

A critical appraisal of the 'Urinary Sodium and Potassium Excretion and Risk of Cardiovascular Events' study cohort, JAMA 2011;306:2229-2238

This critical appraisal is a product of the Scientific Review Sub-group of the Pan American Health Organization/World Health Organization initiative on Cardiovascular Disease prevention through dietary salt reduction. It was reviewed by an international panel of scientists and experts on dietary salt listed at the end of the appraisal.

Numerous highly regarded scientific and health organizations now recommend that dietary sodium should be reduced. This follows the emergence of a large body of evidence documenting a relationship between increased dietary salt and adverse cardiovascular outcomes and death (1-15). Average adult sodium consumption is over 2300 mg/day in most countries and plans are underway to reduce dietary sodium to less than 2000 mg/day in many places (16;17). New research findings have the potential to impact dietary sodium reduction programs. However, research that is scientifically weak is often brought to public attention without broad-based careful scientific consideration and this has the potential to confuse policy makers and the public. Hence a group of international researchers has been formed to appraise new research on dietary sodium in order to assess the potential impact on public health and sodium reduction programs. In the following commentary, this group appraises an article entitled, 'Urinary Sodium and Potassium Excretion and Risk of Cardiovascular Events', recently published in JAMA (18). Methodological problems in the conduct of the study were assessed to be the major determinant of the study findings. Hence, this study should not impact the strong recommendation to reduce dietary sodium in the general population.

In the Nov 23/30, 2011 issue of JAMA, a study was published examining the relationship of dietary sodium to cardiovascular outcomes, with an accompanying editorial (18;19). The study was a *post hoc* analysis relating salt excretion and cardiovascular events, using data from two populations enrolled in drug trials. Participants were individuals with, or at, high risk for cardiovascular disease. The results indicated that both high and low sodium intake was associated with increased cardiovascular events in a 'J' shaped relationship. The study reported an increase in cardiovascular death, stroke or heart attack in those estimated to be consuming more than 6000 mg/day of sodium and less than 4000 mg/day of sodium (for example, those consuming more than 8000 mg/day sodium had a 49% increased risk for the composite of cardiovascular events, while those consuming less than 2000 mg sodium/day had a increased risk of 21%, compared to those consuming 4000 -5999 mg/day). The study also found that estimated potassium intake was protective against stroke.

The study needs to be considered in the context of existing evidence. An extensive body of literature supports the relationship between dietary sodium and adverse health outcomes (14;17;20-32). From an evolutionary standpoint, land animals consumed little sodium and humans less than 1000 mg/day until the advent of mass food processing with salt initially being used as a preservative (33). In carefully conducted animal studies of multiple species, increasing sodium intake above physiological levels causes increases in blood pressure, and most (but not

all) of the increased blood pressure is reversible by reducing sodium intake (34). Hunter-gatherer populations that still consume unprocessed foods have little sodium consumption, have low blood pressures throughout their lifespan, do not develop hypertension with aging and have little if any cardiovascular disease (32). If people from these populations migrate to areas of high salt intake, their blood pressures increase and they develop hypertension (32). Overall in cross sectional and cohort studies, increased sodium intake is associated with increased blood pressure (32;35). In clinical trials of infants/children as well as in normotensive and hypertensive adults, increased dietary salt increases blood pressure (32). In studies of multiple animal species, increased dietary salt causes cardiovascular disease and premature death, most but not all of which is caused by increased blood pressure (36). There are no experimental animal models where decreased sodium intake causes cardiovascular disease and none where high sodium intake prevents disease unless there is an acquired disease causing salt wasting. In a meta-analysis of long term cohort studies of healthy populations, increased salt intake is associated with increased cardiovascular disease and a meta-analysis of clinical trials of normotensive and hypertensive adults shows that lowering dietary salt reduces cardiovascular disease events by 20% (35;37). When the impact of reducing dietary sodium is modeled to estimate the impact on population health, reducing dietary salt is projected to be one of the most effective means of preventing disease. About 30% of hypertension (approximately 300 million people), and 1 in 5 cardiovascular events, are estimated to be caused by excess dietary sodium (37-39). In developed, as well as in emerging countries, reducing dietary sodium is one of the few cost saving population based public health interventions available (40).

In the light of this extensive body of literature, the first question is whether the recently published JAMA results are likely to be true. The increase in cardiovascular events with increased dietary sodium that the authors observed is consistent with the literature summarized above, and will not be discussed further. We will, therefore, focus on the observation that lower sodium intake was also found to result in an increased risk of adverse cardiovascular events.

The studies used in the JAMA article were conducted by investigators, without any apparent conflict of interest, in a clinical trial setting where the participants were carefully monitored and evaluated with almost complete assessment of outcomes. However, their method of estimating dietary sodium is suboptimal, and this is likely to be the principal reason for their paradoxical findings. As discussed below, there are problems both with precision and accuracy, with a large potential for bias. Early morning spot urine and a mathematical correction were used to estimate sodium intake. Presumably the method was used because of the *post hoc* nature of the study. The authors valiantly attempted to validate the method used in their study population. Still, the method used has previously only been validated in a single healthy population and is not currently recommended as a means to determine sodium intake because of evidence that it results in inaccurate classification of dietary sodium (41) (<http://new.paho.org/hq/dmdocuments/2010/pahosaltprotocol.pdf>). Furthermore, correlation coefficients used by the authors are not an appropriate statistical test to assess if the spot urine sodium classification accurately reflects 24 hour urinary sodium classification; a

Bland Altman plot is the standard approach (42). By using the latter method, a recent study has clearly shown the presence of bias (43). Although single 24 hour urinary sodium is recommended as a valid means of assessing salt intake in populations, accurate assessment of intake in individuals requires multiple 24 hour urinary salt evaluations (<http://new.paho.org/hq/dmdocuments/2010/pahosaltprotocol.pdf>).

