ORIGINAL ARTICLE

Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events

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ABSTRACT

BACKGROUND

The optimal range of sodium intake for cardiovascular health is controversial.

METHODS

We obtained morning fasting urine samples from 101,945 persons in 17 countries and estimated 24-hour sodium and potassium excretion (used as a surrogate for intake). We examined the association between estimated urinary sodium and potassium excretion and the composite outcome of death and major cardiovascular events.

RESULTS

The mean estimated sodium and potassium excretion was 4.93 g per day and 2.12 g per day, respectively. With a mean follow-up of 3.7 years, the composite outcome occurred in 3317 participants (3.3%). As compared with an estimated sodium excretion of 4.00 to 5.99 g per day (reference range), a higher estimated sodium excretion (≥7.00 g per day) was associated with an increased risk of the composite outcome (odds ratio, 1.15; 95% confidence interval [CI], 1.02 to 1.30), as well as increased risks of death and major cardiovascular events considered separately. The association between a high estimated sodium excretion and the composite outcome was strongest among participants with hypertension (P=0.02 for interaction), with an increased risk at an estimated sodium excretion of 6.00 g or more per day. As compared with the reference range, an estimated sodium excretion that was below 3.00 g per day was also associated with an increased risk of the composite outcome (odds ratio, 1.27; 95% CI, 1.12 to 1.44). As compared with an estimated potassium excretion that was less than 1.50 g per day, higher potassium excretion was associated with a reduced risk of the composite outcome.

CONCLUSIONS

In this study in which sodium intake was estimated on the basis of measured urinary excretion, an estimated sodium intake between 3 g per day and 6 g per day was associated with a lower risk of death and cardiovascular events than was either a higher or lower estimated level of intake. As compared with an estimated potassium excretion that was less than 1.50 g per day, higher potassium excretion was associated with a lower risk of death and cardiovascular events. (Funded by the Population Health Research Institute and others.)

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Most of the global population consumes between 3.0 and 6.0 g of sodium per day (7.5 to 15.0 g of salt per day).[1,2] Guidelines on cardiovascular disease prevention recommend a maximum sodium intake of 1.5 to 2.4 g per day, but achieving this target will require a substantial change in diet for most people.[3-5]

Although clinical trials have shown a reduction in blood pressure with a reduced sodium intake, to our knowledge, no large randomized trial has been conducted to document reductions in the risk of cardiovascular disease with low sodium intake.[6] Prospective cohort studies have shown inconsistent associations between sodium intake and rates of cardiovascular events and death.[6-11] Several studies have shown an increased risk of cardiovascular disease or death among people consuming less than 3.0 g of sodium per day, as compared with average intake,[7,9,12-15] but many of these studies included people at high cardiovascular risk,[13-15] who were not representative of the general population.[16,17] The association between sodium intake and cardiovascular disease is complex and may be modified by other dietary factors, such as potassium intake, which has also been associated with cardiovascular risk.[18,19]

Because of the need for data from large studies examining the association between sodium intake and cardiovascular disease in general populations,[8,17] we conducted a prospective cohort study that included 101,945 people from five continents. We examined the association of urinary sodium and potassium excretion with death and incident cardiovascular events.

METHODS

STUDY DESIGN AND PARTICIPANTS

The Prospective Urban Rural Epidemiology (PURE) study is a large-scale epidemiologic cohort study that enrolled and followed 156,424 persons, 35 to 70 years of age, residing in 628 urban and rural communities in 17 low-, middle-, and high-income countries (Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, Pakistan, Poland, South Africa, Sweden, Turkey, United Arab Emirates, and Zimbabwe).[20-23] Selection of the participants is described in the Supplementary Appendix, available with the full text of this article at NEJM.org. Recruitment began in January 2003. For the current analysis, we included 101,945 participants who collected early-morning fasting urine samples suitable for analysis. The study was coordinated by the Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada.

PROCEDURES

A morning fasting midstream urine sample was collected from each participant and frozen at −20°C to −70°C. All urine samples were shipped in ambient packaging with the use of STP-250 shipping boxes (Saf-T-Pak) to the Clinical Research Laboratory, Hamilton Health Sciences, Hamilton, Ontario, Canada (the central laboratory for 14 countries), or to the regional laboratory in Beijing; Bangalore, India; or Kocaeli, Turkey, for analyses that used standardized methods. A description of the methods used for performing urinary analyses is provided in the Supplementary Appendix. The Kawasaki formula was used to estimate 24-hour urinary sodium and potassium excretion, and these estimates were used as surrogates for intake.[24,25] A brief description of the validation of the Kawasaki formula is provided in the article by Mente et al. in this issue of the *Journal*.[26]

Information on personal medical history and use of prescription medication was obtained by means of questionnaire. Standardized case-report forms were used to capture data on major cardiovascular events and death during follow-up, which were adjudicated with the use of standardized definitions. A description of the ascertainment and adjudication of the outcome events is provided in the Supplementary Appendix. For the current analysis, we included all adjudicated outcome events in the PURE study database through October 16, 2013.

STUDY OVERSIGHT

The first three authors and the last author conceived the study, supervised all the analyses, assume responsibility for the analyses and the interpretation of data, and wrote the first draft of the manuscript. The study was funded by nonprofit, government, and industry sponsors. The funders of the study had no role in its design or conduct, in the collection, analysis, or interpretation of the data, or in the writing of the manuscript or the decision to submit it for publication. The study was approved by the research ethics committee at each participating center and at Hamilton Health Sciences. All the study participants provided written informed consent.

