Urinary Potassium Excretion and Risk of Developing Hypertension
The Prevention of Renal and Vascular End-Stage Disease Study

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Abstract—Previous prospective cohort studies on the association between potassium intake and risk of hypertension have almost exclusively relied on self-reported dietary data, whereas repeated 24-hour urine excretions, as estimate of dietary intake, may provide a more objective and quantitative estimate of this association. Risk of hypertension (defined as blood pressure ≥140/90 mm Hg or initiation of blood pressure–lowering drugs) was prospectively studied in 5511 normotensive subjects aged 28 to 75 years not using blood pressure–lowering drugs at baseline of the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study. Potassium excretion was measured in two 24-hour urine specimens at baseline (1997–1998) and midway during follow-up (2001–2003). Baseline median potassium excretion was 70 mmol/24 h (interquartile range, 57–85 mmol/24 h), which corresponds to a dietary potassium intake of ≈91 mmol/24 h. During a median follow-up of 7.6 years (interquartile range, 5.0–9.3 years), 1172 subjects developed hypertension. The lowest sex-specific tertile of potassium excretion (men: <68 mmol/24 h; women: <58 mmol/24 h) had an increased risk of hypertension after multivariable adjustment (hazard ratio, 1.20; 95% confidence interval, 1.05–1.37), compared with the upper 2 tertiles (Pnonlinearity=0.008). The proportion of hypertension attributable to low potassium excretion was 6.2% (95% confidence interval, 1.7%–10.9%). No association was found between the sodium to potassium excretion ratio and risk of hypertension after multivariable adjustment. Low urinary potassium excretion was associated with an increased risk of developing hypertension. Dietary strategies to increase potassium intake to the recommended level of 90 mmol/d may have the potential to reduce the incidence of hypertension. (Hypertension. 2014;64:769-776.) ● Online Data Supplement

Key Words: diet ■ epidemiology ■ hypertension ■ potassium ■ primary prevention ■ risk factors ■ sodium

Potassium is an essential mineral which is thought to play an important role in blood pressure (BP) regulation. 1 Potassium supplementation has been shown to significantly reduce BP in some, but not all, randomized controlled trials (RCTs). Although most meta-analyses of these RCTs2–4 found an overall BP-lowering effect, a more comprehensive meta-analysis,5 comprising 21 RCTs that lasted for 4 weeks, observed this effect only among hypertensive subjects.

Long-term prospective cohort studies on the association between dietary potassium and risk of hypertension are limited, and the majority observed no independent relationship.6–10 except one, in which an inverse association was found.11 These observational studies predominantly relied on 24-hour dietary recalls8,11 or food frequency questionnaires6,7,10 to assess potassium intake. Such self-reported dietary methods, however, are less objective than urinary measures to assess dietary intake.12 Although 24-hour urine collections are considered the most direct method for estimating dietary potassium,12 few large epidemiological cohort studies have collected them for reasons of costs, logistics, and burden.

Hence, the aim of this study was to prospectively examine the association between repeated 24-hour urinary potassium excretions and risk of developing hypertension among subjects free of hypertension at baseline in a cohort with long-term follow-up.

Methods

Study Design and Population
The Prevention of Renal and Vascular End-Stage Disease (PREVEND) study is a prospective investigation of albuminuria, urinary excretion of sodium and potassium, and Charlson comorbidity index, which is an important risk factor for blood pressure and cardiovascular disease. 13–15 The Prevention of Renal and Vascular End-Stage Disease Study (PREVEND) is a prospective investigation of albuminuria, urinary excretion of sodium and potassium, and Charlson comorbidity index, which is an important risk factor for blood pressure and cardiovascular disease. 13–15

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In total, 8592 individuals constitute the PREVEND cohort and completed an extensive examination in 1997 and 1998 (baseline).

We excluded subjects with hypertension at baseline (n=3040), subjects requiring dialysis (n=12), and subjects with missing values of urinary analytes at baseline (n=29), leaving 5511 participants for the analyses. Of these, 4546 participants completed a second examination between 2001 and 2003, 3928 participants completed a third examination between 2003 and 2006, and 3528 participants completed a fourth examination between 2006 and 2008. The PREVEND study has been approved by the medical ethics committee of the University Medical Center Groningen. Written informed consent was obtained from all participants.

**Data Collection**

The procedures at each examination in the PREVEND study have been described in detail previously. In brief, each of the examinations included visits to an outpatient clinic separated by 3 weeks. Before the first visit, all participants completed a self-administered questionnaire regarding demographics, cardiovascular and renal disease history, smoking habits, alcohol consumption, and medication use. In the last week before the second visit, subjects had to collect 2 consecutive 24-hour specimens after thorough oral and written instruction. During the urine collection, the participants were asked to avoid heavy exercise as much as possible. Subjects were also instructed to postpone the urine collection in case of urinary tract infection, menstruation, or fever. The collected urine was stored cold (4°C) for a maximum of 4 days before the second visit. After handing in the urine collections, the urine specimens were stored at −20°C. Furthermore, fasting blood samples were provided and stored at −80°C.

