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## Original Contribution

# Associations of Biomarker-Calibrated Sodium and Potassium Intakes With Cardiovascular Disease Risk Among Postmenopausal Women

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Studies of the associations of sodium and potassium intakes with cardiovascular disease incidence often rely on self-reported dietary data. In the present study, self-reported intakes from postmenopausal women at 40 participating US clinical centers are calibrated using 24-hour urinary excretion measures in cohorts from the Women's Health Initiative, with follow-up from 1993 to 2010. The incidence of hypertension was positively related to (calibrated) sodium intake and to the ratio of sodium to potassium. The sodium-to-potassium ratio was associated with cardiovascular disease incidence during an average follow-up period of 12 years. The estimated hazard ratio for a 20% increase in the sodium-to-potassium ratio was 1.13 (95% confidence interval (CI): 1.04, 1.22) for coronary heart disease, 1.20 (95% CI: 1.01, 1.42) for heart failure, and 1.11 (95% CI: 1.04, 1.19) for a composite cardiovascular disease outcome. The association with total stroke was not significant, but it was positive for ischemic stroke and inverse for hemorrhagic stroke. Aside from hemorrhagic stroke, corresponding associations of cardiovascular disease with sodium and potassium jointly were positive for sodium and inverse for potassium, although some were not statistically significant. Specifically, for coronary heart disease, the hazard ratios for 20% increases were 1.11 (95% CI: 0.95, 1.30) for sodium and 0.85 (95% CI: 0.73, 0.99) for potassium; and corresponding values for heart failure were 1.36 (95% CI: 1.02, 1.82) for sodium and 0.90 (95% CI: 0.69, 1.18) for potassium.

cardiovascular disease; energy consumption; hazard ratio; measurement error; odds ratio; potassium; regression calibration; sodium

Abbreviations: BMI, body mass index; CVD, cardiovascular disease; DM-C, usual diet comparison group; FFQ, food frequency questionnaire; NPAAS, Nutrition and Physical Activity Assessment Study; OS, Observational Study; WHI, Women's Health Initiative.

***Editor's note:*** *An invited commentary on this article appears on page 1044, and the authors' response appears on page 1047.*

A high intake of sodium and a high ratio of sodium to potassium have been associated with elevated blood pressure and clinical hypertension in observational studies and randomized controlled trials (1–3), but evidence of associations of these dietary intakes with cardiovascular disease (CVD) incidence and mortality has been inconclusive (4, 5). Despite such uncertainties, excess sodium intake has been projected to contribute to more than 50,000 myocardial infarctions and 30,000 strokes per year in the United States (6).

The 2015 US Dietary Guidelines recommend limiting sodium intake to 2,300 mg/day to help prevent CVD (7). Questions remain about the adequacy of data underlying estimated CVD relationships, and the need for additional research has been emphasized (8). Epidemiologic studies of these associations have typically relied on self-reported dietary intake

data. Earlier reports illustrate substantial biases in self-reported intakes that are related to individual characteristics, including body mass index (BMI, measured as weight (kg)/height (m)$^2$) (9, 10). Sodium intake is particularly difficult to estimate using standard dietary assessment methods because it is ubiquitous in the US food supply, with over 70% derived from packaged and processed foods (7). Accurate assessment of the amounts of hidden sodium in these processed foods, as well as in foods eaten away from home in general, may not be possible using standard self-report methods. Studies that have included timed 24-hour urine collections to provide objective biomarkers of sodium and potassium intake are more reliable (11).

In a meta-analysis of factors associated with blood pressure, Tzoulaki et al. (3) identified the sodium-to-potassium ratio, which was estimated from 24-hour urine measures, as having direct association with systolic blood pressure. The Trials of Hypertension Prevention Collaborative Research Group valuably reported a positive association between the 24-hour urinary sodium-to-potassium excretion ratio and total CVD incidence; however, the study was small, with only 193 incident CVD events (12). More recently, in the large international Prospective Urban Rural Epidemiology (PURE) Study (13, 14), investigators used fasting morning spot urine samples to estimate daily sodium and potassium intakes (15). Positive associations with sodium and inverse associations with potassium were observed for both systolic and diastolic blood pressure (13), but associations with a composite outcome of death or major cardiovascular event tended to be J-shaped. This was especially the case for sodium. Persons estimated to excrete 3–6 g/day of sodium reportedly had lower cardiovascular risk than did those with either higher or lower sodium excretion (14). This work prompted questions about recommendations to lower sodium intake as an isolated public health recommendation (16) and contributed to interest in the reliability of spot urine for assessment of sodium intake (17–19). The Prospective Urban Rural Epidemiology Study reinforces a review from the Institute of Medicine in which researchers found that available studies are insufficient to conclude whether a low sodium intake is associated with a higher or lower risk of CVD in the general population (8). However, it should be noted that in the US population, the average sodium intake is higher than dietary recommendations, and excess sodium is thought to be an important contributor to cardiovascular morbidity and mortality in the US and worldwide (20).