A Quick Take animation is available at NEJM.org

STATISTICAL ANALYSIS

Differences in the baseline characteristics among the study participants in the different categories of estimated sodium and potassium excretion were compared with the use of the chi-square test for categorical variables and analysis of variance for continuous variables. We used restricted-cubic-spline plots to explore the shape of the association between the estimated sodium and potassium excretion and the outcomes, fitting a restricted-cubic-spline function with four knots (at the 5th, 35th, 65th, and 95th percentiles).[27] Our primary outcome measure was the composite of death from any cause and major cardiovascular events (defined as death from cardiovascular causes, stroke, myocardial infarction, or heart failure).

On the basis of our restricted-cubic-spline plots for the primary outcome and the results of previous analyses,[13] we selected a level of 4.00 to 5.99 g per day as the reference category for sodium excretion and a level of less than 1.50 g per day as the reference category for potassium excretion. We performed a multivariable logistic-regression analysis with generalized estimating equation models (to account for clustering)[28] in order to determine the association between estimated urinary sodium and potassium excretion and death and cardiovascular events, using three sequential models. Model 1 (the primary model) was adjusted for age, sex, educational level, ancestry (Asian or non-Asian), alcohol intake (former use, current use, or no use), diabetes mellitus (yes or no), body-mass index (BMI), history of cardiovascular events (yes or no), and current smoking (yes or no), with an additional model that included the ratio of low-density lipoprotein cholesterol to high-density lipoprotein cholesterol. Model 2 also included caloric intake, estimated potassium (or sodium) excretion, and fruit and vegetable intake. In addition to the variables included in models 1 and 2, model 3 included systolic blood pressure, history of hypertension (yes or no), and use of antihypertensive therapy (yes or no) at baseline, because blood pressure is in the putative causal pathway.

To minimize the potential for reverse causation, we conducted analyses that excluded participants with prior cardiovascular disease, those with cancer (at baseline or follow-up), and those with events in the first 2 years of follow-up. We tested for interactions of age, hypertension, sex, ancestry, history of cardiovascular disease, diabetes, BMI, and estimated potassium excretion. We explored the potential influence of unmeasured confounders on our estimates of risk using an array-approach sensitivity analysis to determine how strong and imbalanced a confounding effect would need to be to alter the direction of findings.[29]

To further explore the potential effect of imbalanced confounders, we performed propensity-score–matched sensitivity analyses[30] that compared a high estimated sodium excretion (≥6.00 g per day) with a moderate level (3.00 to 5.99 g per day) and that compared a low estimated sodium excretion (<3.00 g per day) with the moderate level. In a secondary analysis, we examined the association between an estimated "usual" level of sodium or potassium excretion and death and cardiovascular disease, with correction for regression dilution bias (with the use of repeated measurements in 448 participants).[31] All analyses were conducted with the use of SAS software, version 9.2, for the UNIX operating system (SAS Institute).

RESULTS

STUDY PARTICIPANTS AND OUTCOMES

The study included 101,945 participants, 42% of whom were from China. The mean estimated 24-hour sodium excretion was 4.93 g, and the mean estimated 24-hour potassium excretion was 2.12 g (Table 1, and Table S1 in the Supplementary Appendix). The mean systolic and diastolic blood pressures were higher among participants with a higher estimated sodium excretion (P<0.001). The mean duration of follow-up was 3.7 years, with follow-up completed for 95% of the participants. The primary composite outcome of death or a major cardiovascular event occurred in 3317 participants (3.3%): 1976 participants died (650 from cardiovascular causes), 857 had myocardial infarction, 872 had stroke, and 261 had heart failure. Participants may have had more than one cardiovascular event.

ESTIMATED SODIUM EXCRETION AND RISKS OF DEATH AND CARDIOVASCULAR EVENTS

As compared with an estimated sodium excretion of 4.00 to 5.99 g per day (the reference category), estimated excretion of 7.00 g per day or more was associated with increased risks of the primary composite outcome (odds ratio, 1.15; 95% confidence interval [CI], 1.02 to 1.30), death from any

cause (odds ratio, 1.25; 95% CI, 1.07 to 1.48), a major cardiovascular event (odds ratio, 1.16; 95% CI, 1.01 to 1.34), death from cardiovascular causes (odds ratio, 1.54; 95% CI, 1.21 to 1.95), and stroke resulting in death or hospitalization (odds ratio, 1.29; 95% CI, 1.02 to 1.63) on multivariable analysis (Table 2 and Fig. 1, and Table S2 in the Supplementary Appendix). The association between a high estimated sodium excretion (≥7.00 g per day) and the primary composite outcome, major cardiovascular events, and stroke resulting in death or hospitalization was attenuated and was no longer significant after adjustment for blood pressure or prior diagnosis of hypertension but remained significant for death from any cause (Table 2, and Table S2 in the Supplementary Appendix).

As compared with an estimated sodium excretion of 4.00 to 5.99 g per day, an estimated excretion of less than 3.00 g per day was also associated with increased risks of the primary composite outcome (odds ratio, 1.27; 95% CI, 1.12 to 1.44), death from any cause (odds ratio, 1.38; 95% CI, 1.15 to 1.66), a major cardiovascular event (odds ratio, 1.30; 95% CI, 1.13 to 1.50), death from cardiovascular causes (odds ratio, 1.77; 95% CI, 1.36 to 2.31), and stroke resulting in death or hospitalization (odds ratio, 1.37; 95% CI, 1.07 to 1.76) (Table 2, and Table S2 in the Supplementary Appendix). These associations remained significant after adjustment for blood pressure or prior diagnosis of hypertension.

