

Joint Association of Urinary Sodium and Potassium Excretion with Cardiovascular Events and Mortality

A Prospective Cohort Study

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ABSTRACT

Objective: To evaluate the joint association of sodium and potassium urinary excretion (surrogates of intake) with cardiovascular events and mortality, in the context of current World Health Organisation recommendation (<2.0g/day of sodium and >3.5g/day of potassium).

Design: International prospective cohort study.

Setting: PURE study in 18 high, middle and low-income countries, sampled from urban and rural communities.

Participants: We obtained morning fasting urine samples on 103,570 individuals and estimated 24-hour sodium and potassium excretion, surrogates for sodium and potassium intake.

Main Outcome Measures: We examined the association of estimated urinary sodium and potassium excretion with all-cause mortality and major cardiovascular events, employing multivariable Cox regression. A six-category variable for joint sodium and potassium was generated, sodium excretion [low (<3g/day), moderate (3-5g/day) and high sodium (>5g/day) intake], by potassium excretion [above and below median (2.1g/day)].

Results: Mean estimated sodium and potassium urinary excretion were 4.93 g/day and 2.12 g/day, respectively. After a mean follow-up of 8.2± years, 7,884 (6.1%) participants had died or experienced a major cardiovascular event. Increasing urinary sodium excretion was positively associated with increasing potassium excretion (unadjusted $r=0.34$), and only 0.001% had a concomitant urinary excretion of <2.0g/day of sodium and >3.5g/day of potassium. We observed a J-shaped association of sodium excretion, and inverse association of potassium excretion, with death and cardiovascular events. For joint sodium and potassium excretion categories, the lowest risk of death and cardiovascular events occurred in the group with moderate sodium excretion (3-5g/day) and higher potassium excretion (21.9% of cohort). Compared to this reference group, the

combinations of low potassium with low sodium excretion (HR 1.23; 1.11 [to](#)-1.37; 7.4% of cohort) and low potassium with high sodium excretion (HR 1.21; 1.11 [to](#)-1.32; 13.8% of cohort) were associated with the highest risk, followed by high sodium excretion (HR 1.10; 1.02 [to](#)-1.18 [29.6% of cohort]) and low sodium excretion (HR 1.19; 1.02 [to](#)-1.38 [3.3% of cohort]) among those with potassium excretion above median. Higher potassium excretion attenuated the increased cardiovascular risk associated with high sodium excretion (P-interaction=0.007).

Conclusions: Our findings suggest that the simultaneous target of low sodium (<2g/day) with high potassium intake (>3.5g/day) is extremely uncommon. Combined moderate sodium intake (3-5g/day) with high potassium intake is associated with lowest risk of mortality and cardiovascular events.

Key Words: Sodium, Salt, Potassium, Cardiovascular, Mortality

INTRODUCTION

Consumption of sodium and potassium is essential to health, as neither are produced endogenously and both are necessary for critical physiologic processes.¹⁻³ Maintaining homeostasis requires a mutual interdependence of sodium and potassium, meaning that their relationship with health is necessarily linked.¹⁻³ Despite these fundamental physiologic considerations, current public health policy adopts markedly opposing guidance for sodium and potassium intake, with the World Health Organisation (WHO) recommending extremely low sodium intake (<2g/day, while the current average intake is about 4g/day), but high potassium intake (>3.5g/day, while the average intake is about 2g/day) in the entire population.^{4,5,6} There are limited international data reporting the percentage of people with both very low intakes of sodium and simultaneously high potassium intakes⁷, and on their joint effects on health outcomes from large international epidemiologic studies.^{4,5}

Current public health policy is based primarily on small, and mostly short-term, clinical trials evaluating the relationship of changes in sodium and potassium intake with blood pressure.^{4,5} While clinical trials have reported a reduction in blood pressure with reducing sodium intake,^{8,9} many prospective cohort studies have reported a J-shaped association of sodium intake and cardiovascular disease¹⁰⁻¹⁶, with an increased risk emerging at sodium intake under 3g/day, and above 5g/day.¹⁰ The increased cardiovascular risk associated with high sodium intake appears to be largely confined to individuals with hypertension¹⁷, while the increased risk associated with low sodium intake may be mediated through activation of physiologic systems to conserve sodium (e.g. renin-angiotensin-aldosterone system)¹⁸ In contrast, the association of potassium intake with blood pressure and cardiovascular disease is consistent, with both a linear reduction in blood pressure and cardiovascular risk reported with increasing potassium intake,

reported in most studies.⁹ There are some epidemiologic reports of an interactive association of sodium and potassium intake with blood pressure, and studies reporting use of sodium to potassium ratios for predicting risk of cardiovascular events and mortality.¹⁹⁻²⁵ Whether a potential modifying effect of increased potassium intake is directly causal, or simply a marker of improved diet quality²⁶, as diets rich in fruit and vegetables (which are associated with lower cardiovascular risk) are high in potassium, is uncertain.³

The PURE prospective cohort study is the largest international study to evaluate the association of sodium and potassium intake with health outcomes. We have previously reported on the intermediate-term (3.7 years follow-up)^{16,17} association of sodium and potassium intake with mortality and cardiovascular events. In the current analyses, we report on the association of sodium and potassium intake with death and cardiovascular disease in extended follow-up (8 years). The larger event rate facilitates the exploration of the inter-relation of sodium and potassium intake with mortality and cardiovascular events.

METHODS

Study Population

The Prospective Urban Rural Epidemiological Study (PURE Study) is a large-scale epidemiological cohort study that has enrolled individuals (aged 35 to 70 years) residing in 628 urban and rural communities in low, middle and high-income countries (Bangladesh, India, Pakistan, Zimbabwe, Argentina, Brazil, Chile, Malaysia, Poland, South Africa, Turkey, China, Colombia, Iran, Canada, Sweden, and United Arab Emirates).²⁷⁻²⁹ A description of participant selection is provided in the Supplementary Appendix. Recruitment began in January 2003. All participants provided written informed consent. For the current analysis, we included 103,570

participants who collected early morning fasting urine samples suitable for analysis from 18 countries, of which 103,200 (99.6%) had follow-up information available (95% completed at least one follow-up visit). The study was coordinated by the Population Health Research Institute, Hamilton Health Sciences, Hamilton, Ontario, Canada.

Exposure Assessments

A morning fasting mid-stream urine sample was collected from each participant, frozen at -20°C to -70°C, and shipped to a central laboratory in Canada, China, India or Turkey. All urine samples were shipped at ambient temperature using the STP 250 ambient specimen shipping box. A description of the methods used for performing urinary analyses is provided in the Supplementary Appendix. The Kawasaki formula was used to estimate 24-hour urinary sodium and potassium excretion from a fasting morning sample, and these estimates have been validated previously versus measured with 24-hour urine collection.^{30, 31} An international validation study reported an intraclass correlation of Kawasaki formula to actual 24-hour urine collections of 0.71. Therefore, we used the estimates derived from fasting morning urine as surrogates for sodium and potassium intake in the whole study. (Supplementary appendix provides summary details of validation of this approach).

