Association between Sodium Intake and Change in Uric Acid, Urine Albumin Excretion, and the Risk of Developing Hypertension

Running title: Forman et al.; Salt, urate, urine albumin, hypertension

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Journal Subject Codes: [8] Epidemiology; [193] Clinical studies
Abstract:

Background — In non-hypertensive individuals, a high sodium diet has little acute effect on blood pressure but, for unclear reasons, is associated with hypertension if consumed chronically. We hypothesized that a chronically high sodium intake would be associated with increases in biomarkers of endothelial dysfunction, specifically serum uric acid (SUA) and urine albumin excretion (UAE), and that high sodium intake would be associated with incident hypertension among those with higher SUA and UAE.

Methods and Results — We prospectively analyzed the associations between sodium intake and the change in SUA (N=4062) and UAE (N=4146) among participants of the PREVEND study who were not taking antihypertensive medications. We also examined the association of sodium intake with the incidence of hypertension (N=5556) among non-hypertensive participants. After adjusting for confounders, each 1 gram higher sodium intake was associated with a 1.2μmol/L increase in SUA (p=0.01) and a 4.6mg/d increase in UAE (p<0.001). The relation between sodium intake and incident hypertension varied according to SUA and UAE. For each 1 gram higher sodium intake, the adjusted hazard ratio for developing hypertension was 0.98 (0.89-1.08) among those in the lowest tertile of SUA, and 1.09 (1.02-1.16) among those in the highest. Corresponding hazard ratios were 0.99 (0.93-1.06) among participants whose UAE was <10mg/d, and 1.18 (1.07-1.29) among those whose UAE was >15mg/d.

Conclusions — Over time, higher sodium intake is associated with increases in SUA and UAE. Among individuals with higher SUA and urine UAE, a higher sodium intake is an independent risk factor for developing hypertension.

Key words: diet, epidemiology, hypertension, risk factors, sodium
Introduction

Most individuals consume sodium far in excess of the recommendations from major health organizations.\(^1\) A high salt diet is believed to be responsible for 20-40% of all cases of hypertension in the United States,\(^2\) and approximately 6% of myocardial infarctions and strokes annually.\(^3\)

Evidence in non-hypertensive humans and experimental animals indicates that a chronically high sodium intake is associated with increases in blood pressure over time.\(^2,4-8\) Paradoxically, short term sodium loading in these healthy humans and animals does not substantially increase blood pressure.\(^9,10\) How individuals who are not initially salt sensitive can develop hypertension related to chronic sodium loading is not well understood. However, studies in humans and animals have shown that short-term sodium loading is associated with endothelial dysfunction and vascular injury,\(^4,11-16\) and it is possible that such insults, if repeated over the long-term, could explain the increasing blood pressure associated with a chronically high salt diet. A high salt diet may also induce salt-sensitivity, as has been reported in rodents, possibly through endothelial dysfunction.\(^4\)

Higher serum uric acid (SUA) and a higher urinary albumin excretion (UAE) are well established markers of endothelial dysfunction,\(^17-25\) and both are independently associated with an increased risk of hypertension.\(^26-30\) We hypothesized that a higher sodium intake would be positively associated with a longitudinal increase in SUA and UAE, and that higher SUA and UAE would modify the association between sodium intake and hypertension. We investigated this hypothesis in participants of the PREVEND study.
Methods

Study population

The PREVEND (Prevention of REnal and Vascular ENd stage Disease) study is a large, ongoing, prospective cohort initiated in 1997 when 40,856 people from the general population of Groningen, The Netherlands, were screened. Recruitment was based upon the screening urine albumin concentration to enrich the cohort with individuals with albuminuria. A total of 8592 participants completed the first examination between 1997 and 1998.31, 32 Of these, 6894 participants completed a second examination between 2001 and 2003, and 5862 completed a third examination between 2003 and 2006.33

To perform the analyses of sodium intake and risk of hypertension, we limited our study population to 5556 participants who did not have prevalent hypertension (defined below) at the time of their initial examination, and who had available measurements of urine sodium (Figure 1). To examine associations of sodium intake with changes in SUA and UAE between the baseline (first) and third examinations, we excluded individuals who were taking antihypertensive medications at the first or third examinations, since antihypertensive medications can affect the levels of SUA and UAE, and also excluded those with missing data on SUA or UAE. After exclusions, 4062 participants were included in the analysis of change in SUA, and 4146 participants were included in the analysis of change in UAE.