ESTIMATED POTASSIUM EXCRETION AND RISKS OF DEATH AND CARDIOVASCULAR EVENTS

As compared with an estimated potassium excretion of less than 1.50 g per day, a higher estimated excretion of potassium was associated with a reduction in the risks of death and cardiovascular events on multivariable analysis (Fig. 2 and Table 3); this association was largely related to a reduction in the risk of death (Table S3 in the Supplementary Appendix). There was no evidence of an interaction between estimated potassium and sodium excretion with respect to the primary composite outcome (P=0.55) (Table S4 in the Supplementary Appendix).

SUBGROUP AND SENSITIVITY ANALYSES

Hypertension at baseline (defined as a prior diagnosis of hypertension or blood pressure >140/90 mm Hg) modified the association between a high estimated sodium excretion and the composite outcome (P=0.02 for interaction) (Table S4 in the Supplementary Appendix). In further analysis, there was significantly increased risk observed among participants with baseline hypertension and an estimated sodium excretion of 6.00 to 6.99 g per day (odds ratio, 1.14; 95% CI, 1.00 to 1.30) or 7.00 g per day or more (odds ratio, 1.21; 95% CI, 1.05 to 1.40), whereas there was no significant association among those without hypertension. There were no other significant subgroup interactions (Tables S4 and S5 in the Supplementary Appendix).

The exclusion of participants with cardiovascular disease (at baseline) or cancer (at baseline or follow-up) or those who had events in the first year of follow-up did not materially affect the findings from the sodium and potassium analyses. When participants with events in the first 2 years were excluded, the associations of a lower (<3.00 g per day) and higher (6.00 to 6.99 g per day) estimated sodium excretion with the primary outcome were significant (Tables 2 and 3). In a propensity-score–matched analysis that included 21,220 participants, a low estimated sodium excretion (<3.00 g per day), as compared with a moderate level (3.00 to 5.99 g per day), was associated with an increased risk of the composite outcome (odds ratio, 1.26; 95% CI, 1.09 to 1.46). In a similar analysis that included 40,618 participants, a high estimated sodium excretion (≥6.00 g per day), as compared with a moderate level, was associated with an increased risk of the composite outcome (odds ratio, 1.19; 95% CI, 1.06 to 1.34) (Table S6 in the Supplementary Appendix). The results of analyses adjusted for regression dilution bias are presented in Figures S1 and S2 in the Supplementary Appendix. The results of the array-approach sensitivity analysis are provided in Table S7 in the Supplementary Appendix.

DISCUSSION

In this large, international, prospective cohort study, we investigated the association between estimated sodium and potassium excretion (used as surrogates for intake) and the composite of death and cardiovascular outcomes. The lowest risk of death and cardiovascular events was seen among participants with an estimated sodium excretion between 3 g per day and 6 g per day. Both higher and lower levels of estimated sodium excretion were associated with increased risk,

Table 1. Characteristics of the Study Participants at Baseline, According to Estimated Sodium Excretion.*

Characteristic	Estimated Sodium Excretion						P Value†
	All Levels (N=101,945)	<3.00 g/day (N=10,810)	3.00–3.99 g/day (N=21,131)	4.00–5.99 g/day (N=46,663)	6.00–6.99 g/day (N=12,324)	≥7.00 g/day (N=11,017)	
Proportion of participants — %	100.0	10.6	20.7	45.8	12.1	10.8	
Estimated excretion — g/day							
Sodium‡	4.93±1.73	2.44±0.47	3.54±0.28	4.93±0.56	6.45±0.29	8.31±1.46	<0.001
Potassium	2.12±0.60	1.77±0.54	1.94±0.54	2.15±0.55	2.34±0.58	2.46±0.66	<0.001
Age — yr	51.01±9.72	52.16±9.94	51.36±9.86	51.12±9.68	50.39±9.50	49.41±9.42	<0.001
Male sex — no. (%)	43,337 (42.5)	3204 (29.6)	7,356 (34.8)	20,165 (43.2)	6213 (50.4)	6399 (58.1)	<0.001
Asian ancestry — no. (%)§	49,391 (48.4)	3650 (33.8)	8,115 (38.4)	22,286 (47.8)	7300 (59.2)	8040 (73.0)	<0.001
Geographic region — no. (%)							
Asia	55,610 (54.5)	4564 (42.2)	9,600 (45.4)	25,023 (53.6)	8016 (65.0)	8407 (76.3)	<0.001
Africa	2,573 (2.5)	457 (4.2)	563 (2.7)	1,137 (2.4)	244 (2.0)	172 (1.6)	<0.001
Europe or North America	19,866 (19.5)	3353 (31.0)	5,315 (25.2)	8,609 (18.4)	1561 (12.7)	1028 (9.3)	<0.001
Middle East	6,542 (6.4)	735 (6.8)	1,596 (7.6)	3,280 (7.0)	658 (5.3)	273 (2.5)	<0.001
South America	17,354 (17.0)	1701 (15.7)	4,057 (19.2)	8,614 (18.5)	1845 (15.0)	1137 (10.3)	<0.001
Urban area — no (%)	53,760 (52.7)	6305 (58.3)	12,431 (58.8)	25,141 (53.9)	5611 (45.5)	4272 (38.8)	<0.001
INTERHEART Modifiable Risk Score¶	10.74±5.89	10.86±6.01	10.74±5.87	10.75±5.93	10.69±5.80	10.68±5.77	0.17
Hypertension — no./total no. (%)‖	42,056/101,445 (41.5)	4297/10,744 (40.0)	8078/21,012 (38.4)	18,926/46,423 (40.8)	5480/12,281 (44.6)	5275/10,985 (48.0)	<0.001
Blood pressure — mm Hg							
Systolic	131.7±22.31	127.9±22.01	129.0±22.05	131.5±21.83	134.7±22.73	137.7±22.94	<0.001
Diastolic	82.24±15.65	80.27±13.61	80.84±15.96	82.25±15.90	83.86±16.03	84.96±14.81	<0.001
Cholesterol — mmol/liter**							
LDL	3.00±0.89	3.14±0.96	3.09±0.92	3.01±0.89	2.91±0.85	2.80±0.81	<0.001
HDL	1.21±0.35	1.29±0.40	1.25±0.37	1.20±0.34	1.17±0.33	1.15±0.32	<0.001
History of cardiovascular disease — no./total no. (%)	8,485/101,800 (8.3)	997/10,800 (9.2)	1864/21,098 (8.8)	3939/46,586 (8.5)	904/12,310 (7.3)	781/11,006 (7.1)	<0.001
Diabetes mellitus — no. (%)††	9,285/101,918 (9.1)	1166/10,806 (10.8)	1823/21,126 (8.6)	4239/46,649 (9.1)	1127/12,323 (9.1)	930/11,014 (8.4)	<0.001
BMI ≥30 — no./total no. (%)‡‡	18,326/101,540 (18.0)	1878/10,748 (17.5)	3532/21,044 (16.8)	8693/46,515 (18.7)	2297/12,280 (18.7)	1926/10,953 (17.6)	<0.001
Low level of physical activity — no./total no. (%)§§	13,378/94,847 (14.1)	1258/9702 (13.0)	2560/19,444 (13.2)	6212/43,562 (14.3)	1739/11,668 (14.9)	1609/10,471 (15.4)	<0.001
Caloric intake — kcal/day	2149±892.7	2210±1015	2182±941.9	2137±879.4	2104±825.2	2131±794.0	<0.001