**Assessment of Urinary Potassium Excretion**

Determination of urine potassium concentration was performed on the 24-hour urine specimens of the first (baseline) and second examination by indirect potentiometry with a MEGA clinical chemistry analyzer (Merck, Darmstadt, Germany). The potassium concentration in mmol/L was multiplied by the urine volume in L/24 h to obtain a value in mmol/24 h. For each of the 2 examinations, we calculated the average of the paired 24-hour collections.

**Ascertainment of Hypertension**

During both visits of each of the 4 examinations, BP was assessed on the right arm in supine position, every minute for 10 and 8 minutes, respectively, with an automatic Dinamap XL Model 9300 series device (Johnson-Johnson Medical, Tampa, FL) as described previously. The mean of the last 2 recordings from each visit was used. Use of antihypertensive medications was ascertained by a questionnaire at each examination and was complemented by information from a pharmacy-dispensing registry, which has complete information on drug use of >90% of subjects in the PREVEND study.

For this study, incident hypertension was defined as hypertension that occurred after baseline, which included systolic BP of ≥140 mm Hg, a diastolic BP of ≥90 mm Hg, or the use of antihypertensive drugs, in concordance with recommendations from the Seventh Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Antihypertensive medication use, for the definition of hypertension, included 5 second-level Anatomical Therapeutic Chemical codes: C02 (antihypertensives), C03 (diuretics), C07 (β-blockers), C08 (calcium channel blockers), and C09 (inhibitors).

**Assessment of Covariates**

Body mass index (BMI) was calculated as weight (kilograms) divided by height squared (square meter). Smoking status was categorized as never, former, current <6 cigarettes/d, current 6 to 20 cigarettes/d, and current >20 cigarettes/d. Alcohol intake was categorized as none, 1 to 4 drinks/week, 5 to 7 drinks/week, 1 to 3 drinks/d, and ≥4 drinks/d. Education was categorized into low (primary education up to those completing intermediate vocational education), average (higher secondary education), and high (higher vocational education and university).

**Statistical Analyses**

Baseline characteristics are presented according to sex-specific tertiles of urinary potassium excretion. Continuous data are presented as mean with SD or as median and interquartile range (IQR) in case of skewed distribution. Categorical data are presented as percentiles. We calculated the Pearson product–moment correlation coefficient for the paired 24-hour urine specimens at the first and second examination, and for the averaged potassium excretions of the first and the second examination, as estimates of the intraclass correlation coefficient of reliability R..

To study the association between potassium excretion (as a categorical [tertiles] and a continuous variable) and risk of hypertension, we used time-dependent Cox proportional hazards regression analyses. For events occurring before the second examination (ie, between 1997 and 2003), the average of the 2 baseline 24-hour urine excretions of potassium (and sodium alike) was used. For events occurring after the second examination (ie, after 2003), the average of the 2 baseline and 2 follow-up 24-hour urine excretions was used, because using cumulative averages of dietary factors yield stronger associations than either only baseline or most recent dietary factors. Nonlinearity was tested by using the likelihood ratio test, comparing nested models with linear or linear and cubic spline terms. Survival time was defined from baseline until the date of last examination round that participants attended, the incidence of hypertension, death, relocation to an unknown destination, or January 1, 2009 (end of follow-up). Hazard ratios (HRs) are reported with 95% confidence intervals (CIs).

We included covariates in our models as linear variables if appropriate, or as categorical if discrete, or if their association with hypertension was nonlinear. Additional adjustment for income, as marker of socioeconomic status, did not provide further information after accounting for education. Adjustment for race/ethnicity in the multivariable model did not affect the association between urinary potassium excretion and risk of hypertension and was therefore not included as a confounder. We tested for multicollinearity between urinary excretions of electrolytes and creatinine. All variance inflation factors were <5, which indicates that there is no evidence for multicollinearity. We evaluated effect modification by age, sex, BMI, smoking behavior, and 24-hour urinary sodium and albumin excretion in the analyses of risk of hypertension by fitting models containing both main effects and their cross-product terms. The population attributable risk was calculated using the formula: \( \rho = \frac{HR_1 - 1}{1 + \rho[HR_1 - 1]} \), where \( p \) is the prevalence of individuals in the high-risk group (low potassium excretion) and HR is the associated multivariable-adjusted HR. Upper and lower 95% CIs of the population attributable risk were derived using this formula and the upper and lower 95% CI estimates of the multivariable-adjusted HR.