The authors of the Prospective Urban Rural Epidemiology Study stated that "actual measurement of 24-hour urinary excretion…would be ideal" but that "'such an approach is impractical for large scale efforts…" (13, p. 609). Indeed, 24-hour urine collections have typically not been included in large epidemiologic cohort studies. Studies in the Women's Health Initiative (WHI) included 24-hour urine collection in a moderate sized subcohort to develop "calibration" equations that aimed to correct biases in self-reported dietary data (21–23). Calibration equations that explain an appreciable fraction of 24-hour excretion variation can be applied to self-reported dietary data to develop calibrated intake estimates for individuals throughout study cohorts for use in disease association analyses.

This regression calibration approach (24–26) assumes that biomarker consumption estimates (here, log-transformed 24-hour urinary recovery measures) equal log-transformed usual daily intakes over, for example, a 1-year exposure period plus error that has a mean of zero and is independent of the usual daily intake and of other study subject characteristics—a so-called classical measurement model. This measurement model allows the objective measure to differ appreciably from the usual daily intake of interest but in a manner that is independent and random among study subjects. We evaluated the associations of the calibrated ratio of sodium to potassium and of calibrated sodium and potassium jointly with subsequent hypertension and CVD incidence during the follow-up of WHI cohorts.

## METHODS

### Study cohorts

During 1993–1998, a total of 48,835 women were randomized to the WHI Dietary Modification Trial, of whom 29,294 were in the usual diet comparison group (DM-C), and 93,676 women were enrolled in the prospective WHI Observational Study (OS) (27). The calibration equations mentioned above were applied to data collected from food frequency questionnaires (FFQs) 1 year after randomization in the DM-C and at baseline in the OS. These data, rather than baseline data, were used in the DM-C to avoid assessment biases related to the use of the FFQ for eligibility screening (27). OS enrollees who had a diagnosis of myocardial infarction, stroke, or transient ischemic attack within the 6 months before enrollment were excluded to match eligibility criteria in the Dietary Modification Trial. A total of 25,730 women in the DM-C and 73,662 women in the OS provided the requisite FFQ assessments, were without a history of CVD at baseline, and, in the DM-C, were also without CVD during the first year of cohort follow-up. Of these, 21,267 (83%) women in the DM-C and 65,177 (88%) women in the OS provided all covariate data considered for calibration of energy or the ratios of sodium to potassium, sodium to energy, and potassium to energy or to control for confounding in the hypertension or cardiovascular outcomes analyses considered. These 86,444 women comprised the analytic cohort for the calibrated intake analyses reported here. Analyses using FFQ assessments without calibration are also reported. These analyses did not include missing data exclusions based on variables used for calibration and were based on 22,678 DM-C women and 70,924 OS women (93,602 total).

All WHI women were postmenopausal and in the age range of 50–79 years at the study entry (27). All provided answers to core questionnaires at baseline, which included information on medical history, reproductive history, family history, and personal habits, and fasting blood samples. The WHI FFQ (28) was administered at baseline and year 1 in the Dietary Modification Trial and then approximately every 3 years thereafter during the trial intervention period (ended April 8, 2005); it was administered at baseline and year 3 in the OS.

### Nutrition and Physical Activity Assessment Study

To develop the calibration equation, we used data from the Nutrition and Physical Activity Assessment Study (NPAAS) (22), which enrolled 450 postmenopausal women from the OS

during 2007–2009. NPAAS recruited WHI women at 9 clinical centers and included some overrepresentation of minority women and women who had elevated BMIs. The study protocol required 2 clinic visits separated by 2 weeks and various at-home activities. A 20% subsample repeated the protocol approximately 6 months after their initial participation. NPAAS data, as well as data from an earlier WHI Nutrient Biomarker Study (23), were previously used (21) to develop calibration equations for sodium divided by potassium, sodium divided by energy, potassium divided by energy, and total energy intake using a doubly labeled water biomarker. FFQ nutrient content estimates were derived using the University of Minnesota's Nutrition Data Systems for Research (NDS-R version 2005, Minneapolis, Minnesota).

