

HEALTH CARE REFORM

Sodium and Potassium Intake and Mortality Among US Adults

Prospective Data From the Third National Health and Nutrition Examination Survey

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Background: Several epidemiologic studies suggested that higher sodium and lower potassium intakes were associated with increased risk of cardiovascular diseases (CVD). Few studies have examined joint effects of dietary sodium and potassium intake on risk of mortality.

Methods: To investigate estimated usual intakes of sodium and potassium as well as their ratio in relation to risk of all-cause and CVD mortality, the Third National Health and Nutrition Examination Survey Linked Mortality File (1988-2006), a prospective cohort study of a nationally representative sample of 12 267 US adults, studied all-cause, cardiovascular, and ischemic heart (IHD) diseases mortality.

Results: During a mean follow-up period of 14.8 years, we documented a total of 2270 deaths, including 825 CVD deaths and 443 IHD deaths. After multivariable adjustment, higher sodium intake was associated with increased all-cause mortality (hazard ratio [HR], 1.20; 95%

confidence interval [CI], 1.03-1.41 per 1000 mg/d), whereas higher potassium intake was associated with lower mortality risk (HR, 0.80; 95% CI, 0.67-0.94 per 1000 mg/d). For sodium-potassium ratio, the adjusted HRs comparing the highest quartile with the lowest quartile were HR, 1.46 (95% CI, 1.27-1.67) for all-cause mortality; HR, 1.46 (95% CI, 1.11-1.92) for CVD mortality; and HR, 2.15 (95% CI, 1.48-3.12) for IHD mortality. These findings did not differ significantly by sex, race/ethnicity, body mass index, hypertension status, education levels, or physical activity.

Conclusion: Our findings suggest that a higher sodium-potassium ratio is associated with significantly increased risk of CVD and all-cause mortality, and higher sodium intake is associated with increased total mortality in the general US population.

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RANDOMIZED CONTROLLED trials (RCTs) and epidemiologic studies have shown that individuals with higher sodium or lower potassium intakes have increased risk for elevated blood pressure and hypertension.¹⁻⁸ Although elevated blood pressure and hypertension are associated with increased

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risk for cardiovascular diseases (CVDs), the observed association between sodium or potassium intake and CVD incidence or mortality has been inconsistent.^{4,9-12} Recently, several studies suggested that the ratio of sodium to potassium intakes represented a more important risk factor for hypertension and CVD than each factor alone.^{3,11-14}

Examining the joint effects of sodium and potassium intakes on CVD risk is par-

ticularly important because most of the US population consumes more sodium and

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less potassium daily than recommended.¹⁵⁻¹⁸ Herein, we report an analysis of the association between the estimated usual intakes of sodium and potassium, as well as their ratio, with all-cause and CVD mortality among persons 20 years of age and older in the Third National Examination and Nutritional Health Survey (NHANES III) Linked Mortality File.

METHODS

THE THIRD NATIONAL HEALTH AND NUTRITION EXAMINATION SURVEY (NHANES III, 1988-1994)

NHANES III used a stratified, multistage probability design to obtain a nationally represen-

tative sample of the civilian, noninstitutionalized US population.¹⁹ In NHANES III, each survey participant completed a household interview and underwent a physical examination.²⁰ Of the 16 562 nonpregnant adults 20 years or older who attended the medical examination center (MEC) and for whom complete mortality follow-up information was available, we excluded, sequentially, 879 participants with incomplete data on the first or second 24-hour dietary recall; 2693 participants who were on a reduced salt diet for hypertension at baseline; and 723 participants who reported a history of heart attack, stroke, or congestive heart failure. After these exclusions, 12 267 NHANES III participants were available for the present analysis.

ESTIMATING USUAL INTAKES OF SODIUM AND POTASSIUM

Dietary information was obtained from in-person 24-hour dietary recalls with use of a personal computer-based, automated, interactive data collection and coding system.¹⁹ All MEC participants provided a single 24-hour dietary recall, and a subsample of about 8% adult participants (≥ 20 years) provided a second 24-hour dietary recall. Among 12 267 NHANES III participants who were eligible for this analysis, 912 (7.4%) provided reliable second 24-hour dietary recalls. The US Department of Agriculture Survey Nutrient Database (<http://www.cdc.gov/nchs/nhanes/nh3data.htm>) was used to calculate nutrient intakes.

Because dietary data from a single 24-hour recall do not represent usual intake owing to day-to-day variations,^{21,22} we used the method developed by the National Cancer Institute (NCI) to estimate the usual intakes of sodium, potassium, and total energy (calorie) intake.²³ The NCI methods for estimating usual intake involve 2 steps. The first step is a 2-part model for repeated measures of nutrient data with correlated random effects. Because sodium and potassium were consumed by nearly every participant daily, we used only the second part of the 2-part model (MIXTRAN macro). The data on amount were transformed to approximate normality using Box-Cox transformation.²³ The second step in the NCI methods (using the INDIVINT macro) calculates the individual's estimated usual intakes using parameters from the first step.²⁴ The NCI method requires that at least some of the respondents have multiple days of nutrient values to estimate the within- and between-individual variations.^{23,24} In our study, we included 912 participants who provided reliable second-day dietary recalls. For each nutrient, the models included the following covariates: an indicator of sequence number (first- vs second-day recall); day of the week when the 24-hr recall was collected (weekday vs weekends [Friday-Sunday]); race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican American, and others); and age groups (20-30, 31-50, 51-70, and >70 years).¹⁷ We estimated the usual intakes of sodium, potassium, and total calorie intake for men and women separately. We present the median, interquartile range, and sodium-potassium ratio of day 1 and day 2 and the estimated usual intakes of sodium and potassium for total population and by sex (eTable 1; <http://www.archinternmed.com>).