Fruit and vegetable intake — g/day	521.4±434.4	604.7±515.7	571.3±470.5	517.1±427.9	468.6±370.6	427.1±336.3	<0.001
Current smoker — no. (%)	19,133/101,310 (18.9)	1761/10,767 (16.4)	3673/21,015 (17.5)	8,415/46,350 (18.2)	2565/12,235 (21.0)	2719/10,943 (24.8)	<0.001
Current alcohol use — no. (%)¶¶	30,909/101,564 (30.4)	3611/10,787 (33.5)	6988/21,050 (33.2)	13,820/46,479 (29.7)	3383/12,271 (27.6)	3107/10,977 (28.3)	<0.001
Medication use — no. (%)							
Beta-blocker	4,073 (4.0)	657 (6.1)	1,008 (4.8)	1,874 (4.0)	317 (2.6)	217 (2.0)	<0.001
Diuretic	5,016 (4.9)	813 (7.5)	1,067 (5.0)	2,090 (4.5)	549 (4.5)	497 (4.5)	<0.001
Calcium antagonist	3,703 (3.6)	529 (4.9)	696 (3.3)	1,602 (3.4)	421 (3.4)	455 (4.1)	<0.001
ACE inhibitor or ARB	6,326 (6.2)	886 (8.2)	1,412 (6.7)	2,837 (6.1)	672 (5.5)	519 (4.7)	<0.001

* Plus–minus values are means ±SD. Percentages are based on denominators for the specified levels of estimated sodium excretion, except as otherwise noted. The size of this study cohort differs from the size of the cohort in the study by Mente et al.,[26] which examined the association of sodium and potassium excretion with blood pressure, because the analysis in that study excluded participants who did not have baseline blood-pressure data available and included participants from the Occupied Palestinian Territory, for whom only baseline data were available (no follow-up has been completed). Data on caloric intake and fruit and vegetable intake were missing for 766 participants in the group that excreted less than 3.00 g of sodium per day, for 1188 in the group that excreted 3.00 to 3.99 g per day, for 2002 in the group that excreted 4.00 to 5.99 g per day, for 367 in the group that excreted 6.00 to 6.99 g per day, and for 302 in the group that excreted 7.00 g per day or more. Data on systolic blood pressure were missing for 51 participants in the group that excreted less than 3.00 g of sodium per day, for 88 in the group that excreted 3.00 to 3.99 g per day, for 156 in the group that excreted 4.00 to 5.99 g per day, for 28 in the group that excreted 6.00 to 6.99 g per day, and for 19 in the group that excreted 7.00 g per day or more. Data on diastolic blood pressure were missing for 44 participants in the group that excreted less than 3.00 g of sodium per day, for 63 in the group that excreted 3.00 to 3.99 g per day, for 77 in the group that excreted 4.00 to 5.99 g per day, for 17 in the group that excreted 6.00 to 6.99 g per day, and for 11 in the group that excreted 7.00 g per day or more. Data regarding educational level are provided in Table S8 in the Supplementary Appendix. ACE denotes angiotensin-converting enzyme, and ARB angiotensin-receptor blocker.

† The P value is for all between-group comparisons.

‡ To convert the values for estimated sodium excretion to salt intake in grams per day, multiply by 2.5.

§ Ancestry was self-reported.

¶ The INTERHEART Modifiable Risk Scores[32] range from 0 to 48, with higher scores indicating a higher modifiable risk of myocardial infarction.

‖ Hypertension was defined as a self-reported history of hypertension or a blood pressure of more than 140/90 mm Hg at the baseline visit.

** To convert the values for low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol to milligrams per deciliter, divide by 0.02586. Data were missing for 1405 participants in the group that excreted less than 3.00 g of sodium per day, for 2209 in the group that excreted 3.00 to 3.99 g per day, for 4220 in the group that excreted 4.00 to 5.99 g per day, for 882 in the group that excreted 6.00 to 6.99 g per day, and for 646 in the group that excreted 7.00 g per day or more.

