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ORIGINAL INVESTIGATIONS

Sodium Intake and All-Cause Mortality Over 20 Years in the Trials of Hypertension Prevention

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ABSTRACT

BACKGROUND The relationship between lower sodium intake and total mortality remains controversial.

OBJECTIVES This study examined the relationship between well-characterized measures of sodium intake estimated from urinary sodium excretion and long-term mortality.

METHODS Two trials, phase I (1987 to 1990), over 18 months, and phase II (1990 to 1995), over 36 months, were undertaken in TOHP (Trials of Hypertension Prevention), which implemented sodium reduction interventions. The studies included multiple 24-h urine samples collected from pre-hypertensive adults 30 to 54 years of age during the trials. Post-trial deaths were ascertained over a median 24 years, using the National Death Index. The associations between mortality and the randomized interventions as well as with average sodium intake were examined.

RESULTS Among 744 phase I and 2,382 phase II participants randomized to sodium reduction or control, 251 deaths occurred, representing a nonsignificant 15% lower risk in the active intervention (hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.66 to 1.09; p = 0.19). Among 2,974 participants not assigned to an active sodium intervention, 272 deaths occurred. There was a direct linear association between average sodium intake and mortality, with an HR of 0.75, 0.95, and 1.00 (references) and 1.07 (p trend = 0.30) for <2,300, 2,300 to <3,600, 3,600 to <4,800, and ≥4,800 mg/24 h, respectively; and with an HR of 1.12 per 1,000 mg/24 h (95% CI: 1.00 to 1.26; p = 0.05). There was no evidence of a J-shaped or nonlinear relationship. The HR per unit increase in sodium/potassium ratio was 1.13 (95% CI: 1.01 to 1.27; p = 0.04).

CONCLUSIONS We found an increased risk of mortality for high-sodium intake and a direct relationship with total mortality, even at the lowest levels of sodium intake. These results are consistent with a benefit of reduced sodium and sodium/potassium intake on total mortality over a 20-year period. (J Am Coll Cardiol 2016;68:1609–17)

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ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

Numerous randomized trials and observational studies have demonstrated a direct relationship between dietary sodium intake and blood pressure (1,2). Although the effect is strongest among those with hypertension (3), there is also a smaller but consistent effect of lowering sodium on blood pressure among those with high normal or prehypertensive blood pressure levels. The DASH-Sodium (Dietary Approaches to Stop Hypertension) trial, a dose-response trial with 3 levels of sodium intake, found a significant direct relationship between sodium intake and blood pressure levels that was evident among subjects both with and without hypertension (4). A recent Cochrane meta-analysis of data from 35 trials (1) found that a 100 mmol reduction in 24-h urinary sodium led to a reduction in systolic/diastolic blood pressure of 5.4/2.8 mm Hg among hypertensive individuals and 2.4/1.0 mm Hg among normotensive individuals.

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How well this blood pressure reduction translates into a beneficial effect on incidence of cardiovascular disease (CVD) and particularly on total mortality remains controversial. A report from the Institute of Medicine in 2013 (5) found that there was a link between excessive sodium intake and risk of CVD, particularly for stroke. However, that report also found that the evidence for the effects of sodium intake below 2,300 mg/24 h was inconsistent and inconclusive. Few studies have available data in this range of sodium, and several that did report outcomes associated with these levels suffered from limitations due to reverse causation, possible confounding, and measurement error (6).

Since that report, additional observational studies (7,8) and a meta-analysis (9) have reported an increase in cardiovascular disease and mortality among those at the lowest levels of sodium intake, suggesting a U-shaped relationship between sodium and health outcomes. In contrast, data from 10 to 15 years of post-trial follow-up in TOHP (Trials of Hypertension Prevention) participants identified a direct linear relationship between average sodium excretion and CVD down to the lowest levels of intake (10). Unlike other reports, this last study used a gold-standard assessment of sodium intake based on the mean of several 24-h sodium excretions accrued over 1.5 to 4 years of exposure ascertainment. In the current paper, we report the relationship between sodium intake and total mortality during more extended follow-up through 2013, for a total of 23 to 26 years. We include results from analyses based on both the exploration of later effects of the randomized sodium reduction interventions in the TOHP trials and the observational relationship between average 24-h sodium excretion in those who were not randomized to an active sodium intervention.

METHODS

TRIALS OF HYPERTENSION PREVENTION. The TOHP Follow-up Study was an observational follow-up of phases I and II of TOHP and has been described previously (11,12). Phase I of TOHP (TOHP I) took place from September 1987 to January 1990 and evaluated the effects on blood pressure over 18 months of 4 supplement and 3 lifestyle interventions, including weight loss and sodium reduction interventions (13). Participants included 2,182 men and women 30 to 54 years of age with high normal blood pressure. A total of 327 participants were randomized to active sodium reduction, and 417 participants were included in their usual care comparison group (Online Figure 1).

