Epidemiology and Prevention

Lower Levels of Sodium Intake and Reduced Cardiovascular Risk

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Background—Recent studies have raised the possibility of adverse effects of low sodium, particularly <2300 mg/d, on cardiovascular disease; however, these paradoxical findings might have resulted from suboptimal measurement of sodium and potential biases related to indication or reverse causation.

Methods and Results—Phases 1 and 2 of the Trials of Hypertension Prevention (TOHP) collected multiple 24-hour urine specimens among prehypertensive individuals. During extended posttrial surveillance, 193 cardiovascular events or cardiovascular disease deaths occurred among 2275 participants not in a sodium reduction intervention with 10 (TOHP II) or 15 (TOHP I) years of posttrial follow-up. Median sodium excretion was 3630 mg/d, with 1.4% of the participants having intake <1500 mg/d and 10% <2300 mg/d, consistent with national levels. Compared with those with sodium excretion of 3600 to <4800 mg/d, risk for those with sodium <2300 mg/d was 32% lower after multivariable adjustment (hazard ratio, 0.68; 95% confidence interval, 0.34–1.37; \( P \) for trend=0.13). There was a linear 17% increase in risk per 1000 mg/d increase in sodium (\( P=0.05 \)). Spline curves supported a linear association of sodium with cardiovascular events, which continued to decrease from 3600 to 2300 and 1500 mg/d, although the data were sparse at the lowest levels. Controlling for creatinine levels had little effect on these results.

Conclusions—Results from the TOHP studies, which overcome the major methodological challenges of prior studies, are consistent with overall health benefits of reducing sodium intake to the 1500 to 2300 mg/d range in the majority of the population, in agreement with current dietary guidelines. (Circulation. 2014;129:981-989.)

Key Words: cardiovascular diseases ■ diet ■ nutrition ■ primary prevention ■ sodium chloride, dietary

The Institute of Medicine (IOM) recently convened a committee to review the effects of sodium intake on health outcomes other than blood pressure, focusing on intake from 1500 to 2300 mg/d. Although the final report supported population-wide efforts to lower sodium, it concluded that there were insufficient data to support a lowering of sodium intake to <1500 mg/d, as recommended by the American Heart Association, or to <2000 mg/d, as recommended by the World Health Organization. The 2010 Dietary Guidelines for Americans recommend lowering sodium to <1500 mg/d for a majority of adults and to <2300 mg/d for all others. Several observational studies and randomized trials have examined the associations of sodium and subsequent morbidity and mortality and generally suggest a lowering of risk with lower sodium; however, few studies have examined absolute levels of sodium intake down to those considered in the IOM report.

Some recent studies have raised the possibility of adverse effects of very low sodium intake on cardiovascular disease (CVD). Data from the Flemish Study on Genes, Environment, and Health Outcomes (FLEMENGO) and European Project on Genes in Hypertension (EPOGH) cohorts found a higher level of CVD mortality among those in the lowest tertile of sodium intake. In addition, data from patients with CVD or diabetes mellitus suggested a J-shaped curve, with an increase in risk of CVD and mortality at both the upper and lower levels of sodium intake. The IOM concluded, however, that these data were limited and their quality was insufficient to support the assertion of an adverse effect on CVD at very low levels of sodium intake. All of the studies reporting a paradoxical inverse or J-shaped association between sodium intake and CVD were based on secondary analyses of studies that were not designed to assess this relationship. Major concerns included suboptimal measurement of sodium and the potential for bias attributable to indication or reverse causality. Most studies with urinary sodium excretion collected only a spot or single
Phases 1 and 2 of the Trials of Hypertension Prevention (TOHP) collected multiple 24-hour urine specimens over periods of either 18 months or 3 to 4 years. To represent long-term usual intake of sodium, these measures were averaged among those not participating in an active sodium intervention. In extended follow-up, a linear association of the sodium-potassium ratio with CVD was identified. Sodium also showed a linear association, of borderline significance, with CVD. The present report provides more detail on the relationship of sodium to CVD, particularly at the low absolute sodium intake levels considered by the IOM. It also provides more detail regarding the quality of the 24-hour urine collections, particularly the relationship of sodium and creatinine, and the impact of the latter on the association of sodium with CVD.