BASELINE COVARIATES

Race/ethnicity was classified as non-Hispanic white, non-Hispanic black, Mexican American, or other. Educational attainment was classified as less than 12 years, 12 to 15 years, or more than 15 years of formal education. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Smoking status was categorized as never, former, or current. Alcohol consumption was classified as 0, 1 to 2, or 3 or more drinks per week. Physical activity was categorized as 0, 1 to 4, or 5 or more times per week of moderate in-

tensity to vigorous activities including walking, jogging or running, bicycling, swimming, aerobics or aerobic dancing, other dancing, calisthenics, and gardening or yard work. Hypertension was defined as systolic blood pressure of 140 mm Hg or higher or diastolic blood pressure of 90 mm Hg or higher or taking hypertension medication. Family history of CVD was classified into 3 mutually exclusive groups as average risk (absence of family history or, at most, 1 second-degree relative with CVD), moderate risk (only 1 first-degree and 1 second-degree relative with CVD, or only 1 first-degree, or at least 2 second-degree relatives with CVD), and high risk (at least 2 first-degree relatives or 1 first-degree and at least 2 second-degree relatives).²⁵ We included total serum cholesterol (milligrams per deciliter) and high-density lipoprotein cholesterol (HDL-C) as continuous variables in our analysis.

OUTCOME MEASURES

For the linked mortality study, eligible NHANES III participants were matched, using a probabilistic matching algorithm, to the National Death Index through December 31, 2006, to determine their mortality status. A complete, detailed description of the method can be found at http://www.cdc.gov/nchs/data/datalinkage/matching_methodology_nhanes3_final.pdf. The *International Statistical Classification of Diseases, 10th Revision (ICD-10)*, was used to identify patients for whom cardiovascular diseases (CVD) (ICD-10 codes I00-I78) or ischemic heart disease (IHD) (ICD-10 codes I20-I25) were listed as the underlying cause of death. Follow-up of survival time continued until death due to CVD and was censored at the time of death among those who died from causes other than CVD. Participants who were not matched with a death record were considered to have remained alive through the entire follow-up period.

STATISTICAL ANALYSIS

We calculated the weighted mean (SE) of the estimated usual intakes of sodium, potassium, and sodium-potassium ratio across categories of selected covariates. We used Cox proportional hazards regression to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) for all-cause, CVD, and IHD mortality. We used the estimated usual intakes as continuous variables in the nutrient-diseases association. Because the relationships between the estimated usual intakes and all-cause and CVD mortality were approximately linear, we calculated the percentile distributions of the estimated usual intakes as the middle value of each quartile: 87.5, 62.5, 37.5, and 12.5. To present the results, we used the parameters from the continuous models and estimated the adjusted HRs comparing the middle values of each quartile with the lowest quartile (Q4, Q3, Q2, vs Q1).^{26,27} We used the attained age as the timescale in Cox proportional hazards models.²⁸ Multivariable models were adjusted for sex, race/ethnicity, educational attainment, BMI, smoking status, alcohol intake, total cholesterol level, HDL-C level, family history of CVD, and total calorie intake. For the sensitivity analysis, we adjusted for the Healthy Eating Index (HEI). The HEI score ranges from 0 to 100 and contains information on consumption of 10 subcomponents of the diet: fruits, vegetables, grains, dairy, meats, fats, saturated fat, cholesterol, sodium, and dietary variety.²⁹ A higher HEI score indicates a healthier eating pattern. We did not adjust for hypertension or blood pressure in the main analysis because they are intermediate variables on the pathway. However, the results did not alter materially after adjusting for hypertension and blood pressure. To examine the association between estimated usual intakes of sodium, potassium, and sodium-potassium ratio and all-cause and CVD mortality, we used the standard multivar-

Table 1. Estimated Usual Intakes of Sodium, Potassium, and Calories and Sodium-Potassium Ratio at Baseline by Sex, NHANES III Linked Mortality File^a