The PREVEND study has been approved by the medical ethics committee at the University Medical Center Groningen, and the current analysis was approved by the institutional review board at Brigham and Women’s Hospital. All participants gave written informed consent.
Assessment of sodium intake

Throughout this manuscript, we refer to “sodium” rather than “salt” because major societies that issue guidelines, such as the Joint National Committee34 and European Society of Hypertension35 each make recommendations for restriction of “sodium”. Each 43 mmol of sodium is approximately equivalent to 1 gram of sodium or 2.5 grams of salt (sodium chloride).

Sodium intake was assessed by urinary sodium excretion. Participants collected two 24 hour urine specimens at each of the three examinations. Determination of urine sodium concentration was performed on specimens from the first and second examinations by indirect potentiometry using a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany); the sodium concentration was multiplied by the urine volume to obtain a value in mg per 24 hours. For each examination, we used the mean value of the two 24 hour collections. The correlation coefficients among participants’ sodium intake across the longitudinal examinations were 0.55 (in the whole cohort) and 0.66 (in just those who did not develop hypertension).

Assessment of serum uric acid and albumin excretion rate

Serum concentrations of uric acid were measured using a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany) with the uricase PAP method, and expressed as µmol/L (divide by 59.48 to obtain the SUA in mg/dL). Urine albumin concentration was measured on 24 hour urine specimens by nephelometry (Dade Behring Diagnostic, Marburg, Germany); the threshold value was 2.3 mg/L and intra-assay and inter-assay coefficients of variation were less than 2.2% and 2.6%, respectively. The urine albumin concentration was multiplied by the total urine volume to obtain a UAE in mg per 24 hours; the UAE at each examination was defined as the mean value of the two collections. We defined the change in SUA and UAE as the mean values for SUA and UAE at the third examination minus the mean values for SUA and UAE at the first
(baseline) examination.

Assessment of hypertension

At each examination, blood pressure was measured on the right arm with an automated device (Dinamap XL Model 9300: Johnson & Johnson Medical, Tampa, FL) for 8 to 10 minutes while the participant was supine. The blood pressure for the visit was defined as the mean of the last two readings. Use of antihypertensive medications was ascertained by questionnaire at each visit, and was complemented by information garnered from community pharmacies.

Hypertension was defined as a systolic pressure ≥ 140 mmHg, a diastolic pressure ≥ 90 mmHg, or both, or the use of antihypertensive medications, in concordance with recommendations from the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Participants who already had hypertension at the baseline examination were excluded; incident hypertension was defined as hypertension that occurred after the baseline examination.

Assessment of covariates

The procedures at each examination in the PREVEND study have been described in detail previously. Briefly, each of the three examinations included two visits to the outpatient unit separated by three weeks. Participants completed questionnaires that gathered demographic information, as well as detailed information about health-related behaviors (such as smoking and alcohol use), diagnoses of cardiovascular and renal disease, medication use, and family history. In addition to blood pressure measurements, participants had assessments of height and weight, and provided fasting blood samples and 24 hour urine specimens.

Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. Urine potassium was determined by indirect potentiometry using a MEGA
clinical chemistry analyzer (Merck, Darmstadt, Germany). Using the same analyzer, urine calcium was determined by a photometric test with an o-Cresolphthalein complex and urine uric acid was measured with the uricase PAP method. Concentrations of serum and urine creatinine, serum glucose, and serum total cholesterol were determined using enzymatic methods with a Kodak Ektachem dry chemistry autoanalyzer (Eastman Kodak, Rochester, NY). Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. Smoking status was categorized as never, quit less than one year earlier, quit more than one year previously, and active smoking. Alcohol intake was categorized as none, 1 to 4 beverages per month, 2 to 7 beverages per week, 1 to 3 beverages per day, and 4 or more beverages per day.