**Methods**

**TOHP Trials**

The TOHP Follow-up Study was an observational follow-up of TOHP, phases 1 and 2, and has been described previously. TOHP I took place from September 1987 to January 1990 and evaluated the effects of 4 supplement and 3 lifestyle interventions, including weight loss and sodium reduction interventions, on blood pressure in 2182 men and women aged 30 to 54 years with high normal blood pressure. Those in the active sodium reduction intervention were excluded from the present analyses, which left 1855 eligible TOHP I participants. In TOHP II, which took place from December 1990 to March 1995, the effects of sodium reduction and weight loss on blood pressure were tested over a longer 3- to 4-year follow-up period in a 2-by-2 factorial design among 2382 prehypertensive men and women aged 30 to 54 years. Eligible participants had a body mass index (calculated as weight in kilograms divided by height in meters squared) that represented 110% to 165% of desirable body weight. Those in the active sodium reduction group were excluded from the present analyses, which left 1191 eligible TOHP II participants.

During the trial periods, 3 to 7 24-hour urine collections were scheduled over 18 months in TOHP I and over 3 to 4 years in TOHP II. Usual intake of sodium or potassium or their ratio was calculated as the mean of available urinary excretion measures at 5 (lifestyle interventions) or 7 (nutritional supplement interventions) scheduled collections during 18 months in TOHP I and at 3 or up to 5 scheduled collections during 3 years in TOHP II. Mean sodium and potassium excretions, representing usual intake, were computed over all collections among prehypertensive individuals not participating in the sodium reduction intervention. All of the urinary sodium and potassium measures were expressed as milligrams per 24 hours (mg/d). To explore whether the relationships could be affected by undercollection, measures of creatinine were computed over the same collections, along with the creatinine to weight ratio (Cr/Wt), the sodium to creatinine ratio (Na/Cr), the potassium to creatinine ratio (K/Cr), and the sodium to potassium ratio (Na/K).

**TOHP Follow-Up**

The observational follow-up for CVD began in 2000, ≈10 years after the end of TOHP I and 5 years after the end of TOHP II, and included a total of 4526 TOHP I and II participants (with 38 participating in both TOHP I and TOHP II; Figure 1). Of these, 2974 were not in a sodium reduction intervention, had available sodium excretions, and remained alive and CVD free at the end of the trial periods. The follow-up was conducted centrally by mail and phone from the TOHP coordinating center at the Brigham and Women’s Hospital, Boston, MA, and was approved by institutional review boards there and at the participating clinic centers. Follow-up questionnaires focused on...
collection of CVD end points that had occurred after the conclusion of the trials. Additional questionnaires were sent at 2-year intervals, through early 2005, with interim annual postcards sent to collect information on address changes and new study end points.

The primary end point for the follow-up study was CVD or CVD death, including myocardial infarction, stroke, coronary artery bypass graft, percutaneous transluminal coronary angioplasty, and death from CVD. On notification of the occurrence of a primary nonfatal end point, consent was sought to obtain medical records. These were reviewed by a study physician, blinded to the participant’s intervention assignment, to confirm the reported events. Disconfirmed end points were excluded from the subsequent analyses. A search of the National Death Index was performed in the fall of 2001 and summer of 2005 to ascertain deaths from trial termination through December 2003 among nonrespondents to the questionnaires. End-point information was obtained for 2275 participants (2312 including duplicates in both trial phases), for an overall response rate of 76.5%. Response was slightly higher among TOHP II participants (78.4%) than their counterparts in TOHP I (75.8%) but did not differ by sodium quartile either crudely (P=0.39) or in fully adjusted logistic regression analyses (P=0.96; Table I in the online-only Data Supplement).

Statistical Analysis
As described above, sodium levels were averaged across all collections during the course of the trial periods in those not in an active sodium intervention who remained alive and CVD free at the end of the trial periods. Absolute levels were grouped into categories defined as <2300, 2300 to <3600, 3600 to <4800, and ≥4800 mg/d, where 2300 mg/d represents current guideline recommendations for adults5 and 3600 mg/d represents the median sodium intake in the US population aged 31 to 50 years.16 Baseline characteristics were expressed as percentages or means and were tested for trend over sodium categories by use of χ² statistics or regression analysis.

