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Contrasting associations of urinary sodium excretion with cardiovascular events in those with and without hypertension

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Panel: Research in context

Systematic review

We searched PubMed for relevant research published between Jan 1, 1960, and April 1, 2016, using the term “sodium” or “salt” AND “mortality” OR “cardiovascular” OR “myocardial” OR “stroke” OR “heart failure” OR “sudden cardiac death”. We screened papers by title and abstract to identify full-text reports that were relevant to the study aims. We also screened citation lists from these full-text reports to identify other relevant research. We considered papers if they contained an evaluation of the relation between sodium intake and at least one of the outcomes of interest. The papers cited in this report were selected to be representative of the existing evidence base, are not an exhaustive list of relevant research.

Added Value of the Study

Several prospective cohort studies have recently reported that the association between sodium consumption and cardiovascular disease (CVD) or mortality is U-shaped, with increased risk at both high and low sodium intake. Subsequently, the PURE study found similar results in >102,000 people around the world. Whether these associations vary between those with and without hypertension is not known. In this analysis of three large international prospective studies with over 10,000 events and based on an analysis of 133,118 people (63,559 with hypertension and 69,559 without hypertension) selected from 49 countries in 6 continents, we assess whether the association between sodium intake and CVD events and all-cause mortality is modified by hypertension status. To our knowledge, this is the largest study of any kind relating sodium intake to CVD events and mortality.

Interpretation

The results showed that CVD and death are increased with low sodium intake (compared to moderate intake) irrespective of hypertension status, whereas there is a higher risk of CVD and death only in people with hypertension consuming >7g of sodium per day (representing only 11% of the population studied). These data indicate that lowering sodium is best targeted at those with hypertension who also consume high sodium.

ABSTRACT

Background: Several studies reported a U-shaped association between urinary sodium excretion and cardiovascular disease (CVD) events and mortality. Whether these associations vary between those with and without hypertension is not known.

Methods: We studied 133,118 individuals (63,559 with hypertension and 69,559 without hypertension), median age of 55 years, from 49 countries in three large cohort studies and estimated 24-hour sodium excretion. We related this to blood pressure (BP) and the composite outcome of death and major CVD events over a median of 4.2 years.

Findings: Increased sodium intake was associated with greater increases in systolic BP in hypertensives (2.08 mmHg change per g sodium increase) compared to non-hypertensives (1.22 mmHg change per g; P<0.0001 for interaction). In those with hypertension (6835 events), compared with sodium excretion of 4-5 g/day (reference: 24.7% of the population), sodium excretion of >7g/day (7060 [11.1%] of population; hazard ratio [HR] 1.23; 95%CI 1.11-1.37; p<0.0001) and <3 g/day (7006 [11.0%] of population: HR 1.34; 95%CI 1.23-1.47; p<0.0001) were both associated with increased risk. In those without hypertension (3021 events), compared with 4-5 g/day (18,508 [26.6%] of the population), higher sodium excretion was not associated with risk of the primary composite outcome (>7g/day in 6271 [9.0%] of the population; HR 0.90; 95%CI 0.76-1.08; p=0.2547), whereas an excretion of <3g/day was associated with a significantly increased risk (7547 [10.8%] of the population; HR 1.26; 95%CI 1.10-1.45; p=0.0009).

Interpretation: CVD and death are increased with low sodium intake (compared to moderate intake) irrespective of hypertension status, whereas there is a higher risk of CVD and death only

in people with hypertension consuming >7g of sodium per day (representing only 11% of the population studied). These data indicate that lowering sodium is best targeted at those with hypertension who also consume high sodium.

Funding: Full funding sources listed at end of paper (see Acknowledgments).

INTRODUCTION

Several prospective cohort studies (1-7) have recently reported that the association between sodium consumption and cardiovascular disease (CVD) or mortality is U-shaped, with increased risk at both high and low sodium intake. This has been reported in studies conducted in different countries, in studies using different methods of estimating sodium intakes, and in different types of populations (ie, people with diabetes, those with vascular disease, and in the general population). A meta-analysis of 23 epidemiologic studies (n=274,683) also reported a U-shaped relationship (8). Subsequently, the PURE study (7) findings were consistent with this observation such that the collective data on 376,628 people involving >15,000 clinical events demonstrating a U shaped association is robust. Given that increasing sodium intake is related to elevated blood pressure (BP), and that this is steeper in those with hypertension compared to those without hypertension(18,23), we hypothesized that there may be differences in the association between sodium intake and CVD outcomes in hypertensives compared to non-hypertensives. In this analysis, we explore whether the association between sodium intake and CVD events and all-cause mortality is modified by hypertension status. We also compare the observed magnitude (and pattern) of association between sodium intake and CVD events with the predicted hazard ratio derived from modelling the association between sodium intake and BP, and assuming that all reductions in BP should translate into CVD reduction, with no other off-target effects (eg, activation of the renin system or increases in blood lipids).

METHODS

Study Design and Participants

Details of the studies' designs and population characteristics have been published before and are described in **Appendix 1 and 2**. In brief, the Prospective Urban Rural Epidemiological Study (PURE Study) (9-13) is an ongoing large-scale epidemiological cohort study that has enrolled 156,424 individuals between 35 and 70 years from the population in 628 communities in 17 low, middle and high-income countries on five continents. The sampling strategy used in PURE ensures representation from urban and rural communities from different geographic areas.(9-13) For the current analysis, we included 101,511 PURE participants who collected morning fasting urine samples suitable for analysis. The EPIDREAM trial was a prospective cohort study of 17,453 individuals, aged 18 to 85 years, who were screened for eligibility to enter the DREAM clinical trial (a randomized, double-blind trial with a 2×2 factorial design that assigned participants at high risk for type 2 diabetes to receive either ramipril [15 mg/day] vs. placebo or rosiglitazone [8 mg/day] vs. placebo).(14) The EPIDREAM cohort included participants who were screened for the study and includes those who entered DREAM and those who were not included into the trial and agreed to a long-term prospective follow-up.(14,15) For the current analysis, to conserve power and at the same time be efficient on resources, we employed a case-cohort design in selecting all individuals who developed a CVD event (n=478) during the follow-up of the EPIDREAM cohort and a control group comprised of a random sample of individuals (n=2372; 5 controls per case) who did not develop a CVD event. ONTARGET was a randomized, double-blind, parallel trial comparing the effects of ramipril (10 mg/day), telmisartan (80 mg/day), and combination therapy in 25,620 patients, aged ≥55 years, with vascular disease or high-risk diabetes patients. TRANSCEND was a randomized controlled trial

comparing telmisartan (80 mg/day) to placebo in 5926 participants intolerant to angiotensin converting enzyme (ACE) inhibitors.(16,17) All studies were coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Canada, and the studies were approved by the ethics committees at participating centers and at the Hamilton Health Sciences, Hamilton, Ontario, Canada. All participants provided written informed consent.