Despite being considered the gold standard, even 24-hour urine collections may be subject to quality control concerns because of collection errors. To account for potential inadequacies in the timed 24-hour urine collections, we examined the difference between expected and actually measured 24-hour urine volume. We defined potential inadequate 24-hour urine collections (ie, over- or undercollection) 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 = (urinary creatinine × 24-hour urine volume) / (serum creatinine), where creatinine clearance was estimated using the Cockcroft–Gault formula.

In addition to the analyses on urinary potassium excretion and our previous analyses on urinary sodium excretion and risk of hypertension, we also examined the association between the urinary sodium to potassium (Na-K) excretion ratio and risk of hypertension with time-dependent Cox proportional hazards regression analyses. We evaluated effect modification by age, sex, BMI, smoking behavior, and 24-hour urinary albumin excretion by fitting models containing both main effects and their cross-product terms.

All P values are 2 tailed. P value <0.05 was considered statistically significant. All analyses were conducted using the statistical package IBM SPSS (version 20.0.1; SPSS, Chicago, IL) and SAS (version 9.2; SAS Institute, Cary, NC) software.
Results

The median 24-hour potassium excretion for the 2 urine specimens at baseline was 70 mmol (IQR, 57–85 mmol), with a higher value in men (77 mmol; IQR, 63–92) than in women (65 mmol; IQR, 53–78). This median urinary excretion corresponds to a daily dietary potassium intake of ≈91 mmol/24 h (≈3550 mg/d), assuming a gastrointestinal absorption of 77%. Baseline characteristics are shown according to sex-specific tertiles of urinary potassium excretion (Table 1). At baseline, subjects who had a higher potassium excretion were more likely to be younger and had a higher BMI. Men and women in the highest tertile of urinary potassium excretion were less likely to smoke and consumed more alcohol and sodium than men and women in the lowest tertile of excretion. Higher urinary potassium levels were univariately associated with higher plasma levels of aldosterone. The within-subject correlations for potassium excretion between the paired 24-hour urine specimens at the first and second examination

Table 1. Baseline Characteristics According to Sex-Specific Tertiles of Urinary Potassium Excretion in 5511 Participants of the PREVEND Study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Tertiles of Urinary Potassium Excretion, mmol/24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants, n</td>
<td>1836 1838 1837</td>
</tr>
<tr>
<td>Women, %</td>
<td>54.7 54.7 54.7</td>
</tr>
<tr>
<td>Age, y</td>
<td>45.9±11.6 45.7±10.8 44.2±10.1</td>
</tr>
<tr>
<td>Race, whites, %</td>
<td>90.7 96.6 98.4</td>
</tr>
<tr>
<td>Parental history of hypertension, %</td>
<td>27.2 29.1 30.8</td>
</tr>
<tr>
<td>Smoking status, never, %</td>
<td>29.0 30.1 32.9</td>
</tr>
<tr>
<td>Alcohol consumption, none, %</td>
<td>27.6 21.7 17.7</td>
</tr>
<tr>
<td>Education, high, %</td>
<td>27.9 35.7 43.0</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.7±3.8 25.2±3.8 25.4±3.9</td>
</tr>
<tr>
<td>Blood pressure</td>
<td></td>
</tr>
<tr>
<td>Systolic, mmHg</td>
<td>118±11 119±11 119±11</td>
</tr>
<tr>
<td>Diastolic, mmHg</td>
<td>70±7 70±7 70±7</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>5.5±1.1 5.5±1.1 5.4±1.0</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/L</td>
<td>1.3±0.4 1.4±0.4 1.4±0.4</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.1 (0.8–1.5) 1.0 (0.8–1.4) 1.0 (0.8–1.4)</td>
</tr>
<tr>
<td>Lipid-lowering drugs, %</td>
<td>2.9 3.4 2.4</td>
</tr>
<tr>
<td>Glucose, mmol/L</td>
<td>4.7±0.8 4.7±0.9 4.6±0.9</td>
</tr>
<tr>
<td>Glucose-lowering drugs, %</td>
<td>0.6 0.5 0.4</td>
</tr>
<tr>
<td>eGFR, mL/min per 1.73 m²</td>
<td>87 (77–97) 87 (77–98) 87 (78–97)</td>
</tr>
<tr>
<td>Proton-pump inhibitors, %</td>
<td>2.3 3.0 2.5</td>
</tr>
<tr>
<td>Plasma potassium, mmol/L †</td>
<td>4.4±0.6 4.3±0.3 4.4±0.6</td>
</tr>
<tr>
<td>Plasma sodium, mmol/L †</td>
<td>142±2 142±3 142±2</td>
</tr>
<tr>
<td>Plasma renin, μIU/mL ‡</td>
<td>19 (12–29) 18 (12–26) 19 (12–28)</td>
</tr>
<tr>
<td>Plasma aldosterone, pg/ml §</td>
<td>117 (93–149) 118 (93–151) 122 (96–160)</td>
</tr>
</tbody>
</table>

Continuous variables are reported as mean±SD or median (interquartile range), and categorical variables are reported as percentage. BMI indicates body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; and PREVEND, Prevention of Renal and Vascular End-Stage Disease.