Cox regression models estimated the hazard ratio for the linear effect of sodium and for the categories defined above. The baseline hazard was stratified by trial, and those who were in both phases contributed time to the end of TOHP I until entry into TOHP II, as well as any follow-up from the end of TOHP II. Models were adjusted for clinic, age, sex, race/ethnicity, and other treatment assignments (model 1); additionally for education, baseline weight, alcohol use, smoking, exercise, potassium excretion, and family history of CVD (model 2); and also for changes in weight, smoking, and exercise during the trial periods (model 3), as prespecified.14 Penalized splines with 4 degrees of freedom were fit by use of S-Plus to examine linearity of effect14; the introduction of more flexibility did not alter the relation in the lower range of sodium.

We also conducted several sensitivity analyses controlling for Cr/Wt in the multivariable models to adjust for potential inadequacy of the urine collections. First, we estimated the within-person variability of measures of creatinine (mg/d) divided by weight in kilograms (Cr/Wt) using mixed-effects models. The coefficient of variation (CV) was computed for each participant. We then conducted analyses that excluded participants with CVs of ≥0.96; Table I in the online-only Data Supplement).

Finally, we ran models controlling for Cr/Wt or the CV of Cr/Wt in the model.17 Finally, we ran models that included sodium, potassium, and Cr/Wt, as well as Na/Cr, K/Cr, and Cr/Wt, expressed per SD for easier comparison of effect sizes. All analyses were conducted in SAS version 9.2 (SAS Institute, Cary, NC), except as otherwise noted.

Results
Baseline Levels
Sodium and other excretion data were averaged across all measures during the trial periods, with a median of 5 measures (range, 1–7). Median sodium excretion among the participants with follow-up data was 3630 mg/d, with 1.4% of the participants at <1500 and 10% at <2300 mg/d, consistent with national levels.15 Levels were higher in men, with medians of 3934 mg/d in men and 3078 mg/d in women. Those in TOHP II, all with a body mass index that exceeded ideal body weight, had higher levels than participants in TOHP I, with medians of 3666 and 4292 mg/d in TOHP I and II, respectively, in men and 2869 and 3340 mg/d, respectively, in women.

Characteristics of participants by absolute level of sodium excretion are provided in Table 1. Those with the lowest sodium levels were more likely to be college educated, more likely to drink alcohol, and more likely to exercise at least once per week, although these relationships were less consistent in women. Weight was directly correlated with sodium intake, although change in weight during the trial periods was not. Blood pressure levels, which were restricted during enrollment because of eligibility criteria, were not correlated with sodium levels.

Baseline urinary excretion levels are shown in Table 2 by phase and sex. Median potassium excretion was 2327 mg/d and was higher in men (2502 mg/d) than women (1952 mg/d) but was similar by study phase. Median creatinine was 1569 mg/d, again higher in men (1726 mg/d) than women (1155 mg/d). The median Cr/Wt was 19.3 in men and 15.0 in women. Both potassium and creatinine, as well as Cr/Wt, Na/K, and Na/Cr, were positively associated with average sodium excretion.

We computed the CVs for the Cr/Wt data using the within-person SD. These were slightly higher in women and in TOHP II, with medians of 18% and 20% for men and women, respectively, in TOHP I, and 15% and 18% for men and women, respectively, in TOHP II. The CVs declined across absolute levels of sodium in men but were more stable in women, as were the percentages with CVs >20% or >30%.

Association With CVD
During the posttrial follow-up, 193 cardiovascular events or CVD deaths occurred. First events included 68 myocardial infarctions, 77 coronary revascularizations, 22 strokes (1 participant reported both myocardial infarction and stroke), and 27 CVD deaths. Crude proportions of those developing CVD were lowest in the 2 lower sodium excretion groups in each phase (Table 3). In models adjusted for clinic, treatment assignment, and demographic variables (model 1), for these plus baseline covariates (model 2), and additionally for changes in weight, smoking, and exercise over the trial periods (model 3), there was a nonsignificant trend of increasing risk with increasing sodium level. In the fully adjusted model, compared with those with sodium 3600 to <4800 mg/d, risk for those with sodium <2300 mg/d was 32% lower after multivariable adjustment (P for trend=0.13). When sodium was considered as a continuous term, risk increased linearly, with a 17% increase in risk per 1000 mg/d increase in sodium (P=0.054) in the fully adjusted model.

The spline plot (Figure 2) supported a linear association of sodium with CVD (P=0.044), with a P value for nonlinearity of 0.76. In particular, the curve continued to descend from 3600 to 2300 and 1500 mg/d, although the data were sparse at the lowest levels. In this nonlinear curve, compared with those consuming 3600 mg/d, the estimated hazard ratios for those consuming 2300 and 1500 mg/d were 0.78 and 0.69, respectively.

