Sodium Excretion and Risk of Developing Coronary Heart Disease

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Background—Despite compelling evidence for sodium’s adverse effects on blood pressure, it remains uncertain whether excess sodium intake is a risk factor for coronary heart disease (CHD) in the overall population and in potentially more susceptible subgroups.

Methods and Results—We prospectively followed 7543 adults aged 28 to 75 years and free of cardiovascular and kidney disease in 1997/1998 of the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. Sodium excretion was measured in two 24-hour urine collections at baseline. Potential susceptibility factors were blood pressure and plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP). Median 24-hour sodium excretion was 137 mmol (Q1–Q3, 106–171 mmol). During a median follow-up of 10.5 (Q1–Q3; 9.9–10.8) years, 452 CHD events occurred. In the entire cohort, there was no association between each 1-g/d (43 mmol/24 h) increment in sodium excretion and CHD risk (adjusted hazard ratio, 1.07; 95% confidence interval, 0.98–1.18; P=0.15). However, the association of sodium excretion with CHD risk tended to be modified by mean arterial pressure (Pinteraction=0.08) and was modified by NT-proBNP (Pinteraction=0.002). When stratified, each 1-g/d increment in sodium excretion was associated with an increased risk for CHD in subjects with hypertension (adjusted hazard ratio, 1.14; 95% confidence interval, 1.01–1.28; n=2363) and in subjects with NT-proBNP concentrations above the sex-specific median (adjusted hazard ratio, 1.16; 95% confidence interval, 1.03–1.30; n=3771).

Conclusions—Overall, there was no association between sodium excretion and risk of CHD. The association between sodium excretion and CHD risk was modified by NT-proBNP. Higher sodium excretion was associated with an increased CHD risk among subjects with increased NT-proBNP concentrations or with hypertension. (Circulation. 2014;129:1121-1128.)

Key Words: diet ■ epidemiology ■ heart diseases ■ nutrition assessment ■ natriuretic peptides ■ sodium ■ urine specimen collection

A large body of evidence supports the relation of excess sodium intake with higher blood pressure1,2 and risk of stroke.3 Its association with coronary heart disease (CHD), however, is much less well-established. Whereas many studies primarily addressed the association between sodium intake and heterogeneous cardiovascular outcomes,4 studies specifically5-7 or additionally8-13 addressing CHD are relatively sparse with conflicting results varying from positive,5,7,10,13 to no,6,9,11 or inverse associations.4,8,12 Part of the discrepancies may be attributable to the use of suboptimal measures of sodium intake, such as dietary recall or spot urine, and only a few prospective studies had the advantage of repeated 24-hour urine collections.7,10

Considerable between-individual differences are present in the body’s susceptibility to altered sodium intake, that, moreover, have been related to long-term outcome.14 Such differences can be clinically apparent from the responses of blood pressure to altered sodium intake,15,16 but also from differences in the responses of the extracellular volume, in the absence of effects on blood pressure.17 Both increased blood pressure and higher levels of volume markers (ie, N-terminal pro-B-type natriuretic peptide (NT-proBNP) and N-terminal atrial natriuretic peptide) have been identified as conditions with enhanced susceptibility to changes in sodium intake.18,19 Whether increased blood pressure or elevated volume markers could identify individuals susceptible to the effects of excess sodium intake on risk of CHD has not been investigated so far.

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Therefore, the aim of our study was to examine the association between sodium intake, assessed from repeated 24-hour urine collections, and risk of CHD in the general population and in subgroups potentially more sensitive to the effects of sodium intake, i.e., subjects with higher blood pressure or with increased circulating NT-proBNP concentrations.

Methods

Study Design and Population
We followed participants in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study. The PREVEND study is designed to prospectively investigate the natural course of albuminuria and its relation to renal and cardiovascular disease in a large cohort drawn from the general population. Details of this study have been described elsewhere.20 In brief, from 1997 to 1998, all inhabitants of Groningen, the Netherlands aged 28 to 75 years, were sent a questionnaire and a vial to collect a first morning void urine sample. Pregnant women and subjects with type 1 diabetes mellitus were excluded. Urinary albumin concentration was assessed in 40,856 responders. Subjects with a urinary albumin concentration of ≥10 mg/L (n=7768) were invited to participate, of whom 6000 were enrolled. In addition, a randomly selected group with a urinary albumin concentration of <10 mg/L (n=3394) was invited to participate in the cohort, of whom 2592 were enrolled. These 8592 individuals form the PREVEND cohort.

