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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)

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

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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