Procedures

A morning fasting midstream urine sample was collected from each participant and shipped in ambient packaging (Saf-T-Pak) for analysis at the Clinical Research and Clinical Trials Laboratory at Hamilton General Hospital in Hamilton, Ontario, Canada (the central laboratory), or the regional laboratory in Beijing; Bangalore, India; or Kocaeli, Turkey, for analyses with the use of validated and standardized methods. A description of the methods used for performing urinary analyses has been described previously (7,18).

We used the Kawasaki formula (19) to estimate 24-hour urinary excretion of sodium and potassium from a fasting morning specimen and used these estimates as surrogates for daily sodium and potassium intake (in grams). Previous studies have reported that this method provides a reliable estimate of sodium intake in healthy Japanese (r=0.73),(19) and this was replicated later in hypertensive Japanese (r=0.69 in those on BP medication, r=0.66 in those not medicated) (49,50), and more recently in hypertensive Chinese (r=0.64) (51). We conducted further extensive validation of the method in 1083 people from 11 countries,(20) which demonstrated that the estimated sodium excretion from the morning urine specimen shows a strong correlation with direct measures of sodium excretion from the actual 24-hour urine collection (intraclass correlation coefficient of 0.70 [95%CI, 0.61 to 0.77] among people with

hypertension and 0.71 [95%CI, 0.61 to 0.78] among those without hypertension). Further, the BP change per g of sodium was 2.11/0.78 mmHg,(18) which is consistent with the results of a meta analysis of sodium lowering RCTs (21,20).(**Appendices 3 and 4**)

Weight, height, and two recordings of BP after 5-minutes of rest in a sitting position with the use of an Omron automatic digital monitor (Omron HEM-757 used in all studies) were recorded in all participants. Participants were considered hypertensive if their untreated baseline BP was ≥140/90 mmHg or if they were prescribed anti-hypertensive medications at baseline.

The information on study variables was collected The information on study variables was collected using similar approaches to measuring risk factor variables and data collection forms in each of the studies. Information on personal medical history and use of medications were recorded. Standardized case-report forms were used to capture data on major CVD events and death during follow-up. Events were classified according to the definitions used in each study, but they were broadly similar. For the current analysis, we included data from the PURE study (which is ongoing) through March 2015, the complete data from ONTARGET/TRANSCEND, and case-cohort data from EPIDREAM.

Statistical Analyses

Mean estimated excretion values of sodium were computed overall and by hypertension status. Multivariable linear regression was used to obtain estimates of the slope describing the relationship between estimated sodium excretion (exposure) and BP measurements (outcome variable), within each subpopulation, adjusting for age, sex, body-mass index, education, alcohol intake, current smoking, and geographic region (18). We examined the association between an estimated “usual” level of sodium excretion (ie, accounting for the degree of

correlation between sodium levels in urine when measured after 30 and 90 days in 448 individuals; this also allows adjusting for regression dilution bias) (22) and BP. Analysis of covariance was performed, with tests for linear trend, to compare the adjusted mean BP according to sodium excretion level.

The primary outcome was defined as the composite of death, myocardial infarction, stroke and heart failure. We used restricted cubic-spline plots with four knots (at the 5th, 35th, 65th, and 95th percentiles) to explore the shape of the association between the estimated sodium excretion and the outcomes.(43) Participants were categorized into urinary sodium excretion groups, based on 1 g/day increments of excretion. Because few individuals had excretion values <2 or >8 g/day, we truncated excretion values at <3 and >7 g/day to avoid small numbers of individuals at the extreme ends of the distribution (approximately 10% of participants in the lowest and highest excretion categories within each subgroup). We calculated hazard ratios (HR) of time to event with Cox proportional hazards models, using shared frailty models. The clustering variable was the study cohort. The proportional hazards assumption was checked by visual inspection of log-log plots. The primary model included age, sex, ethnicity, BMI, smoking status, diabetes, educational level, alcohol consumption, physical activity, past CVD events, and treatment allocation (ramipril, telmisartan, or both, and treatment with statins, B-blockers, diuretic therapy, and calcium antagonist), as in our previously published papers (4,7). Separate analyses were performed excluding those with previous CV events. Interaction tests were performed to assess whether the slopes of the associations between estimated sodium excretion level and BP, CVD events or deaths differed between those with and without

hypertension. Statistical analyses were conducted using the SAS system Version 9.3 (SAS, Cary, NC).

We modelled the impact of changes in sodium intake on risk of incident CVD events, based on the observed associations between sodium excretion and systolic BP, and between systolic BP and CV events (see **Appendix 5**). For this modelling, we focused on 98,612 participants (3733 CVD events; median 4.2 years of follow-up) without baseline CVD, since this sub-cohort is comprised of generally healthy people from the population among whom few were receiving drugs. We compared these simulated BP-based estimates with directly observed HR of sodium excretion versus clinical outcomes to evaluate the consistency between estimates derived, overall and in those with and without hypertension. Cox regression was used to calculate HR and 95% CI of CVD events (total CVD, stroke and MI) per 1 mmHg increment in systolic BP, within each subgroup of hypertension status.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

A total of 63,559 with hypertension and 69,559 without hypertension were included in the study. There were 98,612 (74.1%) without prior CVD, and 118,232 (88.8%) without diabetes. Baseline characteristic of study participants are shown in **Appendix 6**. Mean (±SD) age was 58.6

(±10.3) years in hypertensives and 50.5 (±10.7) in non-hypertensives. Hypertensive individuals were more likely to be men, heavier, less physically active, and had more prior CVD and diabetes. (**Appendix 6**).

Mean estimated sodium excretion was 4956 ± 1747 g per day in people with hypertension, and 4823 ± 1647 g per day in those without hypertension (p<0.0001).

Among those with hypertension, 7,006 (11.0%) had an estimated sodium excretion of less than 3.0 g per day and 15,126 (23.8%) more than 6 g (7060 [11.1%] more than 7 g), and 41,427 (65%) had a level between 3 and 6 g per day. In those without hypertension, 7547 (10.8%) had an estimated sodium excretion of less than 3.0 g per day and 14,098 (20.3%) more than 6 g per day (6271 [9.0%] more than 7 g), and 47,914 (69%) between 3 and 6 g per day. After adjustment for regression dilution bias, 3039 (<3%) participants had a sodium excretion of less than 3 g per day and 21,240 (16.0%) had more than 6 g per day (11,146 [17.5%] of those with hypertension and 10,094 [14.5%] of those without hypertension, p<0001).