### Ascertainment of outcomes

Descriptions of clinical measurements in the WHI have been reported (27). Blood pressure was measured in a standardized fashion by trained clinical center staff at baseline and annually during the intervention phase of the Dietary Modification Trial and at baseline and year 3 in the OS. Ascertainment of clinical outcomes and adjudication methods in WHI have been described previously (29). Initial self-reports of disease events and hospitalizations were obtained semi-annually in the Dietary Modification Trial during its intervention phase and annually thereafter and were obtained annually in the OS. Potential outcomes were adjudicated by trained physicians. At the end of the WHI intervention period (April 8, 2005), participating women had the opportunity to enroll in additional follow-up through September 30, 2010, and more than 80% of women elected to do so. The average follow-up period was 12.0 years in the cohort considered here. The CVD categories that we considered were coronary heart disease, as well as nonfatal myocardial infarction and coronary death separately; coronary artery bypass graft plus percutaneous coronary intervention; total stroke, as well as ischemic stroke and hemorrhagic stroke separately; total CVD (coronary heart disease plus stroke); total CVD plus coronary artery bypass graft and percutaneous coronary intervention; and heart failure.

### Statistical methods

Hazard ratios for CVD risk in relation to nutrient consumption, adjusted for potential confounding factors, were estimated using Cox regression (30). Follow-up times began with the year-1 visit for women in the DM-C and at enrollment for women in the OS and continued until the earliest of the specific CVD outcomes under analysis, death, loss to follow-up, or September 30, 2010, whichever occurred first. Baseline hazard ratios in the Cox model were stratified by age (year-1 age in the DM-C and baseline age in the OS) in 5-year categories. For women in the DM-C, the hazard ratios were also stratified on their participation in the hormone therapy trial (27) (active estrogen; estrogen placebo; active estrogen plus progestin; estrogen plus progestin placebo; or not randomized). Analyses in which the DM-C and OS cohorts were combined were also stratified by cohort. To control for confounding, the associations of nutrient consumption on risk of each cardiovascular outcome were adjusted for a standard set of baseline CVD risk factors, including age, race/ethnicity, educational level, family history of premature CVD, cigarette smoking status, treated diabetes, statin use, aspirin use, prior postmenopausal hormone therapy use, and an estimate of recreational physical activity. Women for whom there were missing data on 1 or more confounding factors were excluded from analysis. We also conducted additional CVD analyses in which we added baseline prehypertension and hypertension indicators and an indicator for hypertension treatment to the set of "control" variables.

The previously presented calibration equations (21) were updated by considering potential confounding variables in the outcome model for possible inclusion. Conceptually, outcome analyses using calibrated (or uncalibrated) sodium and potassium intakes examine the association of these estimated intakes with the outcome in question at specified values of the confounding control variables, so that their inclusion in calibration equations is solely based on their ability to improve intake estimation at specified values of these other variables. Such variables were included in calibration equations if they contributed to explaining biomarker-assessed usual intake variation at $P < 0.10$. Calibrated estimates for absolute sodium and potassium intakes were obtained by multiplying those for the nutrient divided by energy by the corresponding calibrated total energy estimate. Using these procedures, calibrated estimates of the intake of sodium divided by potassium and for sodium and potassium individually were calculated for DM-C and OS participants. Log-hazard ratios were modeled as a linear function of log-transformed nutritional variables so that the hazard ratio for a fractional increase in intake was then independent of intake level. To facilitate interpretation, we present hazard ratios for a 20% increase in intake.

For uncalibrated dietary intakes, standard errors for regression coefficients were estimated using standard Cox model (30) procedures. For calibrated nutrient consumption, uncertainty in the calibration coefficient estimates needed to be acknowledged. A resampling procedure with 1,000 bootstrap samples was used to obtain standard error estimates. The bootstrap procedure involved resampling of the entire estimation procedure, including calibration equation development with sample selection stratified on cohort and membership in the NPAAS, as well as resampling in its 20% reliability sample subset.

