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REVIEW

Controversies in cardiovascular medicine

The technical report on sodium intake and cardiovascular disease in low- and middle-income countries by the joint working group of the World Heart Federation, the European Society of Hypertension and the European Public Health Association

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Ingestion of sodium is essential to health, but excess sodium intake is a risk factor for hypertension and cardiovascular disease. Defining an optimal range of sodium intake in populations has been challenging and controversial. Clinical trials evaluating the effect of sodium reduction on blood pressure have shown blood pressure lowering effects down to sodium intake of less than 1.5 g/day. Findings from these blood pressure trials form the basis for current guideline recommendations to reduce sodium intake to less than 2.3 g/day. However, these clinical trials employed interventions that are not feasible for population-wide implementation (i.e. feeding studies or intensive behavioural interventions), particularly in low and middle-income countries. Prospective cohort studies have identified the optimal range of sodium intake to reside in the moderate range (3–5 g/day), where the risk of cardiovascular disease and death is lowest. Therefore, there is consistent evidence from clinical trials and observational studies to support reducing sodium intake to less than 5 g/day in populations, but inconsistent evidence for further reductions below a moderate intake range (3–5 g/day). Unfortunately, there are no large randomized controlled trials comparing low sodium intake (< 3 g/day) to moderate sodium intake (3–5 g/day) in general populations to determine the net clinical effects of low sodium intake. Until such trials are completed, it is likely that controversy about optimal sodium intake range will continue. This working group calls for the completion of large definitive clinical trials to clarify the range of sodium intake for optimal cardiovascular health within the moderate to low intake range. We support interventions to reduce sodium intake in populations who consume high sodium intake (> 5 g/day), which should be embedded within an overall healthy dietary pattern.

Keywords Sodium • Hypertension • LMIC

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The impressive reductions in cardiovascular disease (CVD) seen in high-income countries over recent decades have not been seen in low- and middle-income countries (LMICs), where both rates of CVD and, given population growth and ageing, the total disease burden are continuing to increase. The success in high-income countries has been attributed to risk factor modification among most, although not all of the population, especially reductions in smoking, treatment of hypertension and hypercholesterolemia. Yet there are many barriers to extending this success to LMICs, reflecting both limited capacity to develop and implement healthy public policies in areas such as diet and tobacco control and slow progress in extending coverage with effective health care.

There is a renewed imperative to overcome these barriers following the adoption of a United Nations High Level Declaration on Non-Communicable Disease (NCD)[1] and, more recently, the inclusion of a target for reducing by one third premature mortality from NCDs through prevention and treatment by 2030 in the Sustainable Development Goals.[2] Yet, if this ambitious target is to be achieved it will require prioritization of those measures known to be both effective and feasible in LMICs. Given its importance as a risk factor for CVD, such measures must tackle the high global burden of hypertension, among the leading modifiable risk factors for CVD in all parts of the world.[3] While a comprehensive response must include expansion of detection and treatment, attention has also focused on the role of sodium intake, which has been shown to correlate positively with hypertension, albeit with inter-individual variation in the strength of the association.[4] Reducing sodium content, especially when embedded with a healthy cardiovascular diet, exerts short-term reductions in blood pressure.

These considerations have led to the prominence of reducing sodium intake as a strategy in CVD prevention guidelines.[5,6] The WHO recommends a 30% reduction in sodium intake worldwide by 2025, irrespective of the baseline mean sodium intake of a population, and recommends a mean sodium intake target of <2 g/day.[7] Public health initiatives to reduce excess sodium intake in populations have been adopted by numerous countries, but predominantly in high-income countries, with low impact so far in LMICs. However, while there is consistent evidence that high sodium intake (> 5 g/day) is associated with increased CV risk, there is little epidemiologic evidence linking an association between moderate sodium intake and increased CV risk (compared to low sodium intake recommended by WHO, < 2 g/day). There is an ongoing scientific debate about the optimal lower level of sodium intake for CVD prevention,[8] but there is an acceptance that a lower limit is present, since sodium is an essential nutrient. This implies that there must be a 'U'-shaped relationship between dietary sodium intake and cardiovascular events, but there is no consensus of where the minimum risk lies. To add to the complexity, a very recent analysis suggested that sodium reduction might only benefit those persons with hypertension.[9]

There are other major barriers to developing effective interventions for reducing sodium intake. First, the absence of accurate, feasible methods to measure sodium intake in individuals results in current recommendations (e.g. < 2 g/day) that are difficult to interpret and implement in clinical practice. There is disagreement about the validity of those relatively simple methods that are used for measuring mean intake in populations, such as spot urinary sodium measurement and, especially, their interpretation when used to assess individual risk. Second, there are no randomized controlled trials (RCTs) that show that reduction of sodium intake, from moderate to low levels, reduces CVD. Third, while a number of interventions, both at individual such as education, and population-level such as reformulation have been proposed, they have so far not been shown empirically to result in sustained reductions in sodium intake, particularly in LMICs. Fourth, overall dietary pattern is an important determinant of health outcomes, and recommendations based on sole nutrients need to consider the effect on overall dietary pattern, and regional variations in dietary patterns (e.g. sources of sodium intake vary by region, and within regions).

The current statement does not seek to replicate prior guidelines on sodium intake, but attempts to propose a practical approach to sodium intake that can inform public policy and clinical practice in adults in LMICs. We summarize knowledge-gaps in our understanding of association between sodium intake and health, and recommend future areas of research focus in LMICs.