To determine the impact of differences in creatinine levels on the association of sodium and CVD, we conducted several sensitivity analyses (Table 4). We first excluded all those with a CV for Cr/Wt ≥20%, which left a sample size of 1298 participants. The association of sodium with CVD was
slightly stronger, with hazard ratios that were 33% lower in those with sodium <2300 mg/d and 35% higher in those with sodium ≥4800 mg/d, but the trend was not statistically significant. The linear trend also strengthened to a 20% increase in risk per 1000 mg/d increase in sodium ($P=0.09$). When we excluded those with a CV for Cr/Wt ≥30%, or when we controlled for Cr/Wt or the CV of Cr/Wt in the model, there was little change in the estimated coefficients, although the effect of sodium became stronger with control for the CV of Cr/Wt.

For easier comparison, we further considered the excretion variables expressed per SD (Table II in the online-only Data Supplement). The average Cr/Wt ratio was not a predictor of CVD by itself, with a small 4% increase in risk per SD ($P=0.72$). When the first baseline measure of Cr/Wt was used rather than the average over the trial period, however, the risk increased by 20% per SD ($P=0.0087$; data not shown). The risk of CVD increased by 21% per SD of average sodium excretion ($P=0.05$) and decreased by 15% per SD of average potassium excretion ($P=0.12$), with little change after adjustment for Cr/Wt. Similar results were seen with the Na/Cr and K/Cr ratios.

**Discussion**

An extensive body of information documents the presence of a direct relationship between sodium intake and blood pressure. During the past year, 3 new meta-analyses of randomized, controlled clinical trials were published.19–21 Although they differed in their trial inclusion and exclusion criteria, each of the meta-analyses reported a significant and clinically important decrement in blood pressure after a reduction in sodium intake. Consistent with prior knowledge, the reduction...
in blood pressure was greater in those with a higher starting level of blood pressure, older persons, blacks, and those with a more successful intervention. In the meta-analyses that are most generalizable to clinical practice and public health, total cholesterol and catecholamine levels were essentially unchanged, and changes in urinary protein excretion were consistent with a beneficial effect of sodium reduction. Blood pressure is one of the best validated surrogate markers for CVD and has been identified as one of the leading preventable causes of death in the United States.

Direct observations of the relationship between sodium reduction and CVD are more limited, especially at lower absolute levels of sodium intake. A preponderance of reports based on observational epidemiology support the presence of a direct relationship between sodium intake and CVD, especially for stroke. Although the DASH (Dietary Approaches to Stop Hypertension)-Sodium clinical trial demonstrated an increasingly beneficial effect of reduced sodium intake on blood pressure at progressively lower levels of dietary sodium down to 1500 mg/d, some reports have identified null, inverse, or J-shaped relationships with CVD.

In its most recent review of dietary sodium, the IOM committee was charged with examining the effects of very low levels of sodium intake (in the range of 1500 to 2300 mg/d) on health outcomes, defined as clinical CVD events. This and other reviews have uniformly concluded that the underlying data showing adverse effects of sodium in this range are of insufficient quality to support a firm conclusion. Many suffer from some combination of potential for bias in the assessment of sodium intake, reverse causality, residual confounding, and random error. Despite this, reports of a paradoxical inverse or J-shaped association between sodium intake and CVD have received considerable attention from the media and scientific community and have been the basis for the addition of sodium to food products.

Several analyses of CVD or total mortality were based on data from the National Health and Nutrition Examination Survey, which used a single 24-hour diet recall to estimate sodium intake. This approach underestimates sodium intake by failing to measure sodium added at the table, in the kitchen, in supplements, or in drinking water. Falsely low estimation caused by underreporting of food and beverage intake and portion sizes is also a concern. Finally, inaccuracies can result from changes in commercial food composition that are not reflected in the nutrient databases used to estimate sodium content. Use of food frequency questionnaires to estimate sodium intake was greater in those with a higher starting level of blood pressure, older persons, blacks, and those with a more successful intervention. In the meta-analyses that are most generalizable to clinical practice and public health, total cholesterol and catecholamine levels were essentially unchanged, and changes in urinary protein excretion were consistent with a beneficial effect of sodium reduction. Blood pressure is one of the best validated surrogate markers for CVD and has been identified as one of the leading preventable causes of death in the United States.