An elevated BMI is associated with greater underestimation of sodium divided by potassium (21). The inclusion of BMI among the variables used to control for potential confounding in the disease risk model would likely overcorrect the CVD associations. Biases in self-reported energy and in related specific nutrient intakes, including sodium and potassium, are strongly associated with BMI. The FFQ alone provides only a weak signal for these dietary variables, and BMI is a useful component of dietary exposure assessment. As a result, CVD associations with intake estimates are mostly weak or nonexistent at specified BMIs. To address this issue, we did not include BMI in the disease risk model for calibrated (or uncalibrated) intake, thereby using BMI for dietary exposure assessment while making the assumption that BMI is not needed to control for residual confounding after allowing for the other modeled variables listed above. A similar procedure was used for baseline hypertension. Hypertension variables were allowed to strengthen sodium and potassium intake assessments but were not

considered for confounding control. BMI and hypertension may be important mediators of the associations of sodium and potassium with CVD, and their inclusion in the disease risk model may leave little residual association with disease risk because of overcorrection.

Using logistic regression on log-transformed sodium and potassium intakes and their log-transformed ratio, we carried out analyses of "baseline" (year 1 in the DM-C; enrollment in the OS) sodium and potassium intakes with and without calibration in relation to the incidence of hypertension, which was defined as a systolic blood pressure greater than 140 mm Hg or a diastolic blood pressure greater than 90 mm Hg, during follow-up years 1–4 in the DM-C and from baseline to year 3 in the OS. The potential confounding factors that were used in the CVD incidence analyses were also included in the logistic regression models.

The WHI and NPAAS protocols were approved by the institutional review committees of participating institutions and the Fred Hutchinson Cancer Research Center. All participants provided written informed consent for WHI and NPAAS participation.

## RESULTS

Table 1 shows details of the calibration equation for the (natural) logarithm of the ratio of usual intake of sodium to the usual intake of potassium based on the NPAAS study data, where "usual" refers to an approximate 1-year period. Note that this calibration equation explains an estimated 50.5% of the variation among women (adjusted $R^2$) in the dietary variable, corresponding to a correlation of $(0.505)^{1/2} = 0.71$ between the (log-transformed)

**Table 1.** Calibration Equation[a] From Linear Regression of Biomarker Log(Sodium/Potassium) on Self-Reported Log(Sodium/Potassium) and Other Characteristics, Women's Health Initiative Nutrition and Physical Activity Assessment Study ($n = 372$), 2007–2009[a]

| Characteristic | Estimate | SE | $R^2$ | Adjusted $R^2$ |
|---|---|---|---|---|
| Intercept | 0.239 | 0.084[b] | | |
| Log(sodium/potassium) self-report[c] | 0.489 | 0.069[b] | 14.1 | 26.5 |
| Age, years[c] | −0.003 | 0.004 | 0.8 | 1.5 |
| Body mass index[c,d] | 0.011 | 0.004[b] | 3.2 | 5.9 |
| Race/ethnicity (vs. white) | | | 3.7 | 6.9 |
| Black | 0.256 | 0.063[b] | | |
| Hispanic | 0.110 | 0.066 | | |
| Other minority | −0.041 | 0.092 | | |
| Dietary supplement use[e] | −0.071 | 0.042 | 0.5 | 0.9 |
| Current smoker[e] | −0.080 | 0.119 | 0.01 | 0.01 |
| Education (vs. <high school diploma/GED diploma) | | | 2.9 | 5.5 |
| High school diploma/GED diploma | −0.061 | 0.074 | | |
| College degree or higher | −0.223 | 0.081[b] | | |
| Family income, $ (vs. <20,000) | | | 0.7 | 1.3 |
| 20,000–34,000 | 0.006 | 0.080 | | |
| 35,000–49,000 | −0.008 | 0.086 | | |
| 50,000–74,000 | 0.120 | 0.088 | | |
| ≥75,000 | 0.017 | 0.086 | | |
| Aspirin use of ≥80 mg/day[e] | 0.162 | 0.057[b] | 1.1 | 2.0 |
| Total | | | 26.9 | 50.5 |

Abbreviations: GED, General Educational Development; $R^2$, percent of response variable variation explained; SE, standard error.