Ascertainment of Outcomes

Standardized case report forms were used to capture major cardiovascular events (myocardial infarction, stroke and heart failure), cancer and death on follow-up, which were adjudicated using standardized definitions.³² For the current analysis, we included all adjudicated outcome events in the PURE database through September 2017. The primary composite outcome was all-cause mortality, myocardial infarction, stroke and heart failure. Secondary outcome were individual component of the primary composite, and new diagnosis of cancer on follow-up.

Ascertainment of Covariates

Baseline standardised questionnaires were completed by all participants, which included detailed information on age, sex, lifestyle risk factors (e.g. smoking, diet, physical activity, alcohol intake), co-morbidities (e.g. prior history of diabetes, hypertension, cardiovascular disease) physical measurements (blood pressure, heart rate, body mass index [BMI], waist-to-hip ratio) and laboratory measurement of lipoproteins. A modified alternative healthy eating index score (mAHEI) was used to measure overall diet quality, with higher score indicating a healthier diet.³³

Patient Involvement

No patients were involved in setting the research question, outcome measures or design and implementation of the study.

Statistical Analyses

Baseline differences in characteristics between study participants in different categories of estimated sodium and potassium excretion have been reported previously, and included in Supplementary Appendix.¹⁶ Restricted cubic spline plots were used to explore the shape of association between estimated sodium and potassium excretion and outcomes, fitting a restricted cubic spline function with four knots (5th, 35th, 65th and 95th percentiles).³⁴ Our primary outcome measure was the composite of all-cause mortality and major cardiovascular events (cardiovascular death, stroke, myocardial infarction and heart failure). Secondary outcome included individual components of the primary outcome.

Based on our restricted cubic spline plots for the primary outcome, and the results of previous analyses^{10,16}, we selected 4 to 4.99 g/day as the reference category for sodium excretion

and less than 1.5 g/day for potassium excretion. We modelled the time to event outcome using multivariable Cox regression proportional hazards analysis with mixed effect (centre included as a random effect variable to account for clustering by research site) to determine the association between estimated urinary sodium and potassium excretion and outcomes, using three sequential models. Model 1 (the primary model) adjusted for age (included as spline function), sex, education, current and former alcohol intake (units per week), diabetes mellitus, body mass index (BMI), physical activity, history of cardiovascular events, use of cardiovascular medications (blood pressure lowering, statins or diabetes), history of tuberculosis, cancer, HIV, and current and former smoking, which constituted our primary multivariable model (with an additional model that included low-density lipoprotein [LDL] cholesterol/high-density lipoprotein [HDL] cholesterol ratio). Model 2 also included caloric intake, estimated potassium (or sodium) excretion, waist to hip ratio and modified alternative healthy eating index (mAHEI). Model 3 also included history of hypertension and baseline systolic and diastolic blood pressure and heart rate, which are in the putative causal pathway. We performed an analysis of the combined effects of sodium and potassium, in which we generated six categories with sodium excretion into low (<3g/day), moderate (3-5g/day) and high sodium (>5g/day) excretion, and potassium excretion above and below median (2.1g/day). Three categories were selected for sodium excretion, as the estimated association was J-shaped, while two categories were selected for potassium excretion, as the association was linear in analyses. We also completed a stratified subgroup analysis of the association of sodium excretion and outcomes, stratified by groups of urinary potassium excretion and mAHEI divided at their tertiles. We tested for interactions between sodium excretion and potassium excretion and between sodium excretion and mAHEI score. As the association of sodium excretion and composite outcome was non-linear, we tested [for interaction](#)

above and below median sodium excretion (i.e. four tests for interaction) modelling the log hazard ratio as a piece-wise linear function of sodium excretion; two connected lines above and below the median sodium excretion with different slopes which were allowed to interact with the potassium and mAHEI subgroups. We completed an analysis of 'usual' sodium intake, based on repeated measurement in 494 participants, employing methodology used in previous publication.

To minimize the potential for reverse causation, we conducted analyses that excluded participants who had a final follow-up or outcome event within the first 3 years of baseline. All analyses were conducted using R Version 3.4.4 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study Participants and Outcomes

In total, 103,570 participants were included, of which 42% were from China. In the overall population, mean estimated 24-hour sodium excretion was 4.93 g and mean estimated potassium excretion 2.12 g. (Supplementary Table 1) After a mean duration of 8.2 years (IQR 6.0-9.4) there were 4,524 deaths, 4,889 with a major CVD event (1893 myocardial infarctions, 2,526 strokes, 534 heart failure, and 1,293 CVD deaths) and 7,884 had either a CVD event or death, and 3,263 were diagnosed with cancer.

Estimated Sodium Excretion with Mortality and Cardiovascular Events

Compared with estimated sodium excretion of 4 to 4.99 g/day (the reference group), higher estimated sodium excretion (more than 7 g/day) was associated with a greater risk of the primary composite outcome (hazard ratio [HR] 1.23; 95% confidence interval [CI] 1.12 to 1.34), all-cause mortality (HR 1.36; 95% CI 1.20 to 1.53), major cardiovascular events (HR 1.20; 95% CI

1.08 to 1.34), cardiovascular death (OR 1.49; 95% CI 1.21 to 1.84), and fatal stroke (HR 1.76; 95% CI 1.28 to 2.41) on multivariable analysis (Table 1, Supplementary Table 2, Figure 2). Compared with estimated sodium excretion of 4 to 4.99 g/day, lower estimated sodium excretion (less than 3 g/day) was associated with a greater risk of the primary composite outcome (HR 1.19; 95% CI 1.09 to 1.30), all-cause mortality (HR 1.26; 95% CI 1.12 to 1.41), major cardiovascular events (HR 1.19; 95% CI 1.06 to 1.33), cardiovascular mortality (HR 1.35; 95% CI 1.09 to 1.69) and stroke (HR 1.24; 95% CI 1.05 to 1.46). (Supplementary Table 2). There was no association of sodium excretion with cancer or cancer mortality (Supplementary Table 2).

Estimated Potassium Excretion with Mortality and Cardiovascular Events

Compared to estimated potassium excretion of less than 1.5 g/day, higher estimated potassium excretion was associated with lower risk of mortality and cardiovascular events (HR 0.83; 95% CI 0.73 to 0.94 for more than 3g/day) on multivariable analysis (Figure 3, Supplementary Table 3). This associated [reduction in hazard was](#) ~~ion was more related to a lower~~ [greater for](#) -mortality risk (HR 0.71; 95% CI 0.60 to 0.85), than major cardiovascular events (HR 0.87; 0.75 ~~to~~-1.02). There was no [apparent](#) association of potassium excretion with cancer or cancer mortality (Supplementary Table 3).