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intake is prone to many of the same challenges encountered with use of dietary recalls. In addition, sodium content can vary considerably across brands of processed foods, which are typically incompletely assessed in these questionnaires.

The gold standard for sodium assessment in healthy persons is 24-hour urine collection. Overnight and spot urine samples are less burdensome for study participants and research staff; however, they are affected by diurnal variation, and the methods supporting the validity of their use are inadequate. They represent a weak substitute for 24-hour urine collections, especially when they are used to estimate sodium intake and relationships in an individual. Despite being considered the “gold standard,” even 24-hour collections are subject to quality control concerns, particularly undercollection of urine specimens. Measurements based on a single 24-hour urine collection fail to capture day-to-day variability, which makes them less than optimal for study of the within-person relationship between sodium and CVD.

The TOHP Follow-up Study used an average of 3 to 7 carefully collected 24-hour urine collections as a measure of sodium exposure, which greatly reduced bias caused by measurement error and random error attributable to within-person variability over time. We found a continued decrease in CVD events among those with sodium levels as low as 1500 mg/d, with no evidence of a J shape when examining spline curves. Risk reductions among those at the lowest levels of sodium excretion were substantial, with a 32% reduction among those excreting <2300 mg/d, although this was not statistically significant because of the small numbers in this subgroup and limited power.

To further consider the quality of urine specimens, we also adjusted for creatinine using various approaches. Because the rate of creatinine formation is fairly constant in healthy individuals, urinary creatinine serves as a measure of completeness of urine collection. Those with the lowest levels of urinary creatinine excretion are likely to include individuals who have collected an incomplete 24-hour specimen. They may be less likely to exhibit healthy behaviors and more likely to have poorer health outcomes. Creatinine level, however, is also related to other factors, such as age, race, and body mass index. Although average sodium levels in TOHP were positively associated with creatinine levels and the Cr/Wt ratio, these had little impact on the relationship between sodium and CVD in these analyses.

In the present study, the average Cr/Wt was not a predictor of CVD; however, when we used only the first baseline urinary creatinine, it was a strong predictor. This suggests that the use of the average of many measurements over several years, as in these TOHP analyses, adjusts for variations in dilution and removes any effect of undercollection, as well as reducing within-person variability. Estimates based on a single urine collection, however, may be distorted by undercollection of the specimen, and in such a circumstance, creatinine adjustment should be considered.

Reverse causation is another important source of error in observational studies of the relationship between dietary sodium and CVD. This is most likely an issue in studies that include patients with heart failure, coronary heart disease, chronic kidney disease, diabetes mellitus, or even hypertension. Such patients are likely to reduce their sodium intake either because of a poor diet or health advice. This can result in an inverse relationship between sodium intake and CVD that is a consequence of their underlying disease rather than the lower intake of dietary sodium (reverse causation). In many of these studies, the situation is further compounded by the use of potent diuretics and other medications that can distort estimates of sodium intake. Often, the number of CVD events in these studies is small, so that even a trivial number of events resulting from reverse causation can distort the results. Eliminating early periods of follow-up and controlling for...
illness in the analysis may not be a sufficient remedy. Indeed, controlling for blood pressure, hypertension, or hypertension medication in the analysis may eliminate the indirect effect of sodium through blood pressure, which may be the main biological mechanism. A major strength of the TOHP follow-up analyses is that the cohorts were restricted to healthy, free-living, prehypertensive individuals who were not taking blood pressure medications. Thus, reverse causation is very unlikely to have been an issue in the TOHP follow-up study. However, because it did not include those with high blood pressure, it could also have eliminated those who were most sensitive to the effects of sodium on blood pressure and in whom the impact on CVD could be even stronger.

