ORIGINAL ARTICLE

24-Hour Urinary Sodium and Potassium Excretion and Cardiovascular Risk

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ABSTRACT

BACKGROUND

The relation between sodium intake and cardiovascular disease remains controversial, owing in part to inaccurate assessment of sodium intake. Assessing 24-hour urinary excretion over a period of multiple days is considered to be an accurate method.

METHODS

We included individual-participant data from six prospective cohorts of generally healthy adults; sodium and potassium excretion was assessed with the use of at least two 24-hour urine samples per participant. The primary outcome was a cardiovascular event (coronary revascularization or fatal or nonfatal myocardial infarction or stroke). We analyzed each cohort using consistent methods and combined the results using a random-effects meta-analysis.

RESULTS

Among 10,709 participants, who had a mean (±SD) age of 51.5±12.6 years and of whom 54.2% were women, 571 cardiovascular events were ascertained during a median study follow-up of 8.8 years (incidence rate, 5.9 per 1000 person-years). The median 24-hour urinary sodium excretion was 3270 mg (10th to 90th percentile, 2099 to 4899). Higher sodium excretion, lower potassium excretion, and a higher sodium-to-potassium ratio were all associated with a higher cardiovascular risk in analyses that were controlled for confounding factors ($P \leq 0.005$ for all comparisons). In analyses that compared quartile 4 of the urinary biomarker (highest) with quartile 1 (lowest), the hazard ratios were 1.60 (95% confidence interval [CI], 1.19 to 2.14) for sodium excretion, 0.69 (95% CI, 0.51 to 0.91) for potassium excretion, and 1.62 (95% CI, 1.25 to 2.10) for the sodium-to-potassium ratio. Each daily increment of 1000 mg in sodium excretion was associated with an 18% increase in cardiovascular risk (hazard ratio, 1.18; 95% CI, 1.08 to 1.29), and each daily increment of 1000 mg in potassium excretion was associated with an 18% decrease in risk (hazard ratio, 0.82; 95% CI, 0.72 to 0.94).

CONCLUSIONS

Higher sodium and lower potassium intakes, as measured in multiple 24-hour urine samples, were associated in a dose–response manner with a higher cardiovascular risk. These findings may support reducing sodium intake and increasing potassium intake from current levels. (Funded by the American Heart Association and the National Institutes of Health.)

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High sodium consumption, a major cause of hypertension, is considered to be a leading dietary risk factor for cardiovascular disease worldwide.[1,2] Population-wide reduction in sodium intake has been suggested as a cost-effective strategy to prevent hypertension and cardiovascular disease.[3,4] However, several cohort studies have linked both estimated lower (e.g., <3000 mg per day) and higher (e.g., >6000 mg per day) sodium intakes, assessed mainly with the use of spot urine samples, to increased cardiovascular risk.[5-8] Methodologic limitations, including inaccurate estimates of individual sodium intakes and reverse causation related to coexisting conditions or changes in health status, may play a major part in these controversial findings.[9]

Accumulating evidence suggests that daily sodium intake as estimated from spot urine samples leads to a spuriously increased cardiovascular risk at lower estimated sodium intake levels because of inherent systematic error in the estimation formulas and is also subject to substantial random error.[9-11] Furthermore, a single 24-hour urine sample is not sufficiently representative of a participant's usual sodium intake owing to the large day-to-day variations in sodium intake. In addition, participants may reduce sodium intake because of preexisting illness or frail status preceding major diseases and still be at an elevated risk for cardiovascular disease, resulting in a spurious association between low sodium intake and increased disease risk (i.e., reverse causation).[9] Given the interrelationship of sodium and potassium, it is also important to consider their associations jointly.[12] We investigated the relation between sodium and potassium intakes and cardiovascular risk by combining individual-level data from studies in healthy populations in which multiple 24-hour urine samples, the most accurate method for assessing sodium intake, were obtained for each participant.

Methods

Study Population

This study combined individual data from six cohorts: the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II), the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, and the Trials of Hypertension Prevention (TOHP I and TOHP II) Follow-up Studies.[13-18] More details on the study design are provided in Sections S1 and S2 and Figure S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The HPFS, NHS, and NHS II are ongoing prospective cohort studies involving health professionals and registered nurses in the United States.[13] A subgroup of 2282 participants collected two 24-hour urine samples between 2003 and 2007, and an additional subgroup of 1217 participants collected four 24-hour urine samples between 2010 and 2013.[14,15] The occurrence of cardiovascular disease was tracked through January 2016 in the HPFS and through June 2017 in the NHS and NHS II; death was tracked through June 2020.

The PREVEND study was a prospective, population-based cohort of 8592 adults, in which participants collected two consecutive 24-hour urine samples between 1997 and 1998 and another two consecutive 24-hour urine samples between 2001 and 2003.[16] The occurrences of cardiovascular events and death during the study were tracked through January 2011 and January 2017, respectively. Our study excluded 1908 participants in the PREVEND study who had preexisting chronic kidney disease.

The TOHP Follow-up Studies are observational follow-up extensions of TOHP I and TOHP II, in which the effects of dietary supplements and lifestyle interventions, including weight loss and reduction in sodium intake, were evaluated among 2182 participants in TOHP I and among 2382 participants in TOHP II.[17,18] A total of five to seven 24-hour urine samples were obtained per participant in TOHP I (between 1987 and 1990) and three to five 24-hour urine samples per participant in TOHP II (between 1990 and 1995). In the TOHP I and II Follow-up Studies, participants were followed from the end of each trial through early 2005 for cardiovascular events and through December 2013 for death.[19] Participants who had been randomly assigned to the sodium-reduction groups in these two trials (327 participants in TOHP I and 1191 in TOHP II) were excluded from our current analysis.

