Body Mass Index and Associations of Sodium and Potassium With Blood Pressure in INTERSALT

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INTERSALT is an international study of the relations of electrolyte excretion and other factors to blood pressure carried out in 52 centers from 32 countries. Previous reports from INTERSALT indicated that body mass index (BMI), 24-hour urinary sodium and potassium excretions, and the sodium-potassium ratio were all independently related to blood pressure of individuals1-3 and that sodium and potassium excretions of individuals were both positively correlated with BMI.2 In addition, pooled regression coefficients for sodium, potassium, and sodium-potassium ratio with blood pressure that were adjusted only for age and sex when compared with the coefficients also adjusted for alcohol intake and BMI (as well as potassium for sodium, and sodium for potassium) suggested that adjustment for BMI had a substantial effect on observed electrolyte-blood pressure associations in INTERSALT.4

Intervention studies of the effects of weight loss, reduced sodium intake, and potassium supplementation on blood pressure have been inconsistent as to whether weight loss leads to lower blood pressure with or without reduced sodium intake4-14 and in at least one study with or without increased potassium intake.5 Furthermore, although sodium reduction lowers blood pressure,15 it is unclear whether lower sodium intake reduces blood pressure equally in overweight and non-overweight individuals.16,17 Also, combined effects of weight and sodium reduction on blood pressure have not yet been quantified.14

This report uses INTERSALT data to further examine BMI and associations of sodium, potassium, and sodium-potassium ratio with blood pressure by quantifying the effects of adjustment for BMI on these associations and by exploring possible interactions of these variables with BMI in relation to blood pressure.

Methods

Details of the INTERSALT study design and methods have been published.18,19 Briefly, each of the 52 centers recruited 200 men and women aged 20 to 59 years, with 25 in each of eight age-sex groups. Samples were selected randomly from population lists or by chunk sampling of defined populations. Local investigators were trained to implement a common standardized protocol at one of five training meetings, based on a detailed Manual of Operations.19 Data forms were sent to the Coordinating Center in London for review, editing, coding, data entry, and analysis.
Participants in each of the 52 centers provided written or verbal (if not literate) informed consent after approval of all study procedures by local institutional review boards. All procedures were conducted in accordance with institutional guidelines.

Blood pressure (sitting) was measured twice with the use of a random-zero sphygmomanometer (Hawkesley) after participants had emptied their bladders and sat 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). Blood pressure of individual participants was the mean of the two readings.

Both “spot” and 24-hour urine collections were made to estimate electrolyte excretion. The start and end of each 24-hour collection were supervised 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. Sodium and potassium excretions were measured by atomic absorption flame photometry. Individual sodium and potassium excretion values were the products of concentrations in the urine and urinary volume collected to 24 hours.

Height and weight were each measured twice using a stadiometer and beam balance scale where possible. BMI was calculated as weight divided by height squared (kilograms per meter squared). Daily intake of alcoholic drinks over the preceding 7 days was assessed by questionnaire and, based on local information, converted into volume (milliliters) of absolute alcohol.

Repeat urine collections and blood pressure measurements were obtained at a second visit in a random 8% of participants to estimate intrapersonal variability.

To quantify the effect of adjustment for BMI on electrolyte-blood pressure associations, center-by-center linear regressions of blood pressure on sodium, potassium, and sodium-potassium ratio were calculated with and without adjustment for BMI. All regressions included adjustment for age, sex, and alcohol intake. The regressions of blood pressure on sodium excretion also included 24-hour potassium excretion, and those for potassium included sodium. To adjust for alcohol, 7-day intakes were stratified into three groups (0, 1 to 299, and 300+ mL of absolute alcohol per week) with two 0-1 variables, i.e., no alcohol intake versus 1 to 299 mL/Wk (0,1) and no intake versus 300+ mL/Wk (0.1). Five of 10,079 people were excluded from these analyses because of missing data on alcohol intake.