Estimated urinary sodium excretion and clinical outcomes

A total of 133,118 (99.7%) participants had follow-up completed, with a median follow-up of 4.2 years (interquartile range, 3.0 to 5.0 years). The primary composite outcome of all-cause death or a major CVD event occurred in 6835 participants (10.7%) with hypertension and 3021 participants (4.3%) without hypertension. Those with 4 to 5 g of sodium excretion had the lowest risk and this was used as the reference category.

The association between sodium excretion and the primary composite outcome varied significantly by hypertension status (P for heterogeneity=0.0342) (**Figure 1**). In the *hypertension*

group, a J-shaped association between sodium excretion and CV events and mortality was apparent. Compared with sodium excretion of 4-5 g/day (reference category), sodium excretion of >7 g/day (HR 1.23; 95% CI 1.11-1.37; p<0.0001) and <3 g/day (HR 1.34; 95% CI 1.23-1.47; p<0.0001) were both associated with increased risk of the composite outcome (**Table 1 and Figure 1**). After adjusting for BP, the associations between high sodium excretion and the composite outcome (HR 1.21; 95% CI 1.09-1.34; p=0.0006), and the association between low sodium excretion and the composite outcome were unaltered (HR 1.35; 95% CI 1.23-1.49; p<0.0001).

In *those without hypertension*, compared with 4-5 g/day, sodium excretion of >7 g/day was not associated with risk of the primary composite outcome (HR 0.90; 95% CI 0.76-1.08; p=0.2547), whereas an excretion of <3 g/day was associated with a significantly increased risk (HR 1.26; 95% CI 1.10-1.45; p=0.0009) (**Table 1 and Figure 1**). After adjusting for BP, the association between low sodium excretion and the composite outcome remained significant (p=0.0011).

Similar results were found for death from any cause and major CV disease (P for heterogeneity=0.0135 and 0.0432, respectively) (see **Table 1**).

Primary versus secondary prevention populations

The results described above of a J shaped association in those with hypertension was consistent in those with and without vascular disease (**Appendix 7**). Among those without hypertension, an increased risk with sodium excretion of <3 g/day compared with 4-5 g/day was consistent in those with and without vascular disease, whereas a sodium excretion of >7 g/day was associated with increased risk only in those with known vascular disease (**Appendix7**). When we

exclude data from the EPIDREAM study from the analysis (which is a case-cohort study of 2372 individuals), the results of the study overall and by subgroup do not change and the estimates from the PURE study alone by itself are clear (**Appendix 8**). Further, the data from the ONTARGET and TRANSCEND trials are consistent with the data from the two observational studies.

Sensitivity Analyses

Exclusion of those who had an event in the first two years of follow-up did not materially affect the estimates (**Table 1**). Further, in those with hypertension, exclusion of 35,027 individuals who were taking anti-hypertensive medication did not alter the findings.(**Table 1**).

Estimated urinary sodium excretion and blood pressure

Sodium excretion was more strongly associated with increased systolic BP in persons with hypertension (2.08; 95% CI 1.96 to 2.21 mm Hg increment in systolic pressure per g) than in those without hypertension (1.22; 95% CI 1.13 to 1.30 mm Hg increment in systolic pressure per g; P<0.0001 for interaction) (**Figure 2**). Similar results were found for diastolic BP (0.72; 95% CI 0.65 to 0.80 mmHg and 0.52; 95% CI 0.46 to 0.58 mmHg increment in diastolic pressure per g, respectively; P<0.0001 for interaction) (**Figure 2**).

Observed versus BP-modelled association of sodium intake with future CVD events

In the simulation models, where we assumed that the effect of sodium intake on CVD events was solely related to its association through systolic BP, the projected HR of CVD events, stroke and MI increased in a graded fashion. However, there was a more marked increase in risk in

311 people with hypertension, and a more modest association in those without hypertension
312 (p<0.0001 for heterogeneity) (**Figure 3;Appendix 9**).

313 The modelled estimates differed from the observed HR of CVD events both in hypertensives
314 and non-hypertensives. This discordance was marked at lower levels of sodium excretion (ie, <3
315 g/day). The projection model showing *lower* HR estimates with lower sodium excretion,
316 whereas the observed HR estimates show an *increased* risk of events with lower sodium
317 excretion. In people with hypertension, the observed HR was similar to the modelled HR at
318 average or higher levels of sodium excretion (>4 g/day) (**Figure 3; Appendix 10**).

319

320 **DISCUSSION**

321 In this analysis of three large international prospective studies with over 10,000 events and
322 based on an analysis of 133,118 people selected from 49 countries in 6 continents (**Appendix**
323 **2**), we found significant heterogeneity in the association between sodium excretion and the
324 composite outcome by hypertension status. In both those with or without hypertension, there
325 is an increased risk of CVD events and deaths associated with 24 hour urinary sodium excretion
326 below 3 g/day. However, an increase in risk of CVD with high sodium was only seen in people
327 with hypertension (which represents less than 10% of the population included in the 3 cohorts
328 included in this analysis), but not in those without hypertension.

329 Our results are consistent with another recently published cohort study (PREVEND study;
330 n=7543) which reported an association between higher sodium intake and CVD, that was
331 confined to participants with baseline hypertension (P-interaction=0.08) and in those with

baseline pro-BNP (brain natriuretic peptide) levels above the median (23). Other studies have not reported a significant modifying effect of prior hypertension, but these studies have been much smaller than our study. In the current study, the association between low sodium intake (<3g/day) and increased CV and mortality was consistent irrespective of baseline hypertension status and after further adjustment for BP level indicating that mechanisms unrelated to BP may be operational. Our findings are also in keeping with a previous meta-analysis of prospective cohort studies showing a J-shaped association between sodium intake and CVD events, in both healthy and high risk populations (eg those with CVD or diabetes), with consistency across different methods of sodium estimation.(1-8) While the meta-analysis (8) included previous analysis from the ONTARGET/TRANSCEND cohort, it did not include the PURE study and EPIDREAM cohorts, and the PURE study accounts for the majority of the current study population. The current findings replicate previous reports and extend these observations to populations based on baseline hypertension status. Further, they suggest that while there is a limit below which sodium intake would be unsafe, the harm associated with high sodium consumption appears to be confined to those with hypertension. Only about 10% of the population in our study had both hypertension and high sodium consumption (greater than 6 g per day).This argues against a population-wide approach to reducing sodium intake in most countries except those where the mean sodium intake is very (eg some in Central Asia or some parts of China).