For the present study, we excluded subjects with a history of cardiovascular disease (n=451), kidney disease requiring dialysis (n=18), or malignancies (n=124) at baseline. We also excluded subjects with missing baseline data on urine (n=91) and serum (n=220) measurements, or questionnaire data (n=145), leaving 7543 subjects for the analysis. The PREVEND study has been approved by the medical ethics committee of the University Medical Center Groningen and is conducted in accordance with the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Data Collection
Participants underwent 2 visits to the outpatient research unit for the baseline examination. At the first visit, all participants completed a questionnaire on demographics, cardiovascular disease history, smoking habits, alcohol consumption, and medication use. Information on medication use was combined with information from a pharmacy-dispensing database, which has complete information on the drug use of approximately 95% of subjects in the PREVEND study. On the first visit, height and weight were measured, and a fasting blood sample was drawn and stored at −80°C. Blood pressure was assessed during both visits in supine position, every minute for 10 and 10 minutes, respectively, with an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical, Tampa, FL). The mean of the last 2 recordings from each visit was used. In addition, subjects collected two 24-hour urines for 2 consecutive days, after thorough oral and written instruction. Urine samples were stored at −20°C.

Laboratory Measurements and Definitions
Sodium, potassium, and magnesium were determined in these urine samples with a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany). Sodium, potassium, and magnesium were determined by indirect potentiometry. Urinary albumin concentration was determined by nephelometry (Dade Behring Diagnostic, Marburg, Germany). Plasma NT-proBNP was measured on the Roche Modular E170 (Roche Diagnostics, Mannheim, Germany) with commercially available kits as previously described.21 Serum and urinary creatinine, serum total cholesterol, triglycerides, and glucose were determined from fasting blood samples by using Kodak Ektachem dry chemistry (Eastman Kodak, Rochester, NY). High-density lipoprotein (HDL) cholesterol was measured with a homogeneous method (direct HDL, Aeroset TM System, Abbott Laboratories, Abbott Park, IL). Triglycerides were measured enzymatically. High-sensitivity C-reactive protein was determined by nephelometry (BN II, Dade Behring, Marburg, Germany).

Hypertension was defined as systolic blood pressure (SBP) of ≥140 mmHg, a diastolic blood pressure (DBP) of ≥90 mmHg, or both or the use of antihypertensive agents as previously described.22 Diabetes mellitus at the baseline of the study was defined according to the 1997 guidelines of the American Diabetes Association as a fasting plasma glucose ≥7.0 mmol/L, or the use of antidiabetic medication.23 Estimated glomerular filtration rate (eGFR) was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation.24

Ascertaining of Coronary Heart Disease Events
CHD was defined as incident cardiac morbidity and mortality during follow-up. Date and cause of death were obtained by record linkage with the Dutch Central Bureau of Statistics. Information on hospitalization for cardiac morbidity was obtained from PRISMANT, the Dutch national registry of hospital discharge diagnoses and was previously validated.25 Data were coded according to the International Classification of Diseases, 9th Revision (ICD), and the classification of interventions. For our study, CHD was defined as myocardial infarction (ICD code 410), acute and subacute ischemic heart disease (ICD code 411), and coronary artery bypass grafting or percutaneous transluminal coronary angioplasty.

Statistical Analysis
The urinary sodium concentration was multiplied by urine volume to obtain a value in millimoles every 24 hours. To assess the within-subject correlation between the repeated 24-hour urinary sodium excretions, we calculated the Pearson product-moment correlation coefficient. Because the within-subject sodium excretions were highly correlated (r=0.59; P<0.0001), the 2 sodium values of each subject were averaged. Baseline characteristics are presented according to sex-specific quartiles of 24-hour urinary sodium excretion.