For all these studies, baseline was defined as the period during which the prespecified numbers of 24-hour urine samples were obtained. The primary analysis excluded the first year of follow-up because dietary information that was collected close to the occurrence of a cardiovascular

event or death may not reflect habitual sodium intake. Among 11,435 participants who had at least two eligible 24-hour urine samples at baseline, 626 (5.5%) did not respond to the follow-up regarding cardiovascular events, and another 100 participants (0.9%) had less than 1 year of follow-up. Therefore, 10,709 participants were included in the primary analysis. All the studies obtained institutional review board approval and written or oral informed consent from all the participants. The first and last authors of the current study vouch for the accuracy and completeness of the data and for the fidelity of this study to the protocol.

24-HOUR URINARY SODIUM AND POTASSIUM EXCRETION

Our primary exposure measures were the participants' sodium and potassium excretions, which were assessed by averaging the excretions in all available 24-hour urine samples per participant. To reduce measurement error that might arise from the undercollection or overcollection of 24-hour urine samples, we excluded samples that met at least one of the following criteria: the volume of the 24-hour urine sample was less than 500 ml or more than 5000 ml; the duration was less than 20 hours or was more than 28 hours, when the start and end times of urine collection were available; or the volume loss was more than 100 ml if the estimated volume lost was reported. Alternative exclusion criteria were used in the sensitivity analyses.

OUTCOME ASCERTAINMENT

The primary outcome of our study was a cardiovascular event, which was defined as a composite of coronary revascularization (coronary-artery bypass grafting or percutaneous coronary intervention), fatal or nonfatal myocardial infarction, or fatal or nonfatal stroke. Other deaths due to cardiovascular causes were reported in the TOHP I and II Follow-up Studies. Secondary outcomes were stroke, death from any cause, and a composite of coronary revascularization or myocardial infarction. The criteria that were used to ascertain these outcomes have shown high validity in the individual studies (Section S3).

STATISTICAL ANALYSIS

Our primary analysis evaluated the associations of continuous urinary sodium and potassium excretion and the sodium-to-potassium ratio with subsequent risk of a cardiovascular event. We assessed the relations in each study independently using consistent analytic methods and then synthesized the results from each study using a random-effects meta-analysis (i.e., two-stage pooled analyses). For each study, hazard ratios were estimated by Cox proportional-hazards models, with adjustment for potential confounding factors, including age, sex, and race or ethnic group in a partially adjusted model (model 1). The fully adjusted model, which was the primary analytic model (model 2), included additional adjustment for educational level, height, baseline body-mass index, smoking status, alcohol consumption, physical activity, history of diabetes and elevated cholesterol status, and family history of cardiovascular disease, as well as the 24-hour urinary potassium excretion (for sodium as the exposure) and sodium excretion (for potassium as the exposure). Details on the model specifications are provided in Section S4.

Missing covariate values (which occurred in <1% of the participants) were handled with the use of missing indicators. Person-time was calculated from 1 year after all the prespecified 24-hour urine collections were obtained until the occurrence of a cardiovascular event or death or the end of follow-up, whichever occurred first. The proportional-hazard assumptions were tested and verified by the inclusion of an interaction term with time in the model. Results from individual studies were pooled with the use of a random-effects meta-analysis to account for the design differences among these studies. Between-study heterogeneity was statistically assessed with the use of I^2. Our primary analyses were based on a priori hypotheses, but in order to account for the hypothesis tests for three exposures, we present P values that were corrected for multiple comparisons with the use of the Holm–Bonferroni procedure.[20] All the 95% confidence intervals that are presented for the secondary outcomes and sensitivity analyses have not been corrected for multiplicity and should not be used to infer statistical significance.

In the secondary analyses, we repeated the analyses for study-specific quartile-based categorical exposures. We also investigated the associations by combining all the individual-level data in the same models with stratification according to study (i.e., simple pooled analysis). To assess the

Table 1. Baseline Characteristics of the Study Population.*

Characteristic	Overall (N=10,709)	Study Cohorts					
		HPFS (N=1028)	NHS (N=1064)	NHS II (N=1305)	PREVEND (N=5131)	TOHP I (N=1334)	TOHP II (N=847)
Calendar years of baseline measurements	—	2003–2007 or 2010–2013	2003–2007 or 2010–2013	2003–2007 or 2010–2013	1997–2003	1987–1990	1990–1995
Age at baseline — yr	51.5±12.6	68.1±6.1	69.2±5.8	52.1±5.5	47.8±11.5	43.3±6.3	43.5±6.2
Female sex — %	54.2	0	100	100	54.1	28.8	32.5
Race or ethnic group — %†							
White	92.4	94.3	95.5	92.2	95.3	85.0	81.5
Black	3.9	0.5	1.5	3.7	0.9	12.7	15.2
Asian or Pacific Islander	1.3	0.4	0.2	0.5	2.0	1.3	1.2
Hispanic	0.3	0	0.1	0.5	—	0.8	1.5
Other	2.0	4.9	2.7	3.1	1.8	0.2	0.6
Height — cm	172.0±9.6	179.0±6.1	164.0±6.0	165.0±6.5	173.1±9.5	174.3±9.3	174.0±9.1
Body-mass index	26.6±4.5	26.1±3.6	26.5±5.0	27.1±6.2	25.6±4.0	27.5±3.6	30.8±3.1
Educational level — %							
Less than high school graduate	19.1	0	0	0	39.5	1.3	1.1
High school graduate	20.0	0	0	0	26.6	35.2	37.2
Some college or more	60.8	100	100	100	34.0	63.4	61.7
Smoking status — %							
Never smoked	45.5	52.7	48.5	70.7	32.4	57.4	54.8
Former smoking	35.9	44.3	45.6	24.3	36.1	31.8	36.8
Current smoking	18.6	3.0	5.8	5.0	31.6	10.8	8.4
Alcohol consumption — %							
≤1 drink per wk	44.1	24.1	49.0	50.5	38.9	55.2	66.8
2–6 drinks per wk	33.1	36.2	31.4	37.9	35.7	26.4	18.5
≥7 drinks per wk	22.8	39.7	19.6	11.5	25.4	18.4	14.6
Physical activity — %‡							
<1 episode per wk	25.6	9.3	25.8	28.4	25.9	31.2	32.0
1 or 2 episodes per wk	27.5	17.1	30.1	27.9	74.1	28.3	35.3
≥3 episodes per wk	46.9	73.5	44.1	43.8	—	40.5	32.7