We found that most of the world's population (~95%) studied consumes above 3 g/day of sodium, regardless of hypertension status and only 22% consume sodium above 6g/day ---the threshold above which we observe an increase in mortality and CVD risk. Sodium is an essential

cation and critical to the action potential of all cells in the body (24). Sodium homeostasis is under tight physiologic regulation. Further, emerging evidence suggests that inflammatory responses with infections involve mobilizing high concentrations of sodium to the local tissues that are involved and this ability may be part of an essential and necessary defence mechanism to external infections (25-27). Sodium intake is governed by neural mechanisms that regulate intake of sodium and related homeostatic mechanisms (28) and so while extreme reductions in sodium intake are possible in controlled settings for short periods, this is unlikely to be sustainable in free living subjects (29).

Prior modelling studies (42) that have estimated the effect of reducing sodium intake globally on CV mortality are based on the assumption that the BP lowering effects of sodium reduction seen in short term trials will translate into reductions in CVD in the long term. However, it is now known that whether lowering blood pressure results in reductions in CV disease is dependent on the baseline blood pressure of the population, the mechanism of blood pressure lowering and presence or absence of CVD. While the SPRINT trials did report a reduction in heart failure and CV death when lowering blood pressure to a mean of 121mmHg systolic in a primary prevention population (53), a number of other randomised controlled trials have failed to demonstrate a benefit of lowering systolic blood pressure under 130mmHg in primary prevention population (HOPE-3) (58) and secondary prevention populations (ACCORD, SPS3, PRoFESS),(46,54,55) and some have demonstrated harm (56). Three independent meta-analysis of large randomized trials of BP lowering with antihypertensive drugs in those with diabetes (30,31,57) demonstrate that the benefits of BP lowering in reducing clinical events is observed only in those with a systolic BP of >140 mm Hg. This is also supported by the results of the

recent HOPE 3 trial (58), which demonstrated that BP lowering by 6 mm Hg systolic reduced CVD risk by about 25% only those with elevated baseline levels (SBP > 143 mm Hg) but not in those with lower initial SBP despite similar reductions in BP. These data are consistent with our finding that the association of high sodium intake and CVD is confined to those with baseline blood pressure over 140/90mmHg. The mechanism of blood pressure lowering is also important, and non-blood pressure effects, which may be beneficial or harmful. (While high risk people, eg. those with previous MI or stroke have benefitted from ACE inhibitors or beta-blockers, the benefits appear to be only partly due to BP lowering (44); and other drugs which lower BP in high risk people have not been shown to reduce CVD events (45,46). Further, some drugs which were shown to reduce BP to similar extents differed in their impact on CVD or its individual CVD outcomes (47,48). Our data suggest that while a persuasive case can be made for reducing sodium intake in hypertensives, with high sodium intake, it is unclear whether the remaining >90% of the population will benefit from sodium reduction.

Our analyses indicate the limitations of estimates from modelled calculations based solely on projected changes in BP from sodium lowering as the results differ compared to the directly observed data relating sodium to CVD events and supported by a lack of CVD reduction with BP lowering in people without CVD. This suggests that the impact of a given level of sodium intake on clinical outcomes is only partly mediated through its effects on BP and that other mechanisms may also be at play. This is supported by observations of activation of the renin system and of catecholamines with low sodium intake (32,33). High renin levels have been reported in studies of the Yanomamo Indians who reportedly consume very little sodium (40). Several studies have shown that elevation of renin, aldosterone and catecholamines are all

associated with increased CVD events and mortality (34-39). Therefore, predicting the net clinical effect based on solely looking at the effects of sodium on BP may not provide a comprehensive understanding of its effects on CVD and mortality, especially within the range of sodium intake that affects the renin system (<4g/day).

We found that the association of sodium intake with CVD was strong even when adjusted for BP levels. This indicates that the association between sodium and CVD may also be related to non BP mechanisms. Exploration of why hypertensives with high sodium intake have a higher risk of CVD whereas no such relationship is seen in non-hypertensives is puzzling and requires mechanistic investigation in careful physiologic studies. Randomized trials have shown that sodium lowering has only a small impact on BP in non-hypertensive individuals (33) and such individuals may be less sensitive to the effects of salt consumption (52). Furthermore, understanding why low sodium intake is associated with higher event rates despite slightly lower BP is also of importance. Given that sodium is an essential cation, it should not be surprising that there is a "sweet spot" (or optimal range) for its intake. This mirrors the situation of most biological systems and it is only with external toxins (eg tobacco or environmental pollutants) that a linear association is likely.

Despite careful design, follow-up and analyses, observational analyses cannot definitively prove causality. Therefore, ideally large and long-term RCTs of sodium reduction to various levels to assesss the impact on clinical outcomes are essential to guide public policy. Given the absence of such RCTs, large prospective observational studies, (despite their inherent limitations) relating sodium intake to CVD should be considered the best available evidence. Further, we have initiated a pilot RCT to assess feasibility as a prelude to establishing a larger and long term

study to definitively address this question. In the absence of large definitive RCTs showing a clear reduction in CVD, the weight of the substantial epidemiologic studies describing a potentially adverse effect of low sodium should urge caution in making broad public health recommendations as they may lead to little benefit and even some harm. Further, the observation that high sodium intake is only associated with increased CVD in people with hypertension raises questions whether public health policies targeted at reducing sodium in the entire population are appropriate. Therefore, until new robust data emerge from large trials (59), it may be prudent to recommend reduction in sodium intake only in those with high sodium intake and with hypertension. Some may consider large randomized trials of sodium reduction impractical to assess their impact on CVD, but they are essential to definitively resolve the controversy. However, we have recently initiated a feasibility trial in high risk individuals (60) with renal disease as a prelude to designing larger studies.

Strengths of our study include the large size, the international nature of our cohorts, use of validated urinary measure of sodium intake, standardized methods to measure a large number of covariates and careful and standardized measurement of BP. These rigorous methods make our study both valid and generalizable. Our analyses include participants with established CVD recruited into a randomized controlled trial (ie, ONTARGET/TRANSCEND) as well as those without vascular disease identified from the population (eg, PURE) or those screened for a trial (EPIDREAM). This broad range of individuals from 49 countries indicates that our findings are widely applicable and robust as similar findings were observed across all 3 studies. While the collection of a single overnight urine sample to estimate the 24hr urinary sodium excretion may be considered a limitation, it has been validated against 24-hour urine collections in previous

studies of healthy (19) and hypertensive (49-51) participants and in our international validation study (20) with correlations similar to that seen with a BP measured at a clinic visit vs 24 hr ambulatory monitoring. Further, our analyses take into account the day to day variability of sodium intake in individuals by estimating the correlation of two measures taken 30 to 90 days apart and then using statistical adjustments to assess the degree of regression dilution. Adjustments for these day to day variability and the lack of perfect correlation with 24 hr urinary estimates of sodium would "steepen" all the associations (both at the low and high ends of sodium intake) and so would not qualitatively affect the pattern of our results (41). Residual confounding cannot be completely ruled out in any epidemiologic study but extensive multivariable analyses did not change our results. Further sensitivity analyses to minimize the potential for "reverse causality" (where sick people reduce sodium intake) by excluding in turn those with known CVD, hypertension or diabetes or by confining analyses to events beyond 2 years did not change the pattern of our findings. Therefore our results are robust to different forms of analyses.