In phase II of TOHP (TOHP II), which took place from December 1990 to March 1995, a factorial design was used to assess the effects of sodium reduction and weight loss on blood pressure in 2,382 prehypertensive men and women 30 to 54 years of age who were followed carefully for 3 to 4 years (14). Eligible participants in TOHP II had a body mass index (kg/m^2) representing 110% to 165% of desirable body weight. All 1,191 participants in an active sodium reduction intervention and 1,191 in a sodium control group were included in these analyses (Online Figure 1).

USUAL INTAKE OF SODIUM. During the trial periods, 3 to 7 collections of 24-h urine specimens were scheduled during 18 months of follow-up in TOHP I and 3 to 4 years in TOHP II. Usual intake of sodium or potassium or their ratio was calculated as the mean of available urinary excretion measurements at 5 (lifestyle interventions) or 7 (nutritional supplement interventions) scheduled collections in TOHP I and at 3 to 5 scheduled collections during TOHP II. Mean sodium and potassium excretions, representing usual intake, were computed over all collections. All urinary sodium and potassium measurements were expressed as milligrams per 24 h (15). Additional descriptions of these measurements, including creatinine and coefficients of variation have previously been reported (10).

Those who were randomized to an active sodium reduction regimen were excluded from the observational analyses of usual intake because their 24-h urine collections would provide a biased estimate of usual sodium intake due to short-term fluctuations

during the active intervention. Of 2,182 participants in TOHP I, 327 were excluded and of 2,382 participants in TOHP II, 1,191, were excluded for this reason. An additional 8 participants in TOHP I and 7 in TOHP II were excluded due to missing sodium excretion. Finally, 3 participants in TOHP I and 17 in TOHP II were excluded due to the occurrence of an incident CVD event or death during the period of exposure assessment (Online Figure 2). Thus, 1,844 participants in TOHP I and 1,167 participants in TOHP II were included in this observational analysis. Of these, 37 participated in both TOHP I and II, leaving 2,974 unique individuals in the follow-up. For the 37 individuals participating in both phases, follow-up to the beginning of TOHP II contributed to TOHP I person-time, and that from TOHP II on contributed to TOHP II person-time.

MORTALITY FOLLOW-UP. Previously, we conducted a mail-based follow-up of all TOHP participants for CVD endpoints through early 2005, with a search of the National Death Index through December 2003 (11,12). We conducted additional searches of the National Death Index in 2014 and 2015, accruing death information through December 2013. In the analysis of the randomized sodium intervention, all-cause mortality from the time of randomization through 2013 was included in an intention-to-treat analysis. Observational analyses of usual sodium intake included sodium assessed throughout the trial periods as the exposure and examined mortality following the trial periods through 2013.

STATISTICAL ANALYSIS. Analysis of the randomized sodium reduction intervention was based on the intention-to-treat principle. Comparisons of baseline trial characteristics by randomized intervention have previously been conducted (11,13,14). The hazard ratio (HR) for the effect of the randomized sodium intervention on all-cause mortality was estimated using a Cox regression analysis, stratified by trial phase with common predictor effects. Analyses were adjusted for clinic, age, race, and sex and for the weight loss intervention in TOHP II. Cumulative incidence curves, adjusted for clinic, age, and sex, were estimated and plotted for each trial separately. We also estimated cumulative HRs over time in 5-year periods and before and after 10 years of follow-up.

In observational analyses of usual intake, sodium excretion levels from 3 to 7 collections of 24-h urine specimens obtained during the course of the trial periods were averaged. Participants not in an active sodium intervention who remained alive and CVD-free at the end of the trial periods were included in these analyses. Absolute levels of 24-h urinary sodium excretion were grouped into categories of <2,300, 2,300 to <3,600, 3,600 to <4,800, and 4,800 mg or higher. Baseline characteristics by sex were expressed as percentages or means and were tested for trend over sodium categories using chi-square statistics or regression analysis.

Cox regression analysis was used to estimate the association between mortality and the absolute sodium level in a continuous fashion and after data were grouped into the previously mentioned categories. Models were adjusted for clinic, age, sex, race/ethnicity, and other treatment assignments (model 1) and additionally for education, baseline weight, alcohol use and amount, smoking, exercise, potassium excretion, and family history of CVD (model 2). Interactions among time, sex, age, race, and weight loss intervention in TOHP II were examined. Penalized splines with 4 degrees of freedom were used to examine linearity of effect. All analyses were conducted using SAS version 9.2 software (SAS, Cary, North Carolina), except for the cumulative incidence plots and spline analyses, which were conducted using R software (R Foundation for Statistical Computing, Vienna, Austria), using the "coxph" function.