Diabetes — %	2.4	4.3	7.0	4.7	1.6	0	0
Hypercholesterolemia — %	29.8	59.8	66.9	42.3	20.6	0	—
Hypertension — %	23.6	38.3	52.1	24.4	24.5	0	0
Family history of cardiovascular disease — %	16.8	13.1	27.2	20.1	17.9	8.1	9.5
No. of eligible 24-hr urine samples per participant	2–7	2–4	2–4	2–4	2–4	2–7	2–5
Median 24-hr urinary sodium excretion (IQR) — mg	3270 (2615–4042)	3647 (2936–4542)	2843 (2254–3519)	3186 (2599–3956)	3157 (2544–3862)	3450 (2768–4252)	3961 (3200–4783)
Among men	3690 (3013–4486)	3647 (2936–4542)	—	—	3584 (2959–4300)	3689 (3038–4451)	4290 (3578–5073)
Among women	2944 (2385–3610)	—	2843 (2254–3519)	3186 (2599–3956)	2820 (2312–3414)	2902 (2357–3548)	3342 (2770–3915)
Median 24-hr urinary potassium excretion (IQR) — mg	2535 (2067–3069)	2882 (2367–3500)	2301 (1831–2779)	2184 (1755–2672)	2679 (2247–3196)	2334 (1877–2899)	2368 (1968–2891)
Among men	2808 (2323–3371)	2882 (2367–3500)	—	—	2959 (2488–3461)	2511 (2064–3067)	2573 (2142–3073)
Among women	2340 (1911–2798)	—	2301 (1831–2779)	2184 (1755–2672)	2479 (2102–2931)	1962 (1595–2353)	2005 (1589–2390)
Median sodium-to-potassium ratio (IQR)§	2.2 (1.8–2.9)	2.2 (1.7–2.8)	2.2 (1.7–2.8)	2.5 (2.0–3.4)	2.0 (1.7–2.5)	2.7 (2.1–3.3)	3.0 (2.4–3.6)
Median 24-hr urinary creatinine excretion (IQR) — mg	1344 (1110–1648)	1581 (1379–1807)	1030 (909–1186)	1235 (1085–1407)	1346 (1119–1630)	1460 (1156–1761)	1725 (1382–2070)
Median 24-hr urine volume (IQR) — ml	1620 (1283–2028)	1705 (1307–2175)	1796 (1400–2210)	1785 (1326–2345)	1588 (1290–1940)	1459 (1159–1875)	1597 (1246–2055)
Cardiovascular event during study¶							
No. of events	571	80	56	20	242	115	58
Median follow-up (IQR) — yr	8.8 (7.6–10.9)	8.4 (2.8–10.7)	12.1 (5.8–13.0)	11.3 (5.8–12.5)	8.3 (7.8–8.9)	14.7 (12.4–14.7)	9.5 (7.2–9.5)

* Plus–minus values are means ±SD. Percentages may not total 100 because of rounding. Data on height were missing for 0.48% of the participants, on body-mass index (the weight in kilograms divided by the square of the height in meters) for 0.49%, on smoking status for 0.31%, on alcohol consumption for 0.43%, and on physical activity for 0.65%. Data from six studies — the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II), the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, and the Trial of Hypertension Prevention (TOHP) I and II Follow-up Studies — are shown.

† Race and ethnic group were reported by the participant.

‡ In the PREVEND study, physical activity was classified as no more than one episode per week for 25.9% of the participants and as more than one episode per week for 74.1%; these data were not included in the overall descriptive data.

§ The sodium and potassium values used in this ratio were measured in millimoles.

¶ Cardiovascular events were defined as fatal or nonfatal myocardial infarction, coronary revascularization, and fatal or nonfatal stroke.

Table 2. Association of Sodium and Potassium Excretion with Cardiovascular Risk.*

Variable	Quartile of Urinary Biomarker				Hazard Ratio per 1000-mg Increase per Day†	P Value
	Quartile 1	Quartile 2	Quartile 3	Quartile 4		
24-Hr sodium excretion						
Median 24-hr sodium excretion — mg	2212	2942	3588	4692		—
Cardiovascular event — no. of events/ no. of participants	111/2677	139/2677	145/2679	176/2676	—	—
Hazard ratio (95% CI)						
Model 1	Reference	1.15 (0.89–1.49)	1.25 (0.86–1.80)	1.40 (1.07–1.82)	1.12 (1.04–1.21)	—
Model 2	Reference	1.25 (0.96–1.63)	1.44 (0.93–2.23)	1.60 (1.19–2.14)	1.18 (1.08–1.29)	<0.001
24-Hr potassium excretion						
Median 24-hr potassium excretion — mg	1755	2336	2784	3501		—
Cardiovascular event — no. of events/ no. of participants	148/2682	156/2674	140/2677	127/2676	—	—
Hazard ratio (95% CI)						
Model 1	Reference	1.02 (0.81–1.29)	0.88 (0.69–1.11)	0.74 (0.57–0.95)	0.85 (0.76–0.96)	—
Model 2	Reference	1.00 (0.78–1.26)	0.86 (0.67–1.11)	0.69 (0.51–0.91)	0.82 (0.72–0.94)	0.005
Sodium-to-potassium ratio						
Median ratio	1.5	2.0	2.4	3.4		—
Cardiovascular event — no. of events/ no. of participants	113/2676	116/2678	152/2679	190/2676	—	—
Hazard ratio (95% CI)†						
Model 1	Reference	1.02 (0.79–1.33)	1.43 (1.01–2.01)	1.76 (1.37–2.24)	1.27 (1.16–1.40)	—
Model 2	Reference	1.02 (0.78–1.33)	1.40 (0.99–1.99)	1.62 (1.25–2.10)	1.24 (1.12–1.37)	<0.001

* Sodium and potassium excretion was measured with the use of multiple 24-hour urine samples per participant. Model 1 was adjusted for potential confounding factors, including age, sex, and race. Model 2, which was the primary analytic model, was defined as model 1 plus adjustment for educational level, height, body-mass index, smoking status, alcohol consumption, physical activity, history of diabetes and elevated cholesterol status, family history of cardiovascular disease, the 24-hour urinary potassium excretion (for sodium as the exposure) and 24-hour sodium excretion (for potassium as the exposure), and total energy intake and the modified DASH (Dietary Approaches to Stop Hypertension) diet quality score for the HPFS, NHS, and NHS II. The 95% confidence intervals have not been adjusted for multiplicity.

