Does reducing salt intake increase cardiovascular mortality?

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Overwhelming evidence shows that reducing salt intake from 9–12 to 5–6 g/d lowers blood pressure, thereby preventing cardiovascular disease. A recent paper claims that lower salt intake is associated with higher cardiovascular mortality despite lower blood pressure. The study is flawed and cannot refute the evidence for the benefits of salt reduction. The WHO recommends salt reduction as crucial in tackling the global non-communicable-disease crisis. A reduction in population salt intake remains a public-health priority.

There is much evidence that raised blood pressure (BP) throughout its range (that is, starting at 115/75 mm Hg) is a major cause of cardiovascular disease (CVD)[1]—strokes, heart attacks, heart failure, and renal disease. A modest reduction in salt intake lowers BP and, therefore, would reduce CVD. Indeed, both prospective cohort studies and outcome trials have demonstrated that a lower salt intake is related to a reduced risk of CVD.[2,3] Over the past few years, this evidence has been repeatedly reviewed by several independent national and international panels of experts around the world. All have reached the same conclusions and developed recommendations for a population-wide reduction in salt intake to prevent CVD.[4–7]

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Contrary to the above, a recent study by Stolarz-Skrzypek *et al.* in the *Journal of the American Medical Association* claimed that 'lower sodium excretion was associated with higher CVD mortality.'[8] Detailed examination of this study, however, reveals many serious flaws. Most importantly, there are substantial concerns related to the collection of 24-h urine specimens, leading to misclassification and bias. This is a common problem in cohort studies with paradoxical findings.[9–11] Specifically, individuals in the lowest tertile of 24-h urinary sodium also had lower 24-h urine volume, lower potassium, and lower creatinine excretion. This pattern of findings clearly indicates an undercollection of 24-h urine that could not be fully explained by a lower body weight.

Further support for undercollection of 24-h urine is evident in the methods section, where it is reported that 'participants collected an exactly timed 24-h urine sample in a 2500 ml wide-neck plastic container.'[8] It appears that only one 2.5-liter container was provided to the participants, which is not large enough for individuals who drink more fluid. This would lead to undercollection of urine in these people. The standard practice is to give a 5-liter container to adults and a 2.5-liter container to children. Taken together, these issues suggest that many of the individuals in the lowest sodium-excretion tertile were likely misclassified because they did not properly collect a full 24-h urine.

Nonadherence to instructions could also have played a role. If individuals could not collect their urine properly, they may be less compliant with BP or other treatments. It is therefore not surprising that they may have a higher CVD mortality, given that they also had higher cardiovascular risk factor levels—the lowest level of educational attainment, higher baseline systolic BP, higher total cholesterol levels, and a higher prevalence of smoking.[8] An association of increased mortality with low urinary sodium excretion was also reported in a cohort of diabetics, but the levels of urinary sodium excretion were biologically implausible, as low as 20 mmol/d, consistent with undercollection. In this study, the nearly 20-fold increased risk of mortality was most likely due to noncompliance with collection procedures.[10] Overall, incomplete collection of 24-h urine in cohort studies reflects poor adherence to data collection procedures and is similar conceptually to nonadherence in clinical trials, where it is well documented that nonadherence, even to placebo, is associated with high mortality rates.[12] These fundamental errors in collecting complete 24-h urine invalidate the results of the study by Stolarz-Skrzypek *et al.*[8]