[a] Calibration equations were developed based on primary and reliability samples together. $R^2$ and adjusted $R^2$ were computed using primary but not reliability samples from the Nutrition and Physical Activity Assessment Study. Adjusted $R^2$ values were formed by dividing corresponding $R^2$ values by the estimated correlation between the paired biomarker assessments in the Nutrition and Physical Activity Assessment Study reliability subsample ($n = 90$). Sodium and potassium were measured in units of milligrams per day. $n$ is the number of participants with available data for all modeled variables.

[b] Significance level $P < 0.05$.

[c] To interpret the intercept, note that log(sodium/potassium) is centered at −0.044, age is centered at 70.9 years, and BMI is centered at 28.2.

[d] Weight (kg)/height $(m)^2$.

[e] No = 0, yes = 1.

calibrated and targeted intakes. Web Table 1 (available at https://academic.oup.com/aje) shows characteristics of the combined DM-C and OS cohorts according to quartile of the calibrated sodium-to-potassium ratio.

Web Tables 2–4 provide corresponding augmented calibration equations for sodium-to-energy ratio, potassium-to-energy ratio, and (total) energy intake, respectively. Calibrated estimates of absolute sodium and potassium intakes were obtained by multiplying calibrated estimates of the nutrient-to-energy ratio by calibrated energy. Web Tables 5 and 6 show combined cohort characteristics in relation to quartile of calibrated sodium intake and calibrated potassium intake, respectively.

Table 2 shows geometric means with 2.5th and 97.5th percentiles for the 24-hour urine biomarkers, uncalibrated (FFQ) intake, and calibrated intake for each of sodium-to-potassium ratio, sodium, and potassium, overall and broken out by BMI category, in the NPAAS subcohort. Systematic bias related to BMI was evident without calibration but was largely removed by the respective calibration procedures. The width of the 2.5th and 97.5th percentile intervals for the calibrated intake estimates was considerably less than that for the excretion biomarker for each of the sodium-to-potassium ratio, sodium, and potassium, reflecting adjustment for the noise component of the biomarker as an estimate of usual intake. The calibrated estimates (adjusted $R^2$) explain 38.0% of the usual intake variation among NPAAS women for log-sodium and 43.7% of the usual intake variation for log-potassium. The sample correlation between log-sodium and log-potassium was 0.80 without calibration and −0.19 with calibration. Twenty-percent increases, above the respective biomarker geometric mean, translate to increases of 0.34 in the sodium-to-potassium ratio, 521.6 mg/day in sodium intake, and 427.7 mg/day in potassium intake.

Table 3 shows the numbers of participants in the cohorts defined above who developed CVD after year 1 in the DM-C and after enrollment in the OS. Table 4 shows results of analyses relating the calibrated sodium-to-potassium ratio, as well as sodium and potassium jointly, to the incidence of hypertension over a 3-year follow-up period. The calibrated sodium-to-potassium ratio is positively associated with hypertension development. This was even more strongly true for sodium, whereas the associations for potassium were inverse but not statistically significant. Without biomarker calibration, the associations of these nutritional variables with hypertension were each much closer to null. These findings were nearly identical in the DM-C and OS cohorts separately (data not shown).

Table 5 gives hazard ratios and 95% confidence intervals for various CVD outcomes for a 20% increase in the calibrated sodium-to-potassium ratio and 20% increases in calibrated sodium and potassium individually in joint analysis. The calibrated ratio was positively associated with coronary heart disease and with nonfatal MI and coronary death individually, coronary artery bypass graft and percutaneous coronary intervention, heart failure, total CVD, and total CVD including coronary artery bypass graft and percutaneous coronary intervention. Total stroke was not significantly related to this ratio, although there was evidence of a positive association with ischemic stroke and an inverse association with hemorrhagic stroke. When absolute sodium and potassium intakes were analyzed together (Table 5), the hazard ratios for calibrated sodium had a pattern similar to that for the sodium-to-potassium ratio, whereas the hazard ratios for calibrated potassium mostly