Combined Sodium and Potassium Excretion with Mortality and Cardiovascular Events

Table 2 shows the association of sodium excretion with the primary composite outcome, categorised by joint sodium and potassium excretion (6 categories). The lowest risk of death and cardiovascular events occurred in the group with moderate sodium excretion (3-5g/day) and higher potassium excretion (21.9% of cohort). Compared to this reference group, the combinations of low potassium with low sodium excretion (HR 1.23; 1.11 ~~to~~-1.37; 7.4% of cohort) and low potassium with high sodium excretion (HR 1.21; 1.11 ~~to~~-1.32; 13.8% of cohort)

were associated with the highest risk, followed by high sodium excretion (HR 1.10; 1.02 to 1.18 [29.6% of cohort]) and low sodium excretion (HR 1.19; 1.02 to 1.38 [3.3% of cohort]) among those with potassium excretion above median. Moderate sodium excretion with low potassium excretion was associated with an increased risk of the primary outcome (HR 1.10; 1.01 to 1.19, 24.0% of cohort), compared to reference. There were very few individuals (0.001%) with both very low sodium excretion (<2g/day) and high potassium excretion (>3.5g/day)-a target recommended by nutrition guidelines-so that the risk in this subgroup could not be estimated reliably (0.2% for potassium >2.63g/day, assuming that about 75% of potassium is excreted in the urine³⁵ and sodium excretion <2.3g/day). Figure 1b reports results of a heat-map that combines multivariable cubic splines of the association of both sodium excretion and potassium excretion with the primary outcome, with median excretion as reference category. Table 3 and Figure 4 shows a stratified analysis by potassium excretion tertiles, supporting a lower relative risk associated with higher sodium excretion among those with higher potassium excretion. Test for interaction of higher sodium excretion (above median) and potassium excretion was significant (P=0.007) but for lower sodium excretion and potassium excretion was not significant (P=0.939).

Sodium Excretion and Diet Quality (mAHEI)

Figure 4b and Table 3 reports a stratified analysis by mAHEI tertiles, which demonstrates a lower magnitude of risk the association of sodium excretion with mortality and cardiovascular events among those with higher diet quality scores, although P for interactions were not significant (P=0.868 for below median excretion and P=0.297 above median excretion).

Sensitivity Analyses

Exclusion of participants who had events in the first three years of follow-up, and excluding those with baseline cardiovascular disease, cancer (or cancer on first year of follow-up, diabetes and were current smoker), did not materially affect findings. (Table 1) Supplementary Figure 1 reports the association of 'usual' 24-hour urinary sodium excretion and clinical outcomes.

DISCUSSION

In this large international prospective cohort study, we investigated the joint association of estimated sodium and potassium urinary excretion (surrogates for intake) and clinical outcomes over a mean follow-up of 8.1 years. Overall, the lowest risk of death and adverse clinical events was seen in individuals with estimated sodium excretion between 3 and 5 g/day, and with the highest potassium excretions (Table 2, Figure 1). Both higher and lower levels of estimated sodium excretion were associated with higher cardiovascular risk, thereby describing a J-shaped association curve, while the association of potassium excretion and mortality/cardiovascular risk was inverse and linear. Higher potassium intake attenuated the increased cardiovascular risk associated with high sodium intake, and the association of high sodium excretion with cardiovascular risk was most prominent in patients with low potassium intake.

Comparison with Other Studies

Potassium, the most abundant intracellular cation, and sodium, the most abundant extracellular cation, are inextricably linked, with their exchange required for membrane potential of cells (Na-K-ATPase) and their inter-reliance on diet and kidneys to maintain homeostasis.^{2,3} We found that the association of higher sodium excretion with cardiovascular risk was lower among those with higher urinary potassium excretion. While prior studies have reported that higher potassium intake diminishes the association of higher sodium intake with increased blood pressure, no prior

study has been sufficiently large to demonstrate a significant modifying effect of sodium and potassium intake with cardiovascular events and mortality.¹⁹⁻²⁴ As illustrated in Figure 1b and Table 2, extremes of sodium excretion (both high and low) in a setting of low potassium excretion are associated with the highest risk of death and CV events. Low potassium intake not only results in potassium retention from the kidneys, but also induces sodium retention, even in individuals with high sodium intake and in those with increased aldosterone levels.^{36, 37} Renal conservation of sodium in the setting of low potassium diets, is mediated through WNK kinases activating the thiazide-sensitive NaCl cotransporter (NCC), leading to greater increases in blood pressure with salt intake.^{38, 39} Low potassium intake may also reflect poorer diet quality, particularly lower intake of fruits and vegetables, and the association of sodium intake with cardiovascular risk may be confounded by foods that independently increase CV risk. Our subgroup analysis by diet quality (mAHEI) would lend some support to this contention, whereby the magnitude of association of sodium excretion with cardiovascular risk was lower among those consuming the highest third of diet quality, although formal tests of interaction were not significant. (Table 3) Therefore, higher potassium intake may directly affect cardiovascular and mortality risks or is a marker of increased intake of healthier food items that are rich in potassium (e.g. fruit, vegetables, nuts), or a combination of both. The DASH-Sodium trial reported a lower antihypertensive effect of reducing sodium intake, in the setting of higher potassium intake, supporting the contention that the association of higher sodium intake with cardiovascular health may be modified by potassium intake.⁴⁰ A small cluster randomised controlled trial (5 centres), which replaced table salt with low sodium salt substitute (partially replaced with potassium chloride) reported reduced risk of cardiovascular risk in those centres randomized to salt substitution, although findings were not conclusive due to methodologic

limitations of the trial.⁴¹ An ongoing large cluster randomized controlled trial in China, evaluating use of salt substitutes (KCl substituted for NaCl) is expected to provide a more definitive answer.⁴² However, these trials are evaluating simultaneous increased potassium intake with reduction of high sodium intake to moderate intake levels, and it is unlikely to inform whether very low sodium (<2.0g/day) is beneficial or harmful. Finally, increased cardiovascular risk may also be mediated through activation of numerous adaptive renal and neuroendocrine mechanisms to maintain balance of both electrolytes, in response to low potassium and low sodium dietary, especially activation of the renin-aldosterone-angiotensin system, whose activation is known to increase cardiovascular risk. Collectively, these data suggest that the health impact of these two cations cannot be easily assessed separately. Prior studies have reported on use of sodium-to-potassium ratio to predict cardiovascular events and mortality, and most have reported a significant association. However, our findings would argue against an isolated use of a ratio, because of the J-shaped association of sodium intake and clinical outcomes and does not take account for absolute intake levels. For example, the combination of moderate intake of sodium and potassium is associated with lower cardiovascular risk than combined low intake of both sodium and potassium intake, despite the same sodium-to-potassium ratio.