Statistical analyses

Sex adjusted associations between sodium intake and other covariates at baseline were analyzed using linear regression. The associations were displayed visually as medians and interquartile ranges for each covariate stratified by quartile of sodium intake. Urinary sodium excretion as a marker for sodium intake was analyzed as a continuous variable (per one gram higher intake), and also in quartiles. The associations of sodium intake with the longitudinal changes in SUA and UAE were examined among the subset of participants with available data and who were also not using antihypertensive medication at the final visit. These analyses employed linear regression, with sodium intake as the independent variable and changes in SUA and UAE as the dependent variables. Multivariable models adjusted for age, body mass index, sex, alcohol intake, smoking status, systolic and diastolic blood pressure, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine. In addition, models were mutually adjusted for baseline
levels of serum uric acid and urinary albumin.

The association between sodium intake and risk for incident hypertension was analyzed using multivariable Cox proportional hazards regression; stratified models by tertile of SUA or clinical category of UAE (< 10 mg/d [N=3490], 10-15 mg/d [N=1051], and > 15 mg/d [N=1015]) were constructed to examine whether the association between sodium intake and hypertension risk varied according to SUA and UAE. In these proportional hazards regression models, person time was counted from the date of the first examination until the date that hypertension was diagnosed, the date of death, or the date of the last examination, whichever came first. Multivariable models were adjusted for age, body mass index, sex, alcohol intake, smoking status, family history of hypertension, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine.

Multiplicative interaction terms were created between sodium intake and SUA, and between sodium intake and UAE. Effect modification of the associations between sodium intake and hypertension risk by SUA and UAE was then tested by including these interaction terms into unstratified multivariable models that also included terms for the main effects of sodium intake, and either SUA or UAE. The proportional hazards assumption was tested by analyzing the interaction between sodium intake and calendar time; there was no significant interaction between sodium intake and calendar time. Finally, we examined the possibility of a non-linear relation between sodium intake and incident hypertension non-parametrically with restricted cubic splines. Tests for non-linearity used the likelihood ratio test, comparing models with only the linear term to models with both linear and cubic spline terms. SAS version 9.1 (SAS Institute, Cary, North Carolina) was used for all analyses, and all p-values were two-sided.
Results

A total of 5556 participants who did not already have hypertension at the time of the first examination, and had available measurements of urine sodium, were included in the analysis of incident hypertension (Figure 1). The baseline characteristics of this study population, according to quartile of sodium intake, are displayed in Table 1. At baseline, a higher sodium intake was associated with higher SUA and UAE, as well as higher systolic and diastolic pressure, higher BMI, higher serum glucose, and a higher prevalence of active smoking and alcohol use. Women consumed less sodium than men. Age, estimated glomerular filtration rate, plasma total cholesterol, and family history of hypertension were not associated with sodium intake at baseline. The baseline characteristics of the 4062 participants who were analyzed for change in SUA and the 4146 participants who were analyzed for change in UAE were not different from the baseline characteristics of 5556 participants analyzed for incident hypertension.

We analyzed the association between sodium intake and change in SUA among the 4062 participants with available SUA levels both at the first (baseline) examination and third examination, and who did not take antihypertensive medication (Table 2). The median SUA of the entire population increased from the first to the third examination by 17.8 μmol/L, and this increase was larger among those who consumed more sodium. For every 43 mmol (approximately 1 gram) higher sodium intake, the adjusted change in SUA was 1.4 μmol/L larger (95% CI, 0.2-2.6; p=0.01). Compared with those in the lowest quartile of sodium intake (< 123 mmol/d), those in the highest (> 221 mmol/d) had a 6.0 μmol/L (95% CI, 1.3-10.7) larger adjusted change in SUA (Table 2 and Figure 2A).
We also analyzed the association between sodium intake and change in UAE among 4146 individuals who had UAE measured at both the first and third examinations, and who were not treated with antihypertensive medications (Table 2). The median UAE increased for the whole population by 0.4 mg/d during the period of follow-up. The change in UAE was larger among participants who consumed greater amounts of sodium. The adjusted change in UAE was 4.6 mg/d larger for each additional 1 gram of sodium consumed (95% CI, 2.2-7.0; p<0.001). Those in the highest quartile of sodium intake had a 6.5 (95% CI, -2.6-15.6) mg/d larger change in UAE compared with those in the lowest quartile (Table 2 and Figure 2B).