Characteristic ^c	Mean (SE) ^b									
	Sample, No. (%) ^b		Usual Sodium Intakes, mg/d		Usual Potassium Intakes, mg/d		Sodium-Potassium Ratio		Usual Calorie Intake	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
All	5899 (0.52)	6368 (0.52)	4323 (21)	2918 (17)	3373 (14)	2433 (13)	1.31 (0.01)	1.23 (0.01)	2697 (14)	1785 (10)
Age, y										
<60	4444 (85.2)	4904 (81.5)	4450 (20)	3003 (18)	3409 (17)	2418 (15)	1.34 (0.01)	1.27 (0.01)	2792 (14)	1844 (10)
≥60	1455 (14.8)	1464 (18.5)	3593 (30)	2546 (19)	3165 (24)	2501 (15)	1.16 (0.01)	1.03 (0.01)	2147 (16)	1524 (9)
<i>P</i> value			<.001	<.001	<.001	<.001	<.001	<.001	<.001	<.001
Race/ethnicity										
Non-Hispanic white (1)	2269 (76.1)	2631 (76.6)	4377 (23)	2914 (17)	3481 (18)	2503 (13)	1.28 (0.01)	1.19 (0.01)	2735 (14)	1789 (12)
Non-Hispanic black (2)	1540 (9.8)	1752 (10.6)	4098 (33)	2924 (20)	2794 (24)	2020 (11)	1.50 (0.01)	1.48 (0.01)	2586 (20)	1781 (12)
Mexican American (3)	1859 (6.1)	1702 (4.7)	3961 (27)	2781 (16)	3280 (21)	2387 (17)	1.23 (0.01)	1.19 (0.01)	2654 (19)	1787 (8)
Other (4)	231 (8.0)	283 (8.1)	4367 (76)	3023 (75)	3116 (53)	2331 (38)	1.43 (0.02)	1.31 (0.02)	2505 (43)	1742 (35)
<i>P</i> value (1 vs 2)			<.001	.66	<.001	<.001	<.001	<.001	<.001	.59
<i>P</i> value (1 vs 3)			<.001	<.001	<.001	<.001	<.001	.73	<.001	.85
<i>P</i> value (1 vs 4)			.90	.14	<.001	<.001	<.001	<.001	<.001	.18
<i>P</i> value overall			<.001	.04	<.001	<.001	<.001	<.001	<.001	.25
Education, y										
0-11	2391 (23.5)	2195 (20.9)	4101 (40)	2775 (22)	3213 (29)	2325 (13)	1.31 (0.01)	1.22 (0.01)	2531 (22)	1686 (12)
12-15	2660 (52.3)	3316 (59.3)	4414 (28)	2950 (22)	3394 (26)	2424 (18)	1.33 (0.01)	1.25 (0.01)	2770 (21)	1802 (13)
≥16	806 (24.2)	820 (19.8)	4350 (44)	2975 (26)	3488 (30)	2567 (22)	1.27 (0.01)	1.18 (0.01)	2705 (23)	1834 (18)
<i>P</i> value for trend			<.001	<.001	<.001	<.001	.07	.006	<.001	<.001
Smoking status										
Never (1)	2211 (37.8)	3878 (54.2)	4395 (26.0)	2888 (22.0)	3377 (24.0)	2402 (14.0)	1.33 (0.01)	1.23 (0.01)	2735 (17.0)	1754 (13.0)
Current (2)	1959 (33.4)	1478 (26.8)	4403 (32.0)	2985 (28.0)	3353 (29.0)	2416 (23.0)	1.35 (0.01)	1.27 (0.01)	2786 (23.0)	1854 (18.0)
Former (3)	1728 (28.8)	1012 (19.0)	4136 (37)	2910 (22)	3389 (33)	2544 (22)	1.24 (0.01)	1.16 (0.01)	2541 (22)	1773 (16)
<i>P</i> value (1 vs 2)			.84	.002	.55	.54	.39	<.001	.054	<.001
<i>P</i> value (1 vs 3)			<.001	.49	.82	<.001	<.001	<.001	<.001	.35
<i>P</i> value overall			<.001	.003	.68	<.001	<.001	<.001	<.001	<.001
Alcohol intake, drinks/wk ^d										
None (1)	590 (10.1)	1709 (30.4)	4172 (58)	2812 (29)	3135 (55)	2346 (24)	1.37 (0.02)	1.23 (0.01)	2515 (34)	1684 (15)
<3 (2)	1400 (36.2)	1398 (44.4)	4348 (42)	3009 (31)	3373 (38)	2466 (21)	1.32 (0.01)	1.25 (0.01)	2709 (26)	1834 (17)
≥3 (3)	2208 (53.7)	810 (25.1)	4413 (32)	2991 (35)	3420 (25)	2517 (20)	1.32 (0.01)	1.22 (0.02)	2802 (23)	1884 (24)
<i>P</i> value (1 vs 2)			.01	<.001	<.001	<.001	.06	.15	<.001	<.001
<i>P</i> value (1 vs 3)			.001	<.001	<.001	<.001	.07	.73	<.001	<.001
<i>P</i> value overall			.01	<.001	.001	<.001	.11	.16	<.001	<.001

(continued)

iate method adjusting for the total calorie intake.³⁰ A *P* value for trend across the HRs for the quintiles was calculated using a Satterthwaite adjusted *F* test.³¹

We tested for interactions of estimated usual intakes of sodium, potassium, and sodium-potassium ratio with sex, race/ethnicity, BMI (<25 vs ≥25), hypertension, physical activity (nonactive vs active), and educational attainment (<12 vs ≥12 years of education) by including the interactions terms in the Cox models using the Satterthwaite adjusted test.³¹ We conducted several sensitivity analyses. First, we restricted the participants to ages 25 to 74 years at baseline. Second, we conducted stratified analyses by sex, race/ethnicity, BMI, and hypertension status. Third, we analyzed the associations between sodium, potassium intakes, and sodium-potassium ratio obtained from the first-day dietary recalls only and also tested for departure from linearity. The results from these sensitivity analyses are provided in eTables 2, 3, 4, 5, 6, and 7.

The proportional hazards assumption of the Cox models was evaluated with Schoenfeld residuals, which revealed no significant departure from proportionality in hazards over time.³² We compared the goodness of fit for models with sodium, potassium, or sodium-potassium ratio using Akaike information criterion (AIC); a smaller AIC indicates a better fit.³³ We conducted the Cox proportional hazards analyses using SUDAAN statistical software (version 9.2; Research Triangle Park, North Carolina) to take into account the complex sampling design.³¹ All tests were 2-sided, and *P* < .05 was considered statistically significant.

RESULTS

Among the 12 267 participants meeting our eligibility criteria, 2270 deaths over 170 110 person-years of follow-up (median follow-up, 14.8 years) were documented. There were 825 deaths from CVD and 433 from IHD.

Table 1 shows the crude estimated usual intakes of sodium, potassium, sodium-potassium ratio, and total calorie intake by sex and selected characteristics. The sodium-potassium ratio was higher among males, the younger age group, current smokers, minority groups, and those with lower educational attainment (females only), lower physical activity, higher BMI (females only), lower total cholesterol or lower HDL-C (female only), and lower systolic blood pressure.

After multivariable adjustment, higher sodium intake was associated with increased all-cause mortality (HR, 1.20; 95% CI, 1.03-1.41 per 1000 mg/d), whereas higher potassium intake was associated with lower mortality risk (HR, 0.80; 95% CI, 0.67-0.94 per 1000 mg/d (**Table 2**)). The risk of all-cause deaths increased linearly with increasing sodium-potassium ratio: the adjusted HR comparing the highest quartile (Q4) with the lowest quartile (Q1) was HR, 1.46 (95% CI, 1.27-1.67) (*P* value for trend <.001).