Public Health Implications

Guidelines for dietary recommendations, targeting the entire population, should be both feasible and based on clear high-quality evidence of improved health outcomes.^{4,5} Our results suggest that a combined strategy of low sodium intake (<2.0g/day), while simultaneously increasing potassium intake to >3.5g/day, is unrealistic, as only 0.001% of the population were in this range (0.2% for potassium excretion of 2.62g/day, if we assume that about 75% of potassium is

excreted in urine). These estimates are consistent with reports from studies in the UK (0.1%), US (0.3%), Mexico (0.15%) and France (0.5%).⁷ In each of these studies, estimates of sodium intake were based on questionnaire which is known to underestimate intake, meaning that the proportion of the population achieving actual target may be lower than reported.⁷ This finding also meant that we were unable to evaluate the association of these joint dietary intake levels at extreme intake levels with health outcomes, as there were insufficient numbers of participants despite the large sample size. We observed a linear relationship between increased sodium and potassium intake, a consistent finding of other studies.^{7,20} These findings question the feasibility of increasing potassium intake while achieving very low sodium intake through modifying diets. While small Phase II clinical trials, such as DASH-Sodium trial⁴⁰, have achieved these targets in the short-term, they required complete control of dietary intake (by providing all meals), which is impractical in free living populations. In contrast, the PREDIMED study⁴³, which promoted increased potassium-containing foods (fruit, vegetables, nuts) with greater adherence to the Mediterranean diet, without focusing on low sodium intake, reported a significant reduction in CVD and mortality, and adherence to a Mediterranean diet has an inconsistent correlation with sodium intake^{44, 45}. In addition, a recent analysis of the NHANES study reported that sodium intake >2.3g/day was associated with better diet quality, compared to diets consuming less than 2.3g/day, meaning that improving dietary quality is likely to be easier to achieve within a moderate sodium intake range.⁴⁶ These considerations raise considerable doubts about the feasibility, and assumed cardiovascular effects, of current recommendations to reduce sodium intake to very low levels (<2g/day), which may counteract achieving dietary targets of dietary intake and improving overall dietary quality.

Strengths and Limitations of Study

Our estimate of sodium intake is based on a baseline measurement of sodium intake, derived from fasting morning urine, rather than repeated 24-hour urinary collections which would be considered the reference standard for estimating usual sodium and potassium intake. However, our approach has been validated in an international study, against actual 24-hour urine estimates of sodium and potassium excretion.³¹ Other formula-based approaches have been developed for estimating 24-hour urinary sodium and potassium excretion, and one study reported that Kawasaki formula was associated with the largest bias compared to actual 24-hour urine collections. However, in the study by Cogswell et al⁴⁷, a non-fasting spot urine sample was used, which would be expected to produce biased over-estimates since the Kawasaki formula was developed and validated for a fasting urine sample, best reflecting basal excretion. In another study⁴⁸, which used an appropriate fasting sample, the Kawasaki formula approach was reported to be associated with least biased estimates (versus other formula), compared to actual 24-hour urine. Further evidence of the construct validity of our approach is the relationship of estimated 24-hour urine estimates of sodium excretion to blood pressure (2.11/0.78mmHg per gram increase in estimated 24-hour urinary sodium excretion), which are consistent with estimates reported in randomised controlled trials of sodium reduction (~1.93/0.88mmHg per gram increase).⁴⁹

Relating a single time-point estimate of sodium and potassium intake to long-term follow-up of death and cardiovascular events may be problematic if there are interval changes in dietary intake over time, and where repeated dietary measures are required to reduce the risk of regression dilution bias. Our approach is consistent with many other large epidemiologic studies of sodium and potassium intake, and analogous to epidemiologic studies relating blood pressure, glucose and cholesterol to clinical outcomes. For example, the correlation of office blood

pressure and 24-hour ambulatory blood pressure, and that of fasting glucose to HbA1c, is similar to the correlation we report for formula-derived estimates.³¹ We chose this practical approach to estimating population-level sodium and potassium intake in the PURE study, which includes a large representative population of participants from high, middle and low-income countries. We deemed actual 24-hour collections to be unfeasible in many low-income settings and expected to have a greater risk selection bias due to non-completion of 24-hour collections. For example, in a recent NHANES study⁵⁰, completion rates for 24-hour urines were about 75%, and completers differed from non-completed with respect to age, sex, ethnicity, BMI and hypertension status. For these reasons, the WHO suggests⁵¹ use of formula-derived estimates of sodium and potassium intake in population-level studies monitoring intakes over time. Among studies reporting on temporal changes of sodium intake over time, there is stability in mean intake of countries⁶, especially those with mean sodium intake in the moderate range (3-5g/day), while some countries with high mean intakes (>5g/day) have reported reductions in mean intake levels (e.g. China, Finland)⁵², which means that interval changes in sodium intake is less likely to influence our findings in the low to moderate range of sodium intake, but may reduce the magnitude of association in the higher sodium intake range.

Reverse causation has been a criticism of prospective cohort studies evaluating the association of diet and clinical outcomes, which may also occur when individuals with reduce their sodium intake due to illness or medical recommendations. Alternatively, it may occur where individuals with prior cardiovascular disease or risk factors, who are at increased cardiovascular risk, reduce their sodium intake due to medical recommendations. In the PURE study, a minority of participants had a previous cardiovascular disease, and our findings are not materially altered with their exclusion. Moreover, in the current analyses, the exclusion of participants with cancer,

diabetes, current smoking, or participants who had events in the first three years of follow-up did not materially alter findings. Additionally, we did not find an increased risk of death due to cancer with low sodium intake. Finally, given the observational nature of the study, residual confounding is a potential limitation. However, we adjusted for all major confounders of the association of sodium and potassium intake and cardiovascular events. Strengths of our study include the large representative international population in the PURE study, completeness of follow-up, rigorous approach to measurement of baseline variables and adjudicated outcome clinical events.

CONCLUSIONS

In conclusion, our findings suggest that a simultaneous target of low sodium (<2g/day) with high potassium intake (>3.5g/day) in the population is extremely uncommon. The combination of moderate sodium intake (3-5g/day) with high potassium intake is associated with lowest risk of mortality and cardiovascular events, while extremes of sodium intake combined with low potassium urinary excretion were associated with the highest cardiovascular risk. Our data support population-wide increases in dietary potassium intake, with a population-specific (i.e. those consuming sodium intakes over 5g/day) reduction of sodium intake, embedded within an overall healthy dietary pattern.

What is already known on this topic

Current dietary guidelines recommend sodium restriction (<2.0g/day recommended by the WHO) but increased potassium intake (>3.5g/day recommended by the WHO). Studies evaluating the association of sodium intake have reported inconsistent findings, but many report a J-shaped association, while those evaluating potassium intake generally report a linear reduction in mortality with increasing potassium intake. Most observational studies have reported on the effects of sodium and potassium intake separately, although some have reported on the association of sodium-potassium ratio with clinical outcomes.