RESULTS

ANALYSIS BASED ON RANDOMIZED ASSIGNMENT. Detailed comparisons of the randomized groups have been reported (11). Among the 744 participants in TOHP I who were randomized to the sodium reduction intervention or control, the average age was 43 years old, 71% were male, and 20% were African American. Average weight was 191 pounds in men and 160 pounds in women, and average sodium excretion at baseline was 167 mmol/24 h (3,839 mg/24 h) in men and 128 mmol/24 h (2,948 mg/24 h) in women. Among the 2,382 participants in TOHP II, the average age was 44 years old, 66% were male, and 18% were black. Because everyone was eligible for a weight loss intervention in TOHP II, weight was higher, with an average of 218 pounds in men and 184 pounds in women. Average sodium excretion at baseline was 199 mmol/24 h (4,576 mg/24 h) in men and 154 mmol/24 h (3,541 mg/24 h) in women. Baseline characteristics were evenly divided by randomized intervention, except that age was slightly higher in the sodium intervention group in both phases I and II (11).

A total of 77 and 174 deaths occurred in the TOHP I and TOHP II participants, respectively, during the extended follow-up through 2013. Median follow-up time since randomization among survivors was 25.7 years for TOHP I and 22.4 years for TOHP II. Crude

TABLE 1 Total Mortality From Randomization in the TOHP Cohorts Through 2013 by Sodium Intervention Group

	Randomized Intervention			
	Sodium Reduction	Usual Care		
Deaths/total (%)				
TOHP I	33/327 (10.1)	44/417 (10.6)		
TOHP II	82/1,191 (6.9)	92/1,191 (7.7)		
	Hazard Ratio*	95% Confidence Interval	p Value	
Model 1				
TOHP I	0.84	0.54-1.32	0.46	
TOHP II	0.85	0.63-1.14	0.28	
Combined	0.85	0.66-1.09	0.19	
Model 2				
TOHP I	0.86	0.54-1.37	0.52	
TOHP II	0.85	0.63-1.15	0.30	
Combined	0.85	0.66-1.10	0.21	

Values are n/N (%) unless otherwise indicated. *From Cox regression analysis stratified by trial and adjusted for clinic, age, race, sex, and weight loss intervention (Model 1); plus baseline weight and sodium (Model 2).

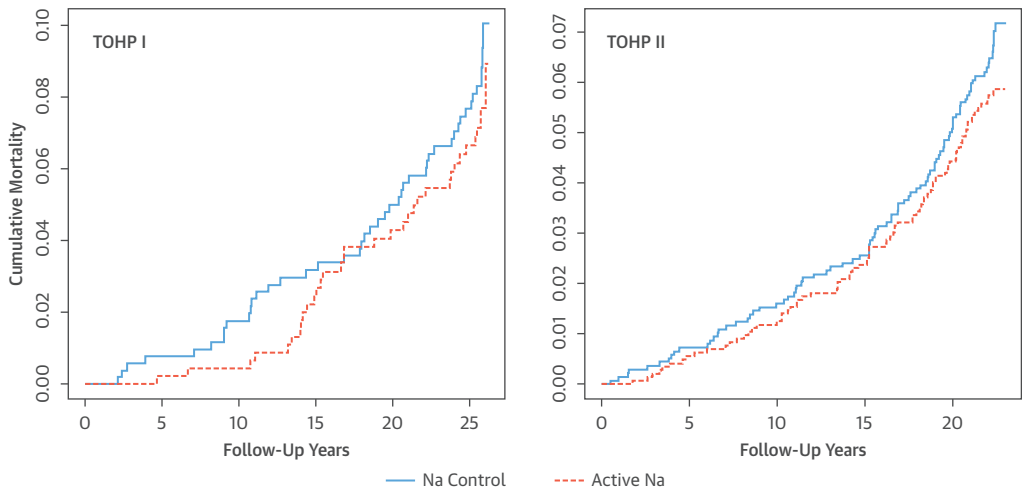
TOHP = Trials of Hypertension Prevention.

rates were slightly lower in the intervention groups (Table 1). In Cox models adjusting for clinic and basic demographic factors, the HR for mortality by randomized intervention group was 0.85 (95% confidence interval [CI]: 0.66 to 1.09; p = 0.19). Cumulative mortality curves showed a consistently lower incidence among those in the active group (Figure 1). Results were virtually identical in phases I and II, as well as after further adjustment for baseline urinary sodium and body weight. When the cumulative HRs were examined over time (Online Figure 3), the differences between randomized groups appeared largest at 10 years (HR: 0.60; 95% CI: 0.34 to 1.06; p = 0.08), followed by attenuation to the null by the end of follow-up after 23 to 26 years. Tests of interaction with time were not significant, however.