Table 1. Estimated Usual Intakes of Sodium, Potassium, and Calories and Sodium-Potassium Ratio at Baseline by Sex, NHANES III Linked Mortality File^a (continued)

Characteristic ^c	Mean (SE) ^b									
	Sample, No. (%) ^b		Usual Sodium Intakes, mg/d		Usual Potassium Intakes, mg/d		Sodium-Potassium Ratio		Usual Calorie Intake	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Physical activity, times/wk										
None	923 (10.4)	1580 (16.9)	4165 (48)	2835 (29)	3215 (40)	2334 (21)	1.33 (0.01)	1.24 (0.01)	2580 (30)	1720 (16)
<5	2378 (42.6)	2762 (46.3)	4357 (27)	2968 (27)	3358 (19)	2406 (14)	1.33 (0.01)	1.26 (0.01)	2708 (18)	1815 (13)
≥5	2565 (47.0)	2005 (36.8)	4327 (26)	2894 (21)	3418 (20)	2511 (17)	1.30 (0.01)	1.18 (0.01)	2711 (18)	1777 (14)
<i>P</i> value for trend			.003	.08	<.001	<.001	.03	<.001	<.001	.001
BMI										
<25	2508 (43.3)	2825 (54.4)	4353 (30)	2961 (23)	3365 (23)	2467 (16)	1.33 (0.01)	1.23 (0.01)	2747 (22)	1824 (16)
25-30	2343 (40.2)	1843 (24.7)	4305 (32)	2846 (22)	3388 (23)	2424 (20)	1.30 (0.01)	1.20 (0.01)	2672 (19)	1731 (12)
>30	1042 (16.6)	1685 (20.9)	4292 (36)	2891 (25)	3357 (33)	2356 (22)	1.31 (0.01)	1.26 (0.01)	2625 (29)	1746 (14)
<i>P</i> value for trend			.12	.03	.85	<.001	.18	.03	<.001	.001
Total serum cholesterol, mg/dL										
<240	4671 (83.7)	4938 (82.1)	4367 (23)	2961 (18)	3396 (16)	2438 (14)	1.32 (0.01)	1.24 (0.01)	2729 (15)	1817 (12)
≥240	952 (16.3)	1114 (17.9)	4173 (39)	2725 (24)	3322 (38)	2434 (20)	1.29 (0.01)	1.14 (0.01)	2569 (24)	1640 (13)
<i>P</i> value			<.001	<.001	.12	.85	.03	<.001	<.001	<.001
Total HDL-C level, mg/dL										
<60	4660 (85.9)	4038 (65.1)	4336 (22)	2919 (20)	3380 (15)	2406 (14)	1.31 (0.01)	1.24 (0.01)	2696 (15)	1782 (11)
≥60	919 (14.1)	1984 (34.9)	4325 (50)	2914 (21)	3408 (38)	2495 (17)	1.30 (0.01)	1.20 (0.01)	2745 (38)	1791 (14)
<i>P</i> value			.84	.84	.53	<.001	.39	<.001	.23	.47
Systolic BP, mm Hg										
<125	3309 (62.6)	4397 (74.6)	4440 (24)	3002 (19)	3423 (22)	2426 (15)	1.33 (0.01)	1.27 (0.01)	2776 (16)	1841 (11)
≥125	2583 (37.4)	1959 (25.4)	4129 (29)	2670 (20)	3294 (22)	2454 (15)	1.28 (0.01)	1.11 (0.01)	2566 (21)	1619 (11)
<i>P</i> value			<.001	<.001	<.001	.14	<.001	<.001	<.001	<.001
Diastolic BP, mm Hg										
<85	4823 (83.1)	5837 (93.1)	4339 (20)	2925 (18)	3382 (15)	2437 (13)	1.31 (0)	1.23 (0.01)	2705 (14)	1790 (11)
≥85	1069 (16.9)	519 (6.9)	4249 (49)	2823 (40)	3339 (33)	2373 (31)	1.30 (0.01)	1.22 (0.01)	2660 (29)	1717 (21)
<i>P</i> value			.06	.03	.21	.06	.46	.55	.13	.01
Hypertension										
Yes	1447 (20.6)	1449 (18.6)	4080 (45)	2719 (25)	3289 (29)	2421 (16)	1.27 (0.01)	1.15 (0.01)	2513 (28)	1650 (15)
No	4452 (79.4)	4919 (81.4)	4387 (21)	2963 (18)	3394 (14)	2436 (14)	1.32 (0)	1.25 (0.01)	2744 (13)	1815 (11)
<i>P</i> value			<.001	<.001	.002	.47	<.001	<.001	<.001	<.001
Familial risk of MI										
Average	4239 (75.8)	4172 (70.5)	4326 (25)	2936 (20)	3374 (17)	2449 (16)	1.31 (0.01)	1.23 (0.01)	2707 (16)	1798 (13)
Moderate	1173 (19.0)	1530 (22.6)	4306 (35)	2881 (25)	3369 (28)	2393 (20)	1.31 (0.01)	1.23 (0.01)	2667 (24)	1757 (13)
High	386 (5.2)	574 (6.9)	4301 (75)	2880 (46)	3394 (77)	2406 (36)	1.30 (0.03)	1.23 (0.02)	2615 (42)	1749 (24)
<i>P</i> value for trend			.76	.27	.81	.32	.76	.84	.04	.10

Abbreviations: BP, blood pressure; HDL-C, high-density lipoprotein cholesterol; MI, myocardial infarction; NHANES III, Third National Health and Nutrition Examination Survey.

SI conversion factor: To convert serum cholesterol to millimoles per liter, multiply by 0.0259.

^a See study by the National Center for Health Statistics, Centers for Disease Control and Prevention.²⁰

^b Mean (SE) and population percentage presented by sex of estimated usual intakes of sodium, potassium, and calorie intake.

^c For categories of the continuous variables in nature (eg, years of education and body mass index), *P* value for difference across the categories. For categorical variables (eg, race/ethnicity), we presented pairwise and overall *P* values. All tests were 2-tailed and based on Satterthwaite adjusted *F* test.

^d Approximately 25% of participants had missing information on frequency and amount of alcohol consumed.