**Table 2.** Geometric Means for the 24-Hour Urinary Excretion Biomarker, Uncalibrated Food Frequency Questionnaire–Based Self-Report, and Biomarker-Calibrated Self-Report, Women's Health Initiative Nutrition and Physical Activity Assessment Study, 2007–2009

| Nutritional Variable and Body Mass Index[a] Category | Biomarker | | | Uncalibrated | | | Calibrated | | |
|---|---|---|---|---|---|---|---|---|---|
| | No.[b] | Geometric Mean | 2.5th, 97.5th Percentile[c] | No.[b] | Geometric Mean | 2.5th, 97.5th Percentile[c] | No.[b] | Geometric Mean | 2.5th, 97.5th Percentile[c] |
| Sodium-to-potassium ratio | 398 | 1.21 | 0.45, 3.37 | 450 | 0.98 | 0.54, 1.69 | 420 | 1.24 | 0.79, 2.24 |
| <25.0 | 139 | 0.98 | 0.38, 2.36 | 156 | 0.93 | 0.60, 1.62 | 145 | 1.04 | 0.76, 1.55 |
| 25.0–29.9 | 105 | 1.28 | 0.53, 2.83 | 121 | 1.00 | 0.50, 1.60 | 113 | 1.25 | 0.82, 2.04 |
| ≥30.0 | 154 | 1.42 | 0.56, 4.03 | 173 | 1.02 | 0.54, 1.73 | 162 | 1.45 | 0.98, 2.57 |
| Total sodium, mg/day | 398 | 2,607.9 | 1,137.1, 5,324.4 | 450 | 2,383.1 | 888.4, 5,046.9 | 413 | 2,566.6 | 1,898.3, 3,544.9 |
| <25.0 | 139 | 2,324.5 | 1,064.7, 4,921.6 | 156 | 2,349.2 | 1,006.6, 4,945.7 | 145 | 2,261.1 | 1,781.3, 2,878.1 |
| 25.0–29.9 | 105 | 2,513.0 | 1,180.8, 4,828.3 | 121 | 2,345.1 | 728.8, 5,057.5 | 109 | 2,562.6 | 2,003.5, 3,200.1 |
| ≥30.0 | 154 | 2,967.4 | 1,244.9, 6,750.7 | 173 | 2,441.3 | 1,079.1, 5,049.4 | 159 | 2,884.2 | 2,205.3, 3,933.5 |
| Total potassium, mg/day | 403 | 2,138.3 | 974.3, 4,586.9 | 449 | 2,432.6 | 988.9, 4,983.6 | 413 | 2,076.6 | 1,452.0, 2,688.9 |
| <25.0 | 140 | 2,364.7 | 1,161.3, 4,819.5 | 156 | 2,531.6 | 1,250.0, 4,625.8 | 145 | 2,180.2 | 1,632.4, 2,732.5 |
| 25.0–29.9 | 109 | 1,948.2 | 945.9, 3,937.8 | 121 | 2,338.2 | 764.7, 4,788.9 | 109 | 2,075.2 | 1,477.4, 2,685.1 |
| ≥30.0 | 154 | 2,084.4 | 870.9, 4,497.0 | 172 | 2,412.4 | 1,056.8, 5,197.5 | 159 | 1,987.4 | 1,419.6, 2,678.4 |

Abbreviation: BMI, body mass index.
[a] Weight (kg)/height $(m)^2$.
[b] Number of women without missing data.
[c] Interval from the empirical 2.5 percentile to the 97.5 percentile for the nutritional variable.

**Table 3.** Numbers of Women Who Developed Cardiovascular Disease Events After Year 1 and Baseline in the Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, Respectively, Through September 2012[a]

| Cardiovascular Disease Outcome | Uncalibrated FFQ Analyses | | | Calibrated FFQ Analyses | | |
|---|---|---|---|---|---|---|
| | DM-C ($n$ = 22,678) | OS ($n$ = 70,924) | Total ($n$ = 93,602) | DM-C ($n$ = 21,267) | OS ($n$ = 65,177) | Total ($n$ = 86,444) |
| Total CHD | 924 | 2,759 | 3,683 | 867 | 2,516 | 3,383 |
| Nonfatal MI | 677 | 2,058 | 2,731 | 640 | 1,878 | 2,518 |
| Coronary death | 290 | 965 | 1,255 | 267 | 877 | 1,144 |
| CABG and PCI | 1,093 | 3,075 | 4,168 | 1,035 | 2,814 | 3,849 |
| Total stroke | 780 | 22,880 | 3,068 | 736 | 2,107 | 2,843 |
| Ischemic stroke | 551 | 1,661 | 2,212 | 517 | 1,537 | 2,054 |
| Hemorrhagic stroke | 133 | 377 | 510 | 126 | 343 | 469 |
| Total CVD (CHD and stroke) | 1,617 | 4,774 | 6,391 | 1,519 | 4,378 | 5,897 |
| Total CVD with CABG and PCI | 2,223 | 6,519 | 8,742 | 2,094 | 5,977 | 8,071 |
| Heart failure | 427 | 1,348 | 1,775 | 399 | 1,228 | 1,627 |