OBSERVATIONAL ANALYSES BASED ON URINARY SODIUM EXCRETION. There were 1,844 participants in TOHP I and 1,167 in TOHP II who had not been randomized to a sodium reduction intervention, with 37 participating in both phases. Of these, 68% were men, 16% were African American, and the average age was 43 years old. Average weight at baseline was 194 pounds in men and 164 pounds in women in phase I and 218 pounds in men and 184 pounds in women in TOHP II. During the trial periods, 3 to 7 24-h urine excretions were scheduled, and 1 to 7 excretions were collected from these individuals. The average number of excretions collected was 4.4 in TOHP I and 3.5 in TOHP II. The overall average sodium excretion during the trial period was 164 mmol/24 h (3,766 mg/24 h). The average was 167 mmol/24 h (3,847 mg/24 h) in men and 131 mmol/24 h (3,003 mg/24 h) in women in TOHP I, and 190 mmol/24 h (4,378 mg/24 h) in men and 147 mmol/24 h (3,386 mg/24 h) in women in TOHP II.

Baseline characteristics by average level of urinary sodium and sex during the trials are presented in Table 2. Many of those at a higher level of urinary sodium excretion were participants in phase II of

FIGURE 1 Cumulative Total Mortality by Randomized Sodium Intervention Group



Cumulative total mortality is shown by randomized sodium intervention group in TOHP I **(left)** and TOHP II **(right)**. Each panel shows a lower but nonsignificant reduction in mortality in the active sodium reduction group (see Table 1). Na = sodium; TOHP = Trials of Hypertension Prevention.

TABLE 2 Baseline Characteristics Among Participants With Follow-Up Information in the TOHP Cohorts by Categories of Sodium, Stratified by Sex

	Sodium Excretion (mg/24 h)				
	<2,300	2,300 to <3,600	3,600 to <4,800	≥4,800	p for Trend
Men					
n	131	679	771	478	
% Phase II	16.8	28.3	39.6	52.3	<0.0001
Age, yrs	42.5	42.7	42.9	42.3	0.49
% Black	16.0	9.7	10.4	8.8	0.11
% College	82.4	69.7	66.8	63.8	0.0002
% Current smokers	14.5	9.9	9.9	9.6	0.31
% Past smokers	30.5	35.6	39.0	40.0	0.026
% Alcohol drinkers	62.6	51.8	48.0	41.6	<0.0001
Alcohol drinks/week among drinkers	7.7	7.8	7.2	6.7	0.018
% Exercise, ≥ once/week	77.8	74.5	69.8	67.5	0.0018
Weight, lbs	181.3	192.1	204.9	221.6	<0.0001
SBP, mm Hg	124.9	125.2	125.7	126.4	0.0039
DBP, mm Hg	84.3	84.4	84.8	85.0	<0.0001
Number of excretions	4.1	4.3	4.2	3.9	0.0014
Sodium, mmol/24 h	83.9	133.2	180.7	253.9	-
Potassium, mmol/24 h	50.3	59.7	67.6	76.0	<0.0001
Sodium/potassium excretion ratio	1.95	2.52	2.94	3.65	<0.0001
Women					
n	181	503	208	60	
% Phase II	24.3	42.7	51.9	51.7	<0.0001
Age, yrs	44.3	43.9	43.0	43.2	0.031
% Black	25.4	28.2	26.9	26.7	0.87
% College	47.5	44.9	41.8	40.0	0.18
% Current smokers	16.6	10.5	12.5	13.3	0.45
% Past smokers	27.6	26.6	22.1	25.0	0.27
% Alcohol drinkers	35.4	24.9	22.1	33.3	0.11
Number of alcohol drinks/week among drinkers	5.6	5.5	4.5	3.5	0.025
% Exercise, ≥ once/week	62.6	59.3	60.6	56.7	0.54
Weight, lbs	156.3	172.2	182.2	191.7	<0.0001
SBP, mm Hg	126.2	126.5	126.8	126.4	0.63
DBP, mm Hg	84.2	84.6	85.0	85.0	0.0037
Number of excretions	3.9	4.1	3.7	3.4	0.0034
Sodium, mmol/24 h	80.2	128.5	176.7	249.8	-
Potassium, mmol/24 h	40.7	48.7	56.7	66.8	<0.0001
Sodium/potassium excretion ratio	2.34	2.96	3.42	4.01	<0.0001

Values are mean or %.
DBP = diastolic blood pressure; SBP = systolic blood pressure; TOHP = Trials of Hypertension Prevention.