† Hazard ratios for the sodium-to-potassium ratio correspond to the per-unit increase in the ratio as assessed on the basis of the sodium and potassium excretion measured in millimoles.

deviation from linearity of the associations, we used penalized splines for the exposures in the simple pooled analysis.[21] We also conducted prespecified stratified analyses and assessed the association of urinary sodium and potassium excretion with secondary outcomes, including total coronary heart disease, total stroke, and death from any cause, separately. The stratified analyses and analyses for components of the primary outcome (i.e., coronary heart disease and stroke) were conducted with the use of a simple pooled analysis owing to small sample sizes in the individual studies. In a post hoc analysis, we used a simple pooled analysis to assess the association of urinary sodium excretion with death from cardiovascular causes and death from noncardiovascular causes separately. In sensitivity analyses, we assessed the effect of measurement error, other

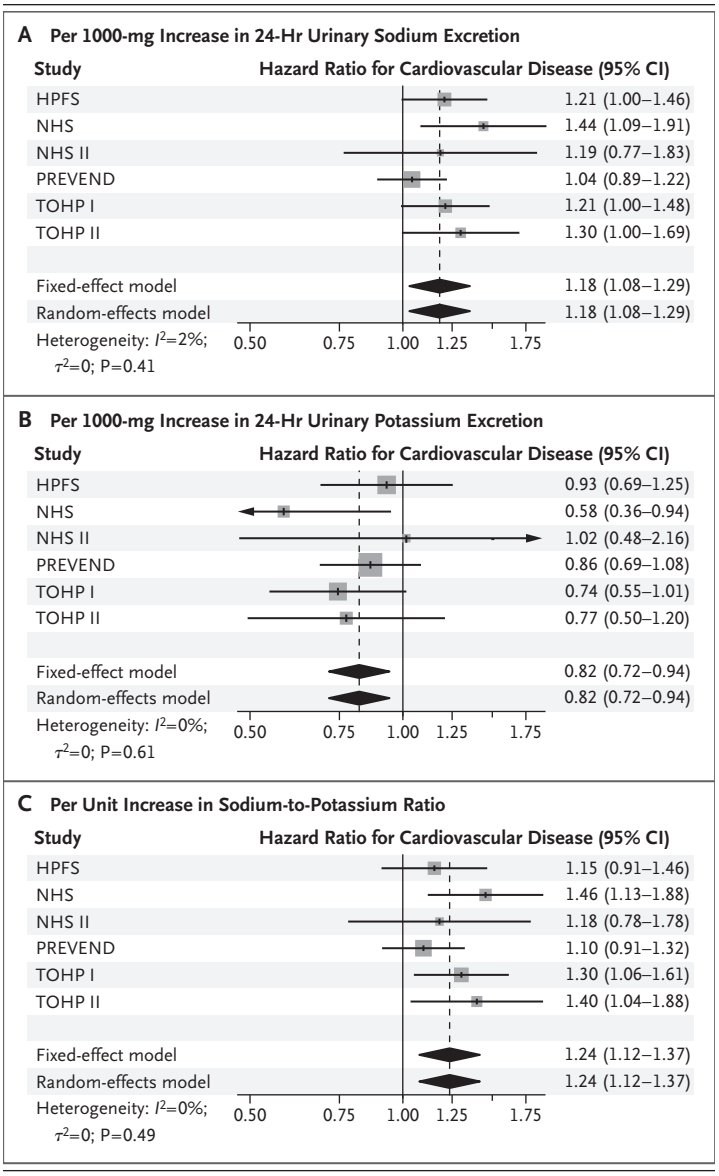


Figure 1. Forest Plots for the Associations of 24-Hour Urinary Sodium and Potassium Excretion and Sodium-to-Potassium Ratio with Cardiovascular Risk.

In two-stage pooled analyses that combined individual-participant data from six studies, each additional 1000 mg of 24-hour urinary sodium excretion (Panel A) was associated with an 18% increase in cardiovascular risk, and each additional 1000 mg of 24-hour urinary potassium excretion (Panel B) was associated with an 18% decrease in cardiovascular risk. The sodium-to-potassium ratio (Panel C) was assessed on the basis of the sodium and potassium excretion measured in millimoles. Data from six studies — the Health Professionals Follow-up Study (HPFS), the Nurses' Health Study (NHS), the Nurses' Health Study II (NHS II), the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, and the Trial of Hypertension Prevention (TOHP) I and II Follow-up Studies — are shown. Hazard ratios have been adjusted for potential confounding factors, including age, sex, race, educational level, height, body-mass index, smoking status, alcohol consumption, physical activity, history of diabetes and elevated cholesterol status, family history of cardiovascular disease, 24-hour urinary potassium excretion (for sodium as the exposure) and 24-hour sodium excretion (for potassium as the exposure), and total energy intake and the modified DASH (Dietary Approaches to Stop Hypertension) diet quality score for the HPFS, NHS, and NHS II. In each graph, the size of the squares indicates the weight given to the study, and the width of the diamond indicates the 95% confidence interval for the overall association estimate. Arrows indicate that the 95% confidence interval extends beyond the scale shown. Between-study heterogeneity was statistically assessed with the use of I^2.

potential confounding factors, missing covariate values, nonresponse, and competing events on the association.