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CVD, cardiovascular disease; DM-C, Dietary Modification Trial comparison group; FFQ, food frequency questionnaire; MI, myocardial infarction; OS, Observational Study; PCI, percutaneous coronary intervention.

[a] Among those for whom covariate data were available for food frequency questionnaire–based association analyses.

showed an inverse association, with hemorrhagic stroke as an exception. Some of the hazard ratios in these latter analyses did not differ significantly from 1. The analyses shown in Table 5 were repeated with baseline prehypertension and hypertension indicator variables and a hypertension treatment indicator variable in the outcome model. Hazard ratios and 95% confidence intervals tended to be somewhat attenuated toward the null compared with those shown in Table 5, although many remained significant (data not shown).

Web Table 7 shows hazard ratios corresponding to Table 5 without intake calibration. Compared with those in Table 5, most hazard ratios were substantially attenuated toward the null, although confidence intervals were shorter because of both this attenuation and statistical variation in calibrated intake hazard ratios due to calibration equation estimation.

Web Table 8 shows hazard ratios for a 20% increase in calibrated sodium divided by potassium, separately for the DM-C and OS. There was quite close agreement between the 2 cohorts.

We also examined whether there was evidence for departure from linear relationships between (log-transformed) odds ratios or hazard ratios and (log-transformed) intakes by including a quadratic term in calibrated intake in the respective outcome models. These analyses did not suggest important departures from linearity and did not suggest increased risks of hypertension or CVD (except hemorrhagic stroke) associated with low sodium or low sodium-to-potassium ratio.

**Table 4.** Odds Ratios for Hypertension[a] Incidence Over a 3-Year Follow-up in Relation to a 20% Increase in the Ratio of Sodium to Potassium Intake and 20% Increases in Sodium and Potassium Jointly, Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, 1994–2001

| Biomarker | Calibrated Intake | | | | Uncalibrated Intake | | | |
|---|---|---|---|---|---|---|---|---|
| | No of Participants | No. of Cases[b] | OR | 95% CI | No of Participants | No. of Cases[b] | OR | 95% CI |
| Sodium-to-potassium ratio | 48,213 | 9,352 | 1.15 | 1.04, 1.26 | 51,925 | 10,073 | 1.03 | 1.01, 1.04 |
| Sodium | 48,034 | 8,953 | 1.29 | 1.11, 1.51 | 51,856 | 10,053 | 1.03 | 1.02, 1.05 |
| Potassium | 48,034 | 8,953 | 0.91 | 0.77, 1.07 | 51,856 | 10,063 | 0.98 | 0.97, 1.00 |

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Hypertension was defined as a systolic blood pressure >140 mm Hg, a diastolic blood pressure >90 mm Hg, or use of hypertension medication.

[b] The numbers of incident cases varied depending on missing dietary data and missing data needed for nutrient calibration.

**Table 5.** Hazard Ratios for a 20% Increase in the Calibrated Ratio of Sodium to Potassium Intake and for 20% Increases in Calibrated Sodium and Potassium Individually, in the Combined Women's Health Initiative Dietary Modification Trial Comparison Group and Observational Study, From Baseline[a] (1994–1998) Through September 30, 2010 ($n$ = 86,444)