Timed 24-hour urinary sodium excretion, considered the gold standard method to estimate sodium intake,26 was analyzed as a continuous term (per 43 mmol/24-hour increase; equivalent to 1 g/d of sodium and 2.5 g/d of salt [sodium chloride]) and in sex-specific quartiles. We also examined the possibility of a nonlinear association between sodium excretion and risk of CHD nonparametrically by using restricted cubic splines and tested nonlinearity by using the likelihood ratio test, comparing nested models with a linear or linear and cubic spline terms. We used Cox proportional hazards regression analysis to examine the association between sodium excretion and risk of CHD. Survival time was defined as the period from the date of urine collection of the participant to the date of first cardiac event or January 1, 2009 (end of follow-up). Subjects were censored if they moved to an unknown destination or died of noncardiac causes. The proportional hazards assumption was tested by analyzing the interaction between sodium excretion and calendar time for the overall cohort and in separate strata; no significant interactions were identified (P=0.62 for the overall cohort; P=0.32 for normotensive, P=0.98 for hypertensive subjects, P=0.30 for subjects with NT-proBNP concentrations below the sex-specific median, and P=0.86 for subjects with NT-proBNP concentrations above the sex-specific median). Adjusted hazard ratios (HRs) are reported with 95% confidence intervals (95% CI). The fully adjusted multivariable Cox proportional hazards regression model included age, sex, body mass index, smoking status (never, former, current <6 cigarettes/d, current 6–20 cigarettes/d, or current >20 cigarettes/d), alcohol consumption (5 categories), family history of CHD, the presence of type 2 diabetes mellitus, total- and HDL-cholesterol ratio, and urinary magnesium, potassium, and creatinine excretion. By controlling for urinary creatinine, we adjusted indirectly for both muscle mass and body dimension. All models took into account the sampling design of the study (presence or absence of albuminuria >10 mg/L) by specifying stratum-specific baseline hazard functions. If an association was present after multivariable adjustment, we also investigated the effect of potential intermediate and other variables by adding ln-transformed eGFR, ln-transformed urine...
albumin, and ln-transformed NT-proBNP (when stratifying on blood pressure), antihypertensive drug use, and SBP (when stratifying on NT-proBNP).

The effect modification of the association between sodium excretion and CHD risk by blood pressure and NT-proBNP was assessed by a likelihood ratio test of the cross-product terms in multivariable models that also included main-effect terms of sodium excretion and blood pressure or NT-proBNP. We fit both blood pressure and NT-proBNP as quadratic splines with 2 knots to optimize model fit. We used mean arterial pressure (MAP; defined as: \[2/3\text{DBP} + 1/3\text{SBP}\]) as an integrative measure of blood pressure. To account for blood pressure–lowering medication use, we added 10 mmHg to the SBP and 5 mmHg to the DBP of treated hypertensive participants. These values are the difference in mean SBP and DBP between treated and untreated hypertensive subjects in our study and correspond with reductions in blood pressure after antihypertensive interventions.27,28

In sensitivity analyses, we excluded 24-hour urine samples with possible over- or undercollections. Such samples were defined as the upper and lower 2.5% of the difference between the estimated and measured volume of a subject’s 24-hour urine sample. The estimated 24-hour urine volume was derived from the formula: Creatinine clearance = ([Urine creatinine]×24-hour urine volume)/[Serum creatinine]), where creatinine clearance was estimated by using the Cockcroft-Gault formula.29 To address potential reverse causation, we also repeated the analyses excluding subjects with incident CHD in the first 2 years of follow-up. Because urinary albumin excretion may be an effect modifier in the association between sodium excretion and CHD risk, we restricted the cohort to the subjects with an albuminuria concentration of ≥10 mg/L. In secondary analyses, we used a less conservative and broader but more general definition for CHD by additionally including old myocardial infarction (ICD code 412), angina pectoris (ICD code 413), and other forms of chronic ischemic heart disease (ICD code 414) in our initial definition.

Statistical analyses were performed with the Statistical Package for Social Sciences (IBM SPSS Statistics, IBM Corporation, Armonk, NY), version 20.0 and SAS (SAS Institute, Cary, NC), version 9.3. We did not adjust for multiple comparisons. Because of the general low power for interaction tests, interaction terms were considered to be statistically significant at 2-sided \(P\) values of <0.10, as recommended by Selvin30 and by the Food and Drug Administration authorities.31 Otherwise, 2-sided \(P\) values of <0.05 were considered statistically significant.

Results

The median 24-hour sodium excretion was 137 mmol (Q1–Q3, 106–171 mmol), which corresponds to a daily intake of 8.4 g of sodium chloride after accounting for nonurinary loss. The mean 24-hour sodium excretion was 142 mmol (standard deviation, 51 mmol). Baseline characteristics of the cohort are presented in sex-specific quartiles of sodium excretion in Table 1. At baseline, a higher sodium excretion was univariately associated with lower age, higher body mass index, lower NT-proBNP, higher eGFR, and higher urine levels of potassium, magnesium, creatinine, and albumin. In univariate models, SBP and DBP, hypertensive medication use and parental history of CHD were not associated with baseline sodium excretion.