* Determined by χ² test (categorical variables), linear regression (continuous variables).
† Available in 4627 subjects.
‡ Available in 5336 subjects.
§ Available in 4847 subjects.
were $r=0.59$ ($P<0.0001$; $n=5489$) and $r=0.64$ ($P<0.0001$; $n=4410$), respectively. The within-subject correlation between the averaged potassium excretions of the first and the second examination (separated by a median of 4.3 years [IQR, 4.0–4.8 years]) was $r=0.49$ ($P<0.0001$; $n=4429$).

During a median follow-up of 7.6 years (IQR, 5.0–9.3 years), 1172 hypertension cases were detected. The association between urinary potassium excretion and risk of hypertension was nonlinear ($P=0.008$ for nonlinearity; Table 2). The multivariable-adjusted spline curve confirmed the nonlinear inverse association of urinary potassium excretion with risk of hypertension (Figure). Because of the nonlinear association between urinary potassium excretion and risk of hypertension, we combined the upper 2 tertiles of the distribution into sex-specific deciles instead of tertiles. The HRs for the lowest 4 deciles of the distribution of potassium excretion were 1.30 (95% CI, 1.06–1.61), 1.12 (95% CI, 0.90–1.37), 1.12 (95% CI, 0.93–1.36), and 1.07 (95% CI, 0.88–1.30), respectively, as compared with the upper 6 deciles.

### Na-K Excretion Ratio

The median Na-K excretion ratio at baseline was 2.0 (IQR, 1.5–2.5) and was slightly lower in women (1.9; IQR, 1.5–2.4) than in men (2.0; IQR, 1.6–2.5). The within-subject correlations for the Na-K excretion ratio between the paired 24-hour urine specimens at the first and second examination were $r=0.49$ ($P<0.0001$; $n=5492$) and $r=0.56$ ($P<0.0001$; $n=4415$), respectively. The within-subject correlation between the averaged Na-K excretion ratios of first and the second examination (4.3 years later) was $r=0.22$ ($P<0.0001$; $n=4431$).

There was no evidence for a deviation from linearity in the association between the Na-K excretion ratio and risk of hypertension ($P=0.49$ for nonlinearity; Table S1). After adjustment for age and sex, a higher Na-K excretion ratio was significantly associated with a higher risk of hypertension ($P=0.005$ for linear trend) with an HR across extreme tertiles of 1.16 (95% CI, 1.01–1.34). The higher age- and sex-adjusted association was no longer significant after additional adjustment for BMI (HR across extreme tertiles, 1.06; 95% CI, 0.92–1.22) or multivariable adjustment (HR across extreme tertiles, 0.99; 95% CI, 0.85–1.15; $P=0.51$ for linear trend). There was no evidence for effect modification by age, BMI, sex, smoking status, alcohol consumption, urinary sodium excretion, or urinary albumin excretion (all $P>0.10$ for interaction). The proportion of hypertension attributable to low potassium excretion was 6.2% (95% CI, 1.7%–10.9%).

Similar results were found when we accounted for potential inadequacies in the timed 24-hour urine collections by excluding subjects with potential over- or undercollections based on the difference between a subject’s estimated and measured volume of 24-hour urine sample (HR first tertile compared with the upper 2 tertiles, 1.23; 95% CI, 1.07–1.40; $n=5239$, $n=1115$). Consistent with the Figure, we observed a curvilinear association between lower levels of potassium excretion and increased risk of hypertension when we divided the population into sex-specific deciles instead of tertiles. The HRs for the lowest 4 deciles of the distribution of potassium excretion were 1.30 (95% CI, 1.06–1.61), 1.12 (95% CI, 0.90–1.37), 1.12 (95% CI, 0.93–1.36), and 1.07 (95% CI, 0.88–1.30), respectively, as compared with the upper 6 deciles.

### Discussion

In this prospective population-based cohort study, 24-hour urinary potassium excretion, as estimate of dietary uptake, was nonlinearly associated with risk of incident hypertension. Subjects in the lowest tertile had a 20% higher risk of developing hypertension compared with the remainder of the cohort. This association remained after adjustment for conventional risk factors and urinary excretions of several...
cations, including sodium, and was consistent across strata of age, BMI, sex, smoking status, and urinary excretion of sodium or albumin. The proportion of hypertension attributable to low potassium excretion appeared to be 6.2%, suggesting that almost 1 in 16 incident cases of hypertension might have been prevented if all subjects were in the low-risk group of potassium excretion. An initial positive association between the urinary Na-K excretion ratio and risk of hypertension after age and sex adjustment lost significance after further adjustment, mainly attributable to BMI.