What this study adds

Our findings suggest that the simultaneous target of low sodium (<2g/day) with high potassium intake (>3.5g/day) may not be associated with lowest cardiovascular risk, although the very low proportion of the population consuming these targets precludes a reliable assessment of the risk in this range. We observed the combination of moderate sodium intake (3-5g/day) with higher potassium intake to be associated with the lowest risk of mortality and cardiovascular events. The J-shaped association of sodium intake with mortality and cardiovascular events does not lend support to the current WHO recommendation to consume low sodium diets (<2.0g/day), and also argues against use of sodium-potassium ratio. While there is a major public health emphasis on reducing sodium intake, our findings suggest that increasing potassium intake may be a more important target, for two reasons. First, increased potassium intake is associated with a reduction in death and major cardiovascular events. Second, our data suggest that higher potassium intake may diminish the association of high sodium intake with cardiovascular events and mortality, meaning that high salt diets may pose a lower risk in the setting of higher potassium intake. Our

data support a dietary target of moderate sodium intake (3-5g/day) with higher potassium intake, embedded within improved overall dietary quality.

Contributors: SY conceived and started the overall Prospective Urban Rural Epidemiology (PURE) study, SR coordinated the study, and KT was the co-principal investigator. MOD, SY and AM designed and SY supervised the present study. NOL and JF did the statistical analysis. MOD, SY and AM wrote the first draft of the manuscript. SY supervised the study conduct and data analysis and provided critical comments on all drafts of the manuscript. All other authors coordinated the study and collected the data in their respective countries and provided comments on drafts of the manuscript. All authors reviewed and provided critical comments on drafts. All authors have approved the submitted version.

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Ethical Approval: The study was approved by research ethics committees at all participating centres and at Hamilton Health Sciences, Hamilton, Ontario, Canada.

Data Sharing: No additional data available.

Transparency: The lead author (MO'D) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted and that any discrepancies from the study as planned have been explained.

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Table 1 Association of Estimated Urinary Sodium Excretion with Mortality and Cardiovascular Events

	Estimated Sodium Excretion g/day					
	<3 g/d (n=11,002)	3-3.99 g/d (n=21,417)	4-4.99 g/d (n=26,012)	5-5.99g/d (n=21,093)	6-6.99 g/d (n=12,458)	≥ 7 g/d (n=11,218)
	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)	HR (95%CI)
Mortality and Cardiovascular Events	949	1562	1816	1640	964	953
Univariate*	1.23 (1.14-1.34)	1.05 (0.98-1.12)	1.00	1.09 (1.02-1.17)	1.07 (0.99-1.16)	1.16 (1.07-1.26)
Multivariable (Primary)**	1.19 (1.09-1.30)	1.06 (0.99-1.14)	1.00	1.08 (1.00-1.16)	1.07 (0.98-1.16)	1.23 (1.12-1.34)
Multivariable (+ Diet)	1.16 (1.05-1.27)	1.06 (0.98-1.14)	1.00	1.09 (1.01-1.17)	1.08 (0.99-1.18)	1.26 (1.15-1.39)
Multivariable (+Blood pressure/Heart Rate)	1.15 (1.04-1.28)	1.06 (0.98-1.14)	1.00	1.08 (1.00-1.16)	1.06 (0.96-1.16)	1.17 (1.06-1.28)
Multivariable† (Excluding CVD, Diabetes, Smoker and Cancer)***	1.16 (1.03-1.31)	1.04 (0.94-1.15)	1.00	1.08 (0.98-1.19)	1.06 (0.95-1.18)	1.12 (0.99-1.25)
Multivariable† (Excluding events in first 3 years)	1.20 (1.07-1.33)	1.11 (1.02-1.21)	1.00	1.12 (1.03-1.21)	1.09 (0.99-1.20)	1.17 (1.06-1.30)
Multivariable† (Primary +Lipids)	1.17 (1.06-1.29)	1.06 (0.98-1.15)	1.00	1.07 (0.99-1.16)	1.05 (0.96-1.15)	1.24 (1.13-1.36)

OR=Odds ratio, CI=confidence intervals. Primary model includes the following covariates at baseline: age, sex, education, alcohol intake, diabetes mellitus, body mass index, a history of cardiovascular events, cancer and COPD, cardiovascular medication at baseline, HIV, tuberculosis or Chagas, physical activity level and smoking status and dosage. Dietary variables: addition of caloric intake, potassium intake, waist-to-hip ratio, and mAHEI. Blood pressure variables: baseline systolic blood pressure and history of hypertension. LDL/HDL ratio available in 88% of cohort. *univariate analysis using Cox proportional hazards model with a random effect for study centre (to address clustering of data), includes 103,200 participants with follow-up data. † adjusted for variables in primary model **major cardiovascular events includes CV mortality, myocardial infarction, stroke and heart failure. **Primary multivariable model included 90% of all participants in univariate model, 10% of participants had missing data for at least one covariate, we did not undertake imputation for missing data. ***excluding those with baseline history of cardiovascular disease, diabetes mellitus, current smoking and cancer (prior history or within first year of follow-up)

Table 2 Association of Joint Urinary Sodium and Potassium Excretion with Mortality and Cardiovascular Events

	Sodium <3g/day	Sodium 3-5g/day	Sodium >5g/day
Potassium (<Median, 2.1g/day)	HR 1.23 (1.11-1.37) 716/7582 *	HR 1.10 (1.01-1.19) 1924/24741 *	HR 1.21 (1.11-1.32) 1260/14259 *
Potassium (≥Median, 2.1g/day)	HR 1.19 (1.02-1.38) 233/3420 *	HR 1.00 (Reference) 1454/22688 *	HR 1.10 (1.02-1.18) 2297/30510 *

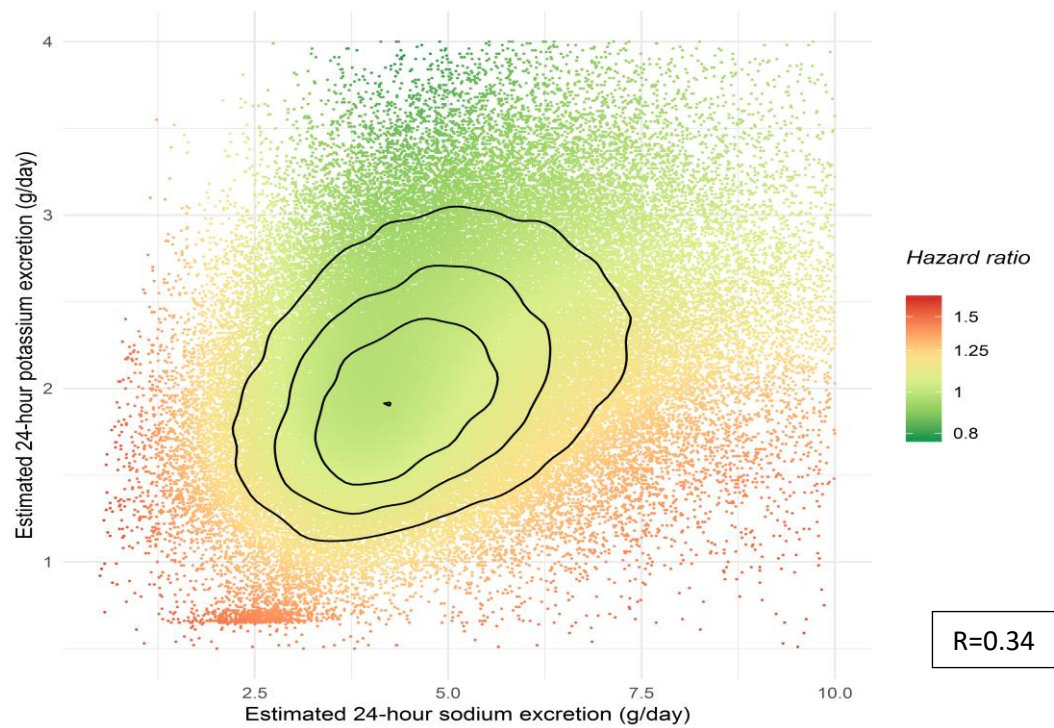
Adjusted for age (included as spline function), sex, education, current and former alcohol intake (units per week), diabetes mellitus, body mass index (BMI), physical activity, history of cardiovascular events, use of cardiovascular medications (blood pressure lowering, statins or diabetes), history of tuberculosis, cancer, HIV, and current and former smoking. *Event proportion for composite outcome of major cardiovascular events or mortality.