RESULTS

STUDY POPULATION

The characteristics of the 10,709 participants are presented according to cohort in Table 1 and according to study-specific quartiles of 24-hour urinary sodium excretion in Table S1. Overall, the median 24-hour sodium excretion as assessed in the 37,896 urine samples was 3270 mg (10th to 90th percentile, 2099 to 4899). Under the assumption of nonrenal losses of 7% for sodium[22] and 23% for potassium,[23] the estimated overall daily sodium intake was 3516 mg (10th to 90th percentile, 2257 to 5268) and the estimated overall daily potassium intake was 3292 mg (10th to 90th percentile, 2162 to 4700).

During a median follow-up of 8.8 years (interquartile range, 7.6 to 10.9), there were a total of 571 cardiovascular events (incidence rate, 5.9 events per 1000 person-years), including 445 coronary heart disease events (232 myocardial infarctions and 213 coronary revascularizations), 136 stroke events (of which 22 also involved coronary heart disease), and 12 additional deaths from cardiovascular causes (as reported in the TOHP I and II Follow-up Studies). A total of 1100 deaths were recorded during a median

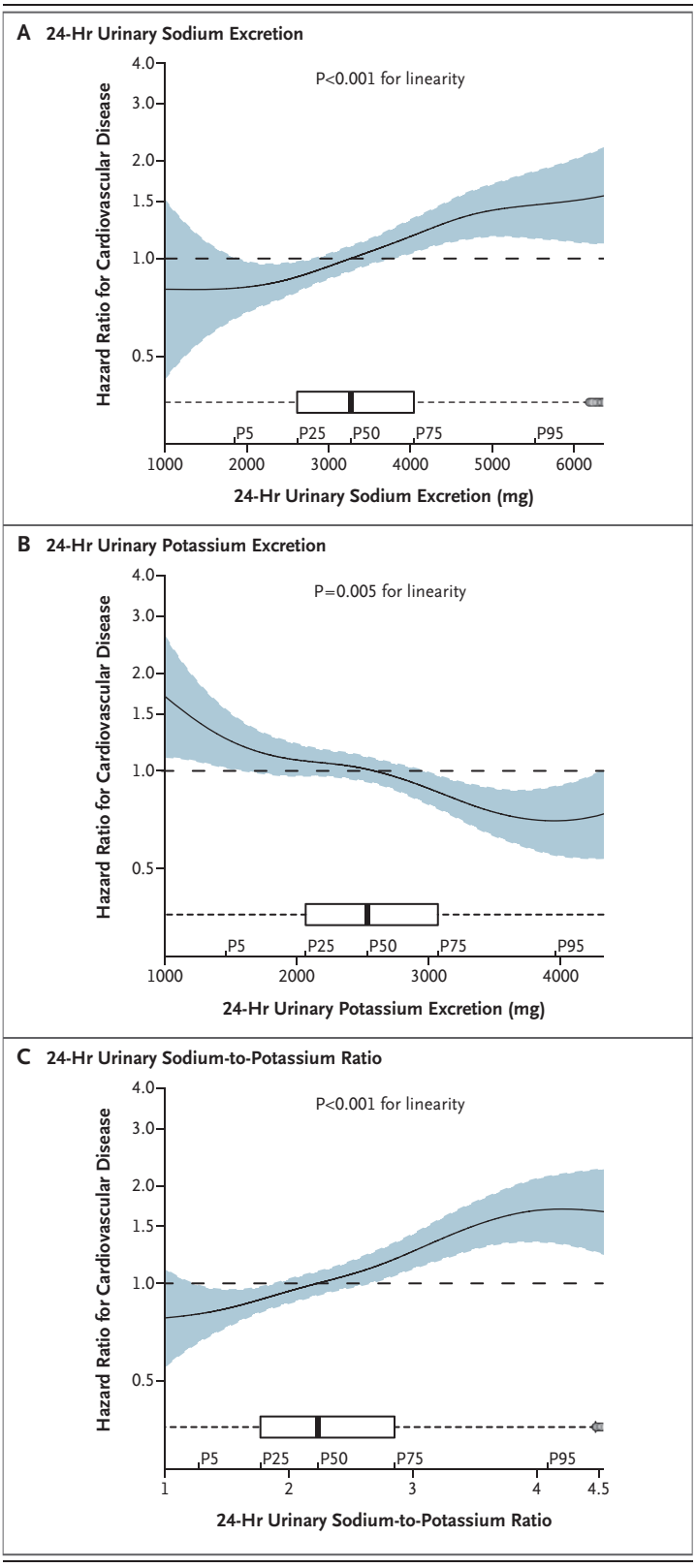


Figure 2. Spline Plots for the Associations of 24-Hour Urinary Sodium and Potassium Excretion and Sodium-to-Potassium Ratio with Cardiovascular Risk.

The spline analysis of pooled data supported a linear association over the range of sodium excretion (Panel A; 5th to 95th percentile, 1846 to 5520 mg) and potassium excretion (Panel B; 5th to 95th percentile, 1462 to 3961 mg) within the overall study population. The sodium-to-potassium ratio (Panel C) was assessed on the basis of the sodium and potassium excretion measured in millimoles. Hazard ratios were estimated from Cox models stratified according to study cohort with adjustment for age, sex, race, educational level, height, body-mass index, alcohol consumption, smoking status, physical activity, history of diabetes and elevated cholesterol status, family history of cardiovascular disease, and mutual adjustment for 24-hour urinary potassium and sodium excretions. Shaded areas indicate 95% confidence intervals, and the dashed line at 1.0 indicates the reference. Box plots at the bottom of the graphs show the distributions of the urinary biomarker. The vertical bar indicates the median, and the ends of the box the interquartile range; the whiskers (dashed lines) extend to values no farther than 1.5 times the interquartile range (which may be past the graphed area), and dots indicate values that are farther than 1.5 times the interquartile range. The 5th, 25th, 50th, 75th, and 95th percentiles (P5, P25, P50, P75, and P95, respectively) are shown at the bottom of each graph.

follow-up of 14.8 years (interquartile range, 13.7 to 16.7).