Although we found that low urinary potassium was associated with a higher risk of hypertension, results from previous prospective studies have been inconsistent. The majority of studies assessed potassium intake by means of self-reported dietary data which hampers a direct comparison. Our results are in keeping with the China Health and Nutrition Survey, which showed a 34% increased prevalence of hypertension associated with lower potassium consumption, when comparing extreme groups of potassium intake. The Nurses’ Health Study, the Health Professionals Follow-Up Study, and the National Health and Nutrition Examination Survey I, on the contrary, did not find a significant association between dietary potassium and risk of hypertension after multivariable adjustment. To date, only 1 observational study has investigated the association between urinary potassium excretion and risk of developing hypertension. Among 1520 ethnic Chinese men and women, 24-hour urinary potassium excretion, extrapolated from a single overnight urine collection, was not associated with risk of incident hypertension (HR extreme groups of potassium excretion, 0.98; 95% CI, 0.78–1.23). A comprehensive meta-analysis comprising 21 RCTs (or 1606 participants) that required 24-hour urinary potassium measurements to estimate potassium intake documented an overall decrease of 3.49 (95% CI, 1.82–5.15) mm Hg in systolic BP and of 1.96 (95% CI, 0.86–3.06) mm Hg in diastolic BP. However, BP reductions were only significant in people with hypertension, perhaps attributable to the limited number of studies (3 RCTs) among normotensive subjects in the meta-analysis. Also, although the largest reductions were seen in the subgroup with achieved potassium intakes of 90 to 120 mmol/d, no (linear) dose–response relationship between potassium intake and BP reductions was observed in this meta-analysis. This seems to corroborate the nonlinear association between potassium excretion and risk of hypertension in the current study.

Our data indicate that potassium is associated with an increased risk of hypertension when potassium excretion is <65 mmol/24 h, which corresponds to a dietary intake of ~84 mmol/d when taking into account an average fractional intestinal absorption of 77%. Such a lower limit seems to support the recommendation of the 2002 Joint WHO/Food and Agriculture Organization Expert Consultation of a minimal potassium intake of ≥3500 mg/d (90 mmol/d) for adults. In this cohort, 48% of the subjects would have been classified as having a potassium intake below this recommendation and even 84% of the subjects would have had a potassium intake below the adequate intake of 4700 mg/d (120 mmol/d) recommended by the Institute of Medicine. A high prevalence of inadequate potassium intake is not only seen in The Netherlands, but also in the United States, Canada, and China. The antihypertensive effect of dietary potassium may have more than one mechanism. One possibility is that dietary potassium enhances natriuresis, thereby lowering BP. Experimental studies have also shown that potassium supplementation may stimulate Na-K-ATPase in vascular smooth muscle cells and adrenergic nerve terminals, resulting in vasodilation or may potentiate endothelium-dependent relaxation. The association between potassium excretion and risk of developing hypertension was not affected by adjustment for plasma aldosterone at baseline. This suggests that low urinary potassium excretion influences development of hypertension by a mechanism that does not involve aldosterone.

Despite stronger associations with BP in cross-sectional analyses than sodium or potassium excretion alone, we and others did not find a prospective association between the urinary Na-K excretion ratio and risk of hypertension, particularly after BMI adjustment. The Na-K excretion ratio has been shown to be independently associated with total body fat, raising the possibility that this ratio is a surrogate of (a poor-quality diet associated with) BMI. Using a ratio makes
the implicit assumption that the regression coefficients for the 2 variables are equal in magnitude but opposite in direction.\textsuperscript{38} This was not the case in our sodium\textsuperscript{33} and potassium data. Furthermore, although the Na-K excretion ratio may offer a correction for characteristics of the urine collection such as completeness during the 24-hour period and correlated measurement errors,\textsuperscript{19} it may also introduce bias because of the combined measurement errors of determining sodium and potassium concentration in urine. Both short-term and long-term within-subject correlations between the 24-hour urinary excretions were lower for the Na-K ratio than for potassium alone, indicating a higher repeatability for urinary excretions of potassium than for the Na-K excretion ratio. Regardless, the null finding for the multivariable-adjusted Na-K excretion ratio and the absence of effect modification by sodium excretion in the potassium–hypertension association both suggest that potassium excretion per se may affect the risk of hypertension, irrespective of sodium. However, the vast majority of our population (81\%) had a sodium excretion of >100 mol/24 h (>2300 mg/d). We thus had limited power to investigate whether low potassium excretion is also associated with a higher risk of hypertension among those whose sodium intake does not exceed dietary recommendations. Also, it might be possible that a high dietary potassium protected against developing hypertension despite a high dietary sodium.