Table 3 Association of Estimated Urinary Sodium Excretion with Mortality and Cardiovascular Events (Subgroup Analysis)

	Estimated Sodium Excretion g/day						P-interaction
	<3 g/d (n=11,002)	3-3.99 g/d (n=21,417)	4-4.99 g/d (n=26,012)	5-5.99g/d (n=21,093)	6-6.99 g/d (n=12,458)	≥ 7 g/d (n=11,218)	
	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	
Potassium Excretion (Tertiles)							
<1.8g/day	1.14 (1.00-1.30)	1.02 (0.91-1.14)	1.00	1.02 (0.89-1.16)	1.15 (0.97-1.36)	1.27 (1.04-1.54)	P=0.929 (Below Median Sodium Excretion) P=0.007 (Above Median Sodium Excretion)
1.8-2.3g/day	1.16 (0.97-1.38)	1.11 (0.97-1.26)	1.00	1.16 (1.03-1.31)	1.17 (1.01-1.36)	1.47 (1.26-1.71)	
>2.3g/day	1.12 (0.91-1.39)	1.02 (0.88-1.18)	1.00	1.08 (0.95-1.22)	1.01 (0.88-1.16)	1.11 (0.96-1.27)	
Modified Alternative Healthy Eating Index (mAHEI) (Tertiles)							
<31.3	1.18 (1.01-1.38)	1.10 (0.97-1.25)	1.00	1.11 (0.98-1.25)	1.07 (0.92-1.25)	1.47 (1.26-1.73)	P=0.868 (Below Median Sodium Excretion) P=0.297 (Above Median Sodium Excretion)
31.3-38.4	1.24 (1.06-1.46)	1.09 (0.96-1.25)	1.00	1.14 (1.01-1.30)	1.12 (0.97-1.30)	1.22 (1.05-1.43)	
>38.4	1.09 (0.92-1.29)	1.03 (0.90-1.17)	1.00	1.00 (0.88-1.14)	0.99 (0.85-1.14)	1.06 (0.91-1.23)	

Adjusted for age (included as spline function), sex, education, current and former alcohol intake (units per week), diabetes mellitus, body mass index (BMI), physical activity, history of cardiovascular events, use of cardiovascular medications (blood pressure lowering, statins or diabetes), history of tuberculosis, cancer, HIV, and current and former smoking.

Figure 1 Scatterplot of Sodium and Potassium Urinary Excretion



Legend: Figure reports scatterplot of estimated 24-hour urinary sodium and potassium excretion in the PURE population. Grey box indicates target guideline intake for combined sodium and potassium intake. Figure demonstrates correlation of increasing sodium and potassium intake. Clustering of intake at 0.5g/day of potassium is related to lower limit of lab measurement in one laboratory (India). Figure illustrates a heat map of risk of risk of composite of cardiovascular events or death that indicates lowest risk in region of moderate sodium intake 3-5g/day and higher potassium intake. Highest risk occurs in regions of extremes of sodium excretion and low potassium excretion. Changes in hazard for various outcomes with changes jointly in both sodium and potassium excretion/intake were modelled using two-dimensional natural cubic splines. For each of sodium and potassium, 2 knot points were selected at the tertiles of the variable's sample distribution. This resulted in a grid of 4 knot points on the two-dimensional (sodium and potassium) spline surface. For a given outcome, the Cox proportional hazard model then included (along with other covariates) natural cubic spline variables for both sodium and potassium separately and also interaction terms between these spline variables. To visualise the two-dimensional relationship, and the putative interaction effect between sodium and potassium on hazards of a given outcome, estimated hazard ratios were evaluated and plotted on a sampling grid (0.01g apart) within the range of observed sodium and potassium was evaluated. The reference hazard for these hazard ratios was set at a value of sodium daily excretion/intake of 5.00g and potassium daily excretion/intake of 2.25g (median excretion of sodium and potassium), marked as 'X'.

Figure 2 Association of Estimated 24-hour Urinary Sodium Excretion with Mortality and Major Cardiovascular Event