| Cardiovascular Disease Outcome | Calibrated Sodium-to-Potassium Ratio | | Calibrated Sodium | | Calibrated Potassium | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| CHD | 1.13 | 1.04, 1.22 | 1.11 | 0.95, 1.30 | 0.85 | 0.73, 0.99 |
| Nonfatal MI | 1.13 | 1.04, 1.22 | 1.09 | 0.93, 1.26 | 0.83 | 0.72, 0.96 |
| Coronary death | 1.16 | 1.02, 1.30 | 1.14 | 0.92, 1.42 | 0.84 | 0.74, 0.98 |
| CABG and PCI | 1.16 | 1.07, 1.25 | 1.17 | 1.02, 1.34 | 0.85 | 0.75, 0.98 |
| Stroke | 1.05 | 0.98, 1.13 | 0.98 | 0.85, 1.13 | 0.88 | 0.78, 1.01 |
| Ischemic stroke | 1.09 | 1.01, 1.18 | 1.02 | 0.87, 1.19 | 0.84 | 0.73, 0.98 |
| Hemorrhagic stroke | 0.88 | 0.78, 0.98 | 0.81 | 0.67, 0.98 | 1.13 | 0.95, 1.35 |
| Total CVD | 1.10 | 1.03, 1.18 | 1.06 | 0.92, 1.23 | 0.86 | 0.75, 0.98 |
| Total CVD with CABG and PCI | 1.11 | 1.04, 1.19 | 1.09 | 0.95, 1.25 | 0.87 | 0.76, 0.99 |
| Heart failure | 1.20 | 1.01, 1.42 | 1.36 | 1.02, 1.82 | 0.90 | 0.69, 1.18 |

Abbreviations: CABG, coronary artery bypass graft; CHD, coronary heart disease; CI, confidence interval; CVD, cardiovascular disease; HR, hazard ratio; MI, myocardial infarction; PCI, percutaneous coronary intervention.

[a] Baseline was defined as 1 year after enrollment in the Dietary Modification Trial Comparison Group and at enrollment in the Observational Study.

## DISCUSSION

These analyses are based on WHI FFQ dietary intake data that were corrected for measurement error by applying calibration equations developed using 24-hour urine excretion biomarkers for sodium and potassium and a doubly labeled water biomarker for total energy in a subcohort of participants. Calibrated estimates of the sodium-to-potassium ratio explained a substantial fraction of the biomarker variation in this subcohort (Table 1), and they related positively to hypertension incidence as well as to several CVD categories. Corresponding stroke results were null overall but positive for ischemic stroke and inverse for hemorrhagic stroke. CVD associations with absolute sodium and potassium intake jointly were mostly positive for sodium and inverse for potassium.

In these analyses, we controlled for a standard set of hypertension and CVD risk factors, which supported a causal interpretation. Baseline BMI and hypertension variables were used for intake assessment but were not considered as potential confounders. These variables are likely mediators of the associations of sodium and potassium with CVD outcomes, and their inclusion in outcome models would likely lead to overcontrol. We have not examined whether the associations identified would be affected by controlling for other aspects of diet. In a previous WHI data analysis, investigators reported stroke associations with uncalibrated potassium that were inverse for ischemic stroke and for total stroke (31).

Questions about the merits of sodium reduction or potassium increase (or both) continue to be debated (7, 8). Results from the analyses in Table 5 suggest that moderate changes in sodium and potassium intakes, such as a 20% decrease in sodium and a 20% increase in potassium, correspond to approximately a 20% decrease in CVD incidence. The contrary associations for hemorrhagic stroke are a surprise for both sodium and potassium. It will be useful for other cohorts to examine whether these hemorrhagic stroke associations are chance findings.

Twenty-four–hour urine excretion has been evaluated as a consumption biomarker for sodium and potassium. Within-person correlations for paired 24-hour urine assessments separated by several months were 0.50 for potassium but only 0.30 for sodium in the Trial of Nonpharmacologic Interventions in Elderly (TONE) (9). In a controlled human feeding study involving randomly fluctuating sodium consumption, Luft et al. (32) found a correlation of 0.55 between 24-hour urine sodium and corresponding actual dietary intake, with improved agreement when using 24-hour urine collections over several days. An experiment involving a constant sodium intake over several months, revealed some rhythmicity among consecutive 24-hour sodium excretions, possibly because of tissue sodium retention variations over time (33). It seems plausible, however, that any such variations can be included in the error component of the classical measurement model used here. Note that 24-hour urinary potassium excretion has been criticized as an intake marker based on possible racial influences (34, 35).

The precision of present analyses are limited by a single 24-hour urine collection in a moderate-sized cohort subset. We relied on the available dietary self-report data having a sufficient "signal" for the targeted dietary variables to support useful calibrated intake estimates. Additional work to strengthen intake assessment for these and other nutritional variables deserves public health research priority.

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