TOHP. Those with lower sodium levels were more likely to have a college education, drink alcohol, exercise, and had lower weight, especially among men. They also tended to have a lower level of systolic and diastolic blood pressure. No association was found with smoking or race. Measurements of urinary sodium and potassium were highly correlated, with an overall r value of 0.49 and significant trends across levels of sodium in both men and women.

During the post-trial follow-up, 272 deaths occurred, 189 among TOHP I participants and 83 among TOHP II participants (Table 3). Median follow-up time following the trial periods among survivors was 23.9 years for TOHP I and 18.8 years for TOHP II. In Cox regression models stratified by phase and adjusted for demographic variables, the HR increased over categories of urinary sodium excretion, but the trend did not reach statistical significance. Compared to the reference category of 3,600 to <4,800 mg/24 h, the HRs were 0.74 for those with <2,300 mg/24 h, 0.90 for those with 2,300 to <3,600 mg/24 h, and 1.13 for those with ≥4,800 mg/24 h (p for trend = 0.092). After further adjustment for baseline variables, these HRs were 0.75, 0.95, and 1.07 (p trend = 0.30) over <2,300, 2,300 to <3,600, and ≥4,800 mg/24 h, respectively.

TABLE 3 Total Mortality in the TOHP Cohorts Through 2013 by Categories of Urinary Sodium Excretion and Urinary Sodium/Potassium Excretion Ratio Among Those not in a Sodium Reduction Intervention

	Sodium Excretion (mg/24 h)						
	<2,300	2,300 to <3,600	3,600 to <4,800	≥4,800	p Trend	HR per 1,000 mg/24 h	p Value
Deaths/total (%)							
TOHP I	22/246 (8.9)	73/775 (9.4)	63/566 (11.1)	31/257 (12.1)			
TOHP II	1/66 (1.5)	32/407 (7.9)	30/413 (7.3)	20/281 (7.1)			
Hazard ratios: model 1							
HR	0.74	0.90	1.00	1.13	0.092	1.13	0.013
95% CI	0.46-1.19	0.67-1.20	(Reference)	0.80-1.59		1.03-1.24	
Model 2							
HR	0.75	0.95	1.00	1.07	0.30	1.12	0.052
95% CI	0.45-1.26	0.70-1.29	(Reference)	0.75-1.54		1.00-1.26	
	Sodium/Potassium Excretion Ratio						
	<2	2 to <3	3 to <4	≥4	p Trend	HR per unit	p Value
Deaths/total (%)							
TOHP I	37/364 (10.2)	81/812 (10.0)	45/458 (9.8)	26/210 (12.4)			
TOHP II	7/127 (5.5)	32/475 (6.7)	27/368 (7.3)	17/197 (8.6)			
Hazard Ratios: model 1							
HR	0.81	0.86	1.00	1.28	0.033	1.19	0.0024
95% CI	0.55-1.20	0.63-1.16	(Reference)	0.86-1.88		1.06-1.33	
Model 2							
HR	0.90	0.86	1.00	1.20	0.14	1.13	0.035
95% CI	0.60-1.34	0.64-1.17	(Reference)	0.81-1.78		1.01-1.27	

Values are n/N (%) unless otherwise indicated. From Cox proportional hazards regression models stratified by trial phase and adjusted for age, sex, race/ethnicity, clinic, and treatment assignment (Model 1), plus education status, baseline weight, alcohol use, smoking, exercise, potassium excretion (in sodium model), and family history of cardiovascular disease (Model 2).

CI = confidence interval; HR = hazard ratio; TOHP = Trials of Hypertension Prevention.

In a corresponding comparison of the lowest (<2,300 mg/24 h) to the highest (≥4,800 mg/24 h) sodium groups, the HR was 0.70 (95% CI: 0.39 to 1.27).

When average urinary sodium excretion was treated as a continuous term, the HR was 1.12 per 1,000 mg/24 h (p = 0.052). In spline analysis, there was a direct linear relationship between intake and later mortality, with no deviation from linearity detected (**Central Illustration**). No significant interactions were identified by time, sex, age, or race or by weight loss intervention in TOHP II.