The study had a median follow-up of 10.5 years (Q1–Q3, 9.9–10.8 years; 71,491 person-years) in which 452 incident cases of CHD occurred. Events included 188 cases of myocardial infarction (of which 22 were fatal), 134 hospitalizations for ischemic heart disease (of which 16 were fatal), and 130 revascularizations. In the entire cohort, there was no significant association \(P=0.15\) between a continuous term of sodium excretion and risk of CHD after multivariable adjustment (Table 2). No significant deviations from linearity were detected for this association \(P_{\text{nonlinear}}=0.79\). The restricted multivariable-adjusted spline plot is presented in the Figure. We also considered a cut point of more extreme sodium excretion. The HRs for the upper 2 deciles of the distribution of sodium excretion in comparison with the lowest half of the distribution were 1.24 (95% CI, 0.88–1.73) and 1.27 (95% CI, 0.89–1.81), respectively, consistent with no significant deviation from linearity and absence of an association at the extreme ends of the distribution.

The association of sodium excretion with CHD risk tended to be modified by MAP \(P_{\text{interaction}}=0.08\) and was modified by NT-proBNP \(P_{\text{interaction}}=0.002\). For clinical relevance and ease of interpretation, we stratified the association by hypertension status and by NT-proBNP concentration above the sex-specific median (22 pg/mL for men; 50 pg/mL for women), respectively. In these stratified analyses, we observed reversed trends across the 2 strata of hypertension status and NT-proBNP status. The associations between sodium excretion and risk of CHD were significant only among subjects with hypertension (HR, 1.14; 95% CI, 1.01–1.28) or with a NT-proBNP concentration above the sex-specific median (HR, 1.16; 95% CI, 1.03–1.30; Table 3) for each 1-g/d increment. Results remained materially unchanged when the cohort was stratified by MAP in groups with sizes similar to those of the normotensive and hypertensive strata. In these analyses, the HRs associated with 1-g/d increment in sodium excretion were 0.96 (95% CI, 0.81–1.14; n=5178) for subjects with a MAP <98 mmHg and 1.14 (95% CI, 1.01–1.28; n=2365) for subjects with a MAP ≥98 mmHg.

We next examined the overlap between the hypertension and higher NT-proBNP subgroups. In total, 1524 of the 2363 hypertensive subjects (64%) also had higher NT-proBNP levels and 1524 of the 3771 subjects with higher NT-proBNP levels (40%) also had hypertension. To formally test whether the effect modification by NT-proBNP was independent of blood pressure, we simultaneously included main effects for sodium excretion, and spline functions of NT-proBNP and MAP and both cross-product terms (ie, sodium-NT-proBNP and sodium-MAP) in multivariable-adjusted models. This analysis showed that the cross-product term of sodium excretion and NT-proBNP slightly attenuated but remained significant \(P_{\text{interaction}}=0.009\) after simultaneously accounting for MAP and the cross-product term of sodium excretion and MAP. However, the effect modification by MAP \(P_{\text{interaction}}=0.30\) attenuated in the model with simultaneous adjustment for effect modification by NT-proBNP. There was no evidence for an interaction between urinary sodium excretion and sex with risk of CHD \(P_{\text{interaction}}=0.43\). Also, sex did not modify the effect modification by NT-proBNP \(P_{\text{interaction}}=0.54\) or by MAP \(P_{\text{interaction}}=0.72\).

The association between sodium excretion and CHD risk among the hypertensive group was attenuated and no longer significant after accounting for antihypertensive drug use and potential mediators such as urine albumin, eGFR, and plasma NT-proBNP (HR, 1.11; 95% CI, 0.99–1.26; \(P=0.08\)). However, the association between 1-g/d increment in sodium excretion and CHD risk among subjects with NT-proBNP levels above the median remained significant.
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In sensitivity analyses, we repeated the analyses per 1-g/d increment in sodium excretion excluding subjects with potential under- or overcollections in 24-hour urine samples or excluding the first 2 years of follow-up. This did not appreciably influence the results (Table I in the online-only Data Supplement). Results were also similar when we restricted the analyses to subjects with a urinary albumin concentration of >10 mg/L. When we defined CHD as ICD codes 410 through 414, the HRs with 1-g/d increment in sodium excretion were 1.07 (95% CI, 0.98–1.17; n=554 events) in the entire cohort, 1.14 (95% CI, 1.02–1.26; n=348 events) among hypertensive subjects, and 1.14 (95% CI, 1.03–1.26; n=383 events) among subjects with higher NT-proBNP.