A second issue is the small number of CVD deaths, probably due to the young age of the participants studied. A total of 3681 participants with an average age of about 40 years were followed up for a median 7.9 years.[8] The number of CVD deaths according to tertiles of baseline 24-h urinary sodium excretion was 50 in the low (mean, 107 mmol), 24 in the medium (168 mmol), and 10 in the high excretion group (260 mmol). Stolarz-Skrzypek *et al.*[8] compared the risk for each of these three groups with the risk for all three groups together. Such analysis is strange, as the usual practice for this type of study is to compare each group with a reference group. It is unclear why Stolarz-Skrzypek *et al.*[8] used such a method; presumably they did so because the number of CVD

deaths in each group (for example, $N = 10$) is too small for valid statistical comparisons. In view of this odd analysis, we assume that a direct comparison between the high and low tertiles or between the medium and low tertiles was not significant. It is extraordinary that, on the basis of such a small number of CVD deaths and one 24-h urinary sodium measured about 8 years earlier, the authors concluded that 'our current findings refute the estimates of computer models of lives saved and health care costs reduced with lower salt intake.'[8]

Third, Stolarz-Skrzypek et al.[8] also reported a separate 'blood pressure cohort' of 1499 participants who were followed up for 6.1 years and in whom 24-h urinary sodium measurement was repeated at the end of follow-up. This analysis showed a significant relationship between 24-h urinary sodium and systolic BP, with a 100-mmol increase in sodium excretion associated with a 1.71-mm Hg increase in systolic BP ($P < 0.001$).[8] Importantly, the authors did not mention whether BP predicted cardiovascular mortality. If not, there would be a fundamental problem with the study, as they would have to claim, on the basis of their reasoning about salt, that BP is not a determinant of cardiovascular events.

Stolarz-Skrzypek et al.[8] tried to ascribe the higher CVD mortality with a lower salt intake to the activation of the renin–angiotensin–aldosterone system and the sympathetic nervous system, as well as a decrease in insulin sensitivity. They cited the meta-analysis by Graudal et al.[13] as the evidence for these claims. However, this meta-analysis included a very large number of trials with conditions ranging from acute salt loading to abrupt and severe salt restriction—for example, from 20 to less than 1 g/d for only a few days. Such acute salt loading and depletion experiments are not relevant to public-health recommendations for a modest reduction in salt intake for a prolonged period of time. Indeed, randomized trials have demonstrated that, with a longer-term modest reduction in salt intake, there was only a small increase in plasma renin activity,[14] and no substantial change in the sympathetic nervous activity,[15] glucose tolerance, or insulin sensitivity.[16] Stolarz-Skrzypek et al.[8] failed to cite these more relevant papers.

Furthermore, salt reduction lowers BP by a similar mechanism to that of thiazide diuretics. Both stimulate the renin–angiotensin system and, in the short term, the sympathetic nervous system. However, outcome trials have demonstrated that thiazide diuretics significantly reduced cardiovascular morbidity and mortality in hypertensive individuals.[17] It could be argued that long-term treatment with thiazide diuretics may increase the risk of diabetes.[18] However, this is likely to be due to the lower serum potassium that occurred.[18] Concomitant treatment with potassium supplementation or use of potassium-sparing diuretics has been shown to lessen the glucose intolerance and possibly prevent the development of thiazide-induced diabetes.[18] The advantage of modest salt reduction over thiazide diuretics is that salt reduction does not have a significant effect on serum potassium but has a similar BP-lowering effect in hypertensive individuals, as demonstrated by randomized trials.[19]

Finally, there are several additional problems with the study by Stolarz-Skrzypek et al.[8] A large number of participants had missing or incomplete data or were lost to follow-up. The presentation of results was also confusing. For example, one cohort was analyzed as three separate cohorts with different eligibility criteria, different numbers of participants, and different durations of follow-up. This confusing presentation makes it extremely difficult to judge the validity of the study methodology. The study also has other paradoxical results. The finding of low urinary potassium in those excreting low sodium is unanticipated, as the major mechanism for marked reduction in sodium intake is the eating of unprocessed foods, which are high in potassium. The presence of low potassium excretion in the group with low sodium excretion, therefore, suggests either substantive residual confounding possibly due to overall food intake and poverty or nonadherence to the urine collection procedure, as previously noted. Another paradoxical finding is the 'inverse' association between urinary sodium-to-potassium ratio and CVD outcomes, a finding at variance with the vast majority of population studies reported so far.