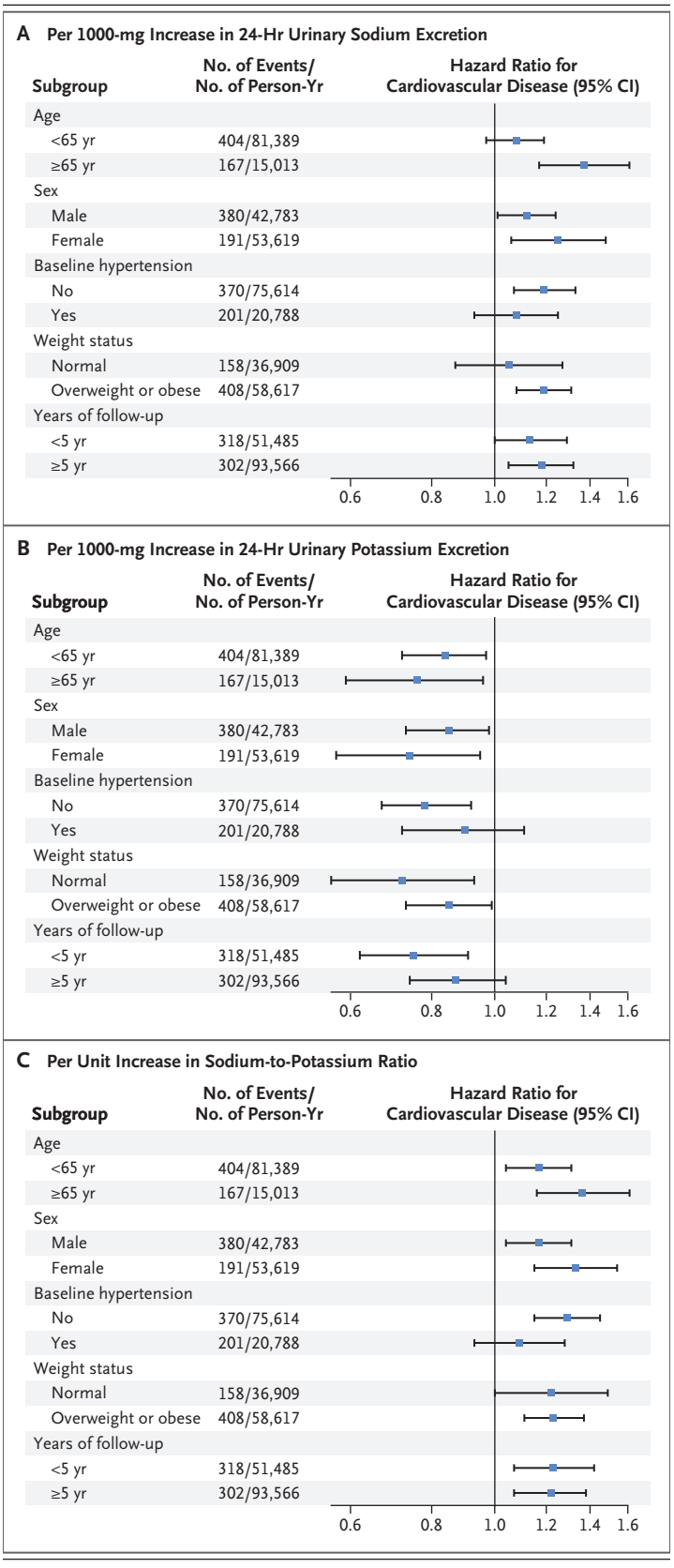
SODIUM AND POTASSIUM EXCRETION AND CARDIOVASCULAR RISK

Table 2 shows a graded association between sodium excretion and cardiovascular risk (hazard ratio for quartile 4 of the urinary biomarker [highest] vs. quartile 1 [lowest] in the fully adjusted model, 1.60; 95% confidence interval [CI], 1.19 to 2.14). Each additional 1000 mg of daily sodium excretion was associated with an 18% increase in cardiovascular risk (adjusted hazard ratio, 1.18; 95% CI, 1.08 to 1.29) (Fig. 1). The spline analysis with pooled data further supported a linear association over the range of sodium excretion within this population (P<0.001 for linearity) (Fig. 2A).

Higher potassium excretion was associated with lower cardiovascular risk in the comparison of quartile 4 with quartile 1 (adjusted hazard ratio, 0.69; 95% CI, 0.51 to 0.91) (Table 2). Each

Figure 3. Subgroup Analyses for the Associations of 24-Hour Urinary Sodium and Potassium Excretion and Sodium-to-Potassium Ratio with Cardiovascular Risk.

Normal weight was defined as a body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) of 18.5 to 24.9. Overweight or obesity was defined as a BMI of 25 or higher. In the subgroup analyses that were stratified according to the length of study follow-up, events that were censored within the first year of follow-up (which were excluded in the primary analysis) were included. Hazard ratios were estimated from Cox models with stratification according to study cohort with adjustment for age, sex (except for the analyses stratified according to sex), race, educational level, height, BMI, alcohol consumption, smoking status, physical activity, history of diabetes and elevated cholesterol status, family history of cardiovascular disease, and mutual adjustment for 24-hour urinary potassium and sodium excretions. The sodium-to-potassium ratio was assessed on the basis of the sodium and potassium excretion measured in millimoles.



additional 1000 mg of daily potassium excretion was associated with an 18% lower cardiovascular risk (hazard ratio, 0.82; 95% CI, 0.72 to 0.94) (Fig. 1). The spline plot also showed a linear trend (Fig. 2B). There was a 24% increase in cardiovascular risk for each unit increase in the sodium-to-potassium ratio, which was calculated on the basis of sodium and potassium excretion measured in millimoles (hazard ratio, 1.24; 95% CI, 1.12 to 1.37). The associations were consistent across subgroups defined according to age, sex, baseline hypertension, weight status, and years of follow-up (Fig. 3). Sex-specific associations are presented in Figure S2.