Table 1. Baseline Characteristics According to Sodium Excretion Among 7543 Participants of the Prevention of Renal and Vascular End-stage Disease (PREVEND) Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>&lt;95</th>
<th>95–121</th>
<th>122–151</th>
<th>155–190</th>
<th>&gt;190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n</td>
<td>1885</td>
<td>1886</td>
<td>1886</td>
<td>1886</td>
<td></td>
</tr>
<tr>
<td>Male sex, %</td>
<td>48.7</td>
<td>48.7</td>
<td>48.7</td>
<td>48.7</td>
<td>48.7</td>
</tr>
<tr>
<td>Age, y</td>
<td>50±13</td>
<td>49±13</td>
<td>48±12</td>
<td>47±11</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25.0±3.7</td>
<td>25.5±3.7</td>
<td>26.1±4.1</td>
<td>27.5±4.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking status, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>30.1</td>
<td>32.1</td>
<td>28.6</td>
<td>29.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Former</td>
<td>31.6</td>
<td>33.9</td>
<td>39.2</td>
<td>37.5</td>
<td></td>
</tr>
<tr>
<td>Current &lt;6 cigarettes/d</td>
<td>6.2</td>
<td>5.8</td>
<td>5.7</td>
<td>5.4</td>
<td></td>
</tr>
<tr>
<td>Current 6–20 cigarettes/d</td>
<td>24.6</td>
<td>22.3</td>
<td>20.8</td>
<td>20.8</td>
<td></td>
</tr>
<tr>
<td>Current &gt;20 cigarettes/d</td>
<td>7.5</td>
<td>5.9</td>
<td>5.7</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>129±22</td>
<td>128±20</td>
<td>128±20</td>
<td>129±20</td>
<td>0.76</td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>74±10</td>
<td>74±10</td>
<td>74±10</td>
<td>74±9</td>
<td>0.84</td>
</tr>
<tr>
<td>Hypertension, %*</td>
<td>32.8</td>
<td>30.4</td>
<td>31.4</td>
<td>30.7</td>
<td>0.28</td>
</tr>
<tr>
<td>Antihypertensive therapy, %</td>
<td>14.3</td>
<td>12.6</td>
<td>12.4</td>
<td>12.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Diuretic therapy, %</td>
<td>3.6</td>
<td>4.0</td>
<td>4.4</td>
<td>4.0</td>
<td>0.74</td>
</tr>
<tr>
<td>ACEI and ARB therapy, %</td>
<td>4.2</td>
<td>3.5</td>
<td>4.1</td>
<td>4.4</td>
<td>0.71</td>
</tr>
<tr>
<td>Plasma NT-proBNP, pg/mL</td>
<td>39.9 (17.6–78.3)</td>
<td>37.0 (17.3–69.1)</td>
<td>34.9 (15.5–68.6)</td>
<td>31.0 (14.0–59.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum HDL cholesterol, mmol/L</td>
<td>1.34±0.40</td>
<td>1.33±0.39</td>
<td>1.34±0.39</td>
<td>1.31±0.41</td>
<td>0.03</td>
</tr>
<tr>
<td>Serum total cholesterol, mmol/L</td>
<td>5.63±1.15</td>
<td>5.62±1.10</td>
<td>5.61±1.15</td>
<td>5.70±1.11</td>
<td>0.06</td>
</tr>
<tr>
<td>Serum triglycerides, mmol/L</td>
<td>1.11 (0.82–1.59)</td>
<td>1.12 (0.82–1.63)</td>
<td>1.12 (0.81–1.64)</td>
<td>1.22 (0.88–1.83)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum C-reactive protein, mg/L</td>
<td>1.21 (0.51–2.86)</td>
<td>1.19 (0.53–2.72)</td>
<td>1.13 (0.51–2.74)</td>
<td>1.39 (0.59–3.22)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, %</td>
<td>2.2</td>
<td>2.5</td>
<td>2.9</td>
<td>4.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Alcohol intake, %</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>27.5</td>
<td>24.0</td>
<td>24.5</td>
<td>21.8</td>
<td>0.001</td>
</tr>
<tr>
<td>1–4 drinks/mo</td>
<td>15.7</td>
<td>15.9</td>
<td>14.6</td>
<td>16.9</td>
<td></td>
</tr>
<tr>
<td>2–7 drinks/week</td>
<td>30.2</td>
<td>35.5</td>
<td>35.7</td>
<td>35.7</td>
<td></td>
</tr>
<tr>
<td>1–3 drinks/d</td>
<td>20.2</td>
<td>19.4</td>
<td>20.4</td>
<td>20.5</td>
<td></td>
</tr>
<tr>
<td>≥4 drinks/d</td>
<td>6.4</td>
<td>5.2</td>
<td>4.8</td>
<td>5.1</td>
<td></td>
</tr>
<tr>
<td>Parental history of CHD, %</td>
<td>20.7</td>
<td>21.5</td>
<td>20.1</td>
<td>22.7</td>
<td>0.21</td>
</tr>
<tr>
<td>eGFR, mL/min×1.73 m⁻¹†</td>
<td>84±16</td>
<td>84±15</td>
<td>85±15</td>
<td>86±14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine potassium, mmol/24 h</td>
<td>59 (47–73)</td>
<td>67 (56–81)</td>
<td>73 (61–86)</td>
<td>80 (66–95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine magnesium, mmol/24 h</td>
<td>3.3 (2.4–4.1)</td>
<td>3.7 (2.9–4.6)</td>
<td>4.0 (3.0–4.9)</td>
<td>4.3 (3.3–5.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine creatinine, mmol/24 h</td>
<td>10.3 (8.4–12.7)</td>
<td>11.5 (9.5–13.8)</td>
<td>12.3 (10.1–15.1)</td>
<td>13.6 (11.1–16.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urine albumin, mg/24 h</td>
<td>8.1 (5.5–14.7)</td>
<td>9.1 (6.3–16.4)</td>
<td>9.4 (6.4–17.1)</td>
<td>10.3 (7.0–19.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Values are presented as means with standard deviations, median with Q1–Q3, or percentages. To convert millimoles of sodium to milligrams of sodium, multiply millimoles of sodium by 23. To convert millimoles of sodium to milligrams of sodium chloride, multiply millimoles of sodium by 58.5. ♀ indicates women; ♂, men; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*Defined as a systolic blood pressure ≥140 mmHg, a diastolic blood pressure ≥90 mmHg, or an antihypertensive medication use.
†The eGFR was calculated with the Chronic Kidney Disease Epidemiology Collaboration equation.