Limitations of the present analyses should also be considered. First, the response rate to the TOHP follow-up questionnaires was <80%. However, much of this was attributable

Table 4. Cardiovascular Events After the Trials of Hypertension Prevention by Categories of Urinary Sodium Excretion

<table>
<thead>
<tr>
<th>Sodium Excretion, mg/d</th>
<th>Excluding those with CV Cr/Wt ≥20%* (CVD events/total=104/1298)</th>
<th>Excluding those with CV Cr/Wt ≥30%* (CVD events/total=141/1780)</th>
<th>Controlling for Cr/Wt in model (CVD events/total=193/2312)</th>
<th>Controlling for CV Cr/Wt in model* (CVD events/total=180/2218)</th>
</tr>
</thead>
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<td></td>
<td>HR</td>
<td>95% CI</td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>&lt;2300</td>
<td>0.67</td>
<td>0.23–1.91</td>
<td>0.71</td>
<td>0.30–1.68</td>
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<td>2300 to &lt;3600</td>
<td>0.83</td>
<td>0.48–1.44</td>
<td>0.79</td>
<td>0.50–1.24</td>
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<tr>
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<td>(Reference)</td>
<td>1.00</td>
<td>(Reference)</td>
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<td>≥4800</td>
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<td>P Value</td>
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</table>

From Cox proportional hazards regression models stratified by trial phase and adjusted for age, sex, race/ethnicity, clinic, and treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, potassium excretion, and family history of cardiovascular disease, as well as changes in weight, smoking, and exercise during the trial periods. Sensitivity analyses adjusted for creatinine. CI indicates confidence interval; Cr/Wt, creatinine/weight ratio; CV, coefficient of variation; and HR, hazard ratio.

*In those with ≥2 urine excretions.
to changes in address after 5 to 10 years of no contact; the response rate was 85% among those with a valid address. We also collected information on cardiovascular deaths for all participants through the National Death Index. In addition, there was no difference in response by sodium level, which reduces the likelihood of bias. Second, it is unclear whether sodium levels were maintained throughout follow-up; however, this concern is shared by most observational studies, and our repeat 24-hour urine collections over 1 to 4 years represent very accurate assessments of usual sodium intake. Third, we cannot rule out residual confounding. Those on a low-sodium diet may exhibit other healthy lifestyle behaviors, including better diet quality and increased exercise. We adjusted for weight, exercise, and smoking in our models, as well as changes in these during the intervention periods, but uncontrolled confounding remains a possibility.

Approximately 37% of US adults have prehypertension, and these data show that they would benefit from sodium reduction. Given the strong impact of sodium on blood pressure among hypertensives, the 16% of US adults with hypertension would also be expected to benefit. Thus, these results are consistent with the overall health benefits of reducing sodium intake to the 1500 to 2300 mg/d range in the majority of the population, in agreement with current dietary guidelines. Although there is likely a biological benefit to lowering sodium to these levels, however, only 1% of US adults have a sodium intake as low as 1500 mg/d currently, and <10% have intakes <2300 mg/d. Reasonable questions remain about the practical implementation of such low sodium targets, but even a small reduction in the population’s average intake of dietary sodium could result in a major improvement in cardiovascular health.

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**Disclosures**
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**References**
22. Desai M, Stockbridge N, Temple R. Blood pressure as an example of a biomarker that functions as a surrogate. AAPS J. 2006;8:E146–E152.
Several observational studies and randomized trials have examined the associations of sodium with subsequent morbidity and mortality and generally suggest a lowering of risk with lower sodium; however, few studies have examined absolute levels of sodium intake down to recommended target intakes of 1500 to 2300 mg/d. Some recent studies have raised the possibility of adverse effects of low sodium, but these paradoxical findings might have resulted from suboptimal measurement of sodium and potential biases related to indication or reverse causation. The extended follow-up of the Trials of Hypertension Prevention (TOHP) provided the opportunity to examine the effects of low sodium intake as measured with several 24-hour sodium excretions collected over periods of 1.5 to 4 years. In this healthy cohort of 2275 prehypertensive individuals, there was a significant linear decrease in risk of cardiovascular disease with decreasing sodium levels. There was no deviation from linearity at the lowest intake levels, which suggests that cardiovascular risk continues to decline at the lowest levels of sodium intake. These data are consistent with the health benefits of reducing sodium intake to the 1500 to 2300 mg/d range in the majority of the population and are in agreement with current dietary guidelines.
Lower Levels of Sodium Intake and Reduced Cardiovascular Risk
Nancy R. Cook, Lawrence J. Appel and Paul K. Whelton

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Supplemental Material
Supplemental Table 1. Follow-up response after the Trials of Hypertension Prevention by categories of urinary sodium excretion (mg/24hr).