Sodium intake was not statistically significantly associated with CVD or IHD mortality (**Table 3**). However, potassium intake was significantly inversely associated with the incidence of CVD or IHD death: the adjusted HR, 0.39 (95% CI, 0.19-0.80), for CVD mortality and HR, 0.26 (95% CI, 0.10-0.71), for IHD mortality comparing the highest quartile with the lowest quartile of potassium intake. Higher sodium-potassium ratio was significantly associated with risk of CVD and IHD mortality: the adjusted HRs comparing the highest quartile with the lowest quartile were 1.46 (95% CI, 1.11-1.92) and 2.15 (95% CI, 1.48-3.12) for CVD and IHD mortality, respectively. The models with the sodium-potassium ratio had consistently smaller AIC compared with the models with either sodium or potassium for all-cause, CVD, and IHD mortality (AIC: 19199, 6244, and 3618 vs 19214, 6246, and 3623), suggesting a better fit for the model with the sodium-potassium ratio.

Additional adjustment for the HEI did not alter the results substantially: the adjusted HRs were 1.38 (95% CI, 1.14-1.67), 1.37 (95% CI, 0.99-1.89), and 1.94 (95% CI, 1.36-2.76) comparing the highest quartile with the lowest quartile of sodium-potassium ratio for all-cause, CVD, and IHD mortality, respectively. After adjustment for calorie intake by the residual method,³⁰ the observed associations were slightly strengthened (adjusted HRs: 1.50 [95% CI, 1.29-1.75], 1.52 [95% CI, 1.17-1.98], and 2.34 [95% CI, 1.53-3.58] comparing the highest quartile with the lowest quartile of sodium-potassium ratio for all-cause, CVD, and IHD mortality, respectively).

The increased risk for all-cause, CVD, or IHD mortality associated with higher sodium-potassium ratio remained largely consistent across sex, race/ethnicity, BMI, hypertension status, physical activity, and educational attainments (**Figure**). We tested statistical interactions between estimated usual intakes of sodium and potassium

Table 2. Adjusted HRs of Estimated Usual Intakes of Sodium, Potassium, and Sodium-Potassium Ratio for All-Cause Mortality,^a NHANES III^b

Characteristic	Midvalue of Quartile of Estimated Usual Intakes in Population, %				P Value ^c	Total ^d
	Q1: 12.5	Q2: 37.5	Q3: 62.5	Q4: 87.5		
Usual sodium intake, mg (range, 839-8555)	2176	3040	3864	5135	NA	NA
HR adjusted for sex and race/ethnicity only	1 [Reference]	1.16 (1.02-1.30)	1.33 (1.05-1.68)	1.64 (1.08-2.49)	.02	1.18 (1.03-1.36)
Fully adjusted HR ^e	1 [Reference]	1.17 (1.13-1.33)	1.37 (1.28-1.74)	1.73 (1.54-2.63)	.02	1.20 (1.03-1.41)
Usual potassium intake, mg (range, 609-8839)	1793	2476	3108	4069	NA	NA
HR adjusted for sex and race/ethnicity only	1 [Reference]	.81 (.71-.91)	0.66 (0.52-0.83)	0.49 (0.32-0.73)	<.001	0.73 (0.61-0.87)
Fully adjusted HR ^e	1 [Reference]	.86 (.77-.97)	0.75 (0.60-0.95)	0.61 (0.41-0.91)	.01	0.80 (0.67-0.94)
Sodium-potassium ratio (range, 0.46-2.98)	0.98	1.17	1.33	1.57	NR	NA
Usual sodium intake (range, 839-8555)	2728	3295	3650	3757	NR	NA
Usual potassium intake (range, 609-8839)	2940	2936	2918	2699	NR	NA
HR adjusted for sex and race/ethnicity only	1 [Reference]	1.15 (1.10-1.21)	1.30 (1.19-1.42)	1.55 (1.33-1.81)	<.001	2.11 (1.63-2.74)
Fully adjusted HR ^e	1 [Reference]	1.13 (1.08-1.18)	1.25 (1.15-1.35)	1.46 (1.27-1.67)	<.001	1.89 (1.50-2.37)

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable; NHANES III, Third National Health and Nutrition Examination Survey Linked Mortality File; NR, not reported.

^aTotal number of deaths, 2270; total person-years, 170 110.

^bUnless otherwise reported, data are given as HRs (95% CIs) or milligrams per day. See study by the National Center for Health Statistics, Centers for Disease Control and Prevention.²⁰

^cP value for trend across percentiles of estimated usual intakes of sodium, potassium, or sodium-potassium ratio based on Satterthwaite adjusted F test; all tests were 2-tailed.

^dFor the estimated usual intakes of sodium or potassium, HRs are for per 1000 mg/d intake. For sodium-potassium ratio, HRs are per unit change.

^eAdjusted for sex, race/ethnicity, educational attainment, body mass index, smoking status, alcohol intake, total cholesterol, high-density lipoprotein cholesterol, physical activity, family history of cardiovascular disease, and total calorie intake.

Table 3. Adjusted HRs of Estimated Usual Intakes of Sodium, Potassium, and Sodium-Potassium Ratio for CVD and IHD Mortality,^a NHANES III Linked Mortality File^b