SECONDARY ANALYSES

Similar associations with sodium and potassium excretion and the sodium-to-potassium ratio were also observed for coronary heart disease (Table S2). The estimates for stroke showed a similar linear trend but with wider confidence intervals, probably owing to the small number of cases (Table S3). The secondary analysis with simple pooled analyses yielded estimates that were almost identical to those from the two-stage pooled analysis for cardiovascular events (Table S4). Sodium excretion was not associated with death from any cause (hazard ratio per 1000-mg increase, 1.02; 95% CI, 0.95 to 1.10), but both higher potassium excretion and a lower sodium-to-potassium ratio were associated with a lower risk of death from any cause

(Table S5 and Fig. S3). The linear trend of the association of sodium excretion with death from cardiovascular causes (which accounted for 22% of the deaths from any cause) was consistent with the results regarding the incidence of cardiovascular events (Table S6 and Fig. S4).

SENSITIVITY ANALYSES

The association of sodium excretion with cardiovascular risk was attenuated (hazard ratio per daily 1000-mg increase, 1.10; 95% CI, 1.03 to 1.17) when only one 24-hour urine sample per participant was used, although the association was attenuated to a lesser degree after the exclusion of urine samples that met the prespecified exclusion criteria (Table S7). The linear association of sodium excretion with cardiovascular risk remained essentially unchanged in the following sensitivity analyses: analyses with additional adjustment for baseline hypertension status, urinary creatinine excretion, other dietary factors, and neighborhood socioeconomic status separately; analyses that excluded participants who had diabetes or were underweight or that excluded coronary revascularization from the study end points regarding cardiovascular events; analyses for which data for missing covariates were imputed with the use of multiple imputation; analyses that accounted for nonresponse to follow-up with the use of inverse probability weighting; and analyses that assessed competing risk of death with the use of subdistribution hazard models (Table S8). The results of the sensitivity analyses for potassium excretion and the sodium-to-potassium ratio were similar to those from the primary results (Tables S9 and 10).

DISCUSSION

In a study involving 10,709 adults whose data were pooled from six prospective cohort studies across the United States and Europe, with a median follow-up of 8.8 years, we found that higher sodium intake, measured by multiple 24-hour urine samples, was significantly associated with higher cardiovascular risk in a dose–response manner with a daily sodium intake of approximately 2000 to 6000 mg. Lower potassium intake and higher sodium-to-potassium ratio were also associated with higher cardiovascular risks.

Several meta-analyses of prospective cohort studies and randomized trials have shown a linear relationship between sodium intake and cardiovascular risk,[24-28] whereas a few other meta-analyses and more recent cohort studies have shown that both low and high sodium intakes were associated with higher risk (i.e., a J-shaped association).[5-8,29] A key limitation of previous studies is the assessment of sodium intake by methods that are prone to measurement errors, such as questionnaires, spot urine samples, and single 24-hour urine samples.[30] The J-shaped association is probably due to confounding variables that were used in the equations to estimate the 24-hour urinary sodium excretion from spot urine samples (e.g., age, sex, body weight, and urinary creatinine concentration), all of which are related to cardiovascular risk and may contribute in part to the increased cardiovascular risk that has been associated with lower sodium intake in observational studies.[31] Another methodologic issue of previous studies is the inclusion of participants with existing chronic diseases such as heart failure,[32] which resulted in the potential for reverse-causation bias.

To overcome these limitations, we combined data from six prospective cohorts involving generally healthy participant populations for which multiple 24-hour urine samples were available from the participants. There was no evidence of heterogeneity in the results across individual studies, although the estimates were weaker in the PREVEND study than in the other studies. The participants in the PREVEND study had lower sodium and higher potassium intakes than those in other cohorts. In addition, the proportion of participants with albuminuria was high in the PREVEND study; in our study, we excluded participants with chronic kidney disease. Although we found a strong and consistent association of sodium excretion with cardiovascular events and the association with death from cardiovascular causes showed a consistent linear trend, sodium excretion was not associated with death from any cause, which we speculate may be due to the occurrence of deaths from noncardiovascular causes diluting the relation between sodium intake and mortality. In contrast, the Salt Substitute and Stroke Study (SSaSS)[33] showed that use of a salt substitute that contained reduced sodium and increased potassium led to significantly lower rates of cardiovascular disease and death from any cause in a high-risk population in China, in which death from cardiovascu-

lar causes accounted for nearly 60% of the deaths; in our study, 22% of the deaths were from cardiovascular disease.

Our study offers new insights concerning current methodologic challenges in sodium assessment. For example, when a single 24-hour urine sample per participant was used, the magnitude of the linear association with cardiovascular risk was attenuated, a finding that is consistent with results of a previous report.[34] A single measurement is not sufficient to reflect a person's usual sodium intake owing to large day-to-day variations in sodium consumption and excretion.[14,35] When sodium and potassium were considered together, higher sodium excretion and lower potassium excretion were associated with a higher cardiovascular risk, which suggests an additive role of higher sodium intake and lower potassium intake in increasing cardiovascular risk.[12] By combining individual-level data from cohort studies with multiple 24-hour urine samples, our study constitutes a large study on cardiovascular risk and sodium intake as assessed by a very reliable method. By studying generally healthy populations, we also reduced confounding and potential reverse-causation bias. The use of individual-level data and the same methods for covariate adjustments and modeling renders our findings robust.