In summary, our results indicate an association between low sodium intake (versus moderate intake) and increased risk of clinical outcomes in those with and without hypertension while high sodium intake (above 6 g) was associated with an increased risk in people with hypertension. Our findings suggest that sodium reduction should be confined to only those with hypertension and high sodium intake.

Contributors

AM designed the present study, performed its statistical analysis, and wrote the first draft of the manuscript. SY designed the present study, conceived and initiated the Prospective Urban Rural Epidemiology (PURE) study, supervised its conduct and data analysis, and provided critical comments on all drafts of the manuscript. M'JO reviewed and provided critical comments on drafts. SR coordinated the worldwide PURE study and reviewed and commented on drafts. KT was the coprincipal investigator of the PURE study and reviewed and commented on drafts. All other authors coordinated the study and collected the data in their respective countries and provided comments on drafts of the manuscript. SA, HG and SY lead the EPIDREAM study and SY and KT lead the ONTARGET and TRANSCEND trials. SY is currently the President of the World Heart Federation but this paper does not necessarily reflect the position of the WHF or any other organization.

Declaration of interests

We declare no competing interests.

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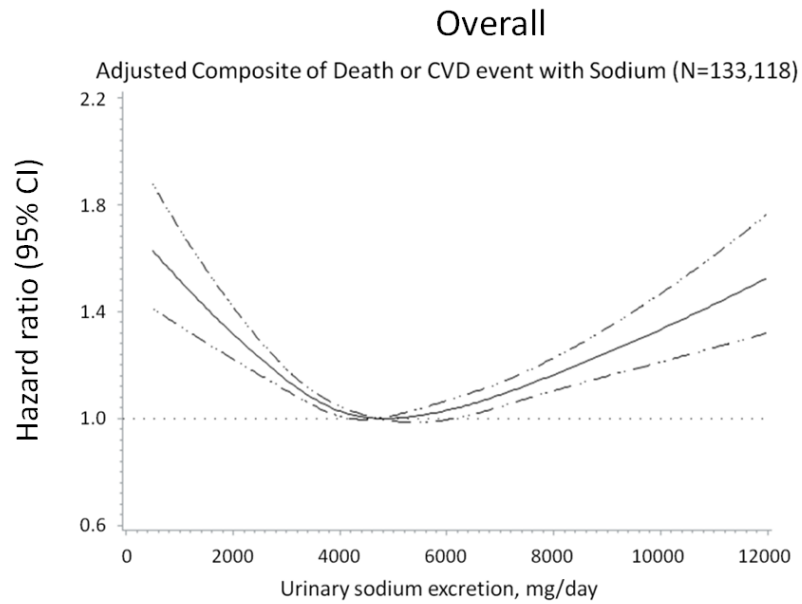
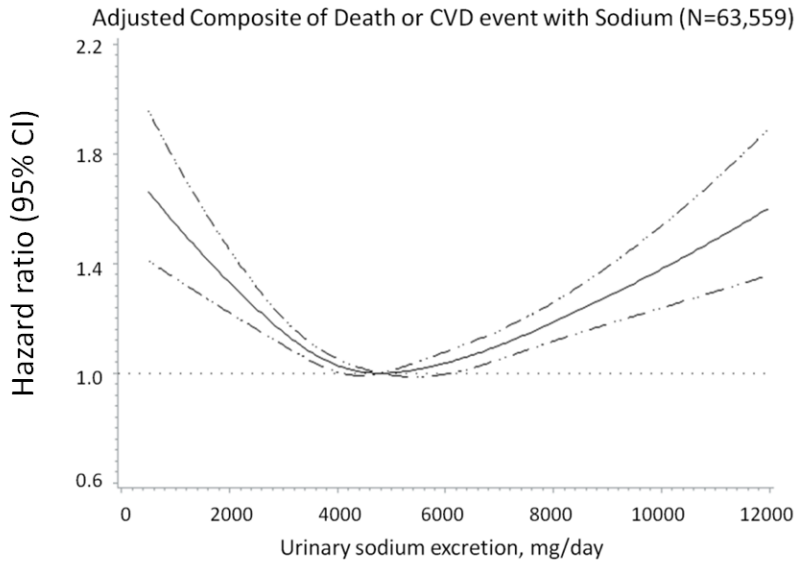
705

Figure 1. Sodium excretion versus composite outcome events



Events	296	3023	4452	1666	319	100
No. at risk	2644	39372	61878	23384	4607	1233



Events	226	2032	2983	1253	259	82
No. at risk	1464	17839	29130	11976	2498	652

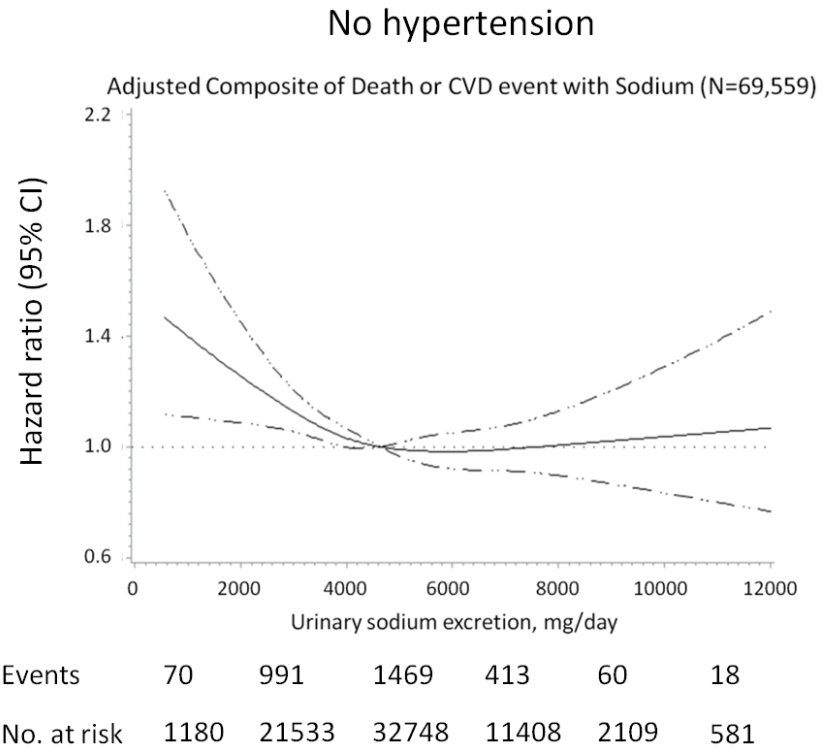
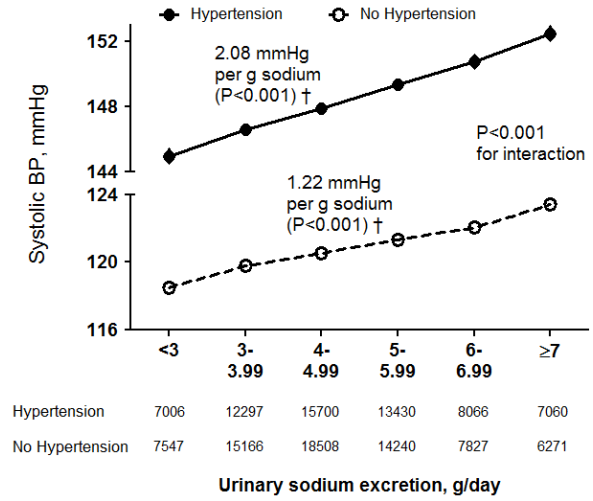


