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How robust is the evidence for recommending very low salt intake in entire populations?

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Salt has been regarded as precious and essential to life from prehistoric times. It is needed to maintain livestock on farms and used to preserve foods since early times. Salt was highly valued in ancient China, Rome and other parts of Europe and became an early trading commodity and source of tax revenue. Protests against the salt tax were integral to the Indian movement for independence, and chosen for its symbolic importance by Mahatma Gandhi, stating, “next to air and water, salt is perhaps the greatest necessity of life”. Salt deprivation was thought responsible for many summer deaths in India during British rule.

Salt (sodium chloride) accounts for 95% of sodium intake. Sodium is an essential nutrient, crucial to the action potential of cell sand involved in first response to cutaneous injuries to prevent infections. Sodium is required to maintain intravascular volume, and an important determinant of blood pressure (BP). While excess sodium intake is a risk factor for hypertension, extreme salt depletion causes hypotension and lethargy, and increased sodium intake is recommended in patients with symptomatic orthostatic hypotension.

Our appetite for sodium is controlled by neural mechanisms in response to peripheral hormonal signals (principally angiotensin II and aldosterone). Reductions in sodium intake to low levels (<3g/day) markedly activates the renin–angiotensin–aldosterone system (RAAS) to conserve sodium. Although extreme reductions in sodium intake are possible in controlled settings for short periods, this is not sustainable long term in free living individuals. This, along with increased intake of non-discretionary sources of salt, may explain why the amount of sodium intake in the US has remained unchanged for over 5 decades (~3.5 g/day), despite public policy efforts to reduce sodium intake to <2.3 g/day.

The idea that salt intake could pose a threat to the general population has only emerged in the past 3 decades, although the first case report of managing severe hypertension with salt restriction was published in 1948. One of the most influential studies was INTERSALT, which reported a weak association between sodium excretion and BP(0.94/0.03 mmHg per 1g of sodium) in ecologic analyses across 52 centers. This association was not reproduced in an individual-level analysis of another large and well-conducted study, the Scottish Health Study (n=7354), which was published in the same issue of the British Medical Journal, but was much less influential (638 versus 101 citations, as per Web of Science, accessed August 1st, 2016). Further, there was no significant association between salt intake and blood pressure in
INTERSALT when 4 outlier centers from primitive societies (Yanomamo Indians and tribes in Africa) were removed from the analyses. The very low mean sodium intake (<1g/day) reported in some of these primitive societies is often cited as evidence to support the safety of very low sodium intake, despite the fact that the life expectancies of people living in these primitive societies were relatively short (e.g. 40 years in the Yanomamo Indians)\textsuperscript{16} and additional studies have demonstrated extreme activation of RAAS in these populations.\textsuperscript{17} Moreover, data provided in the appendix of the study suggests incomplete collection of 24-hour urine based on implausibly low urinary creatinine levels.\textsuperscript{14} Nonetheless, the totality of observational research studies, including the recent PURE study (n=102,216)\textsuperscript{18} confirm a nonlinear association between increased sodium intake and blood pressure, and the magnitude of the latter association is largest in those consuming high sodium diets, and low in potassium or those with hypertension.

In the late 1990s, findings from two clinical trials (TON\textsuperscript{E} and TOHP-II trials)\textsuperscript{19,20} demonstrated that an intensive behavioral dietary intervention could reduce sodium intake (mean reduction of \~1g/day) and result in a modest reduction in blood pressure (-1.2/0.7mmHg in TOHP-II at 36 months). Although both clinical trials targeted a sodium intake of less than 1.8g/day, neither intervention group achieved this target (mean intake in TONE was about 2.4g/day and in TOHP-II was 3.1g/day on final follow-up).\textsuperscript{19,20} Both clinical trials implemented a resource intensive dietary counseling intervention to reduce dietary sodium, through changing dietary patterns which is expected to result in other dietary changes, such as greater fruit intake, and fewer processed foods. Neither employed a control dietary intervention. To date, these clinical trials are the largest to evaluate sodium reduction (enveloped within a change in dietary pattern) on blood pressure. In 2001, the DASH-Sodium trial,\textsuperscript{21} which was a Phase IIa clinical trial (n=412) that demonstrated a BP lowering effect of reduced sodium intake to very low levels (<1.5g/day) over a 30-day period using pre-prepared meals. Despite its small size, and proof-of-concept design, findings from the DASH-Sodium trial have exerted more influence on guideline recommendations than any other trial (including TONE and TOHP-II), as many guidelines currently recommend very low sodium intake levels (e.g. <1.5g/day recommended by AHA)\textsuperscript{22} although this was not achieved by either TONE or TOHP trials.\textsuperscript{19,20} Despite the absence of clinical trials demonstrating the effect of low sodium intake on CVD,\textsuperscript{23} or any study showing the feasibility of sustained low sodium intake in the general population,\textsuperscript{18} the effect of sodium reduction on BP was considered sufficiently robust for most guidelines to endorse low sodium
intake for the entire population. It was assumed that all reductions in sodium intake would result in reductions in blood pressure in all populations, which in turn would be expected to translate directly into predictable reductions in CVD incidence.\textsuperscript{24}