Some limitations of this study should be noted. First, we had no information on the dietary origin of the excreted potassium because no dietary records were obtained in the PREVEND study. Potassium is mostly present in fruits, vegetables, meat, potatoes, and dairy products.\textsuperscript{39} Potassium homeostasis is complex; several factors play a role including electrolytes (sodium and magnesium) and several hormones such as not only insulin, norepinephrine, but also aldosterone and renin. Also, other (dietary) components that are closely associated with potassium intake, such as alkali and dietary fiber, could potentially be involved in the lower risk for hypertension.\textsuperscript{6} However, we did adjust for urinary sodium, magnesium, and calcium excretion and for BMI as a proxy for energy intake. Second, participants with mildly elevated levels of urinary albumin, an indicator of kidney impairment, were over-represented in the PREVEND study. However, similar results were obtained after stratification for urinary albumin, showing that mild kidney impairment is unlikely to modify the association of potassium excretion with incident hypertension. Third, >95\% of the individuals of the PREVEND study are white and our results of a nonlinear association between urinary potassium excretion and risk of hypertension may not be readily generalizable to different demographic populations. Blacks, for instance, typically show a lower urinary excretion rate of potassium than do whites.\textsuperscript{40,41} Fourth, we did not have additional information on recreational drug use other than alcohol consumption and tobacco use. Uncontrolled confounding by unmeasured factors, if associated with potassium excretion and risk of hypertension, remains a possibility. Fifth, there is variation in dietary potassium absorption. In carefully performed balance studies, the mean (SEM) potassium absorption was 77.0\% (1.7\%), consistent with a 95\% CI of absorption of 73.7\% to 80.3\%, with most extreme values in this report ranging from 64\% to 95\%.\textsuperscript{25} Also, ageing of the intestine may have influenced potassium absorption. Sixth, because the subjects of PREVEND study were in a long-term observational trial, their behavior might have been affected. However, the participants were unaware of their urinary potassium excretion, which limits the possibility that subjects changed their diets because of a low potassium excretion. Finally, we studied subjects who were normotensive at baseline. Thus, subjects who had already developed hypertension before their inclusion in PREVEND study, possibly representing the population subgroup with this highest risk, were not included in our analysis.

One of the strengths of this study is the use of multiple 24-hour urine collections updated over time to estimate habitual dietary potassium uptake (and indirectly, intake). Twenty-four hour urine collections are regarded as the gold standard to assess dietary potassium and provide an objective and quantitative measure of intake on a population level. Furthermore, dietary potassium based on urine collections tends to have higher repeatability than those based on 24-hour dietary recall, as characterized by within-subject correlations.\textsuperscript{19} Our within-subject correlations for the paired 24-hour urine assessments for potassium were also similar or higher than those observed in the Trials of Hypertension Prevention (TOHP),\textsuperscript{42} the Trial of Nonpharmacological Interventions in the Elderly (TONE),\textsuperscript{19} and the International Cooperative Study on Salt, Other Factors, and Blood Pressure (INTERSALT) study.\textsuperscript{43,44} Despite being considered the gold standard, even 24-hour collections are subject to certain concerns. To evaluate the quality and completeness of the urine specimens, we performed a sensitivity analysis to correct for possible over- or undercollections. This did not appreciably alter the results. Also, although greatly reducing bias because of measurement error and random error because of within-person variability over time, two 24-hour urinary collections at baseline and 2 during follow-up may have been suboptimal to represent habitual potassium uptake and to sufficiently reduce the day-to-day variation in urinary potassium excretion. Other strengths of this study were the prospective design, the use of multiple measured BPs and participant and pharmacy information on antihypertensive medication to define hypertension, the use of a large sample size, and the availability of detailed and updated (midway through the period of follow-up to reduce potential misclassification) information on the exposure and potential confounders.

**Perspectives**

In this large population-based cohort of men and women, low urinary excretion of potassium was associated with a higher risk of hypertension. This association persisted after adjustment for both dietary and nondietary factors and was consistent across several subgroups. A higher consumption of potassium, particularly by those with the lowest potassium excretion, while concurrently not exceeding dietary recommendations on sodium intake, may be a promising approach for the primary prevention of hypertension. These data reinforce the importance of dietary potassium in BP control.

**Sources of Funding**

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conduct of the study, collection, analysis, or interpretation of the data, or the preparation and approval of the manuscript.

Disclosures

None.