†† Diabetes mellitus was defined as a history of diabetes mellitus or diagnosis of diabetes mellitus during follow-up.

‡‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§§ A low level of physical activity was defined as less than 600 metabolic equivalents per week.

¶¶ Current alcohol use was defined according to the participant's response to the question "What best describes your history of alcohol use?" with the following response options: "formerly used alcohol," "currently use alcohol," and "never used alcohol products."

Table 2. Association of Estimated Urinary Sodium Excretion with Death and Major Cardiovascular Events.*

Variable	Estimated Sodium Excretion				
	<3.00 g/day (N=10,810)	3.00–3.99 g/day (N=21,131)	4.00–5.99 g/day (N=46,663)	6.00–6.99 g/day (N=12,324)	≥7.00 g/day (N=11,017)
Death or cardiovascular event — no. of participants (%)	462 (4.3)	662 (3.1)	1437 (3.1)	391 (3.2)	365 (3.3)
Analysis — odds ratio (95% CI)					
Univariate analysis†	1.24 (1.09–1.41)	0.96 (0.89–1.05)	1.00	1.07 (0.96–1.19)	1.18 (1.05–1.32)
Multivariate analysis					
Primary analysis‡	1.27 (1.12–1.44)	1.01 (0.93–1.09)	1.00	1.05 (0.94–1.17)	1.15 (1.02–1.30)
Analysis including LDL:HDL ratio	1.30 (1.15–1.48)	1.00 (0.92–1.09)	1.00	1.06 (0.94–1.19)	1.18 (1.04–1.33)
Analysis including dietary factors§	1.19 (1.04–1.35)	1.00 (0.92–1.09)	1.00	1.06 (0.95–1.18)	1.15 (1.02–1.30)
Analysis including dietary factors and blood pressure¶	1.19 (1.05–1.36)	1.01 (0.93–1.10)	1.00	1.03 (0.92–1.15)	1.08 (0.96–1.22)
Analysis excluding cardiovascular disease at baseline‖	1.24 (1.07–1.42)	1.00 (0.91–1.10)	1.00	1.06 (0.95–1.19)	1.14 (1.01–1.29)
Analysis excluding cancer‖	1.26 (1.11–1.43)	1.02 (0.93–1.11)	1.00	1.06 (0.95–1.18)	1.15 (1.02–1.29)
Very-low-risk cohort‖**	1.62 (1.29–2.05)	1.07 (0.90–1.26)	1.00	1.15 (0.98–1.35)	1.14 (0.95–1.36)
Analysis excluding events in yr 1‖	1.33 (1.17–1.52)	1.02 (0.93–1.13)	1.00	1.12 (0.99–1.27)	1.16 (1.01–1.33)
Analysis excluding events in yr 1 and 2‖	1.34 (1.14- 1.57)	1.04 (0.93–1.16)	1.00	1.15 (1.00–1.32)	1.11 (0.96–1.28)

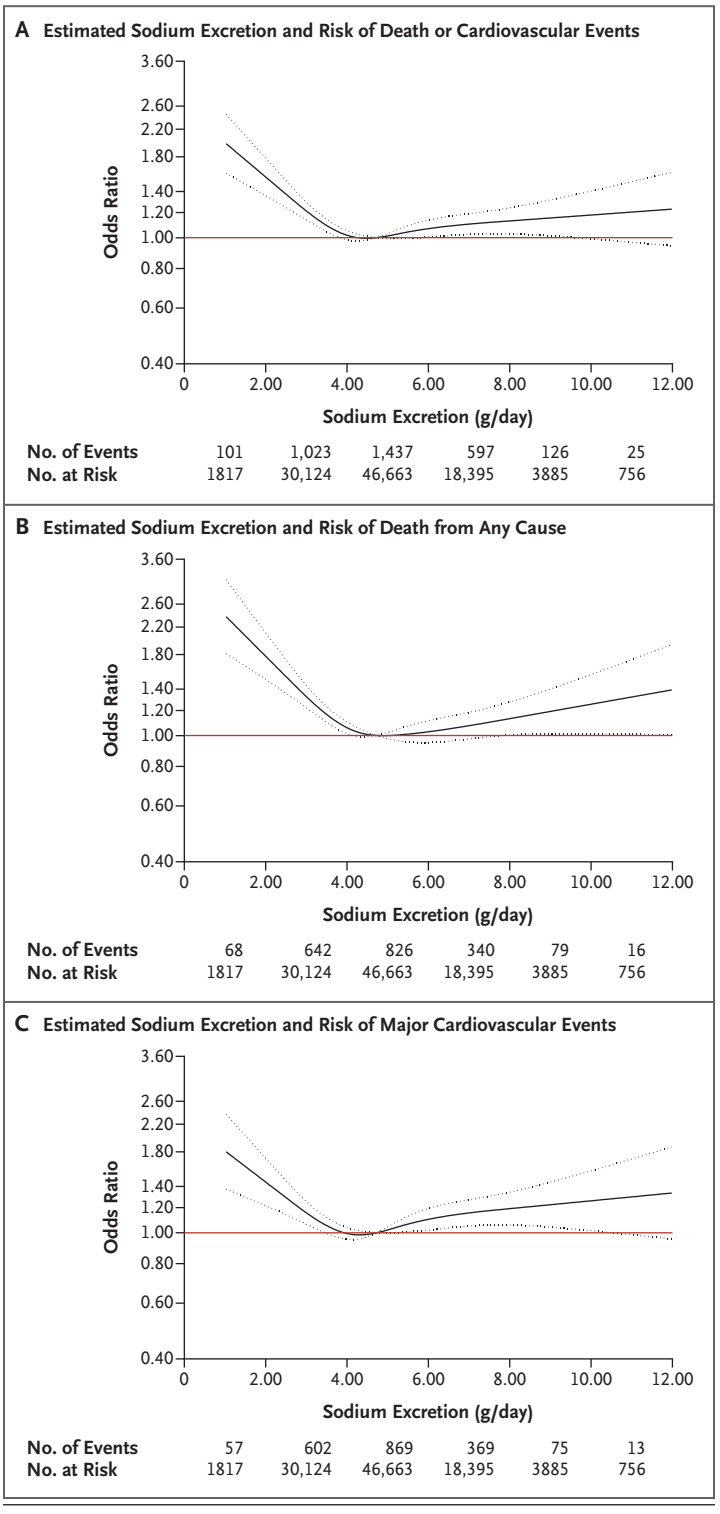
* Major cardiovascular events included death from cardiovascular causes, myocardial infarction, stroke, and heart failure.
† The univariate analysis was performed with the use of a generalized-estimating-equation model to address clustering of data.
‡ The primary model included age, sex, educational level, ancestry (Asian vs. non-Asian), alcohol intake, body-mass index, and status with respect to diabetes mellitus, a history of cardiovascular events, and current smoking. Additional sensitivity analyses with physical activity (measured in metabolic equivalents per week) included in the model did not materially alter estimates of association (in the cohort with physical-activity data available).
§ Dietary variables included caloric intake, potassium intake, and fruit and vegetable intake.
¶ Blood-pressure variables included baseline systolic blood pressure, history of hypertension (yes or no), and use of antihypertensive therapy (yes or no).
‖ The analysis was adjusted for the variables in the primary model.
** The very-low-risk cohort included 57,988 participants and excluded participants who had prior cardiovascular disease, who had been prescribed medications for cardiovascular disease, who had a history of cancer or a diagnosis of cancer on follow-up, who were smokers, or who had diabetes.