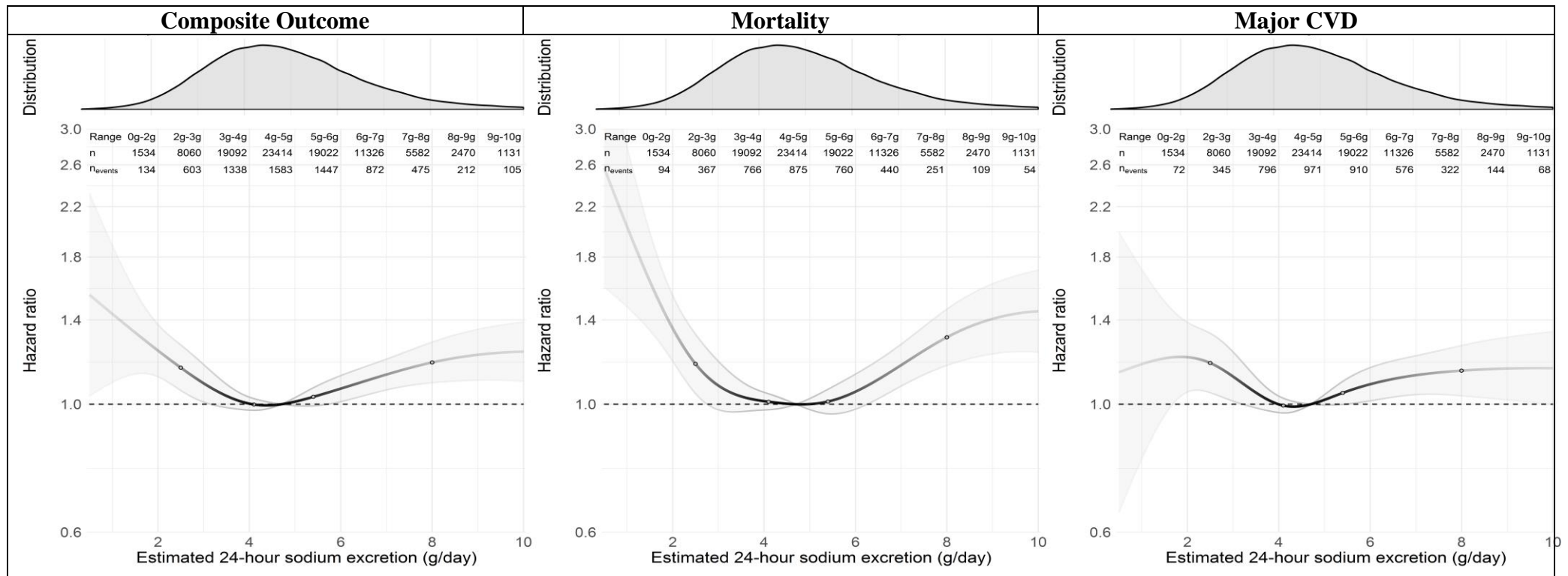


Figure 2a, restricted cubic spline plot of association of estimated 24-hour urinary sodium excretion (X-axis) with composite of all-cause mortality and major cardiovascular events. Spline curve truncated at 10 g per day.

Figure 2b, restricted cubic spline plot of association of estimated 24-hour urinary sodium excretion (X-axis) with mortality. Spline curve truncated at 10 g per day.

Figure 2c, restricted cubic spline plot of association of urinary sodium excretion (X-axis) with major cardiovascular events (which is a composite of cardiovascular death, myocardial infarction, stroke and heart failure). Spline curve truncated at 10 g per day.

All plots adjusted for age (included as spline function), sex, education, current and former alcohol intake (units per week), diabetes mellitus, body mass index (BMI), physical activity, history of cardiovascular events, use of cardiovascular medications (blood pressure lowering, statins or diabetes), history of tuberculosis, cancer, HIV, and current and former smoking. Dashed lines indicate 95% confidence intervals (CI). Median intake is reference standard (4.91g/day). Salt approximates 2.5 X sodium g per day.

Figure 3 Association of Estimated 24-hour Urinary Potassium Excretion with Mortality and Major Cardiovascular Events

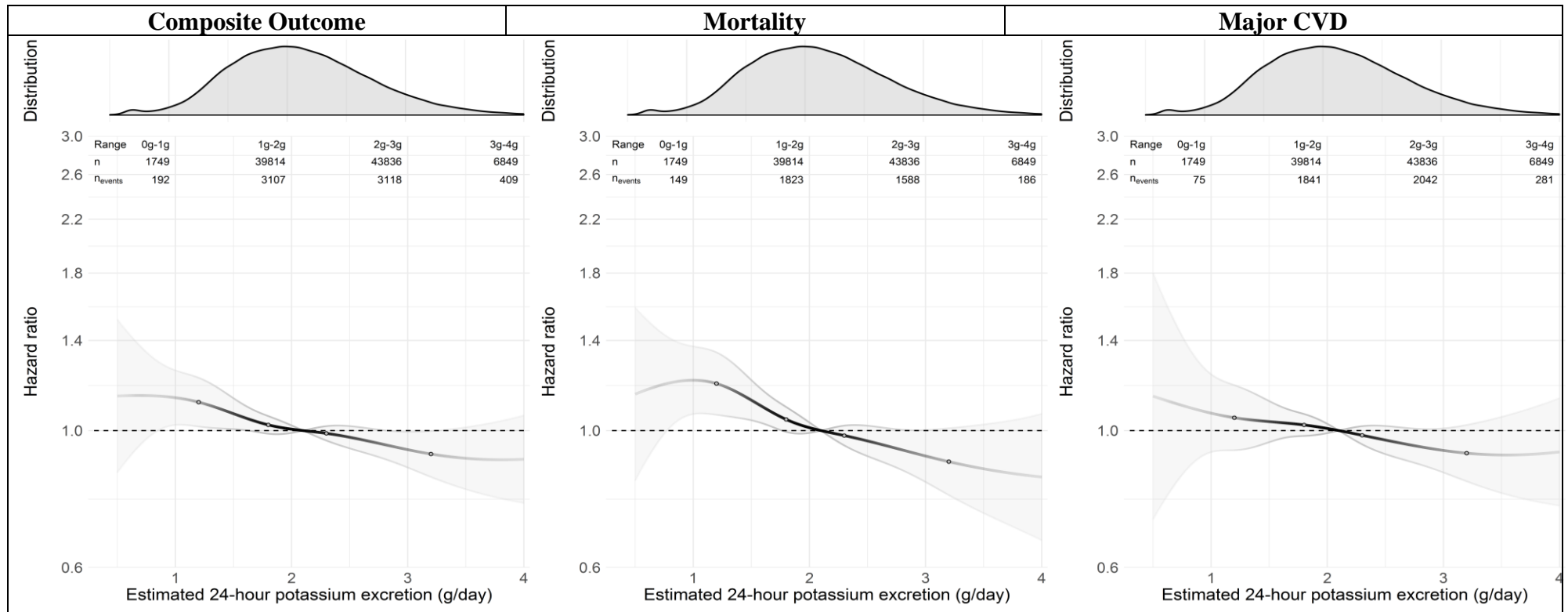


Figure 3a, restricted cubic spline plot of association of estimated 24-hour urinary potassium excretion (X-axis) with composite of all-cause mortality and major cardiovascular events. Spline curve truncated at 4 g per day.

Figure 3b, restricted cubic spline plot of association of estimated 24-hour urinary potassium excretion (X-axis) with mortality. Spline curve truncated at 4 g per day.

Figure 3c, restricted cubic spline plot of association of urinary potassium excretion (X-axis) with major cardiovascular events (which is a composite of cardiovascular death, myocardial infarction, stroke and heart failure). Spline curve truncated at 4 g per day.

All plots adjusted for age (included as spline function), sex, education, current and former alcohol intake (units per week), diabetes mellitus, body mass index (BMI), physical activity, history of cardiovascular events, use of cardiovascular medications (blood pressure lowering, statins or diabetes), history of tuberculosis, cancer, HIV, and current and former smoking.