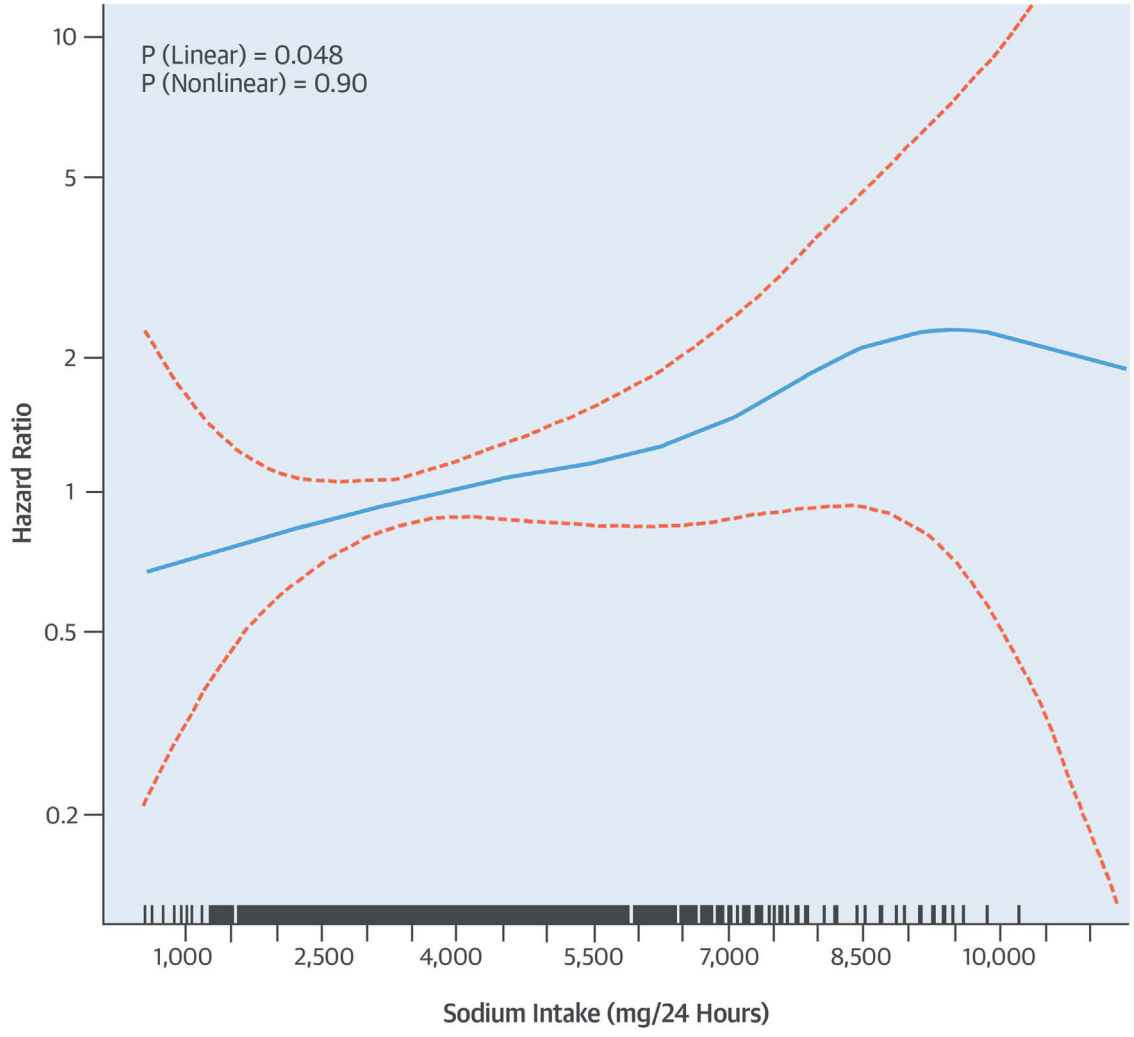
In analyses of the sodium/potassium ratio, there was a significant trend across categories of <2, 2 to <3, 3 to <4, and 4+ with HRs of 0.81, 0.86, 1.00 (reference), and 1.28, respectively (p for trend = 0.033). The trend was slightly attenuated after further adjustment for baseline characteristics to 0.90, 0.86, 1.00, and 1.20, respectively (p for trend = 0.14). In a comparison of the lowest (<2) to the highest (≥4) category, the HR was 0.75 (95% CI: 0.47 to 1.20). There was also a linear relationship to mortality with an HR of 1.13 per unit increase in the ratio (p = 0.035), with no significant deviation from linearity found in spline analysis (Online Figure 4). There were no significant interactions with time, sex, age, or race, or with the weight loss intervention in TOHP II.

DISCUSSION

The health effects of sodium intake remain controversial despite clear effects on blood pressure. Many studies have found conflicting results when examining effects of sodium consumption on incidence of CVD or on CVD or total mortality. Much of the controversy results from unique methodological challenges arising from the study of sodium (6). Unlike macronutrients, which can be assessed with food frequency questionnaires, sodium is typically hidden in processed foods and can vary from brand to brand. Studies using questionnaires to assess sodium intake (8) are thus using an instrument that may be biased due to both random and systematic errors. In addition, while 24-h diet recalls or food records can assess intake at the population or group level, these are inadequate to assess individual consumption because of large day-to-day variation in diet (16).