During a median follow-up of 6.4 years, 878 incident cases of hypertension accrued. Sodium intake was significantly associated with incident hypertension. The crude hypertension incidence rate for the entire population without hypertension at baseline was 38 cases per 100,000 person-years. The incidence rate was 99 cases per 100,000 person-years among participants in the highest quartile of sodium intake and 28 cases per 100,000 person-years among those in the lowest quartile.

After adjusting for age, the hazard ratio for incident hypertension per one gram higher sodium intake was 1.06 (95% CI, 1.02-1.11). Compared with the lowest quartile of sodium intake, the age-adjusted hazard ratio for incident hypertension among those in the highest quartile of sodium intake was 1.29 (95% CI, 1.05-1.60). After additionally controlling for BMI, sex, alcohol intake, smoking status, family history of hypertension, estimated glomerular filtration rate, serum levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine, the hazard ratio was 1.05 (95% CI, 1.00-1.10) for each one gram higher sodium intake and 1.21 (95% CI, 0.98-1.51) comparing the highest with lowest quartile of sodium intake.
The association of sodium intake with incident hypertension was modified by both SUA and UAE (Table 3 and Figure 3). A one gram higher sodium intake was associated with an adjusted hazard ratio of 0.98 (95% CI, 0.89-1.08) among those in the lowest tertile of SUA (<255.8 μmol/L), and with an adjusted hazard ratio of 1.09 (95% CI, 1.02-1.16) among those in the highest tertile of SUA (>309.3 μmol/L); the p-value for the interaction between sodium intake and SUA was <0.001. When we stratified by category of UAE, the hazard ratio of developing hypertension for each one gram higher sodium intake was 0.99 (95% CI, 0.93-1.06) among participants whose UAE was <10 mg/d, and was 1.18 (95% CI, 1.07-1.29) among those whose UAE was >15 mg/d; the p-value for the interaction between sodium intake and UAE was 0.007. Further controlling for baseline systolic and diastolic blood pressure did not materially alter these results. The association of sodium intake with incident hypertension was close to linear in our non-parametric analysis (p-value for linearity = 0.06), and was linear among those participants in the highest tertile of SUA (p-value for linearity = 0.05) and the highest category of UAE (p-value for linearity = 0.02).

**Discussion**

In this prospective, population-based cohort, we found that a higher sodium intake was independently associated with larger increases in markers of vascular endothelial dysfunction over time, specifically SUA and UAE. In addition, the association between sodium intake and incident hypertension was modified by these markers of vascular endothelial dysfunction, and sodium intake was only an independent risk factor among those with higher levels of SUA and UAE. Thus, a high sodium diet may lead to biological changes favoring the development of hypertension if the high sodium diet is continued.
More than thirty years ago, Guyton et al. drew attention to the contradiction between the short-term and long-term effects of sodium loading on blood pressure. In the short-term, a high sodium diet has a minimal effect on the blood pressure of normal individuals and experimental animals. However, sodium loading led to substantial increases in the blood pressure of those who had a reduction in kidney mass, infusion of angiotensin II, or endothelial dysfunction (i.e., individuals who are ‘salt sensitive’). In contrast to acute sodium loading, chronic sodium loading is associated with the development of hypertension in initially normal populations. This has been demonstrated in various natural experiments, notably in the Cook Islanders specifically, lifetime blood pressure remained low among the residents of one island where access to sodium rich food was limited, while blood pressure increased with age among a population of genetically similar inhabitants of a nearby island with ample access to sodium rich food. Identical observations have been made in rodents who, after weaning, were randomly assigned to consume high sodium or low sodium chow. Thus, a high sodium diet may have minimal acute effects on blood pressure, but if continued over long periods of time, may ultimately result in progressive increases in blood pressure.