In addition, the results for diastolic blood pressure with adjustment for age, sex, alcohol intake, and BMI differ slightly from those previously reported because of the exclusion from regression analyses for diastolic pressure of 17 people with diastolic blood pressures recorded as less than 30 mm Hg. Within-center regression coefficients were averaged (pooled) across centers to yield study-wide estimates of associations between blood pressure and each electrolyte variable with and without adjustment for BMI. Each center coefficient was weighted by the inverse of its variance.

Regression coefficients for sodium are expressed as millimeters of mercury per 100 mmol (1 mmol = 1 mEq = 23 mg) sodium, coefficients for potassium as millimeters of mercury per 30 mmol (1 mmol = 1 mEq = 39 mg) potassium, and coefficients for the sodium-potassium ratio as millimeters of mercury per 2 U. These values for sodium, potassium, and the sodium-potassium ratio were chosen for these reasons. First, 100 mmol (mEq) sodium, 30 mmol (mEq) potassium, and 2 U of the sodium-potassium ratio are approximately the interquartile ranges for these variables in the INTERSALT sample of 10,074 people used in these analyses, i.e., 97 mmol (mEq) for sodium, 32 mmol (mEq) for potassium, and 2.13 U for the sodium-potassium ratio. Second, these values also generally reflect the changes that would be required in sodium and potassium intake in the US population and/or the INTERSALT sample to achieve the goals for intake suggested by the National Research Council.2 For sodium, the National Research Council recommends a reduction in daily intake from the current US consumption of 10 to 14.5 g salt (171 to 248 mmol sodium intake) to no more than 6.0 g salt (103 mmol sodium), with a goal of 4.5 g (77 mmol sodium).21 Hence, the average reduction in sodium intake from current levels required to achieve this goal is approximately 100 mmol (mEq).

For potassium, the National Research Council recommends an intake of 3500 mg (90 mmol) which represents an average increase of approximately 35 mmol (mEq) over current INTERSALT levels of intake. Changes of this magnitude in sodium and potassium intake would reduce the average sodium-potassium ratio in INTERSALT by approximately 2 U.

To explore possible interactions of electrolyte variables and BMI in relation to blood pressure, two sets of analyses were performed. First, the 52 centers were divided into two groups of 26 centers based on whether the median BMI at the center was less than 24.5 kg/m² (lower-BMI centers) or greater than or equal to 24.5 kg/m² (higher-BMI centers). There were 2518 men and 2492 women in the 26 lower-BMI centers and 2524 men and 2540 women in the 26 higher-BMI centers. Within each center, linear regressions of blood pressure on each electrolyte variable were calculated and adjusted for age, sex, alcohol intake, and BMI. Regressions for sodium also included potassium, and those for potassium included sodium. Within-center regression coefficients, weighted by the inverse of their variances, were averaged across centers to yield estimates of the associations between blood pressure and each variable within each set of 26 centers.

In the second set of analyses for interactions, individuals within the 52 centers were classified as lower-BMI if their BMI was less than or equal to 24.1 kg/m² and higher-BMI if their BMI was greater than or equal to 24.1 kg/m². The cut point for determining higher- and lower-BMI individuals was chosen to approximately equalize the number of individuals in each subgroup after exclusion of any center in a center with fewer than 20 individuals.) Within each center, linear regressions of blood pressure on each electrolyte variable were calculated for individuals in each group. Regressions were not run for any BMI subgroup in a center if that subgroup contained fewer than 20 people. This resulted in 4 centers and 57 people being excluded from analyses in the higher-BMI groups. There were 2349 men and 2661 women included in the analyses for the lower-BMI groups and 2658 men and 2349 women included in the analyses for the higher-BMI groups. In these analyses, adjustment was also made for age, sex, alcohol intake, and BMI within each BMI subgroup. Potassium excretion was also included in regressions of blood pressure on sodium, and sodium in those for potassium. Regression coefficients were averaged across centers for all higher-BMI groups and all lower-BMI groups, with weights equal to the inverse of the variance.

BMI was included as a possible confounder in these two sets of analyses for two reasons. First, adjustment for BMI within BMI subgroups allows comparison of the results reported here with previously reported results. Second, analyses in individuals classified as lower and higher BMI constitutes an adjustment for BMI that was not present in analyses in lower- and higher-BMI centers. Hence, to make these two sets of analyses comparable, BMI was included as an independent variable in all BMI subgroup analyses.

