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EDITORIAL COMMENT

# 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 has been used to preserve foods since early times (1). Salt was highly valued in ancient China and Rome and other parts of Europe, and it became an early trading commodity and a source of tax revenue. Protests against the salt tax were integral to the movement for independence in India, and salt was 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 to be responsible for many summer deaths in India during British rule (2,3).

Salt (sodium chloride) accounts for 95% of sodium intake. Sodium is an essential nutrient, crucial to the action potential of cells and involved in first response to cutaneous injuries to prevent infections (4,5). Sodium is required to maintain intravascular volume and is an important determinant of blood pressure (BP). Although 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 (4,6).

Our appetite for sodium, which is controlled by neural mechanisms in response to peripheral hormonal signals (principally angiotensin II and aldosterone), has been unchanged since the 1960s (~3.5 g/day) (7), despite public policy efforts to reduce sodium intake to <2.3 g/day (8). Reductions in sodium intake to low levels (<3 g/day) markedly activate the renin-angiotensin-aldosterone system to conserve sodium (9–11). Although extreme reductions in sodium intake are possible in controlled settings for short periods, they are not sustainable over the long term in free-living persons (12). This lack of sustainability, along with increased intake of nondiscretionary sources of salt, may explain why the amount of sodium intake in the United States has remained steady to this day (7).

The idea that salt intake could pose a threat to the general population emerged only in the 1980s, although the first case report of managing severe hypertension with salt restriction was published in 1948 (13). One of the most influential studies was INTERSALT (International Study of Sodium, Potassium, and Blood Pressure) (14), which reported a weak association between sodium excretion and BP (0.94/0.03 mm Hg/1 g of sodium) in ecological analyses across 52 centers. This association was not reproduced in an individual-level analysis of another large, well-conducted study, the Scottish Health Study (n = 7,354) (15), which was reported in the same issue of *BMJ*, but that analysis was much less influential (638 vs. 101 citations on Web of Science, accessed August 1, 2016). Further, there was no significant association between salt intake and BP 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 (<1 g/day) reported in some of these primitive societies is often cited as evidence to support the safety of very low sodium intake, even though the life expectancies of people living in these primitive societies were relatively short

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(e.g., 40 years in the Yanomamo Indians) (16), and additional studies demonstrated extreme activation of the renin-angiotensin-aldosterone system in these populations (17). Moreover, data provided in the appendix of the study suggest incomplete collection of 24-h urine, given the implausibly low urinary creatinine levels (14). Nonetheless, the totality of observational research studies, including the more recent PURE (Prospective Urban Rural Epidemiological) study (n = 102,216) (18), confirms a nonlinear association between increased sodium intake and BP, and the magnitude of that association is greatest in persons consuming diets that are high in sodium and low in potassium or in persons with hypertension.

In the late 1990s, findings from 2 clinical trials (TONE [Trial of Nonpharmacologic Interventions in Elderly] and TOHP-II [Trials of Hypertension Prevention II] trials) (19,20) demonstrated that an intensive behavioral dietary intervention could reduce sodium intake (mean reduction ~1g/day) and result in a modest reduction in BP (–1.2/0.7 mm Hg in TOHP-II at 36 months). Although both clinical trials targeted a sodium intake of <1.8 g/day, neither intervention group achieved this target (mean intake in TONE was ~2.4 g/day, and in TOHP-II it was 3.1 g/day on final follow-up) (19,20). Both clinical trials implemented a resource-intensive dietary counseling intervention to reduce dietary sodium levels through changing dietary patterns that was expected to result in other dietary changes, such as greater fruit intake and consumption of fewer processed foods. Neither trial used a control dietary intervention. To date, these clinical trials are the largest to evaluate sodium reduction (within a change in dietary pattern) on BP.

In 2001, the DASH (Dietary Approaches to Stop Hypertension)-Sodium trial (21), which was a phase IIa clinical trial (n = 412), demonstrated a BP-lowering effect of reduced sodium intake to very low levels (<1.5 g/day) over a 30-day period by using previously prepared meals. Despite the study's small size and its 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) because many guidelines currently recommend very low sodium intake levels (e.g., <1.5 g/day recommended by the American Heart Association) (22), although this target was not achieved by either the TONE trial or the TOHP trials (19,20). Despite the absence of clinical trials demonstrating the effect of low sodium intake on cardiovascular disease (CVD) (23), or any study showing the feasibility of sustained low sodium intake in the general population (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 lowered BP in all populations, which in turn would be expected to translate directly into predictable decreases in CVD incidence (24).

A major challenge to the assumed benefit of low sodium intake on CVD events came from prospective cohort studies reporting, in 2011 and 2014, an increased risk of CVD and death with low sodium intake (compared with moderate intake) (25–31). A 2014 meta-analysis of studies (n = 274,683) (32) identified an increased CVD risk associated with sodium intake lower than 2.7 g/day and higher than 5.0 g/day. Clearly, findings from these studies directly contradict recommendations for lowering sodium intake to <2.3 g/day, and they suggest that moderate sodium intake is associated with the lowest CVD risk, thus mirroring what is known of sodium physiology. No prospective cohort study reported a significantly lower CVD risk with low sodium intake, compared with moderate intake, in general populations (33). The methodology used by these contradictory prospective cohort studies came into sharp focus, especially the method of measuring sodium intake, although an increased CVD or 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-h urine collections, morning fasting urine, or dietary questionnaires) (25–31,34–37).

SEE PAGE 1609

Against this backdrop, in this issue of the *Journal,* Cook et al. (38) report on the 25-year observational follow-up of the TOHP-I and TOHP-II clinical trials to determine the effect of sodium reduction on mortality rates, by recognizing that "the health effects of sodium intake remain controversial despite clear effects on blood pressure." The analyses by Cook et al. (38) of the randomized comparison are most relevant because TOPH-II is the largest clinical trial to evaluate a sodium reduction intervention. It used the reference standard to measure sodium intake (repeated 24-h urine collections), and it had long-term follow-up for mortality outcome, through data linkage. In the randomized comparison, Cook et al. (38) did not find a significant difference in mortality rates between groups (hazard ratio: 0.85; 95% confidence interval: 0.66 to 1.09). This finding is disappointing given the intensive nature of the dietary behavioral intervention used in the TOHP trials, the anticipated effects of sodium reduction reported by simulation modeling studies (24), and the emphasis