The mechanisms that underlie the association between chronic sodium loading and hypertension are incompletely understood. Rodent data suggest that sodium loading leads to suppression of nitric oxide synthase in vascular beds, generating endothelial dysfunction. In humans, sodium loading also seems to produce endothelial dysfunction. As an example, the effect of a high sodium diet on brachial endothelium-dependent vasodilation was determined in 16 healthy, non-hypertensive individuals in a randomized double-blind cross-over trial. Compared with a low sodium diet (76 mmol/d), endothelium-dependent vasodilation was 36% reduced (p<0.05) when daily sodium intake was supplemented (mean total intake of 225
mmol/d). In addition to endothelial dysfunction, a high sodium diet may lead to anatomic capillary rarefaction. Capillary rarefaction, or a decrease in the number of capillaries, is a well established abnormality in people with hypertension, and may also predate the onset of hypertension. Since, as noted earlier, individuals with endothelial dysfunction and vascular damage are more likely to be sodium sensitive, it is possible that a chronic high sodium intake may create a state of sodium sensitivity. Indeed, this phenomenon has been noted in rats who “transitioned” from sodium resistant to sodium sensitive after eight weeks on a high sodium diet. Thus, chronic sodium loading may lead to endothelial dysfunction and vascular damage, which in turn may exacerbate the pressor effects of a high sodium diet in an amplification loop.

Higher SUA and UAE are markers of endothelial dysfunction in humans, and therefore may also be markers of sodium sensitivity. The association of SUA with endothelial dysfunction was illustrated in 217 individuals with mild untreated hypertension who underwent measurement of endothelium-dependent brachial artery vasodilation. Compared with participants whose SUA was 3.5 mg/dL or less, endothelium-dependent vasodilation was 33% worse among those with SUA levels of 5.5 mg/dL or more; other studies have found similar associations. In rats, induction of hyperuricemia by inhibiting the uricase enzyme for just nine weeks induces persistent sodium sensitivity, even after the SUA is lowered to normal. In humans, an association between SUA and sodium sensitivity was documented in a small study of 21 healthy volunteers; the correlation coefficient was 0.31, although not statistically significant. The relation between UAE and endothelial dysfunction is well established. In addition, higher UAE is associated with sodium sensitivity. In 177 healthy volunteers, for example, the prevalence of sodium sensitivity was significantly higher in those whose UAE was 15 to 20 mg/d compared with those whose UAE was 10 mg/d or less (67% vs. 24%). Taken together,
these data suggest that higher levels of SUA and UAE indicate the presence of endothelial
dysfunction and, as a result, may identify those at higher risk for hypertension when sodium
intake is high.

We found that a higher sodium intake was associated with greater longitudinal increases
in SUA and UAE. To our knowledge, the relation between sodium intake and increasing SUA is
novel. However, the effects of sodium intake on albumin excretion have been documented in
several clinical trials,\textsuperscript{51-53} and in observational studies.\textsuperscript{54} In the largest of these trials, 71 white,
69 black, and 29 Asians received sodium supplements for six weeks and placebo for six weeks,
given in random order.\textsuperscript{51} UAE increased significantly with sodium supplements from 9.1 mg/d
to 10.2 mg/d; this increase may have been due to a change in blood pressure, which also
increased with sodium supplements. In our study, a 1 gram higher sodium intake over a median
of 6.4 years was associated with a 4.6 mg/d increase in UAE that was independent of blood
pressure.

Overall, a higher sodium intake was also associated with a modestly increased risk of
developing hypertension. This finding is consistent with some,\textsuperscript{5,55} but not all,\textsuperscript{56} prospective
cohort studies. Among 1520 Taiwanese men and women followed for an average of 7.9 years,
for example, the risk of developing hypertension was 26\% higher (95\% CI, 1-57\%) among those
whose baseline 24 hour urinary sodium excretion was 178 mmol/d or more compared with those
whose sodium intake was estimated to be less than 123 mmol/d.\textsuperscript{5} On the other hand, there was
no association between urinary sodium excretion and incident hypertension in 2096 Europeans
followed for a median of 6.5 years.\textsuperscript{56} However, the confidence intervals were wide and
incorporated the hazard ratio that we observed. Furthermore, the hypertension incidence rates
according to category of urinary sodium excretion began to diverge after approximately six years
of follow-up, and the incidence thereafter was higher among those who consumed more sodium. Our finding is also consistent with the combined experience from randomized trials of sodium reduction, which indicate that long-term reductions in sodium reduce blood pressure.6,57

We found that the association between sodium intake and risk for developing hypertension depended upon SUA and UAE. In stratified models, sodium intake was independently associated with incident hypertension in participants who were in the highest tertile of SUA, or who had UAE >15 mg/d. The dependence of the sodium – hypertension association upon SUA and UAE may reflect differences in sodium sensitivity, which, in and of itself, is a significant and independent predictor of hypertension incidence.58 Modification of the effect of sodium intake on blood pressure has been described previously in meta-analyses. As an example, a modest reduction in sodium intake lowered systolic blood pressure by 5.2 mmHg in 28 trials of hypertensive individuals, and by 1.3 mmHg in 19 trials of non-hypertensive individuals (p-interaction <0.001).57 In addition, the effect of sodium on blood pressure tended to be larger in older compared with younger individuals.57 To our knowledge, however, no studies have examined whether the association between sodium intake and risk for hypertension is modified by markers of endothelial dysfunction, which could be indicators of a sodium sensitive state.