Figure 4a Association of Estimated 24-hour Urinary Sodium Excretion with Composite Outcome, Stratified by Potassium Excretion

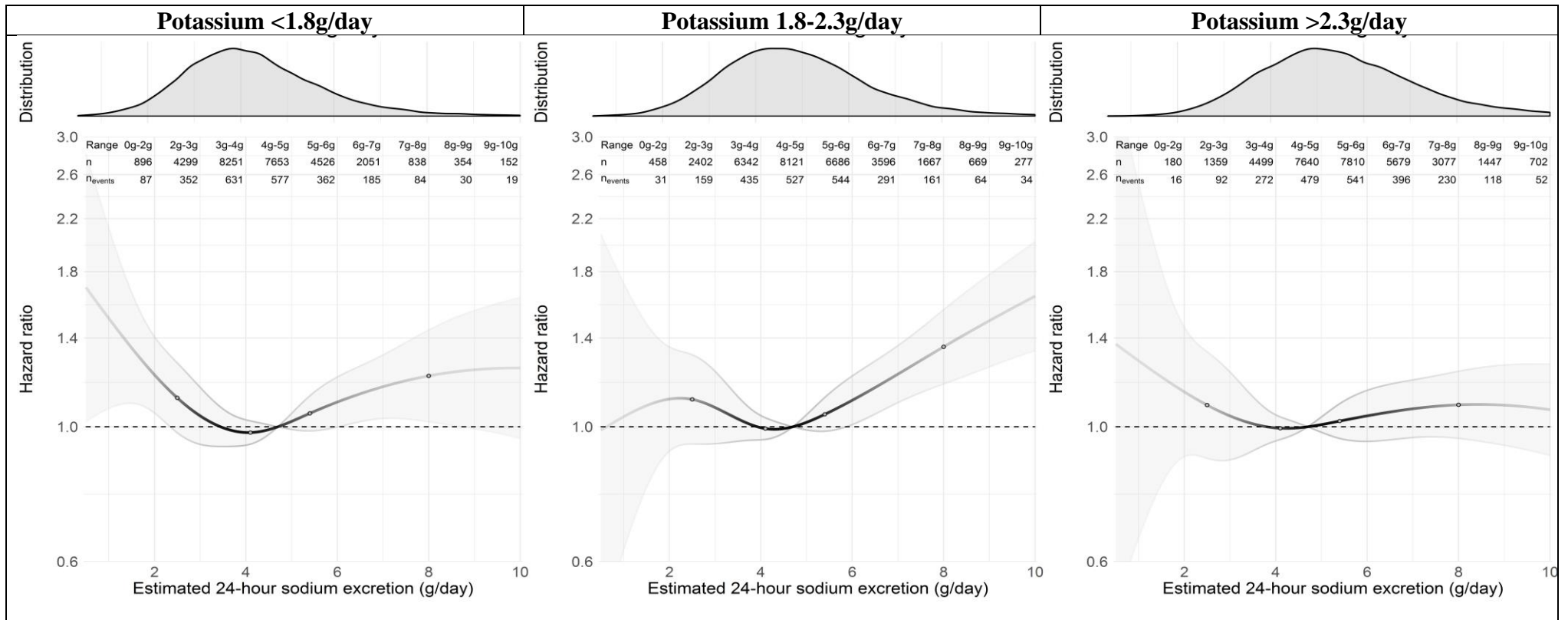


Figure 4b Association of Estimated 24-hour Urinary Sodium Excretion with Composite Outcome, Stratified by mAHEI

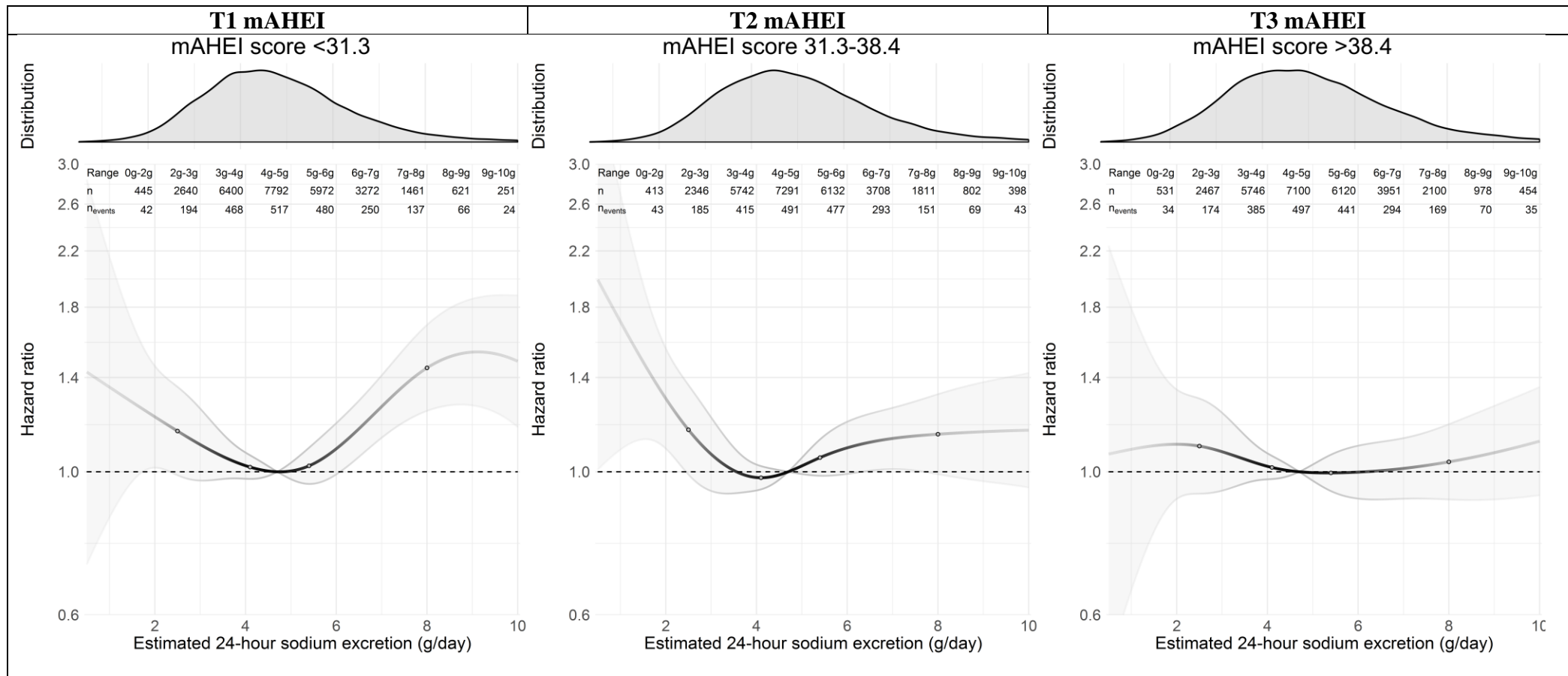


Figure 4 reports association of urinary sodium excretion and composite of mortality and major cardiovascular events, by subgroups of urinary potassium excretion and mAHEI score. Top panel demonstrates association of urinary sodium excretion within tertiles of urinary potassium excretion. P-interaction is significant ($P=0.007$) for urinary potassium excretion*urinary sodium excretion above median intake, with lower magnitude of association with higher urinary potassium excretion. Lower panel demonstrates association of urinary sodium excretion within tertiles of mAHEI. P-interactions not significant. All plots adjusted for age (included as spline function), sex, education, current and former alcohol intake (units per week), diabetes mellitus, body mass index (BMI), physical activity, history of cardiovascular events, use of cardiovascular medications (blood pressure lowering, statins or diabetes), history of tuberculosis, cancer, HIV, and current and former smoking.