Regression coefficients for electrolyte variables were corrected for reliability ("regression dilution bias") according to methods previously described for INTERSALT. The estimates of reliability used in these corrections were 0.3747 for 24-hour sodium excretion, 0.4717 for 24-hour potassium excretion, and 0.3422 for the sodium-potassium ratio. The corrections for models containing both sodium and potassium also require an estimate of the proportion of the covariance.
Dyer et al. BMI, Sodium, Potassium, and Blood Pressure

Results

Electrolyte–Blood Pressure Associations With and Without Adjustment for BMI

Table 1 gives the pooled regression coefficients relating 24-hour sodium (millimeters of mercury per 100 mmol) and potassium (millimeters of mercury per 30 mmol) excretions and sodium-potassium ratio (millimeters of mercury per 2 U) to systolic and diastolic blood pressure with and without adjustment for BMI. The table also gives the standard error of each coefficient, the coefficient divided by its standard error (Z score), and the coefficient corrected for reliability ("regression dilution bias"). Without adjustment for BMI, the pooled regression coefficient relating sodium to systolic blood pressure without correction for reliability was twice as large as the coefficient from the analysis that included BMI, ie, 1.12 and 0.99 mm Hg per 30 mmol (mEq) for the models with and without BMI adjustment, respectively. For diastolic blood pressure, the coefficients indicated average pressure less by 1.12 and 0.99 mm Hg per 30 mmol (mEq) for the models with and without BMI adjustment, respectively.

For potassium, unlike for sodium, the uncorrected regression coefficients for both systolic and diastolic blood pressures were smaller without adjustment for BMI than with adjustment, and the coefficient for diastolic pressure from the model without BMI did not differ significantly from zero. However, when corrected for regression dilution bias, the difference due to inclusion of BMI in the model essentially disappeared for systolic pressure and was reduced for diastolic. For systolic blood pressure, the corrected regression coefficients indicated average pressure less by 2.02 and 1.97 mm Hg for potassium excretion higher by 30 mmol (mEq) for the models with and without BMI adjustment, respectively. For diastolic blood pressure, the corrected coefficients indicated average pressure less by 1.12 and 0.99 mm Hg per 30 mmol (mEq) higher potassium excretion, respectively.

Adjustment for BMI also had a substantial effect on the regression coefficients for the sodium-potassium ratio and blood pressure. For systolic blood pressure, both the corrected and uncorrected regression coefficients were approximately 33% larger in the model without than with adjustment for BMI, whereas for diastolic pressure, coefficients were twice as large without adjustment for BMI. With correction for reliability, the regression coefficient relating sodium to diastolic blood pressure indicated average pressure greater by 2.52 mm Hg for sodium higher by 100 mmol (mEq) without adjustment for BMI and 0.14 mm Hg per 100 mmol (mEq) with adjustment.

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Table 2 gives the medians and 25th and 75th percentiles for systolic and diastolic blood pressures, 24-hour urinary sodium and potassium excretions, sodium-potassium ratio, and BMI for participants from higher- and lower-BMI centers as well as for all higher- and lower-BMI individuals. Table 2 also gives the percentages of participants in these BMI subgroups who reported consuming 1 to 299 mL absolute alcohol in the week before the exam and the percentage who reported consuming 300+ mL. Medians in each center were divided into those with BMI <24.1 kg/m² (lower-BMI) and those with BMI ≥24.1 kg/m² (higher-BMI).