(HR, 1.15; 95% CI, 1.02–1.29) even after adjustment for eGFR, SBP, antihypertensive drug use, and urinary albumin excretion.

In sensitivity analyses, we repeated the analyses per 1-g/d increment in sodium excretion excluding subjects with potential under- or overcollections in 24-hour urine samples or excluding the first 2 years of follow-up. This did not appreciably influence the results (Table I in the online-only Data Supplement).
Table 2. Association Between Sodium Excretion and Risk of Coronary Heart Disease

<table>
<thead>
<tr>
<th>Continuous Sodium Excretion, per 1-g/d Increase</th>
<th>Sex-specific Quartiles of Sodium Excretion, mmol/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>♀: &lt;95</td>
</tr>
<tr>
<td>No. of cases</td>
<td>452</td>
</tr>
<tr>
<td>Person-years</td>
<td>71 491</td>
</tr>
<tr>
<td>Age and sex-adjusted HR</td>
<td>1.06 (0.98–1.15) P=0.16</td>
</tr>
<tr>
<td>Multivariable-adjusted HR</td>
<td>1.07 (0.98–1.18) P=0.15</td>
</tr>
</tbody>
</table>

Hazard ratios (HR) and 95% confidence intervals were derived from Cox proportional hazards regression models. The multivariable model is, in addition to age and sex, also adjusted for body mass index, smoking status, alcohol intake, parental history of coronary heart disease, type 2 diabetes mellitus, total to high-density lipoprotein cholesterol ratio, and urinary potassium, magnesium, and creatinine excretion. To convert millimoles of sodium to milligrams of sodium chloride, multiply millimoles of sodium by 58.5. To convert millimoles of sodium to milligrams of sodium, multiply millimoles of sodium by 23.

Discussion

In this large prospective population-based study, there was no association between urinary sodium excretion and risk of CHD in the overall cohort. The association between sodium excretion and risk of CHD was modified by NT-proBNP, a marker of myocardial stretch and volume overload. We found positive associations between sodium excretion and risk of CHD among individuals with higher concentrations of NT-proBNP and among individuals with hypertension. Furthermore, the association between sodium excretion and CHD risk among subjects with higher NT-proBNP concentrations seemed to be independent of blood pressure, eGFR, the ratio of total to HDL cholesterol, and urinary albumin excretion at baseline.

Our data suggest that subjects already at higher risk of developing cardiovascular diseases, ie, subjects with higher NT-proBNP levels or with hypertension, may be prone to the increased risk of CHD associated with high dietary sodium. Indeed, the positive association between sodium intake and CHD risk has generally appeared to be more pronounced in high-risk populations, eg, with higher blood pressure\(^3\) or existing cardiovascular diseases\(^4\) although not consistently\(^4\) and less so in otherwise healthy subjects.\(^6\,\,9\,\,12\) However, besides differences in subject characteristics, it cannot be excluded that the inconsistencies between studies for this association may also be attributable, in part, to differences in the assessment of sodium intake, study design including adjustment for confounding variables, or CHD ascertainment and definitions.