Figure 1. Cubic splines for the association between sodium excretion and composite outcome events (risk of death and major cardiovascular events), overall and by hypertension status in the 4 included studies (N=133,118). The analyses were adjusted for the variables in the primary model which included age, sex, ancestry (Asian vs. non-Asian), body-mass index, educational level, alcohol intake, current smoking, physical activity, status with respect to diabetes mellitus, a history of cardiovascular events, treatment allocation (ramipril, telmisartan, or both, and treatment with statins, B-blockers, diuretic therapy, and calcium antagonist).

Figure 2. Blood pressure by sodium excretion

Systolic blood pressure



Diastolic blood pressure

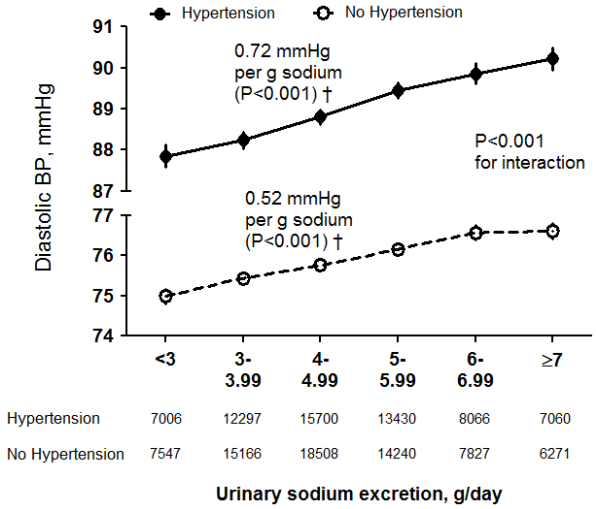
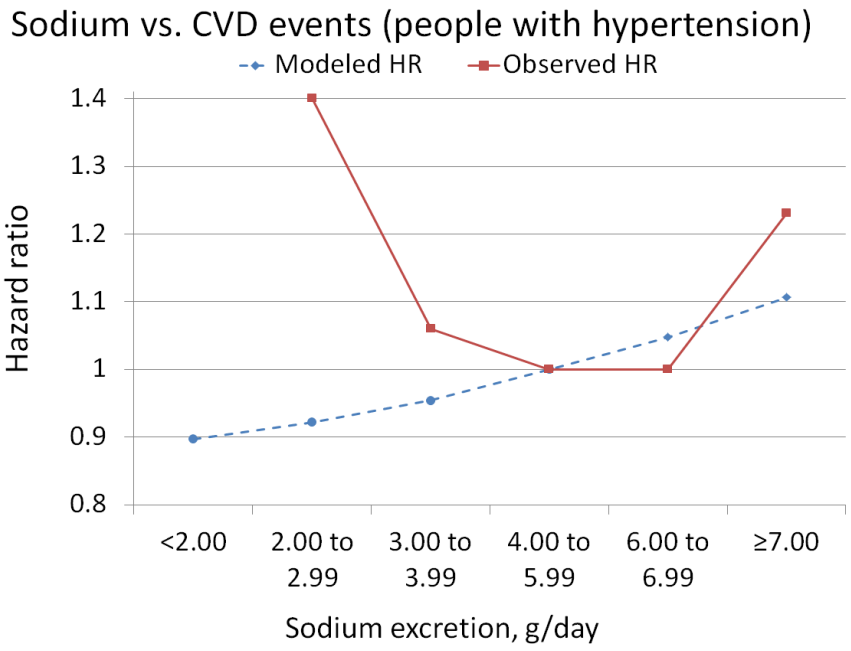


Figure 2. Mean (95% CI) systolic and diastolic blood pressure by sodium excretion and hypertension status, adjusting for age, sex, body-mass index, education, alcohol intake, current smoking, and geographic region (N=133,118). These covariates were selected since they were included in the INTERSALT Study and in our previous PURE analysis.(18) Linear regression

766 assumptions were checked using standard plots (residuals versus predicted values plots,

767 residual time series plots, and normal probability plots), with no detected violations.

Figure 3



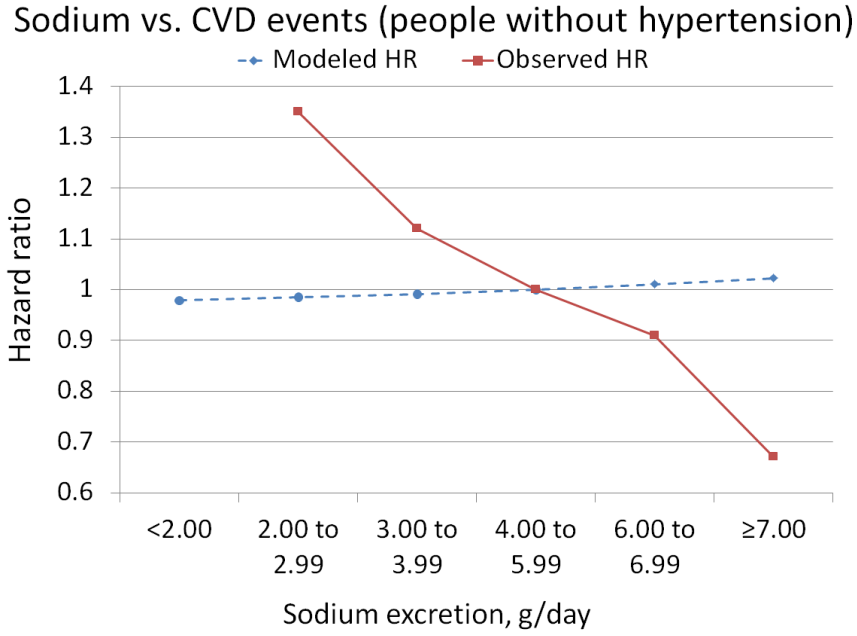


Figure 3. Simulation modelled versus observed hazard ratio estimates of the association between sodium excretion and CVD events in those without CVD (N=98,612), overall and

778 stratified by hypertension status. There were 40,547 people with hypertension and 58,065

779 people without hypertension.