Sodium and Blood Pressure in BMI Subgroups

Table 3 gives the results of the regression analyses to assess possible interactions of sodium with BMI in relation to blood pressure. With multivariate adjustment, 24-hour sodium excretion was positively and significantly related to systolic pressure. For analyses based on centers, the regression coefficient was larger for lower-BMI centers compared with higher-BMI centers. Without correction for reliability, the pooled regression coefficients indicated average systolic pressure greater by 1.32 mm Hg for each 100 mmol (mEq) increment in sodium excretion in lower-BMI centers and 0.73 mm Hg greater in higher-BMI centers, a difference that was not statistically significant. With correction for reliability, the coefficients indicated average systolic pressure greater by 3.98 and 2.41 mm Hg, respectively, per 100 mmol (mEq) sodium. This difference was also not...
TABLE 3. Pooled Regression Coefficients (mm Hg per 100 mmol) Relating 24-Hour Urinary Sodium Excretion to Blood Pressure in Body Mass Index Subgroups

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<tr>
<th>Variable</th>
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<td>Z score</td>
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| Diastolic Pressure        | Lower-BMI                     | Higher-BMI      | Lower-BMI       | Higher-BMI      |
|                           | 0.198                         | -0.095          | 0.279           | 0.253           |
|                           | 0.710                         | -0.374          | 0.610           | -0.270          |
|                           | 0.710                         | -0.374          | 0.610           | -0.270          |
|                           | 0.710                         | -0.374          | 0.610           | -0.270          |
|                           | 0.710                         | -0.374          | 0.610           | -0.270          |

BMI indicates body mass index. Fifty-two centers were divided into 26 with median BMI <24.5 kg/m² (lower-BMI centers) and 26 with median BMI ≥24.5 kg/m² (higher-BMI centers). Individuals in each center were divided into those with BMI <24.1 kg/m² (lower-BMI) and those with BMI ≥24.1 kg/m² (higher-BMI).

*Adjusted for age, sex, BMI, alcohol intake, and 24-hour potassium excretion.
†Corrected for reliability of both 24-hour sodium and potassium excretions and intraindividual correlation of sodium and potassium.
§P<.05, ||P<.01, ||P<.001.

statistically significant. With correction for reliability, the regression coefficients were 3.81 and 2.96 mm Hg per 100 mmol (mEq).

For diastolic pressure, none of the four regression coefficients were significantly different from zero. This finding is consistent with results in Table 1 for the full INTERSALT sample showing no significant association of sodium with diastolic pressure when adjustment was made for age, sex, alcohol intake, BMI, and potassium excretion. The coefficients for sodium and diastolic pressure also did not differ significantly between lower- and higher-BMI centers or individuals.

**Potassium and Blood Pressure in BMI Subgroups**

Table 4 gives the results of regression analyses relating 24-hour potassium excretion to blood pressure in higher- and lower-BMI centers and individuals. With multivariate adjustment, potassium was inversely and significantly related to systolic pressure in both higher- and lower-BMI centers and higher- and lower-BMI individuals. Potassium was also significantly related to diastolic pressure in higher-BMI centers and higher- and lower-BMI individuals. Although these inverse associations for higher-BMI centers and individuals were larger than those for lower-BMI centers and individuals, the differences were not statistically significant. Without correction for reliability, the pooled regression coefficients indicated average systolic pressure less by 0.54 mm Hg per 30 mmol (mEq) increment in potassium excretion in lower-BMI centers and 1.13 mm Hg less for higher-BMI centers. With correction for reliability, the coefficients indicated average pressure less by 1.52 and

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</tr>
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</table>

| Diastolic Pressure        | Lower-BMI                     | Higher-BMI      | Lower-BMI       | Higher-BMI      |
|                           | -1.130                        | -0.310          | -0.507          | -0.556          |
|                           | -1.130                        | -0.310          | -0.507          | -0.556          |
|                           | -1.130                        | -0.310          | -0.507          | -0.556          |
|                           | -1.130                        | -0.310          | -0.507          | -0.556          |
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Definitions are as in Table 3.

*Adjusted for age, sex, BMI, alcohol intake, and 24-hour sodium excretion.
†Corrected for reliability of both 24-hour sodium and potassium excretions and intraindividual correlation of sodium and potassium.
§P<.05, ||P<.01, ||P<.001.
2.82 mm Hg, respectively, per 30 mmol (mEq). The comparable estimates for diastolic pressure were 0.38 and 0.69 mm Hg per 30 mmol (mEq) potassium without correction for reliability and 0.87 and 1.46 mm Hg with correction.