Many studies that have examined the health effects of dietary sodium are based on urinary sodium excretion data. In these studies, quality of the exposure assessment has varied substantially. Overnight or spot urine samples may not adequately reflect intake compared to "gold-standard" 24-h urine specimens (17,18). Several studies that have found a

CENTRAL ILLUSTRATION **Sodium and All-Cause Mortality Over 20 Years**



Cook, N.R. et al. J Am Coll Cardiol. 2016;68(15):1609–17.

Spline plot of average sodium intake based on multiple 24-h excretions and total mortality in observational analysis of usual intake in the TOHP cohorts. HRs are shown for total mortality over >20 years as a function of usual sodium intake averaged over 3 to 7 urine collections over 1 to 3 years at baseline. Mortality is lowest among those with usual sodium intake <2,300 mg/24 h and highest among those with levels >6,000 mg/24 h. There is a significant direct linear effect of sodium on mortality ($p = 0.048$) with no evidence of nonlinearity ($p = 0.90$) in spline analysis.

U- or J-shaped relationship between sodium intake and CVD or mortality have used overnight or urinary spot samples to estimate dietary sodium intake (7,19,20), but these estimates could be affected by error in estimation of dietary sodium. Even a single 24-h urine specimen may not be sufficient to accurately estimate usual sodium consumption. In a simulated space flight, urinary sodium excretion demonstrated considerable variability despite a constant sodium intake (21,22). Researchers estimated that 3 24-h collections would improve accuracy to 75% compared to sodium ingestion and that 7 would be needed to improve accuracy to 92% (23). The TOHP study reported here used up to 7 excretion measurements and used the most accurate sodium exposure assessment in relationship to outcomes to date.

Another issue that may lead to bias in effect estimates is the possibility of reverse causation. Some studies include participants with prior cardiovascular (7,19) or other diseases, including diabetes (24,25). These individuals may have been advised to limit their sodium intake or have reduced caloric intake

and consequently have reduced sodium intake related to their underlying illness, leading to apparent increased risk among those with low levels. The same is true for those with hypertension (26), due to the well-known relationship between sodium and blood pressure. Participants in the TOHP trials did not previously have hypertension, diabetes, or CVD, and these results should not suffer from this problem of reverse causation.

STUDY LIMITATIONS. First, in the randomized comparison while TOHP participants were randomized to an active sodium intervention or usual care, it is not clear how well they maintained the intervention over time, particularly over more than 20 years. In fact, there was some indication of a difference between randomized groups through 10 years that was not maintained with longer follow-up. On our previous follow-up for incident CVD conducted in 2004 to 2005 (11), those in the sodium intervention arm reported a stronger preference for low-sodium foods at 14 to 17 years post-randomization. Whether this difference was maintained over an additional 9 years, however, is unknown.

Second, in our observational analysis while we have accurate measurements of sodium intake during the trial periods, we have no later measurements of sodium intake during the course of follow-up. It is likely that there were changes in usual diet over the long course of follow-up, a limitation that is shared with most observational analyses of excretion data and long-term outcomes. We did not, however, find any significant interaction with time.

Finally, it is possible that some of the effect of our estimate of usual sodium intake may be related to other dietary factors, such as more fruit and vegetable intake and less consumption of saturated fat. Although some dietary information was available in TOHP I, this was collected in only a small subset in TOHP II. We were thus unable to control for such factors in our analyses with sufficient power. All of our analyses, however, controlled for the weight loss intervention in TOHP II as well as for baseline weight, which should be correlated with energy intake. Potassium excretion may be another marker for a more healthy dietary pattern and was included in our adjusted models.

CONCLUSIONS

In contrast to some other studies, we found a direct linear relationship of an accurate measure of usual sodium intake to total mortality over a period of 23 to 26 years, with higher risk at high sodium intake and no evidence of a U or J shape, although as in other studies, power is limited to estimate effects at the tails of the sodium distribution. The relationship was slightly stronger for the sodium/potassium ratio, 2 electrolytes that are suspected of playing joint roles in the pathogenesis of hypertension (27). Our analysis of the randomized sodium interventions was also consistent with an effect on mortality, with an estimated 15% reduced risk, albeit nonsignificant, among those randomly assigned to the active sodium reduction intervention versus those in usual care.