A major challenge to the assumed benefit of low sodium intake on CVD events came from prospective cohort studies reporting an increased risk of CVD and mortality with low sodium intake (compared to moderate intake), mostly published in the past 6 years.\textsuperscript{25-31} A 2014 meta-analysis of studies (n=274,683)\textsuperscript{32} identified an increased CVD risk for sodium intake under 2.7g/day, and above 5.0g/day. Clearly, findings from these studies directly contradict recommendations for lowering sodium intake to below 2.3 g/d, and suggest that moderate sodium intake is associated with lowest CVD risk, mirroring what is known of its physiology. Importantly, no prospective cohort study reported a significantly lower CVD risk with low sodium intake, compared to moderate intake, in general populations.\textsuperscript{33} The methodology employed by these contradictory prospective cohort studies came into sharp focus, especially the method of measuring sodium intake, although an increased CVD/mortality risk associated with low sodium intake has been reported in studies using different methods of estimating sodium intake (e.g., single or multiple 24-hour urine collections, morning fasting urine, or dietary questionnaires).\textsuperscript{25-31,34-37}

Against this backdrop, Cook and colleagues\textsuperscript{38} report on the 25-year observational follow-up of the TOHP-I and II clinical trials to determine the effect of sodium reduction on mortality, recognizing that ‘the health effects of sodium intake remain controversial despite clear effects on blood pressure’. Their analyses of the randomized comparison are most relevant, since TOPH-II is the largest clinical trial to evaluate a sodium reduction intervention, employed the reference standard to measure sodium intake (repeated 24-hour urine collections) and had long-term follow-up for mortality outcome, through data linkage. In the randomized comparison, the authors did not find a significant difference in mortality between groups (RR 0.85; 0.66-1.09). This finding is disappointing, given the intensive nature of the dietary behavioral intervention employed in the TOHP trials, the anticipated effects of sodium reduction reported by simulation modeling studies\textsuperscript{24} and emphasis placed on sodium reduction in guidelines. Non-significance may be related to insufficient power to detect a 15% risk reduction in mortality, which is a plausible treatment effect of a dietary intervention that targets sodium reduction through a healthier dietary pattern. In fact, as TOHP did not have a control intervention (e.g. advice on a
healthy diet), it may be that much of the potential reduction in mortality could be due to changes in overall diet rather than sodium intake alone. Another contributor to the absence of a mortality benefit may be non-adherence with dietary recommendations beyond the period of intensive intervention, although this reflects real-life. In addition, all-cause mortality includes conditions which may not be modifiable through dietary modification, and effects may be more evident on CVD, though not reported. In particular, these findings do not provide evidence of the safety or efficacy of low sodium intake (<2.3g/day), as low sodium intake was not achieved in the intervention group.

In a secondary observational analyses of the control group (n=2,974, with 272 deaths), Cook et al.\(^\text{38}\) evaluated the association of sodium intake (and sodium:potassium ratio) with mortality, to determine whether there was evidence of a J-shaped association. Unfortunately, the small sample size, and low number of events (particularly in the low sodium intake group), precluded a reliable analysis of the pattern of association between sodium intake and mortality, irrespective of how sodium intake was measured. Their failure to identify a J-shaped association is not surprising, as detecting non-linear association between exposure and health outcomes requires much larger sample sizes and larger numbers of events than in the Cook et al. study. None of their analyses provide robust evidence to support low sodium intake; in particular the death rate was not significantly lower between low(<2.3g/day) and moderate sodium intake categories. Of note, the authors place considerable emphasis on the importance of repeated 24-hour urine collections in measuring sodium intake, claiming that use of alternative methods to measure sodium intake may result in a spurious J-shaped association reported by numerous other studies. Providing the results using sodium intake based on baseline 24-hour urine versus multiple collections in relation to mortality would have been helpful. It is noteworthy that the recent CRIC cohort study, including 3757 individuals with CKD, which also completed multiple 24-hour urinary collections, described an increased risk of CVD with sodium intake over 4.5g/day (a similar threshold to other prospective cohort studies), along with evidence of an increased risk of myocardial infarction and congestive heart failure with sodium intake below 2.9g/day, consistent with a J shaped association.\(^\text{37}\)

These latest analyses of the TOHP trials, and those of prospective cohort studies, support modest reductions in sodium intake among individuals consuming high sodium diets, enveloped within healthy dietary patterns. However, the null effect of low sodium intake on mortality adds to the
growing uncertainty about the health effects of low sodium intake, and reinforces the need for large definitive RCTs of low sodium intake (versus moderate).

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**References**