resulting in a J-shaped association curve. The association between a high estimated sodium excretion and increased risk, which was significant only among participants with hypertension, was attenuated after adjustment for blood pressure, suggesting that the adverse effects of high sodium intake may be mediated to some degree by the effects of sodium intake on blood pressure.[9,10] By contrast, the association between a low estimated sodium excretion and increased risk, which was seen among both patients with hypertension and those without hypertension, was unaffected by adjustment for blood pressure, suggesting that mechanisms other than blood-pressure effects may play a role.

Current guidelines, which recommend a maximum sodium intake of 1.5 to 2.4 g per day, are based on evidence from largely short-term clinical trials showing that reducing sodium intake from a moderate to a low level results in modest reductions in blood pressure.[3,4] The projected benefits of low sodium intake with respect to cardiovascular disease are derived from models of data from these blood-pressure trials that assume a linear relationship between sodium intake and blood pressure and between blood pressure and cardio-

Figure 1. Association of Estimated 24-Hour Urinary Sodium Excretion with Risk of Death and Major Cardiovascular Events.

Panel A shows a restricted-cubic-spline plot of the association between estimated 24-hour urinary sodium excretion and the composite outcome of death from any cause and major cardiovascular events. The spline curve is truncated at 12.00 g per day (event rate among participants with sodium excretion >12.00 g per day, 8 events in 305 participants). Panel B shows a restricted-cubic-spline plot of the association between estimated sodium excretion and death. The event rate among participants with sodium excretion of more than 12.00 g per day was 5 events in 305 participants. Panel C shows a restricted-cubic-spline plot of the association between estimated sodium excretion and major cardiovascular events (defined as death from cardiovascular causes, myocardial infarction, stroke, or heart failure). The event rate among participants with sodium excretion of more than 12.00 g per day was 6 events in 305 participants. All plots were adjusted for age, sex, geographic region, educational level, ancestry (Asian vs. non-Asian), alcohol intake, body-mass index, and status with respect to diabetes mellitus, history of cardiovascular events, and current smoking. Dashed lines indicate 95% confidence intervals. The median sodium excretion (4.72 g per day) was the reference standard, indicated by the red line. To convert the values for estimated sodium excretion to salt intake in grams per day, multiply by 2.5.



vascular events.[33,34] Implicit in these guidelines is the assumption that there is no unsafe lower limit of sodium intake. However, sodium is known to play a critical role in normal human physiology,[35] and activation of the renin–angiotensin–aldosterone system[36,37] occurs when sodium intake falls below approximately 3.0 g per day.

A J-shaped association between sodium intake and cardiovascular disease or death has been shown in previous studies.[7,9,13,14] However, some of these studies included participants at high cardiovascular risk[13,14] and were vulnerable to biases from reverse causation. Reverse causation may occur when persons with prior cardiovascular disease or increased cardiovascular risk reduce their sodium intake owing to illness or medical recommendations. In the PURE study, the vast majority of participants did not have a history of cardiovascular disease. Although diabetes and history of cardiovascular disease were more common in the group of participants with a low estimated sodium excretion, these participants had a similar overall mean INTERHEART Modifiable Risk Score,[32] as compared with those who had a moderate estimated sodium excretion. Moreover, the exclusion of participants with prior cardiovascular disease or cancer, diabetes, or current smoking and the exclusion of those who had events in the first 2 years of follow-up did not

