considered along with those, the INTERSALT data lend further substantive support to the judgment that the habitually high salt intake common in most populations (at levels several times above physiological need) is among the key etiological factors producing the rise in blood pressure found in a majority of people in these populations over the decades from youth through middle age. This elevated salt intake is one of the key mass exposures accounting for the high prevalence rates of frank hypertension in most contemporary societies.

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Appendix

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