Table 1. Hazard ratios (95% CI) for the association of estimated urinary sodium excretion with death and major cardiovascular events.*						
	Estimated sodium excretion					
	<3 g/day	**3.00-3.99 g/day**	**4.00-4.99 g/day**	**5.00-5.99 g/day**	**6.00-6.99 g/day**	**≥7.00 g/day**
All participants (N=133,118)	**(N=14553)**	**(N=27463)**	**(N=34208)**	**(N=27670)**	**(N=15893)**	**(N=13331)**
Death or cardiovascular event, no. of individuals (%)	1323 (9.09)	1996 (7.27)	2487 (7.27)	1965 (7.10)	1148 (7.22)	937 (7.03)
Univariable analysis †	1.26 (1.17 to 1.36)	1.04 (0.98 to 1.11)	1.00	1.00 (0.93 to 1.06)	1.09 (1.01 to 1.18)	1.28 (1.18 to 1.39)
Multivariable analysis ‡§	1.31 (1.21 to 1.42)	1.08 (1.01 to 1.16)	1.00	0.98 (0.91 to 1.05)	1.04 (0.96 to 1.13)	1.18 (1.08 to 1.29)
Excluding CVD at baseline	1.38 (1.23 to 1.55)	1.14 (1.03 to 1.26)	1.00	1.02 (0.92 to 1.13)	1.02 (0.91 to 1.16)	1.14 (1.003 to 1.30)
Excluding events in year 1 and year 2	1.27 (1.15 to 1.40)	1.09 (1.002 to 1.19)	1.00	1.00 (0.92 to 1.09)	1.06 (0.96 to 1.17)	1.17 (1.05 to 1.31)
Major CVD events, no. of individuals (%)	1001 (6.88)	1472 (5.36)	1852 (5.41)	1461 (5.28)	857 (5.39)	725 (5.44)
Univariable analysis †	1.27 (1.17 to 1.38)	1.03 (0.96 to 1.11)	1.00	1.00 (0.93 to 1.07)	1.10 (1.01 to 1.21)	1.37 (1.25 to 1.50)
Multivariable analysis ‡§	1.34 (1.23 to 1.47)	1.06 (0.98 to 1.15)	1.00	0.96 (0.88 to 1.04)	1.03 (0.94 to 1.13)	1.21 (1.10 to 1.34)
Excluding CVD at baseline	1.36 (1.18 to 1.57)	1.14 (0.98 to 1.29)	1.00	1.03 (0.91 to 1.17)	1.04 (0.89 to 1.20)	1.15 (0.98 to 1.35)
Excluding events in year 1 and year 2	1.30 (1.16 to 1.46)	1.05 (0.95 to 1.16)	1.00	0.95 (0.86 to 1.05)	1.03 (0.92 to 1.16)	1.21 (1.06 to 1.37)

All cause mortality, no. of individuals (%)	812 (5.58)	1177 (4.29)	1377 (4.03)	1102 (3.98)	644 (4.05)	573 (4.30)
Univariable analysis †	1.38 (1.27 to 1.51)	1.11 (1.03 to 1.20)	1.00	1.01 (0.93 to 1.09)	1.10 (1.00 to 1.22)	1.42 (1.28 to 1.58)
Multivariable analysis ‡§	1.41 (1.28 to 1.54)	1.15 (1.06 to 1.24)	1.00	1.00 (0.91 to 1.09)	1.05 (0.95 to 1.17)	1.31 (1.17 to 1.47)
Excluding CVD at baseline	1.52 (1.32 to 1.74)	1.18 (1.05 to 1.32)	1.00	1.02 (0.89 to 1.18)	1.03 (0.88 to 1.22)	1.28 (1.08 to 1.51)
Excluding events in year 1 and year 2	1.34 (1.19 to 1.51)	1.15 (1.04 to 1.27)	1.00	1.01 (0.91 to 1.15)	1.06 (0.93 to 1.22)	1.28 (1.11 to 1.48)
Participants without hypertension (N=69,559)	**(N=7547)**	**(N=15166)**	**(N=18508)**	**(N=14240)**	**(N=7827)**	**(N=6271)**
Death or cardiovascular event, no. of individuals (%)	393 (5.21)	668 (4.40)	837 (4.52)	632 (4.44)	293 (3.74)	198 (3.16)
Univariable analysis †	1.23 (1.08 to 1.40)	1.04 (0.94 to 1.16)	1.00	1.00 (0.90 to 1.12)	0.95 (0.82 to 1.09)	0.95 (0.81 to 1.12)
Multivariable analysis ‡§	1.26 (1.10 to 1.45)	1.05 (0.94 to 1.18)	1.00	0.99 (0.88 to 1.11)	0.92 (0.79 to 1.07)	0.90 (0.76 to 1.08)
Excluding CVD at baseline	1.38 (1.15 to 1.66)	1.10 (0.94 to 1.29)	1.00	1.03 (0.87 to 1.21)	0.81 (0.65 to 1.00)	0.81 (0.64 to 1.03)
Excluding events in year 1 and year 2	1.22 (1.02 to 1.44)	1.07 (0.93 to 1.23)	1.00	1.00 (0.87 to 1.16)	0.91 (0.76 to 1.09)	0.91 (0.73 to 1.13)
Major CVD events, no. of individuals (%)	262 (3.47)	452 (2.98)	573 (3.10)	409 (2.87)	209 (2.67)	131 (2.09)
Univariable analysis †	1.18 (1.01 to 1.38)	1.03 (0.91 to 1.17)	1.00	0.95 (0.83 to 1.08)	1.02 (0.86 to 1.20)	0.98 (0.80 to 1.20)
Multivariable analysis ‡§	1.28 (1.09 to 1.51)	1.05 (0.91 to 1.21)	1.00	0.92 (0.79 to 1.06)	0.97 (0.81 to 1.15)	0.90 (0.72 to 1.11)
Excluding CVD at baseline	1.34 (1.04 to 1.71)	1.16 (0.94 to 1.43)	1.00	0.99 (0.79 to 1.23)	0.89 (0.67 to 1.17)	0.69 (0.49 to 0.96)
Excluding events in year 1 and year 2	1.31 (1.07 to 1.61)	1.07 (0.90 to 1.27)	1.00	0.95 (0.80 to 1.14)	0.94 (0.75 to 1.18)	0.90 (0.70 to 1.18)