References


**Novelty and Significance**

What Is New?
- Potassium supplementation lowers blood pressure in randomized controlled trials, but the long-term effect of dietary potassium on risk of hypertension remains to be established.
- Previous prospective cohort studies have almost exclusively relied on self-reported dietary data, whereas repeated 24-hour urine excretions, as estimate of dietary uptake, may provide a more objective and quantitative estimate of this association.

What Is Relevant?
- Low urinary potassium excretion is associated with a higher risk of developing hypertension.
- Six percent of all incident hypertension cases seemed to be attributable to suboptimal dietary potassium.
- Dietary strategies to increase potassium intake to the recommended level of 90 mmol/d may have the potential to reduce the incidence of hypertension.

**Summary**

During a median follow-up of 7.6 years, 1172 participants developed hypertension. Low urinary potassium excretion, a reflection of dietary potassium intake, was associated with a 20% higher risk of hypertension after adjustment for both dietary and nondietary risk factors.
Urinary Potassium Excretion and Risk of Developing Hypertension: The Prevention of Renal and Vascular End-Stage Disease Study
Lyanne M. Kieneker, Ron T. Gansevoort, Kenneth J. Mukamal, Rudolf A. de Boer, Gerjan Navis, Stephan J.L. Bakker and Michel M. Joosten

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URINARY POTASSIUM EXCRETION AND RISK OF DEVELOPING HYPERTENSION: THE PREVENTION OF RENAL AND VASCULAR END-STAGE DISEASE STUDY

Running title: Kieneker et al; Potassium and Risk of Hypertension

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Total number of figures: 1
Additional methods
Study design and population
In summary, from 1997 to 1998, all inhabitants of the city Groningen, the Netherlands, aged 28 to 75 years (n=85,421), were sent a vial to collect a first morning void urine sample and a short questionnaire on demographics and renal and cardiovascular morbidity. Altogether, 40,856 people (48%) responded and their urinary albumin concentration was assessed. After exclusion of pregnant women and subjects with type I diabetes mellitus, subjects with a urinary albumin concentration of ≥10 mg/L (n=7,768) were invited to participate, of whom 6,000 did so. In addition, a randomly selected group with a urinary albumin concentration of <10 mg/L (n=3,394) was invited to participate in the cohort, of whom 2,592 joined. These 8,592 individuals constitute the PREVEND cohort and completed an extensive examination in 1997 and 1998 (baseline).

Laboratory assays
Sodium, calcium, magnesium, creatinine and albumin in urine and circulating potassium, sodium, total cholesterol, HDL cholesterol, triglycerides and glucose were determined as previously described.\textsuperscript{1, 2} Estimated glomerular filtration rate (eGFR) was calculated from the Chronic Kidney Disease Epidemiology Collaboration equation.\textsuperscript{3} Plasma renin was measured using an automated sandwich immunochemiluminescent assay (LIAISON, Diasorin, DiaSorin Ltd, Schiphol Rijk, The Netherlands) as described previously.\textsuperscript{4} Plasma aldosterone was measured using an enzyme immunoassay (Alpco Diagnostics, Catalog Number: 11-ALDHU-E01, Alpco, Salem, NH).
References
Figure Legend:

**Figure S1.** Association between low urinary potassium excretion (men: <68 mmol/24-hour; women: <58 mmol/24-hour) and risk of hypertension in the overall population and stratified by selected characteristics (N=number of subjects, n=number of cases). Multivariable-adjusted hazard ratios (95% confidence intervals) for risk of hypertension for the lowest tertile compared with the upper two tertiles. A hazard ratio higher than 1 indicates that the lowest tertile of urinary potassium excretion is associated in the direction of a higher risk for developing hypertension. Hazard ratios were derived from Cox proportional hazards regression models with time-varying covariates and adjusted for age, sex, body mass index, smoking status, parental history of hypertension, alcohol consumption, education, and urinary excretion of sodium, calcium, and magnesium. The P-values denote the P for interaction.
<table>
<thead>
<tr>
<th>Measures</th>
<th>Tertiles of sodium-potassium excretion ratio</th>
<th>P-value for linear association†</th>
<th>P-value for non-linear association‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>&lt;1.7</td>
<td>0.92 (0.80-1.06)</td>
<td>0.005</td>
</tr>
<tr>
<td></td>
<td>1.7-2.3</td>
<td>1.00 (reference)</td>
<td>0.50</td>
</tr>
<tr>
<td></td>
<td>&gt;2.3</td>
<td>1.07 (0.93-1.23)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&lt;1.6</td>
<td>0.97 (0.85-1.12)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>1.6-2.2</td>
<td>1.00 (reference)</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>&gt;2.2</td>
<td>0.98 (0.85-1.13)</td>
<td>0.49</td>
</tr>
</tbody>
</table>