Characteristic	Midvalue of Quartiles of Estimated Usual Intakes In Population, HR (95% CI)				P Value for Trend ^c	Total/HR per 1000 mg/d ^d
	Q1: 12.5	Q2: 37.5	Q3: 62.5	Q4: 87.5		
Usual sodium intake, mg (range, 839-8555)	2176	3040	3864	5135	NA	NA
CVD mortality						
HR adjusted for sex and race/ethnicity only	1 [Reference]	1.02 (0.76-1.37)	1.04 (0.59-1.85)	1.08 (0.40-2.95)	.88	1.03 (0.73-1.44)
Fully adjusted HR ^e	1 [Reference]	0.95 (0.71-1.27)	0.90 (0.51-1.60)	0.83 (0.31-2.28)	.72	0.94 (0.67-1.32)
IHD mortality						
HR adjusted for sex and race/ethnicity only	1 [Reference]	1.25 (.88-1.76)	1.54 (0.78-3.01)	2.12 (0.65-6.88)	.21	1.29 (0.87-1.92)
Fully adjusted HR ^e	1 [Reference]	1.17 (0.84-1.62)	1.36 (0.71-2.58)	1.70 (0.55-5.27)	.36	1.20 (0.81-1.77)
Usual potassium intake, mg (range, 609-8839)	1793	2476	3108	4069	NA	NA
CVD mortality						
HR adjusted for sex and race/ethnicity only	1 [Reference]	0.68 (0.55-0.84)	0.48 (0.32-0.72)	0.28 (0.14-0.56)	<.001	0.57 (0.42-0.78)
Fully adjusted HR ^e	1 [Reference]	0.75 (0.61-0.94)	0.58 (0.38-0.88)	0.39 (0.19-0.80)	.005	0.63 (0.46-0.87)
IHD mortality						
HR adjusted for sex and race/ethnicity only	1 [Reference]	0.58 (0.43-0.79)	0.35 (0.20-0.63)	0.16 (0.06-0.45)	<.001	0.45 (0.29-0.70)
Fully adjusted HR ^e	1 [Reference]	0.67 (0.50-0.90)	0.46 (0.26-0.82)	0.26 (0.10-0.71)	.005	0.51 (0.32-0.81)
Sodium-potassium ratio (range, 0.46-2.98)	0.98	1.17	1.33	1.57	NR	NA
Usual sodium intake (range, 839-8555)	2728	3295	3650	3757	NR	NA
Usual potassium intake (range, 609-8839)	2940	2936	2918	2699	NR	NA
CVD mortality						
HR adjusted for sex and race/ethnicity only	1 [Reference]	1.17 (1.08-1.27)	1.34 (1.15-1.56)	1.64 (1.27-2.13)	<.001	2.32 (1.50-3.59)
Fully adjusted HR ^e	1 [Reference]	1.13 (1.03-1.23)	1.25 (1.07-1.47)	1.46 (1.11-1.92)	.01	1.90 (1.20-3.03)
IHD mortality						
HR adjusted for sex and race/ethnicity only	1 [Reference]	1.33 (1.19-1.48)	1.69 (1.38-2.06)	2.41 (1.72-3.38)	<.001	4.45 (2.51-7.89)
Fully adjusted HR ^e	1 [Reference]	1.28 (1.13-1.44)	1.57 (1.26-1.97)	2.15 (1.48-3.12)	<.001	3.66 (1.94-6.90)

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; IHD, ischemic heart disease; NA, not applicable; NHANES III, Third National Health and Nutrition Examination Survey; NR, not reported.

^aTotal number of CVD deaths, 825; total number of IHD deaths, 443; total person-years, 170 110.

^bUnless otherwise reported, data are given as HRs (95% CIs) or milligrams per day. See study by the National Center for Health Statistics, Centers for Disease Control and Prevention.²⁰

^cP value for trend across percentiles of estimated usual intakes of sodium, potassium, or sodium-potassium ratio based on Satterthwaite adjusted F test; all tests were 2-tailed.

^dFor the estimated usual intakes of sodium or potassium, HRs are for per 1000 mg/d intake. For sodium-potassium ratio, HR are per unit change.

^eAdjusted for sex, race/ethnicity, educational attainment, body mass index, smoking status, alcohol intake, total cholesterol, high-density lipoprotein cholesterol, physical activity, family history of CVD, and total calorie intake.