The null findings between sodium excretion and CHD risk in the overall cohort or in the less susceptible groups do not necessarily imply that excess sodium may have no adverse health consequences in these subjects. A challenge in studying the impact of excess sodium intake in humans is that target-organ damage often develops slowly, likely over many years.\(^32\) Besides, susceptibility to the effects of sodium, such as salt sensitivity, is not limited to hypertensive subjects but is also prevalent among nonhypertensive subjects.\(^6\,\,9\,\,12\) However, besides differences in subject characteristics, it cannot be excluded that the inconsistencies between studies for this association may also be attributable, in part, to differences in the assessment of sodium intake, study design including adjustment for confounding variables, or CHD ascertainment and definitions.

The effect of sodium excretion on CHD risk among subjects with higher NT-proBNP levels appeared to only be minimally related to other known CHD risk factors such as eGFR and blood pressure. It suggests that also other mechanisms besides kidney function and blood pressure may play a role in the sodium-induced pathogenesis of CHD. Sodium intake is reversibly associated with coronary flow reserve, a measure

![Figure. Association between urinary sodium excretion and the risk of coronary heart disease (CHD). Association estimated by Cox proportional hazards regression analysis based on restricted cubic splines (P=0.15). Sodium excretion of 75 mmol/24 hours is the reference standard. Dashed lines indicate the 95% confidence interval (CI). Model is adjusted for age, sex, smoking status, body mass index, alcohol consumption, total to high-density lipoprotein cholesterol ratio, parental history of coronary heart disease, type 2 diabetes mellitus, and urinary potassium, magnesium, and creatinine excretion. The spline curve is truncated at the 0.5th percentile and 99.5th percentile of the distribution curve (n=7469). To convert millimoles of sodium to milligrams of sodium, multiply millimoles of sodium by 23. To convert millimoles of sodium to milligrams of sodium chloride, multiply millimoles of sodium by 58.5.](http://circ.ahajournals.org/doi/10.1161/CIRCULATIONAHA.117.029210)
Table 3. Association Between Sodium Excretion and Risk of Coronary Heart Disease Stratified by Hypertension Status and Median NT-proBNP Concentration

<table>
<thead>
<tr>
<th>Continuous Sodium Excretion, per 1-g/d Increase</th>
<th>Quartiles of Sodium Excretion, mmol/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>♂:&lt;95</td>
</tr>
<tr>
<td></td>
<td>♂:&lt;122</td>
</tr>
<tr>
<td>Hypertension status</td>
<td></td>
</tr>
<tr>
<td>Normotensive</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>162</td>
</tr>
<tr>
<td>Person-years</td>
<td>49,822</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.97 (0.82–1.15)</td>
</tr>
<tr>
<td>Hypertensive</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>290</td>
</tr>
<tr>
<td>Person-years</td>
<td>21,669</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.14 (1.01–1.28)</td>
</tr>
<tr>
<td>NT-proBNP level*</td>
<td></td>
</tr>
<tr>
<td>≤Sex-specific median</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>132</td>
</tr>
<tr>
<td>Person-years</td>
<td>36,241</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>0.91 (0.76–1.09)</td>
</tr>
<tr>
<td>&gt;Sex-specific median</td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>320</td>
</tr>
<tr>
<td>Person-years</td>
<td>35,250</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.16 (1.03–1.30)</td>
</tr>
</tbody>
</table>

Hazard ratios (95% confidence intervals) were derived from Cox proportional hazards regression models and were adjusted for age, body mass index, smoking status, sex, alcohol intake, parental history of coronary heart disease, type 2 diabetes mellitus, total to high-density lipoprotein cholesterol ratio, and urinary potassium, magnesium, and creatinine excretion. The P for interaction between sodium excretion and mean arterial pressure was P=0.08. The P for interaction between sodium excretion and NT-proBNP was P=0.002. To convert millimoles of sodium to milligrams of sodium by 23. To convert millimoles of sodium to milligrams of sodium chloride, multiply millimoles of sodium by 58.5. <sup>*</sup> indicates women; ♂, men; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

<sup>*</sup>Cutoff concentrations for sex-specific medians of NT-proBNP are 22 pg/mL for men and 50 pg/mL for women.