Person-years  10,847  10,751  10,213
Number of events  372  412  388
Age- and sex-adjusted  0.92 (0.80-1.06)  1.00 (reference)  1.07 (0.93-1.23)  0.005  0.50
Multivariable model 1  0.97 (0.85-1.12)  1.00 (reference)  1.01 (0.88-1.16)  0.17  0.17
Multivariable model 2  0.99 (0.86-1.14)  1.00 (reference)  0.98 (0.85-1.13)  0.51  0.49

* Hazard ratios were derived from Cox proportional hazards models. Multivariable model 1 was an age-adjusted model and was additionally adjusted for sex, body mass index, smoking status, alcohol consumption and parental history of hypertension. Multivariable model 2 was adjusted as model 1 plus adjusted for education and urinary magnesium and calcium excretion.
† Derived from a Cox proportional hazards model by using urinary potassium excretion as a continuous linear term.
‡ Derived by using the likelihood ratio test, comparing nested Cox proportional hazards regression models with a linear or linear and cubic spline terms. Abbreviations: PREVEND, Prevention of Renal and Vascular End-Stage Disease.
Table S2. Systolic blood pressure, diastolic blood pressure and pulse pressure at time of follow-up.

<table>
<thead>
<tr>
<th>Time of follow-up</th>
<th>Systolic blood pressure (mm Hg)</th>
<th>Diastolic blood pressure (mm Hg)</th>
<th>Pulse pressure (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (N=5,511)</td>
<td>119 ± 11</td>
<td>70 ± 7</td>
<td>49 ± 8</td>
</tr>
<tr>
<td>Screening two (N=4,546)</td>
<td>119 ± 13</td>
<td>71 ± 8</td>
<td>48 ± 9</td>
</tr>
<tr>
<td>Screening three (N=3,928)</td>
<td>120 ± 14</td>
<td>72 ± 8</td>
<td>49 ± 10</td>
</tr>
<tr>
<td>Screening four (N=3,528)</td>
<td>122 ± 15</td>
<td>73 ± 9</td>
<td>49 ± 11</td>
</tr>
</tbody>
</table>
Figure S1. Association between low urinary potassium and risk of hypertension in the overall population and stratified by selected characteristics

Overall (N=5311; n=1172)
Age at baseline, y
  ≤49 (N=3697; n=622)
  >49 (N=1514; n=550)
Body mass index, kg/m²
  ≤25 (N=2985; n=444)
  >25 (N=2526; n=717)
Gender
  Male (N=2497; n=596)
  Female (N=3014; n=576)
Smoking status
  Nev./for. (N=3460; n=737)
  Current (N=2051; n=435)
Urine albumin, mg/24 h
  <9.3 (N=3254; n=586)
  ≥9.3 (N=2257; n=586)
Urine sodium, mmol/24 h
  ≤136 (N=3112; n=588)
  >136 (N=2399; n=584)
尿钾排泄量和高血压患病风险
——肾脏和血管终末期疾病防治的研究

Urinary Potassium Excretion and Risk of Developing Hypertension
The Prevention of Renal and Vascular End-Stage Disease Study

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张抒扬 译

在先前多个关于钾盐摄入量和高血压患病风险关系的前瞻性队列研究中，钾摄取量的统计均依靠患者的自我饮食报告数据，而通过重复检查24小时尿钾排泄量来估计钾的每日摄入量，可以提供一个更为客观的定量数据，从而评估钾摄取量和患高血压患病风险之间的关系。高血压患病风险定义为：血压≥140/90 mm Hg，或者血压≥起始血压减去降压药物降低的血压。在一项称为肾脏和血管终末期疾病防治（Prevention of Renal and Vascular End-Stage Disease, PREVEND）的研究项目中，有5511例年龄为28~75岁且不使用降压药物的正常研究对象，分别利用每位研究对象的两份24小时的尿液样本，测量其基线水平（1997~1998）和随访过程中的尿钾排泄情况（2001~2003）。基线水平的尿钾排泄为70 mmol/24 h（四分位间距57~85 mmol/24h），相应的钾摄取量约为91 mmol/24 h；在中位期为7.6年的随访时间（四分位间距5.0~9.3年）后，约1172例出现高血压。按尿钾排泄量将研究对象分为3组，分析其中尿钾排泄最低的一组（男<68 mmol/24h；女<58 mmol/24h），与另外两组相比，校正多个变量后，该组高血压患病风险增加（RR值1.20，95%可信区间为1.05~1.37）。回归危险分析，6.2%的高血压由低尿钾排泄引起（95%可信区间为1.7%~10.9%）。多个变量的校正分析显示，钠/钾排泄比值和高血压患病风险之间没有相关性。低尿钾排泄增加高血压发病率。

(1Hypertension. 2014;64:769-776.)