The differences in regression coefficients for higher- and lower-BMI individuals were smaller than those for higher- and lower-BMI centers. The regression coefficients for systolic pressure indicated average pressure less by 0.76 and 0.86 mm Hg, respectively, in lower- and higher-BMI individuals without correction for reliability and 1.92 and 2.39 mm Hg per 30 mmol (mEq) with correction. For diastolic pressure, the coefficients without correction for reliability were 0.51 and 0.56 mm Hg and were 1.05 and 1.36 mm Hg with correction.

### Sodium-Potassium Ratio and Blood Pressure in BMI Subgroups

Table 5 gives the results of regression analyses relating the 24-hour sodium-potassium ratio to blood pressure in BMI subgroups. With multivariate adjustment, the sodium-potassium ratio was significantly related to systolic pressure in both higher- and lower-BMI centers and individuals and to diastolic pressure in lower-BMI centers and higher-BMI individuals. Although the coefficients for both systolic and diastolic blood pressure were larger in lower-BMI compared with higher-BMI centers but were larger in higher-BMI than in lower-BMI individuals, none of these differences was statistically significant. Without correction for reliability, the pooled regression coefficients indicated average systolic pressure greater by 1.50 and 1.00 mm Hg for the sodium-potassium ratio higher by 2 U for lower- and higher-BMI centers and by 1.33 and 1.41 mm Hg for lower- and higher-BMI individuals. With correction for reliability, the coefficients indicated average systolic pressure greater by 4.48 and 2.96 mm Hg in lower- and higher-BMI centers and by 3.93 and 4.19 mm Hg for lower- and higher-BMI individuals. The uncorrected coefficients for diastolic pressure ranged from 0.22 mm Hg in lower-BMI individuals to 0.57 mm Hg in higher-BMI individuals and the corrected coefficients from 0.65 to 1.69 mm Hg.

### Discussion

The purpose of these analyses was to further examine BMI and associations of sodium, potassium, and sodium-potassium ratio with blood pressure in INTERSALT. The relation of BMI to these associations is of interest because of the suggested effect of adjustment for BMI on the sodium-blood pressure relations in INTERSALT and other studies and because of the inconsistencies in the results of intervention trials on the independent effects of sodium reduction and weight loss on blood pressure. These questions were addressed by quantifying the effect of adjustment for BMI on associations of sodium, potassium, and sodium-potassium ratio with blood pressure and by exploring possible interactions of these variables with BMI in relation to blood pressure.

Adjustment for BMI had a substantial effect on the size of regression coefficients relating sodium and the sodium-potassium ratio to blood pressure. Adjustment for BMI, in addition to adjustment for age, sex, alcohol intake, and potassium excretion, reduced the uncorrected regression coefficient for sodium with systolic blood pressure by more than 50% and the corrected coefficient by almost 50%. For diastolic pressure, adjustment for BMI made a significant association (P<.001) nonsignificant. For the sodium-potassium ratio, adjustment for BMI reduced both corrected and uncorrected regression coefficients for systolic pressure by approximately 25% and for diastolic by approximately 50%. For potassium, adjustment for BMI increased the size of uncorrected regression coefficients but left corrected coefficients little changed from the analyses that did not include BMI.

An important issue in regard to these and other analyses of the sodium–blood pressure association is whether it is really appropriate to adjust for BMI. Although BMI is a variable measured essentially without error, this is not the case for 24-hour sodium...
excretion; indeed, for sodium excretion in INTERSALT, the intraindividual variation was greater than the interindividual variation, as indicated by a coefficient of reliability that was less than 0.50. Furthermore, given the positive correlation of BMI with sodium excretion, a portion of the association between BMI and blood pressure may be due to the higher sodium intake in overweight individuals. Hence, the inclusion of BMI as a potential confounder in previous INTERSALT analyses may have resulted in an overadjustment for that variable.