All cause mortality, no. of individuals (%)	257 (3.41)	403 (2.66)	475 (2.57)	374 (2.63)	166 (2.12)	122 (1.95)
Univariable analysis †	1.42 (1.21 to 1.67)	1.11 (0.97 to 1.28)	1.00	1.05 (0.91 to 1.20)	0.95 (0.79 to 1.14)	1.04 (0.84 to 1.27)
Multivariable analysis ‡§	1.39 (1.17 to 1.66)	1.10 (0.95 to 1.28)	1.00	1.04 (0.90 to 1.21)	0.95 (0.78 to 1.15)	1.00 (0.80 to 1.24)
Excluding CVD at baseline	1.50 (1.19 to 1.90)	1.10 (0.90 to 1.36)	1.00	1.03 (0.83 to 1.28)	0.78 (0.59 to 1.04)	0.93 (0.69 to 1.24)
Excluding events in year 1 and year 2	1.18 (0.94 to 1.48)	1.06 (0.88 to 1.27)	1.00	1.02 (0.85 to 1.23)	0.91 (0.71 to 1.16)	0.96 (0.73 to 1.26)
Participants with hypertension (N=63,559)	**(N=7006)**	**(N=12297)**	**(N=15700)**	**(N=13430)**	**(N=8066)**	**(N=7060)**
Death or cardiovascular event, no. of individuals (%)	930 (13.27)	1328 (10.80)	1650 (10.51)	1333 (9.93)	855 (10.60)	739 (10.47)
Univariable analysis †	1.28 (1.17 to 1.41)	1.05 (0.97 to 1.14)	1.00	0.97 (0.90 to 1.05)	1.11 (1.01 to 1.21)	1.31 (1.19 to 1.45)
Multivariable analysis ‡§	1.34 (1.23 to 1.47)	1.09 (1.002 to 1.19)	1.00	0.97 (0.89 to 1.05)	1.07 (0.97 to 1.18)	1.23 (1.11 to 1.37)
Excluding CVD at baseline	1.37 (1.19 to 1.58)	1.16 (1.01 to 1.32)	1.00	0.99 (0.87 to 1.14)	1.12 (0.96 to 1.30)	1.26 (1.08 to 1.47)
Excluding events in year 1 and year 2	1.29 (1.14 to 1.45)	1.10 (0.99 to 1.23)	1.00	0.99 (0.89 to 1.10)	1.11 (0.98 to 1.25)	1.24 (1.09 to 1.41)
Excluding users of anti-hypertension medication	1.70 (1.39 to 2.06)	1.26 (1.07 to 1.50)	1.00	1.02 (0.86 to 1.20)	1.07 (0.88 to 1.29)	1.13 (0.93 to 1.37)
Major CVD events, no. of individuals (%)	739 (10.55)	1020 (8.29)	1279 (8.15)	1052 (7.83)	648 (8.03)	594 (8.41)
Univariable analysis †	1.30 (1.18 to 1.44)	1.03 (0.95 to 1.13)	1.00	1.00 (0.91 to 1.09)	1.08 (0.97 to 1.19)	1.37 (1.24 to 1.53)
Multivariable analysis ‡§	1.35 (1.21 to 1.50)	1.06 (0.97 to 1.17)	1.00	0.97 (0.88 to 1.06)	1.02 (0.92 to 1.14)	1.26 (1.12 to 1.42)
Excluding CVD at baseline	1.36 (1.14 to 1.63)	1.13 (0.96 to 1.32)	1.00	1.03 (0.88 to 1.21)	1.06 (0.89 to 1.27)	1.27 (1.06 to 1.52)
Excluding events in year 1 and year 2	1.29 (1.12 to 1.47)	1.05 (0.93 to 1.18)	1.00	0.95 (0.84 to 1.07)	1.04 (0.91 to 1.20)	1.26 (1.09 to 1.45)
Excluding users of anti-	1.64 (1.30 to 2.08)	1.21 (0.99 to 1.48)	1.00	1.04 (0.85 to 1.27)	0.96 (0.76 to 1.21)	1.15 (0.91 to 1.45)

hypertension medication						
All cause mortality, no. of individuals (%)	555 (7.92)	774 (6.29)	902 (5.75)	728 (5.42)	478 (5.93)	451 (6.39)
Univariable analysis †	1.37 (1.23 to 1.54)	1.12 (1.01 to 1.24)	1.00	0.98 (0.88 to 1.08)	1.13 (1.01 to 1.28)	1.50 (1.33 to 1.70)
Multivariable analysis ‡§	1.39 (1.23 to 1.58)	1.17 (1.05 to 1.31)	1.00	0.97 (0.87 to 1.08)	1.08 (0.95 to 1.23)	1.39 (1.22 to 1.59)
Excluding CVD at baseline	1.52 (1.25 to 1.86)	1.25 (1.05 to 1.49)	1.00	1.00 (0.84 to 1.20)	1.17 (0.95 to 1.43)	1.43 (1.17 to 1.75)
Excluding events in year 1 and year 2	1.43 (1.23 to 1.68)	1.22 (1.06 to 1.40)	1.00	1.01 (0.88 to 1.16)	1.12 (0.96 to 1.32)	1.39 (1.17 to 1.64)
Excluding users of anti-hypertension medication	1.77 (1.38 to 2.27)	1.37 (1.11 to 1.70)	1.00	1.00 (0.80 to 1.24)	1.11 (0.86 to 1.42)	1.27 (0.99 to 1.63)

* Major cardiovascular events included death from cardiovascular causes, myocardial infarction, stroke, and heart failure.

† The univariable model included age, sex and ancestry (Asian vs. non-Asian).

‡ The primary model included age, sex, ancestry (Asian vs. non-Asian), educational level, alcohol intake, body-mass index, current smoking, physical activity, status with respect to diabetes mellitus and a history of cardiovascular events, treatment allocation (ramipril, telmisartan, or both, and treatment with statins, B-blockers, diuretic therapy, and calcium antagonist).

§ Additional sensitivity analyses with estimated potassium excretion included in the model or exclusion of participants from the EPIDREAM study (case-cohort design) did not materially alter estimates of association.

End