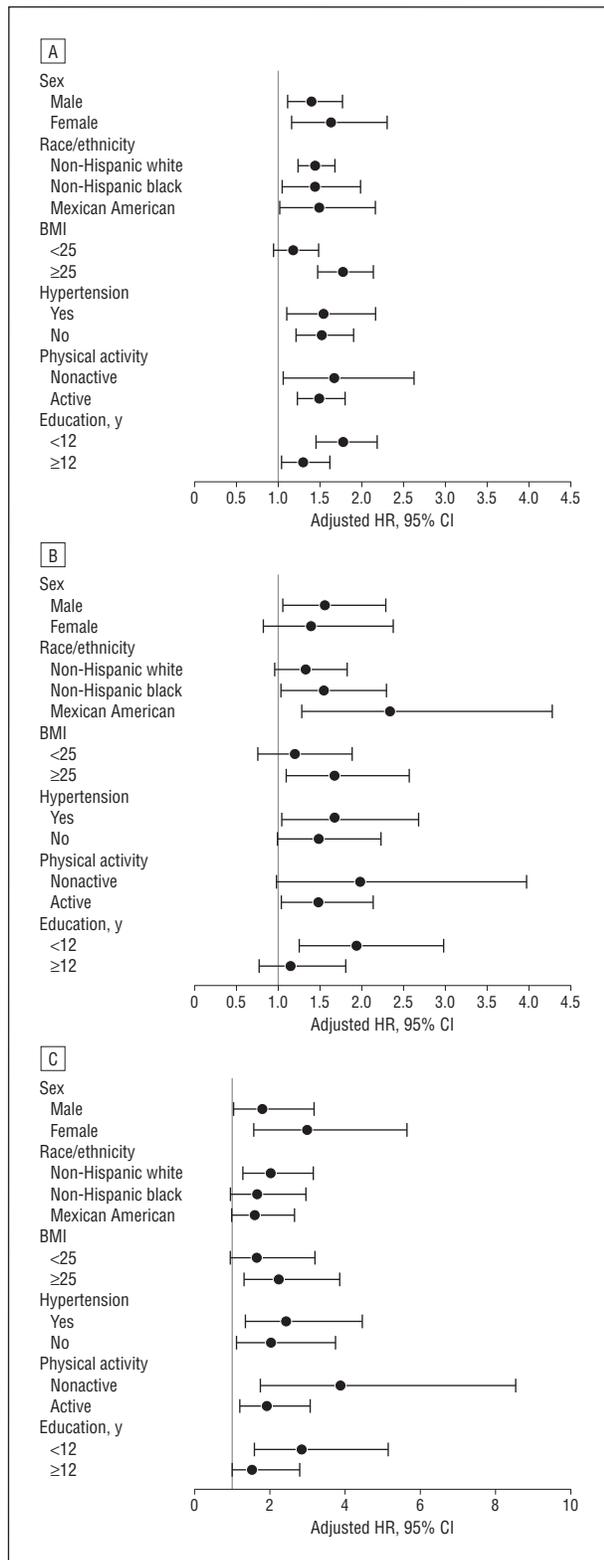


Figure. Association between the estimated usual intake of sodium-potassium ratio and all-cause, cardiovascular, and ischemic heart diseases mortality and selected characteristics. Adjusted hazard ratios (HRs) (95% confidence intervals [CIs]) for all-cause (A), cardiovascular (B), and ischemic heart diseases (C) mortality comparing the highest quartile with the lowest quartile of sodium-potassium ratio by sex, race/ethnicity, body mass index (BMI, calculated as weight in kilograms divided by height in meters squared), hypertension status, physical activity, and educational attainments, Third National Health and Nutrition Examination Survey (NHANES III) Linked Mortality File.²⁰

or sodium-potassium ratio and selected covariates in relation to all-cause or CVD mortality and found no evidence of significant interactions ($P > .05$ for all comparisons) (eTables 2-6).

COMMENT

In this cohort of a nationally representative sample of US adults followed for an average of 14.8 years, we observed a significant monotonic association between increasing sodium-potassium ratio and risk for all-cause, CVD, or IHD mortality. This association was independent of age, sex, race/ethnicity, and other covariates.

Numerous epidemiologic studies and randomized clinical trials have found that high sodium³⁴⁻³⁷ or low potassium intake^{1,6,38,39} was associated with increased risk for hypertension, with a stronger association observed for potassium. However, less consistent results have been observed for incidence of CVD or mortality. For instance, moderately inverse,⁴⁰⁻⁴² moderately positive,^{2,4,12,43-46} or non-significant associations^{3,4,47,48} were observed for sodium intake and incidence of CVD or mortality. The inconsistency in the results of these studies may be attributable to the variability of CVD end points and differences in measurement of nutrient intake, adjustment for confounding variables, and analytic methods. In an earlier analysis of NHANES III data, a modest and insignificant association between sodium intake and CVD mortality was observed.⁴¹ However, this analysis used only 1-day dietary recall data, with a much shorter duration of follow-up (1988-2000), and it did not examine the associations with potassium. We observed a positive association between sodium intake and CVD mortality among normotensive persons but a slightly inverse association among hypertensive persons, raising the possibility that patients with hypertension might have reduced their sodium intake. However, these associations were modest and nonsignificant; the interaction between hypertension and sodium intake was not significant either (eTable 6). A pooled estimate obtained in the meta-analysis of 19 independent cohort samples with 177 025 participants (range of follow-up, 3.5-19.0 years) showed that higher salt intake was significantly associated with greater risk of stroke and cardiovascular disease.⁴ A stronger association was observed in studies with a larger range of sodium intake and a longer duration of follow-up.

Several epidemiologic studies examined the joint effects of sodium and potassium and the incidence or mortality of CVD.^{3,11,12} In our study, the positive association between the sodium-potassium ratio and mortality was consistent across different sex and racial/ethnic groups as well as different categories of other covariates. A stronger association was observed for IHD mortality (HR, 2.15; 95% CI, 1.48-3.12) comparing the highest quartile with the lowest quartile of the sodium-potassium ratio) than for CVD mortality (HR, 1.46; 95% CI, 1.11-1.92), but we could not obtain the stable estimates for stroke mortality owing to the limited number of stroke deaths ($n = 139$). In a multicenter cross-sectional study in men, involving 25 cooperative study centers across 16 countries, stroke mortality was strongly associated with a higher sodium-potassium ratio.⁴⁹

The observed stronger and more consistent associations between the sodium-potassium ratio and mortality than between each nutrient separately and mortality may be due to complex interactions between potassium and sodium at cellular levels.^{13,14,50} High sodium levels induce increased blood pressure and hypertension by stiffening endothelial cells, thickening and narrowing resistance arteries, and blocking nitric oxide synthesis, whereas high potassium levels can counteract these effects by activating nitric oxide release.⁵¹ The opposite biological effects of sodium and potassium may explain stronger associations of sodium-potassium ratio with CVD mortality than either sodium or potassium intake alone. Future laboratory and clinical studies could shed additional light on this observation from our study.

Because sodium is added to many foods, especially processed foods, while potassium is naturally present in most foods, a low sodium-potassium ratio may be a marker of high intake of plant foods and lower intake of processed foods. For example, cheeses, cooked meats, breads, soups, fast foods, pastries, and sugary products tend to have a higher sodium-potassium ratio, whereas fruits, vegetables, dairy products, and hot beverages tend to have a lower ratio.⁵² In our study, additional adjustment for the HEI did not materially alter the results, suggesting that the benefits of potassium intake might be independent of a healthy dietary pattern that includes fruits and vegetables. From a public health point of view, reduced sodium intake accompanied by increased potassium intake could achieve greater health benefits than restricting sodium alone.³⁹ In community settings, increased neighborhood availability of supermarkets and grocery stores and fruit and vegetable stores and decreased availability of confectionery stores and bakeries has been associated with favorable sodium-potassium ratio.^{52,53}

Our study has several strengths. These include the availability of dietary sodium and potassium intakes from a cohort based on a nationally representative sample of the US adult population, adjustment for a large number of potential confounding variables, and ascertainment of all-cause and CVD mortality over a long duration of follow-up (median duration, 14.8 years). In addition, we used a validated method developed by the NCI to estimate the usual intakes of sodium and potassium using information from two 24-hour dietary recalls.^{23,24,27} Many studies have indicated that a single 24-hour dietary recall does not provide a reliable measure of usual nutrient intakes owing to large day-to-day variation. These errors tend to attenuate observed nutrient-disease relationships (eTable 7).^{22,26,54} Several studies indicated that estimating usual intakes using the NCI methods provides significant improvement in assessing nutrient-disease associations.^{26,27}