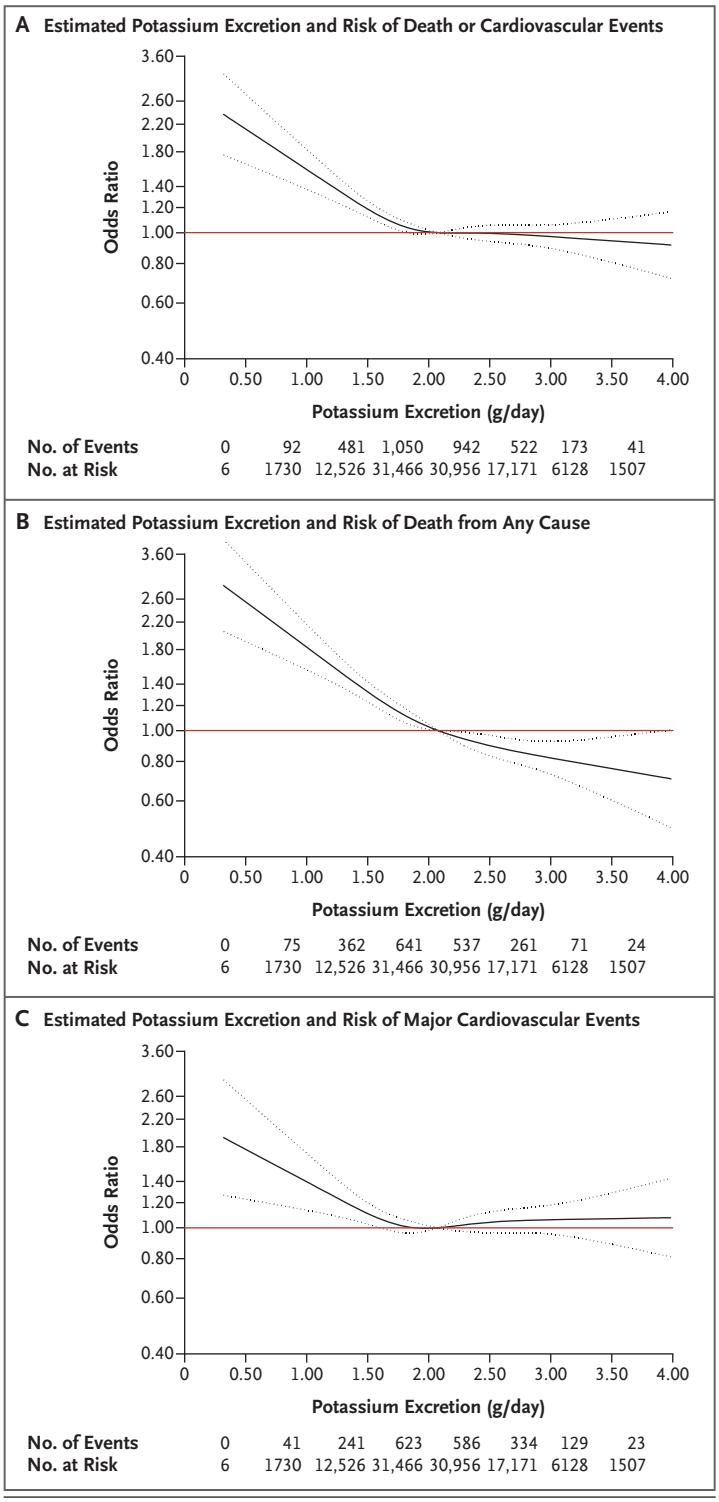


Figure 2. Association of Estimated 24-Hour Urinary Potassium Excretion with Risk of Death and Major Cardiovascular Events.

Panel A shows a restricted-cubic-spline plot of the association between estimated 24-hour urinary potassium excretion and the composite of death from any cause and major cardiovascular events. The spline curve was truncated at 4.00 g per day (event rate among participants with potassium excretion >4.00 g per day, 13 events in 397 participants). Data on potassium excretion were missing for 58 participants (0.1%). Therefore, the sample included in the analysis for the composite outcome of death and major cardiovascular events was 101,887 participants with 3314 events. Panel B shows a restricted-cubic-spline plot of the association between estimated potassium excretion and death from any cause. The event rate among participants with potassium excretion of more than 4.00 g per day was 4 events in 397 participants. Panel C shows a restricted-cubic-spline plot of the association between estimated potassium excretion and major cardiovascular events (defined as death from cardiovascular causes, myocardial infarction, stroke, or heart failure). The event rate among participants with potassium excretion of more than 4.00 g per day was 11 events in 397 participants. All plots were adjusted for age, sex, geographic region, educational level, ancestry (Asian vs. non-Asian), alcohol intake, body-mass index, and status with respect to diabetes mellitus, history of cardiovascular events, and current smoking. Dashed lines indicate 95% confidence intervals. The median level of potassium excretion (2.07 g per day) was the reference standard, indicated by the red line.

materially alter our findings. Nonetheless, we acknowledge that reverse causation cannot be completely ruled out and may account in part for the increased risk observed in the group of participants with a low estimated sodium excretion.[17]

We also found that a higher estimated potassium excretion was associated with a lower risk of the composite of death and major cardiovascular events. A small, cluster-randomized, controlled trial, in which participants increased potassium consumption and reduced high sodium consumption through the use of potassium-enriched salt, showed a reduction in cardiovascular mortality among those assigned to the higher-potassium group and could serve as a template for larger, definitive trials.[38] An increased potassium intake may reduce the risk of death and cardiovascular disease through its effects on blood pressure, or it may simply be a marker of healthy dietary patterns that are rich in potassium (e.g., high consumption of fruit and vegetables).[39] In our analysis, the association between potassium excretion and the composite outcome was attenuated after adjustment for fruit and vegetable intake and blood pressure.