Average levels of sodium intake in the United States remain too high (28) and even appear to be increasing (29). In 2010, the Institute of Medicine recommended a gradual reduction in sodium levels (30), which would be more palatable to consumers. Such reductions appear feasible (31) and would serve to reduce the population level of blood pressure and incidence of hypertension and help prevent subsequent morbidity and mortality.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Studies that used accurate measurements have found lower sodium intake beneficial.

TRANSLATIONAL OUTLOOK: New strategies are needed to reduce the amount of sodium in the food supply and to educate people about the importance of dietary sodium restriction.

REFERENCES

1. He FJ, Li J, MacGregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. BMJ 2013;346:f1325.

2. Aburto N, Ziolkovska N, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. BMJ 2013;346:f1326.

3. Whelton PK, Appel LJ, Espeland MA, et al. Sodium reduction and weight loss in the treatment of hypertension in older persons: a randomized controlled trial of nonpharmacologic interventions in the elderly (TONE). TONE Collaborative Research Group. JAMA 1998;279:839–46.

4. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. N Engl J Med 2001;344:3–10.

5. Institute of Medicine. Sodium intake in populations: assessment of evidence. Washington, DC: the National Academies Press; 2013.

6. 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.

7. 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.

8. Kalogeropoulos AP, Georgiopoulou VV, Murphy RA, et al. Dietary sodium content, mortality, and risk for cardiovascular events in older adults: the Health, Aging, and Body Composition (Health ABC) Study. JAMA Intern Med 2015;175:410–9.

9. Graudal N, Jurgens 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.

10. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. Circulation 2014;129:981–9.

11. Cook NR, Cutler JA, Obarzanek E, et al. The long-term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the Trials of Hypertension Prevention. BMJ 2007;334:885–8.

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 (TOHP) follow-up study. Arch Intern Med 2009;169:32–40.

13. 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.

14. 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. The Trials of Hypertension Prevention Collaborative Research Group. Arch Intern Med 1997;157:657–67.

15. Brown IJ, Tzoulaki I, Candeias V, Elliott P. Salt intakes around the world: implications for public health. Int J Epidemiol 2009;38:791–813.

16. Caggiula AW, Wing RR, Nowalk MP, Milas NC, Lee S, Langford H. The measurement of sodium and potassium intake. Am J Clin Nutr 1985;42: 391–8.

17. Ji C, Sykes L, Paul C, et al. Systematic review of studies comparing 24-hour and spot urine collections for estimating population salt intake. Rev Pan Salud Publica 2012;32:307–15.

18. Ji C, Miller MA, Venezia A, Strazzullo P, Cappuccio FP. Comparisons of spot vs 24-h urine samples for estimating population salt intake: validation study in two independent samples of adults in Britain and Italy. Nutrition, metabolism, and cardiovascular diseases: Nutri Metab Cardiovasc Dis 2014;24:140–7.

19. O'Donnell MJ, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. JAMA 2011;306: 2229–38.

20. Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. Eur J Heart Fail 2014;16:394–402.

21. Rakova N, Juttner K, Dahlmann A, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. Cell Metab 2013;17:125–31.

22. Titze J, Dahlmann A, Lerchl K, et al. Spooky sodium balance. Kidney Int 2014;85:759–67.

23. Lerchl K, Rakova N, Dahlmann A, et al. Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. Hypertension 2015;66:850–7.

24. Ekinci EI, Clarke S, Thomas MC, et al. Dietary salt intake and mortality in patients with type 2 diabetes. Diabetes Care 2011;34:703–9.

25. Thomas MC, Moran J, Forsblom C, et al. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. Diabetes Care 2011;34:861–6.

26. Stolarz-Skrzypek K, Kuznetsova T, Thijs L, et al. Fatal and nonfatal outcomes, incidence of hypertension, and blood pressure changes in relation to urinary sodium excretion. JAMA 2011; 305:1777–85.

27. Adrogue HJ, Madias NE. Sodium and potassium in the pathogenesis of hypertension. N Engl J Med 2007;356:1966–78.

28. Cogswell ME, Zhang Z, Carriquiry AL, et al. Sodium and potassium intakes among US adults: NHANES 2003–2008. Am J Clin Nutr 2012;96: 647–57.

29. Pfeiffer CM, Hughes JP, Cogswell ME, et al. Urine sodium excretion increased slightly among U.S. adults between 1988 and 2010. J Nutr 2014; 144:698–705.

30. Institute of Medicine. Strategies to reduce sodium intake in the United States. Washington, DC: The National Academies Press; 2010.

31. Levings JL, Cogswell ME, Gunn JP. Are reductions in population sodium intake achievable? Nutrients 2014;6:4354–61.

KEY WORDS diet, mortality, nutrition, potassium, sodium

APPENDIX For supplemental figures, please see the online version of this article.