Our study has multiple strengths, including the use of a large prospective community-based cohort, the use of multiple 24 hour urine specimens to estimate each participant’s sodium intake and to define their UAE, the use of multiple measured blood pressures along with participant and pharmacy information regarding antihypertensive medication to define hypertension, extensive adjustment for covariates that are associated with hypertension and thus potential confounders, and updating of sodium intake and covariate information mid-way.
through the period of follow-up to reduce potential misclassification. Our study also has important limitations. First, approximately 30% of those who participated in the first examination did not participate in the third examination, in large part because of refusal or death. However, the baseline characteristics of those who were lost to follow-up and those who completed the third examination were only marginally different (data not shown), and therefore the likelihood for survival bias is low. Moreover, because individuals with hypertension may be more likely to be lost to follow-up owing to cardiovascular disease, any survival bias that was introduced would likely lead to an underestimation of the true association between sodium intake and hypertension. Second, this PREVEND cohort is almost entirely white, therefore limiting the generalizability of our findings. Nevertheless, several of our findings, namely the association between sodium intake and changes in albuminuria, and the relation between sodium intake and incident hypertension, have been previously observed in black populations. Third, our definition of hypertension was based in part on measurement of supine blood pressure, whereas consensus recommendations (such as from the Joint National Committee) recommend ascertainment of seated blood pressure. However, with the exception of elderly individuals and those with hypovolemia, supine and seated blood pressure should differ only minimally.

Finally, as with any observational study, residual confounding may explain our findings, at least in part. As an example, a higher sodium intake may be a marker for other unhealthy lifestyle choices that we did not measure and therefore could not include in our multivariable models, such as physical activity or intake of sugar-sweetened beverages. On the other hand, we did adjust for numerous known risk factors for hypertension, including adiposity, and there are extensive physiologic and experimental studies that provide a plausible mechanism linking sodium intake with hypertension.
In conclusion, a higher sodium intake over time is associated with greater increases in two markers of endothelial dysfunction, namely SUA and UAE. In addition, a higher sodium intake is associated with an increased risk of developing hypertension, principally in those individuals who have higher levels of SUA and UAE. Taken together, high sodium diet over the long term may lead to endothelial dysfunction and vascular damage, generating a biological state in which continuance of the high sodium diet may produce hypertension (a sodium amplification loop). These findings should be tested in other prospective cohorts, and if possible, in randomized trials.

**Funding Sources:** This work was funded by the American Heart Association (2009A050171) and the National Institutes of Diabetes Digestive and Kidney disease (DK091417). The PREVEND study has been made possible by grants from the Dutch Kidney Foundation. The funders of this work had no role in the conception, execution, or analysis of the research, and had no role in drafting of the manuscript. We also thank Dade Behring (Marburg, Germany) for supplying equipment (specifically the Behring Nephelometer II) and reagents for nephelometric measurement of urinary albumin concentration.