<table>
<thead>
<tr>
<th>Sodium Excretion (mg/24hr)</th>
<th>P Value for Trend</th>
<th>OR per 1000 mg/d</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2300</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2300-&lt;3600</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3600-&lt;4800</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4800</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TOHP I**

Responded/ Total (%) | 189/246 (76.8) | 590/775 (76.1) | 427/566 (75.4) | 191/257 (74.3) | 0.39* |

**TOHP II**

Responded/ Total (%) | 47/66 (71.2) | 303/407 (74.4) | 341/413 (82.6) | 224/281 (79.7) |

**Model 1**

| OR† | 0.88 | 0.86 | 1.00 | 0.82 | 0.95 | 1.01 | 0.84 |
| 95%CI | 0.64-1.22 | 0.70-1.07 (Reference) | 0.63-1.07 | 0.93-1.09 |

**Model 2**

| OR | 0.88 | 0.85 | 1.00 | 0.82 | 0.85 | 1.02 | 0.73 |
| 95%CI | 0.62-1.26 | 0.68-1.06 (Reference) | 0.62-1.09 | 0.93-1.11 |

**Model 3**

| OR | 1.05 | 0.82 | 1.00 | 0.84 | 0.96 | 1.01 | 0.85 |
| 95%CI | 0.69-1.58 | 0.64-1.06 (Reference) | 0.62-1.15 | 0.91-1.12 |

* From Cochran-Mantel-Haenszel analysis of trend.
† From logistic regression models stratified adjusted as follows: Model 1 (phase, age, sex, race/ethnicity, clinic, and treatment assignment), Model 2 (Model 1 variables plus education status, baseline weight, alcohol use, smoking, exercise, potassium excretion, and family history of cardiovascular disease), and Model 3 (Model 2 variables plus changes in weight, smoking, and exercise during the trial periods). CVD indicates cardiovascular disease; OR, odds ratio; CI, confidence interval.
**Supplemental Table 2.** Cardiovascular events after the Trials of Hypertension Prevention – Sensitivity analyses of linear effects of average urinary excretions expressed in standard deviation units.

<table>
<thead>
<tr>
<th>Model</th>
<th>HR</th>
<th>95% CI</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Model A</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr/Wt (per SD)</td>
<td>1.04</td>
<td>0.86-1.25</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>Model B</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na (per SD)</td>
<td>1.13</td>
<td>0.95-1.35</td>
<td>0.18</td>
</tr>
<tr>
<td><strong>Model C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K (per SD)</td>
<td>0.85</td>
<td>0.70-1.04</td>
<td>0.12</td>
</tr>
<tr>
<td>Na (per SD)</td>
<td>1.21</td>
<td>1.00-1.48</td>
<td>0.054</td>
</tr>
<tr>
<td><strong>Model D</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr/Wt (per SD)</td>
<td>1.03</td>
<td>0.82-1.30</td>
<td>0.80</td>
</tr>
<tr>
<td>K (per SD)</td>
<td>0.84</td>
<td>0.68-1.04</td>
<td>0.12</td>
</tr>
<tr>
<td>Na (per SD)</td>
<td>1.20</td>
<td>0.98-1.48</td>
<td>0.085</td>
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<tr>
<td><strong>Model E</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Na/Cr (per SD)</td>
<td>1.12</td>
<td>0.94-1.32</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>Model F</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K/Cr (per SD)</td>
<td>0.83</td>
<td>0.67-1.02</td>
<td>0.078</td>
</tr>
<tr>
<td>Na/Cr (per SD)</td>
<td>1.16</td>
<td>0.98-1.39</td>
<td>0.088</td>
</tr>
<tr>
<td><strong>Model G</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cr/Wt (per SD)</td>
<td>1.04</td>
<td>0.86-1.26</td>
<td>0.67</td>
</tr>
<tr>
<td>K/Cr (per SD)</td>
<td>0.83</td>
<td>0.67-1.03</td>
<td>0.087</td>
</tr>
<tr>
<td>Na/Cr (per SD)</td>
<td>1.17</td>
<td>0.98-1.40</td>
<td>0.079</td>
</tr>
</tbody>
</table>

From Cox proportional hazards regression models stratified by trial phase and adjusted for age, sex, race/ethnicity, clinic, and treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, potassium excretion, and family history of cardiovascular disease, and changes in weight, smoking, and exercise during the trial periods. Na indicates sodium; K, potassium; Cr, creatinine; Wt, weight; HR, hazard ratio; CI, confidence interval.