Possible interactions of these electrolytes with BMI in relation to blood pressure were addressed by examining electrolyte-blood pressure associations in centers classified as lower- or higher-BMI based on the median BMI at the center being less than or greater than or equal to 24.5 kg/m² and by examining these same associations in individuals classified as lower- or higher-BMI based on individual BMI of less than or greater than or equal to 24.1 kg/m². In these analyses sodium and the sodium-potassium ratio were positively and significantly related to systolic pressure, and potassium was inversely and significantly related in all four BMI subgroups. The sodium-potassium ratio was also positively and significantly related to diastolic pressure in two subgroups and potassium inversely and significantly related in three. Pooled regression coefficients did not differ significantly between higher- and lower-BMI centers or individuals for any of these electrolyte variables.

It has been suggested that the low blood pressures found in populations with low sodium intake might reflect lower body weight rather than low sodium intake, thus implying that an association between sodium and blood pressure should be absent or reduced among lower-body-weight populations and individuals. As indicated above, no evidence to support this assertion was found in the present study. Thus, the findings of this report are concordant with other epidemiologic studies showing significant associations between sodium and blood pressure in lean Far Eastern populations and in Western populations with higher BMI. The combined effects of weight and sodium reduction on blood pressure have not been quantified, and it is unclear whether lower sodium intake reduces blood pressure equally in overweight and non-overweight individuals. In addition, it has been suggested that weight loss without a concomitant reduction in sodium intake does not lead to reductions in blood pressure. Although the present analyses cannot address these issues directly, results from previous analyses showing that BMI was significantly related to both systolic and diastolic blood pressures, independent of sodium and potassium excretion, and the present results showing that sodium and potassium excretions were significantly related to systolic pressure throughout the range of BMI indicate that the effects of sodium intake and overweight on blood pressure are additive. Thus, for most populations consuming salt in excess of 5.8 g/d (ie, >100 mmol/d sodium), the inference from the analyses presented here is that reduction in both salt intake and weight will have additive effects in lowering blood pressure. However, these cross-sectional observational data are limited in regard to resolving the issue posed by the apparently contradictory results of intervention trials; ie, with maintenance of high salt intake, is weight reduction in obese individuals ineffective in lowering blood pressure? Further well-designed and well-executed trials are needed to resolve this matter.

The related question also remains as to whether a high salt intake is a primary, essential, necessary cause for a population rise of blood pressure with age from youth through middle and older age and for high prevalence rates of hypertension, and whether other factors (eg, obesity, high alcohol consumption, low potassium intake) are secondary, adjuvant, contributory causes operating only if salt intake is high. No "experiments of nature" in populations are available yielding data to resolve this issue definitively. Data on the four low sodium centers in INTERSALT were not consistent as to whether BMI is directly related to blood pressure in populations with habitual low salt intake. Thus, for men from all four of these samples—the Yanomamo and Xingu Indians in Brazil, Papua, New Guinea, and Kenya—with median 24-hour sodium excretion ranging from 0.2 to 51.3 mmol (mEq) per 24 hours, BMI was positively related to blood pressure, significantly so in the Yanomamo for both systolic and diastolic blood pressure and in Kenya for diastolic pressure. However, in women there were no significant associations between BMI and blood pressure, and three of the eight within-center regression coefficients relating BMI to blood pressure were negative. Moreover, for men from these isolated low sodium samples, higher BMI could reflect musculature rather than adiposity, ie, that the meaning of the direct BMI-blood pressure relation may be different than in most populations, for which greater BMI is predominantly due to greater adiposity. Hence, the INTERSALT data are not definitive in regard to this question.

In any case, the overall results of INTERSALT indicate that for most populations, with high average salt intake, effects of blood pressure of sodium reduction and weight loss should be independent and additive.

In conclusion, these INTERSALT results do not support the concept of important interactions of sodium and potassium with BMI in relation to blood pressure. Furthermore, they indicate that associations of sodium (positive) and potassium (inverse) with blood pressure occur across the BMI range. These findings have implications for the primary prevention of high blood pressure in populations; ie, they lend further support to recommendations for a combined approach, including lower sodium intake, higher potassium intake, reduction in the prevalence of heavy drinking, and prevention and control of obesity.

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