One potential limitation of our study is that our validated method of estimating sodium and potassium intake used a formula-derived estimate

Table 3. Association of Estimated Urinary Potassium Excretion with Death and Major Cardiovascular Events.*

Variable	Estimated Potassium Excretion				
	<1.50 g/day (N=14,262)	1.50–1.99 g/day (N=31,466)	2.00–2.49 g/day (N=30,956)	2.50–3.00 g/day (N=17,171)	>3.00 g/day (N=8032)
Death or cardiovascular event — no. of participants (%)	573 (4.0)	1050 (3.3)	942 (3.0)	522 (3.0)	227 (2.8)
Analysis — odds ratio (95% CI)					
Univariate analysis†	1.00	0.92 (0.81–1.04)	0.89 (0.78–1.01)	0.91 (0.79–1.05)	0.83 (0.71–0.98)
Multivariate analysis					
Primary analysis‡	1.00	0.86 (0.77–0.97)	0.81 (0.73–0.91)	0.86 (0.75–0.98)	0.78 (0.67–0.91)
Analysis including LDL:HDL ratio	1.00	0.86 (0.77–0.97)	0.81 (0.72–0.91)	0.84 (0.74–0.96)	0.80 (0.68–0.94)
Analysis including dietary factors§	1.00	0.89 (0.79–1.00)	0.84 (0.74–0.94)	0.88 (0.77–1.00)	0.81 (0.69–0.96)
Analysis including dietary factors and blood pressure¶	1.00	0.89 (0.80–1.00)	0.86 (0.77–0.97)	0.92 (0.80–1.05)	0.86 (0.73–1.02)
Analysis excluding cardiovascular disease at baseline‖	1.00	0.87 (0.77–0.98)	0.79 (0.70–0.90)	0.87 (0.75–1.00)	0.76 (0.63–0.91)
Analysis excluding cancer‖	1.00	0.87 (0.78–0.97)	0.81 (0.72–0.90)	0.86 (0.75–0.98)	0.78 (0.66–0.92)
Very-low-risk cohort‖**	1.00	0.72 (0.60–0.85)	0.71 (0.59–0.86)	0.77 (0.61–0.96)	0.70 (0.53–0.92)
Analysis excluding events in yr 1‖		0.89 (0.79–1.00)	0.80 (0.71–0.91)	0.81 (0.70–0.94)	0.77 (0.65–0.92)
Analysis excluding events in yr 1 and 2‖	1.00	0.85 (0.74–0.98)	0.74 (0.63–0.86)	0.79 (0.67–0.94)	0.75 (0.62–0.92)

* Data on potassium excretion were missing for 58 participants (0.1%). Therefore, the sample included in the analysis for the composite outcome of death and major cardiovascular events was 101,887 participants with 3314 events. Major cardiovascular events included death from cardiovascular causes, myocardial infarction, stroke, and heart failure.
† The univariate analysis was performed with the use of a generalized-estimating-equation model to address clustering of data.
‡ The primary model included age, sex, educational level, ancestry (Asian vs. non-Asian), alcohol intake, body-mass index, and status with respect to diabetes mellitus, a history of cardiovascular events, and current smoking. Data regarding the characteristics of the study participants at baseline and missing data, according to estimated potassium excretion, are provided in Table S1 of the Supplementary Appendix. Additional sensitivity analyses with physical activity (measured in metabolic equivalents per week) included in the model did not materially alter estimates of association (in the cohort with physical-activity data available).
§ Dietary factors included the addition of caloric intake, sodium intake, and fruit and vegetable intake.
¶ Blood-pressure variables included baseline systolic blood pressure, history of hypertension, or use of antihypertensive therapy.
‖ The analysis was adjusted for the variables in the primary model.
** The very-low-risk cohort included 57,954 participants and excluded participants who had prior cardiovascular disease, who had a history of cancer or a diagnosis of cancer on follow-up, who had been prescribed medication for cardiovascular disease, who were smokers, or who had diabetes.

of 24-hour urinary excretion and not actual 24-hour urinary collection. This issue, which also applies to the study by PURE investigators Mente et al.[26] regarding the association between estimated sodium excretion and blood pressure, is discussed further in that article. Our approach is probably less reliable for estimating potassium intake than for estimating sodium intake, since a lower proportion of consumed potassium, as compared with sodium, is excreted in the urine.[40]

Another potential limitation of our study is that a true probability-sampling approach was not undertaken to select our study population. Such a method was not deemed to be feasible, given the many practical constraints of studying sodium excretion in a wide range of countries and settings. The fact that sampling was not random should be considered when interpreting the generalizability of our findings but should not compromise the internal validity of our findings.

An additional potential limitation of our study, as with all observational studies, is the possibility of residual confounding from unmeasured or poorly measured variables. However, our array-approach analysis showed that a confounder effect would need to be quite large to alter the direction of association in the primary multivariable model, especially for the increased risk with low sodium intake. For example, even a strong confounder effect (odds ratio, ≥2.0) would need to be considerably imbalanced (a difference of >30 percentage points) between the low and moderate sodium-intake categories to result in an ad-

justed odds ratio below 1.0, although a smaller imbalance (a difference of 20 percentage points) would alter the direction of the association for high sodium intake.

Finally, our study provides an epidemiologic comparison of groups that consume different levels of sodium, and it does not provide information on the effect on clinical outcomes of reducing sodium intake. Therefore, our findings should not be interpreted as evidence that the intentional reduction of sodium intake would alter the risk of death or cardiovascular disease.

In conclusion, we investigated the association of estimated sodium and potassium excretion with the risk of death and cardiovascular events in a large, international, prospective cohort study. An estimated sodium intake between 3 g per day and 6 g per day was associated with a lower risk of death and cardiovascular events than either a higher or lower estimated level of sodium intake. As compared with an estimated potassium excretion of less than 1.50 g per day, higher potassium excretion was associated with a reduction in the risk of the composite outcome.

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

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APPENDIX

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