Strengths of our study are the prospective design, long duration of follow-up, the large number of subjects, elaborate information on subject characteristics including multiple measured blood pressures and medication use, extensive adjustment for potential confounders, and the robustness of the associations in several sensitivity analyses. Another strength is the use of 2...
consecutive 24-hour urine collections. By repeating the 24-hour urine collections, we reduced the intraindividual variability. Moreover, the correlation between the 2 sodium excretions, and thus the repeatability of the sodium assessment, was relatively high, even in comparison with those reported in previous studies; perhaps because of the shorter time span between the 2 urine collections in this study in comparison with the <2 weeks in the other studies.29–51

Conclusion
In this large population-based cohort of men and women, we found no association between urinary sodium excretion and risk of CHD in the overall cohort. However, the association between sodium excretion and risk of CHD was modified by NT-proBNP. A higher sodium excretion was associated with an increased risk of CHD among subjects with higher levels of NT-proBNP and among subjects with hypertension, both potential indicators of susceptibility to high dietary sodium. Our results are in line with the notion that excess sodium intake is associated with an increased risk of CHD, particularly among vulnerable groups who constitute a large portion of the population.

Sources of Funding
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Disclosures
None.

References

**CLINICAL PERSPECTIVE**

The health effects of dietary sodium have generated considerable interest and debate in the public and healthcare community. Despite compelling evidence for sodium’s adverse effects on blood pressure and risk of stroke, it remains uncertain whether excess sodium intake is a risk factor for coronary heart disease (CHD). In a prospective cohort study of nearly 8000 Dutch men and women, sodium excretion was measured in two 24-hour urine collections (considered the gold standard to assess sodium intake). The median 24-hour sodium excretion was 137 mmol, approximately equivalent to an intake of 8.4 g/d of sodium chloride or 3.3 g/d of sodium after accounting for nonurinary loss (for comparison, the American Heart Association recommends a sodium intake of <1.5 g/d). During a median follow-up of 10.5 years, 452 CHD events occurred. In the entire cohort, sodium excretion was not associated with risk of CHD. However, the association between sodium excretion and CHD risk was modified by plasma N-terminal pro-B-type natriuretic peptide, a marker of myocardial stretch and volume overload, and tended to be modified by blood pressure. In subjects with high N-terminal pro-B-type natriuretic peptide or with hypertension, each 1-g/d increment in sodium excretion was associated with a 16% and 14% increased CHD risk, respectively. These results are in line with the notion that excess sodium intake is associated with an increased risk of CHD, particularly among vulnerable groups who constitute a large portion of the population.
Sodium Excretion and Risk of Developing Coronary Heart Disease
the PREVEND Study Group

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Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2014/01/14/CIRCULATIONAHA.113.004290.DC1

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**Supplemental Table 1.** Sensitivity analyses of the association between sodium excretion and risk of coronary heart disease

<table>
<thead>
<tr>
<th>Sodium excretion, per 1 g/d increase</th>
<th>Excluding 24h urine specimens with potential under or over collection</th>
<th>Excluding the first two years of follow-up</th>
<th>Excluding subjects with a urinary albumin concentration &lt;10 mg/L</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>427</td>
<td>370</td>
<td>353</td>
</tr>
<tr>
<td>Person-years</td>
<td>68,297</td>
<td>57,433</td>
<td>49,138</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.09 (1.00-1.19) P=0.06</td>
<td>1.07 (0.96-1.19) P=0.22</td>
<td>1.10 (0.99-1.22) P=0.09</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension stratum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>275</td>
<td>240</td>
<td>239</td>
</tr>
<tr>
<td>Person-years</td>
<td>20,669</td>
<td>17,352</td>
<td>16,624</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.12 (1.00-1.24) P&lt;0.05</td>
<td>1.15 (1.01-1.31) P=0.04</td>
<td>1.13 (1.00-1.29) P=0.06</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NT-proBNP level &gt;sex-specific</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>median stratum</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of cases</td>
<td>303</td>
<td>265</td>
<td>253</td>
</tr>
<tr>
<td>Person-years</td>
<td>33,581</td>
<td>28,357</td>
<td>24,441</td>
</tr>
<tr>
<td>Hazard ratio</td>
<td>1.14 (1.03-1.27) P=0.01</td>
<td>1.16 (1.03-1.31) P=0.02</td>
<td>1.18 (1.04-1.34) P=0.01</td>
</tr>
</tbody>
</table>
Hazard ratios were derived from Cox proportional hazards regression models and were adjusted for age, sex, body mass index, smoking status, alcohol intake, parental history of coronary heart disease, urinary potassium, magnesium, and creatinine excretion, type 2 diabetes, and total to high-density lipoprotein cholesterol ratio. Abbreviation: NT-proBNP, N-terminal pro-B-type natriuretic peptide. Cut-off concentrations for sex-specific medians of NT-proBNP are 22 pg/mL for men and 50 pg/mL for women. To convert mmol of sodium to mg of sodium, multiply mmol of sodium by 23. To convert mmol of sodium to mg of sodium chloride, multiply mmol of sodium by 58.5.