Our study has several limitations. First, although we were able to reduce the degree of heterogeneity by the use of consistent analytic approaches in individual studies, between-study heterogeneity that is inherent in the design of the original studies exists — for example, health profiles of participants, numbers and intervals of 24-hour urine samples, and available information on covariates. Second, this observational study does not allow us to rule out potential residual confounding, such as other dietary factors, energy intake, and socioeconomic status, for which data were available in only some of the included studies. Third, given within-participant variation in sodium excretion, the observed association may have underestimated the true association. Fourth, our study was based on study populations that comprised mainly generally healthy White participants (Table S11), so the generalizability of our results to other racial and ethnic groups and to other patients with specific conditions is not possible.

Our study showed a significant linear association between sodium intake, as measured with the use of multiple 24-hour urine samples, and cardiovascular risk in a dose–response manner with a daily sodium intake of approximately 2000 to 6000 mg. Higher potassium intake was associated with a lower cardiovascular risk. These findings may support reducing sodium intake and increasing potassium intake from current levels.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

REFERENCES

1. GBD 2017 Diet Collaborators. Health effects of dietary risks in 195 countries, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2019;393:1958-72.
2. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. N Engl J Med 2014;371:624-34.
3. Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. Lancet 2007;370:2044-53.
4. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010;362:590-9.
5. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 2014;371:612-23.
6. O'Donnell MJ, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. JAMA 2011;306:2229-38.
7. Mente A, O'Donnell M, Rangarajan S, et al. Urinary sodium excretion, blood pressure, cardiovascular disease, and mortality: a community-level prospective epidemiological cohort study. Lancet 2018;392:496-506.
8. Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. Am J Hypertens 2014;27:1129-37.
9. Cobb LK, Anderson CA, Elliott P, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. Circulation 2014;129:1173-86.

10. He FJ, Campbell NRC, Ma Y, MacGregor GA, Cogswell ME, Cook NR. Errors in estimating usual sodium intake by the Kawasaki formula alter its relationship with mortality: implications for public health. Int J Epidemiol 2018;47:1784-95.
11. Dougher CE, Rifkin DE, Anderson CA, et al. Spot urine sodium measurements do not accurately estimate dietary sodium intake in chronic kidney disease. Am J Clin Nutr 2016;104:298-305.
12. Cook NR, Obarzanek E, Cutler JA, et al. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. Arch Intern Med 2009;169:32-40.
13. Bao Y, Bertoia ML, Lenart EB, et al. Origin, methods, and evolution of the three Nurses' Health Studies. Am J Public Health 2016;106:1573-81.
14. Sun Q, Bertrand KA, Franke AA, Rosner B, Curhan GC, Willett WC. Reproducibility of urinary biomarkers in multiple 24-h urine samples. Am J Clin Nutr 2017;105:159-68.
15. Yuan C, Spiegelman D, Rimm EB, et al. Relative validity of nutrient intakes assessed by questionnaire, 24-hour recalls, and diet records as compared with urinary recovery and plasma concentration biomarkers: findings for women. Am J Epidemiol 2018;187:1051-63.
16. Kieneker LM, Eisenga MF, Gansevoort RT, et al. Association of low urinary sodium excretion with increased risk of stroke. Mayo Clin Proc 2018;93:1803-9.
17. The Trials of Hypertension Prevention Collaborative Research Group. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure: the Trials of Hypertension Prevention, phase II. Arch Intern Med 1997;157:657-67.
18. The Trials of Hypertension Prevention Collaborative Research Group. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels: results of the Trials of Hypertension Prevention, phase I. JAMA 1992;267:1213-20.
19. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the Trials of Hypertension Prevention. J Am Coll Cardiol 2016;68:1609-17.
20. Holm S. A simple sequentially rejective multiple test procedure. Scand J Stat 1979;6:65-70.
21. Durrleman S, Simon R. Flexible regression models with cubic splines. Stat Med 1989;8:551-61.
22. Lucko AM, Doktorchik C, Woodward M, et al. Percentage of ingested sodium excreted in 24-hour urine collections: a systematic review and meta-analysis. J Clin Hypertens (Greenwich) 2018;20:1220-9.
23. World Health Organization. Guideline: potassium intake for adults and children. December 25, 2012 (https://www.who.int/publications/i/item/9789241504829).
24. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. BMJ 2009;339:b4567.
25. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. Lancet 2011;378:380-2.
26. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 2013;346:f1326.
27. Li XY, Cai XL, Bian PD, Hu LR. High salt intake and stroke: meta-analysis of the epidemiologic evidence. CNS Neurosci Ther 2012;18:691-701.
28. National Academies of Sciences, Engineering, and Medicine. Dietary reference intakes for sodium and potassium. Washington, DC: National Academy Press, 2019:514.
29. Taylor RS, Ashton KE, Moxham T, Hooper L, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). Am J Hypertens 2011;24:843-53.
30. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary sodium and cardiovascular disease risk — measurement matters. N Engl J Med 2016;375:580-6.
31. He FJ, Ma Y, Campbell NRC, MacGregor GA, Cogswell ME, Cook NR. Formulas to estimate dietary sodium intake from spot urine alter sodium-mortality relationship. Hypertension 2019;74:572-80.
32. Paterna S, Gaspare P, Fasullo S, Sarullo FM, Di Pasquale P. Normal-sodium diet compared with low-sodium diet in compensated congestive heart failure: is sodium an old enemy or a new friend? Clin Sci (Lond) 2008;114:221-30.
33. Neal B, Wu Y, Feng X, et al. Effect of salt substitution on cardiovascular events and death. N Engl J Med 2021;385:1067-77.
34. Olde Engberink RHG, van den Hoek TC, van Noordenne ND, van den Born BH, Peters-Sengers H, Vogt L. Use of a single baseline versus multiyear 24-hour urine collection for estimation of long-term sodium intake and associated cardiovascular and renal risk. Circulation 2017;136:917-26.
35. Birukov A, Rakova N, Lerchl K, et al. Ultra-long-term human salt balance studies reveal interrelations between sodium, potassium, and chloride intake and excretion. Am J Clin Nutr 2016;104:49-57.