However, there are several limitations to our study. First, the consumption of sodium and potassium was not updated during the follow-up, and thus baseline exposure might not capture changes in intakes over time. Second, only 912 of the analytic sample (7.4%) provided the second-day dietary recalls, which were used in our estimate of usual intakes. However, data were available for approximately 100 participants in each sex-age group (20-30, 31-50, 51-70, and >70 years of age), which should provide a robust

estimate of the usual intakes.^{21,23} Third, the calculated sodium intake from NHANES III did not include discretionary salt use. The survey asked the participants about use of table salt, but the information on the amount of intake was lacking. Because it is estimated that American adults consume on average about 80% of their sodium from processed or restaurants foods and only 6% from table salt,⁵⁵ adding table salt to the estimate is unlikely to change our results appreciably. Although lower reported sodium intake from foods might be associated with increased use of table salt, diminishing the true exposure between low and high intakes, the adjustment for the use of table salt in the sensitivity analysis did not change the results. Fourth, the associations reported in our study may be due in part to confounding by other dietary variables.⁵⁶ However, the observed association did not change after adjusting for a healthy dietary pattern. Fifth, the measurement of sodium excretion in the 24-hour urine collection method is considered to be the most reliable but is not available in NHANES III. Finally, given the longitudinal study design and these limitations, caution should be taken in interpretation of results from this and other similar studies. Although these studies are important in improving our understanding of nutrient-disease relationship and are often included in meta-analyses, it should be stressed that dietary guidelines and public health recommendations are based on combination of evidence drawn from various types of studies (laboratory, epidemiologic studies, and clinical trials, etc).⁵⁷ The nonsignificant associations between sodium intake and CVD mortality observed in our study do not undermine a well-established relationship between sodium intake and high blood pressure or the potential benefits of sodium reduction at the population level.⁵⁸ The finding of a significant association between estimated usual intake of sodium and all-cause mortality adds weight to a direct sodium-mortality relationship.

In summary, our findings indicate that higher sodium-potassium ratio is associated with significantly increased risk of CVD and all-cause mortality in the general US population. Public health recommendations should emphasize simultaneous reduction in sodium intake and increase in potassium intake.

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Author Contributions: Dr Yang and Mr Liu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Yang, Liu, Flanders, Gillespie, Khoury, and Hu. *Analysis and interpretation of data:* Yang, Liu, Flanders, Kuklina, Hong, Chang, Gwinn, Dowling, and Hu. *Drafting of the manuscript:* Yang. *Critical revision of the manuscript for important intellectual content:* Yang, Liu, Kuklina, Flanders, Hong, Gillespie, Chang, Gwinn, Dowling, Khoury, and Hu. *Statistical analysis:* Yang, Liu, Flanders, Gillespie, and Chang. *Administrative, technical, and material support:* Hong, Chang, Dowling, Khoury, and Hu. *Study supervision:* Yang and Hu.

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INVITED COMMENTARY

Sodium and Potassium Intake

Mortality Effects and Policy Implications

In this issue of the *Archives*, Yang et al¹ report on their analysis of the relationship between mortality and usual intakes of sodium and potassium. Among more than 12 000 US adults whose dietary intake was assessed in the Third National Health and Nutrition Examination Survey (NHANES III), they identified large relationships between higher sodium intake and higher all-cause mortality and between lower potassium intake and higher all-cause, cardiovascular (CVD), and ischemic heart disease (IHD) deaths. Most important, higher sodium to potassium ratios were strongly associated with increased all-cause, CVD, and IHD mortality.

This article strengthens the already compelling evidence of the relationship between sodium intake and mortality. A considerable body of work supports the links between higher sodium and lower potassium intake and hypertension, cardiovascular events, and mortality.² Some studies diverge, such as that by Cohen et al.³ However, the work of Yang et al, with methodological improvements, reached almost opposite conclusions using the same data set.

Sodium-potassium ratios can be improved by lowering sodium intake, by raising potassium intake, or both. Changes in blood pressure from these 2 approaches are interdependent and probably not additive, with potassium offering the greatest benefits when sodium intake is high.² In the study by Yang et al, men and women, respectively, consumed 4323 and 2918 mg/d of sodium, far above the 1500 mg/d maximum recommended for most adults, and 3373 and 2433 mg/d of potassium, far below the 4.7 mg/d recommended adequate intake.

More than three-quarters of sodium in the US diet is added during processing,⁴ making it hard for individu-

als to reduce their intake. A 2010 Institute of Medicine⁵ report called on the US Food and Drug Administration to regulate sodium in the food supply, while endorsing voluntary efforts currently under way. The report highlighted the National Salt Reduction Initiative (NSRI), a partnership of over 70 organizations that seeks to lower sodium in packaged and restaurant food by 25% by 2014. Twenty-eight major food companies have already made voluntary commitments to NSRI sodium reduction targets. Other efforts to lower sodium in the food supply are occurring internationally. Finland and the United Kingdom, for example, have made progress in lowering population sodium intake. In Finland, with decades of voluntary work and 18 years since regulatory measures were put into effect, a one-third decrease in sodium intake was observed concurrently with decreasing hypertension and premature mortality from stroke and coronary heart disease.⁶

Optimizing population potassium intake also is of great public health importance, but implementation poses important questions regarding potential unintended negative consequences. In a traditional, largely plant-based diet, potassium content is high and sodium content low. As foods are processed, typically sodium is added and potassium is removed, reversing the sodium-potassium ratio. Encouraging consumption of unprocessed, potassium-rich fruits and vegetables is the safest and preferred pathway to increasing potassium intake.² However, despite years of educational campaigns, consumption of fruits and vegetables in the United States is far below recommended levels and has remained relatively stable or even declined slightly.