**Conflict of Interest Disclosures:** None.

**References:**


4. Carlstrom M, Sallstrom J, Skott O, Larsson E, Persson AE. Uninephrectomy in young age or


<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartile of Urine Sodium, mmol/day (median, interquartile range)</th>
<th>Sex-adjusted p-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N=1389</td>
<td>N=1389</td>
</tr>
<tr>
<td>Uric acid, μmol/L</td>
<td>261.7 (220.1-321.2)</td>
<td>279.6 (237.9-327.1)</td>
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<td>Urine albumin excretion, mg/d</td>
<td>7.3 (5.3-11.7)</td>
<td>7.9 (5.8-12.5)</td>
</tr>
<tr>
<td>Age, years</td>
<td>43 (36-52)</td>
<td>43 (36-52)</td>
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<tr>
<td>BMI, kg/m²</td>
<td>23.7 (21.7-26.2)</td>
<td>24.2 (22.2-26.7)</td>
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<tr>
<td>Systolic blood pressure, mmHg</td>
<td>116 (108-126)</td>
<td>118 (110-127)</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>69 (64-74)</td>
<td>70 (65-75)</td>
</tr>
<tr>
<td>Estimated GFR, mL/min/1.73 m²</td>
<td>87 (77-97)</td>
<td>87 (77-96)</td>
</tr>
<tr>
<td>Serum Glucose, mmol/L</td>
<td>4.5 (4.2-4.9)</td>
<td>4.6 (4.2-4.9)</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.3 (3.9-7.7)</td>
<td>5.4 (4.7-6.2)</td>
</tr>
<tr>
<td>Urine calcium, mg/d</td>
<td>114 (78-158)</td>
<td>140 (97-188)</td>
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<td>Urine potassium, mg/d</td>
<td>56 (43-72)</td>
<td>73 (59-91)</td>
</tr>
<tr>
<td>Urine uric acid, mg/d</td>
<td>229 (151-286)</td>
<td>273 (198-344)</td>
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<tr>
<td>Urine creatinine, g/d</td>
<td>1.1 (0.9-1.3)</td>
<td>1.3 (1.1-1.5)</td>
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<tr>
<td>Female (%)</td>
<td>67.5</td>
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<tr>
<td>Family history of hypertension (%)</td>
<td>30.8</td>
<td>31.0</td>
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<td>Alcohol intake, none (%)</td>
<td>29.8</td>
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<tr>
<td>Smoking status, never (%)</td>
<td>31.5</td>
<td>30.5</td>
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Estimated GFR calculated using the CKD-EPI equation. P-values for were determined by linear regression with urine sodium as the dependent variable, and adjusted for sex.
Table 2. Association between sodium intake and longitudinal changes in serum uric acid and urine albumin excretion

<table>
<thead>
<tr>
<th>Model</th>
<th>Continuous urine sodium (per each 43 mmol increase)</th>
<th>Quartile of Urine Sodium, mmol/day (median, interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Linear regression coefficients and standard errors for longitudinal change in uric acid (μmol/L)</td>
<td>Linear regression coefficients and standard errors for longitudinal change in urine albumin excretion (mg/d)</td>
</tr>
<tr>
<td></td>
<td>Age-adjusted change in uric acid (SE)</td>
<td>97 (79-110)</td>
</tr>
<tr>
<td>Multivariable change in uric acid (SE)</td>
<td>1.61 (0.48)**</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>1.37 (0.59)*</td>
<td>Referent</td>
</tr>
<tr>
<td></td>
<td>Age-adjusted change in albumin excretion(SE)</td>
<td>3.48 (0.88)**</td>
</tr>
<tr>
<td>Multivariable change in albumin excretion (SE)</td>
<td>4.59 (1.21)**</td>
<td>Referent</td>
</tr>
</tbody>
</table>

43 mmol is approximately 1 g of sodium.
Multivariable models were adjusted for age, body mass index, sex, alcohol intake, smoking status, systolic and diastolic blood pressure, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine. In addition, models were mutually adjusted for baseline levels of serum uric acid and urinary albumin.

*p<0.05
**p<0.01

Table 3. Association between sodium intake and hazard ratio of hypertension according to level of uric acid or albumin excretion

<table>
<thead>
<tr>
<th>Model</th>
<th>Continuous urine sodium (per each 43 mmol increase)</th>
<th>Quartile of Urine Sodium, mmol/day (median, interquartile range)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Multivariable HR (95% CI) according to category of uric acid</td>
<td>Multivariable HR (95% CI) according to category of albumin excretion</td>
</tr>
<tr>
<td>Uric acid</td>
<td></td>
<td>97 (79-110)</td>
</tr>
<tr>
<td>Tertile 1 (&lt;255.8 μmol/L)</td>
<td>0.98 (0.89-1.08)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Tertile 2 (255.8-309.3 μmol/L)</td>
<td>1.05 (0.96-1.15)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Tertile 3 (&gt;309.3 μmol/L)</td>
<td>1.09 (1.02-1.16)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>Urine albumin</td>
<td></td>
<td>97 (79-110)</td>
</tr>
<tr>
<td>&lt;10 mg/d</td>
<td>0.99 (0.93-1.06)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>10-15 mg/d</td>
<td>1.02 (0.92-1.12)</td>
<td>1.0 (ref)</td>
</tr>
<tr>
<td>&gt;15 mg/d</td>
<td>1.18 (1.07-1.29)</td>
<td>1.0 (ref)</td>
</tr>
</tbody>
</table>