Because of the serious flaws described above, the study by Stolarz-Skrzypek et al.[8] cannot be used to refute the strong evidence that a modest reduction in population salt intake is extremely beneficial to health and could prevent millions of deaths from strokes, heart attacks, heart failure, and kidney disease each year.[4–7,20]
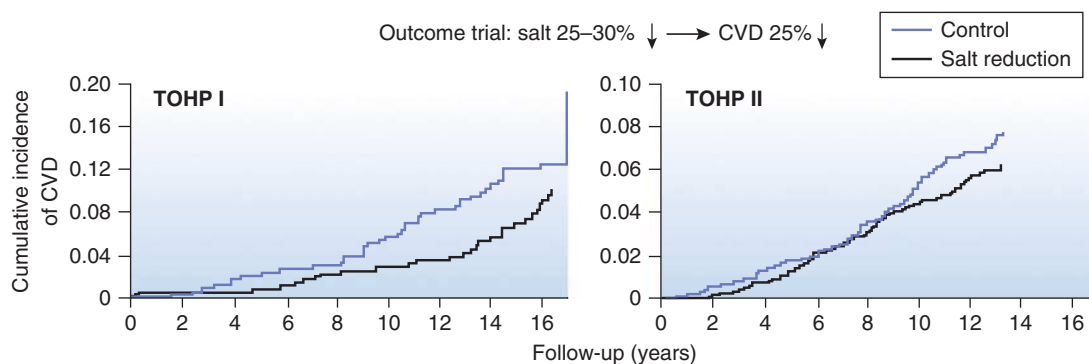

Figure 1 | Cumulative incidence of cardiovascular disease (CVD) by salt intervention group in the Trial of Hypertension Prevention (TOHP) I and II, adjusted for age, sex, and clinic. Adapted from Cook et al.[3]

A meta-analysis of all prospective cohort studies has demonstrated a direct relationship between salt intake, stroke, and CVD risk.[2] This association remained significant even when the study by Stolarz-Skrzypek *et al.* was included in an updated meta-analysis. The pooled results showed that an increase of approximately 5 g/d in salt intake (that is, 2 g/d or 85 mmol/d of sodium) was related to a 20% increase in the risk of stroke ($P = 0.026$) and a 14% increase in total CVD ($P = 0.07$). Stronger evidence comes from outcome trials.[3,21] A follow-up study of individuals who took part in two large randomized salt reduction trials demonstrated that a 25–30% reduction in salt intake resulted in a 25% decrease in cardiovascular events (Figure 1).[3] Another outcome trial of more than 2.5 years in elderly Taiwanese veterans ($N = 1981$) showed that switching from the usual salt (sodium chloride) to potassium-enriched salt (49% sodium chloride, 49% potassium chloride, 2% other additives) with a subsequent reduction of 17% in salt intake and an increase of 76% in potassium intake resulted in a 40% decrease in CVD mortality.[21]

In conclusion, the totality of the evidence for a causal relationship of chronic high salt intake with elevated BP and CVD is robust and persuasive.[4–7,20] The paper by Stolarz-Skrzypek *et al.*[8] and other papers[9–11] with paradoxical findings related to methodologic flaws should not divert us from reducing salt intake worldwide. A reduction in salt from the current intake of 9–12 g/d to the recommended level of less than 5–6 g/d will have major beneficial effects on health along with major cost savings in all countries around the world.[4–7,20] At a recent high-level policy meeting of the World Health Organization, salt reduction has been recommended as one of the top priority actions to tackle the global non-communicable-disease crisis.[22,23] Rather than pursuing the question of *whether* salt intake should be reduced to prevent CVD, the global health priority is and should remain *how* to reduce population salt intake to save lives.

DISCLOSURE

This publication does not necessarily represent the decisions or the stated policy of the WHO (World Health Organization), and the designations employed and the presentation of material do not imply the expression of any opinion on the part of the WHO. All the authors declared no competing interests.

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