There are also concerns about accuracy. Many of the people in the study were consuming diuretics, especially in the low sodium intake group. Loop diuretics, if taken prior to the urine collection, could increase estimated sodium intake through increased urinary sodium excretion. Hence the study may be, in part, examining timing of diuretic ingestion rather than sodium intake (44). Potentially those participants who were taking high doses of diuretic during the day might avidly retain urinary sodium, in turn resulting in low early morning urinary sodium levels. As such, these low levels may simply be a marker for high daytime diuretic use and poor outcomes. The investigators indicate that the findings were similar in those not taking diuretics but do not provide relevant data. Also, it should be noted the study populations were older and predominantly male. It is likely that many individuals had benign prostatic hypertrophy leading to reduced urine output and also at greater risk for adverse outcomes.

In observational studies, people select their own sodium intake and are observed over time. One of the most likely reasons for the unexpected findings of the JAMA study is that people who are more ill are more likely to consume less sodium than persons who are otherwise healthy. There are many possible reasons for the reduced sodium intake. For example, persons who are ill consume fewer calories, which is a major determinant of sodium intake. Several studies have demonstrated a positive correlation between sodium intake and caloric intake. Also, persons who are ill may adopt healthier habits including a reduced sodium diet. This phenomenon is called 'reverse causation' where, rather than causing disease, low dietary sodium may be a marker of more severe disease and thus poorer outcomes. Consistent with this, the study population consuming less sodium also had differences in several cardiovascular risk factors and surprisingly did not have higher dietary potassium intake. Potassium intake is usually inversely related to sodium intake since the main mechanism to reduce sodium intake is to increase unprocessed food consumption, which is relatively rich in potassium. The finding in this observational study that there are unusual characteristics of people who eat low salt diets and some higher cardiovascular risk factors (hypertension, diabetes, sedentary behaviour, atrial fibrillation, higher heart rate, more diuretic and calcium channel blocker use), is also found in the few cohort studies that find adverse cardiovascular outcomes with low salt intake. This strongly suggests that unidentified confounding factors, such as those related to poverty or poor health which both increase the risk of cardiovascular disease and lower sodium intake, may explain the anomalous findings in the JAMA article (45-48). Exploration of observational studies from the NHANES data base may provide insights, as studies of this database have had diametrically opposing findings (48;49). Those that were conducted by a team that included a consultant of the Salt Institute showed increased cardiovascular disease with low salt intake (44; 47; 48) while 2 groups of independent investigators refuted those findings reporting lower cardiovascular events or total mortality with lower sodium intake also using the NHANES data

(49,50). Carefully examining the different methods of assessing and adjusting for confounding in the NHANES data bases by the different investigators may identify the confounders that are critical to account for. In the most recent analysis the NHANES data, additional follow-up was included, leading to substantially improved power (49). In addition, statistical methods were used to reduce measurement errors in the assessment of sodium intake

The possibility that the trial results reflect a true risk of increased cardiovascular events in those consuming lower amount of dietary sodium also needs to be considered. The trial population included only people with cardiovascular disease or at high risk of cardiovascular disease, a group that has not been extensively studied. In addition, the interventions in both clinical trials were blood pressure lowering drug treatments and surprisingly (inconsistent with meta-analyses of blood pressure lowering drug treatments) produced no benefit or resulted in harm (51-55). Some have expressed concern that the drug therapies in one of the trials lowered blood pressure too far in some subgroups thus creating adverse effects, and low dietary sodium would have substantively increased the hypotensive effects of the interventions (56;57). Seeing the results of the impact of dietary sodium in the placebo groups compared to the intervention groups could have helped assess if the adverse effects may have been related to hypotension or related to other interactions with the drug interventions. Lower dietary sodium has been demonstrated to increase counter regulatory hormones that have the potential to cause cardiovascular disease in those at risk, but this is seen at lower levels of dietary sodium than were estimated in the trial reported in JAMA (18;58). Perhaps most importantly is that at best, *post hoc* analyses are hypothesis generating and must not be used to infer causation. Such results need to be interpreted carefully even when they are methodologically sound.

Of concern, the authors cite a very unusual trial as providing corroborating evidence. The cited trial evaluated the impact of low sodium diets in people with severe heart failure who were simultaneously treated with massive doses of furosemide and fluid restriction (59;60). Such a trial design is likely to lead to adverse outcomes, and would not be likely to pass a scientific or clinical review committee in most settings. In addition, several findings of the heart failure trial are not clinically plausible in the context of severe heart failure and the treatment provided. Further, it does not provide evidence that could be applied to the general population.

In summary, the published study suffers from crucial methodological concerns. A wide body of existing data consistently demonstrates the benefits of salt reduction on lowering cardiovascular disease and premature death in human populations, and such efforts must be continued in the interest of the public health.

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