43 mmol is approximately 1 g of sodium.
Multivariable models were adjusted for age, body mass index, sex, alcohol intake, smoking status, family history of hypertension, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine.
The interaction p-values were <0.001 for the interaction between sodium intake and SUA, and 0.007 for the interaction between sodium intake and UAE.
Figure Legends:

Figure 1. Assembly of the three study populations. SBP, systolic blood pressure. DBP, diastolic blood pressure. SUA, serum uric acid. UAE, urine albumin excretion. Relevant data, information on urinary sodium excretion, SUA, or UAE. Analyses of the change in SUA and UAE included individuals who had available data at baseline and 3rd screening exam, and who were not taking antihypertensives at either time point. Analyses of incident hypertension included non-hypertensive individuals at baseline.

Figure 2. Adjusted change in serum uric acid and urine albumin excretion during follow-up according to sodium intake. The adjusted mean change (± standard error) is shown for each quartile of urinary sodium excretion compared with the lowest quartile. Panel A displays results for change in serum uric acid. Panel B displays results for change in urine albumin excretion.

Figure 3. Adjusted hazard ratio for incident hypertension according to sodium intake and either baseline serum uric acid or urine albumin excretion. Hazard ratios are compared with a common reference group (the lowest quartile of sodium intake and either the lowest tertile of serum uric acid or the lowest category of urine albumin excretion). Hazard ratios are adjusted for age, body mass index, sex, alcohol intake, smoking status, family history of hypertension, estimated glomerular filtration rate, plasma levels of glucose and cholesterol, and urinary levels of potassium, calcium, and creatinine. Panel A displays results for the hazard ratio of hypertension according to quartile of urinary sodium excretion and tertile of serum uric acid; a common reference group was used, specifically those participants in the lowest quartile of urinary sodium excretion and the lowest tertile of serum uric acid. Panel B displays results for the hazard ratio of hypertension according to quartile of urinary sodium excretion and category of urine albumin excretion; a common reference group was used, specifically those participants in the lowest quartile of urinary sodium excretion and the lowest category of urine albumin excretion. A common reference group, which was employed here, was not used in Table 3.
PREVEND cohort
(Baseline exam)
N=8592

Use of antihypertensives at baseline (N=1250)

SBP ≥ 140, DBP ≥ 90 mmHg, or both at baseline, not already excluded (N=1628)
Relevant data missing at baseline, not already excluded (N=158)
Relevant data missing at baseline and 3rd screening exam, not already excluded (N=28)
Non-hypertensive at baseline, analysis of incident hypertension N=5556

Lost to follow-up (N=2265)
Use of antihypertensives at 3rd screening exam (N=903)

Relevant data missing at baseline and 3rd screening exam, not already excluded (N=112)

Analysis of change in SUA (baseline vs 3rd screening exam) N=4062
Analysis of change in UAE (baseline vs 3rd screening exam) N=4146

Censored if lost to follow-up, death, or completed 3rd screening exam

New hypertension cases (N=878)
A

P-trend = 0.03

Quartile of urine sodium (mmol/day)

Change in uric acid (mg/dL)

B

P-trend < 0.001

Quartile of urine sodium (mmol/day)

Change in urine albumin (mg/day)
A

Adjusted hazards for hypertension

Quartile of urine sodium

B

Adjusted hazards for hypertension

Quartile of urine sodium

Serum uric acid (μmol/L)

Urine albumin (mg/day)
Association between Sodium Intake and Change in Uric Acid, Urine Albumin Excretion, and the Risk of Developing Hypertension
John P. Forman, Lieneke Scheven, Paul E. de Jong, Stephan J.L. Bakker, Gary C. Curhan and Ron T. Gansevoort

Circulation. published online June 18, 2012;

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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