Physiology of sodium

Sodium is an essential nutrient, required for numerous physiologic processes. It is tightly regulated by numerous physiologic (renal, endocrine, immune) systems which act to maintain serum sodium within normal range. Sodium exchange with potassium is a key part of the action potential of human cells. In most people, normal kidneys are capable of excreting large amounts of sodium, or excrete almost no sodium, in settings of high and low sodium intake, respectively. Niche populations with very low sodium intake have been studied, and have a low prevalence of hypertension,[10] although long-term effects of low intake on health have not been evaluated as mean life expectancy in these population was short (~40 years). There is a positive association between increasing sodium intake and blood pressure, in observational and experimental research studies, with inter-individual variability. Reductions in sodium also appear to affect cardiovascular dynamics, with animal models demonstrating low sodium intake associated with attenuated pressor responses during stress (e.g. septic shock).[11,12] Our understanding of the physiology of sodium intake, storage and excretion is continuing to evolve. For example, recent evidence suggests that sodium excretion demonstrates cyclic variations, and the majority of sodium is stored in skin, subcutaneous lymphatic networks and in muscle, and partly regulated by the immune system.[13,14] These observations raise issues related to measurement of sodium and need to gain better understanding of potential effects of manipulating sodium intake on the immune system. A recent study also suggests that sodium that is still well within the 'normal' range may be more hazardous than previously thought in hospitalized subjects.[15]

Measurement of salt intake

Individual level assessment of sodium consumption

A prerequisite for effective programmes to modify risk factors, is an ability to accurately measure the exposure using simple methods (e.g. blood pressure, cholesterol, smoking). A key obstacle to making quantitative individual-level recommendations on sodium intake targets, is the lack of valid and reliable methods to objectively quantify sodium intake in individuals. At present, there is no routine approach to accurately measuring sodium intake in individuals. Accurate objective

measurement requires multiple 24-h urine collections, which is impractical in clinical practice.[16] Therefore, while guidelines may recommend an intake of sodium < 2.3 g/day, this target is relatively meaningless to both clinician and patient, as it is not supported by an available objective measurement. In contrast, recommendations on blood pressure targets are based on simple measurements, which are suitable for both screening and monitoring change over time, which are readily interpreted and implemented by clinician and patient, and can be applied in all settings given the ease of blood pressure measurement. In contrast to other dietary recommendations (e.g. increased consumption of fruits and vegetables) where intake is directly observable, self-assessment of sodium intake range is poor, which may be related to the fact that much of sodium intake is hidden (embedded within foods, particularly in high-income countries), and the accuracy of self-predicted sodium intake appears to be independent of knowledge and attitudes to sodium intake.[17] Even subjective categorization of individuals into high, medium and low sodium intake is poor, although dietary questionnaires are generally good at identifying groups and individuals who consume high sodium, but these require validated questionnaires to specific populations as different populations have distinct dietary patterns. Moreover, standard food composition tables developed in one setting may not apply to others, where the same descriptors may include differently constituted foodstuffs.[18] The implication, therefore, is that a policy targeting individual consumption should incorporate recommendations for individuals, which are not dependent on numeric targets, but based on practical assessment of diet to identify high sodium foods and those consuming high sodium diets. In such individuals, reduction of sodium intake can, in theory, be facilitated by recommendations to avoid/reduce sodium in food preparation and at the table, and avoid (or replace) specific foods that are high in sodium, rather than targeting a specific quantitative target for sodium intake. However, such an approach requires a detailed knowledge of food items with a high sodium content, taking account of the dietary variations that exist not only between countries but also among different regions of a country. Even with common foods, such as breads, sodium content can vary widely, but there are also many foodstuffs that are common in some settings but rare in others (e.g. salted fish such as bacalhau and its variants). Examples of dietary screening tools exist, but very few have been validated in LMICs.

Population-level assessment of sodium consumption

Employing multiple 24-h urinary collections is considered to be the reference standard for measuring sodium intake in populations, but challenging to complete in large population studies . Recent research has suggested that use of spot urine, or particularly fasting urine samples, which employ a formula-derived approach, appears suitable to estimate mean intakes at a population-level or subdivide large populations into those who, on average, have high, moderate and low sodium intakes.[19] Spot or fasting urine measurement offers the potential to achieve more representative samples in a population (external validity), since use of 24-h collections are burdensome and associated with a high rate of non-adherence for complete collections. This creates an inherent risk of selection bias (i.e. individuals who are adherent with 24-h collections differ from those who are not). Intraclass correlation (ICC) for single urine-formula derived estimates of 24-h urinary sodium excretion are good (0.71 in largest validation study of fasting urine) and comparable to the ICC for single office blood pressure measure compared to 24-h ambulatory blood pressure measurements. However, while there is acceptance that blood pressure measured during office visits is suitable for large epidemiologic studies, there is debate about whether spot or fasting urines are appropriate in large epidemiologic studies to estimate mean intake or report on association with clinical outcomes. WHO does consider spot/fasting urine assessment in populations to be appropriate for measuring mean sodium intake. Dietary questionnaires, using either food frequency questionnaire or 24-h dietary recall, are more convenient but more time-consuming to complete than single urine measures. Dietary questionnaires require validation in population with distinct dietary patterns and different sources of sodium intake. Generally dietary assessments provide a lower, and less reliable, quantification of sodium intake, compared to urinary measurements, which presents special challenges for between-study comparisons. A main advantage of dietary assessment is the identification of food items that are high in sodium, and measurement of overall dietary quality to guide other types of dietary recommendations.

Regional variations in sodium intake

Globally, the mean intake of sodium is estimated at 3.95 g/day by the Global Burden of Disease (GBD) collaboration, in a meta-analysis of surveys from 187 countries, using 24-h urine collections.[20] Intakes were highest in East Asia, Central Asia and Eastern Europe (mean >4.2 g/day) and in Central Europe and Middle East/North Africa (3.9–4.2 g/day). Mean intakes in North America, Western Europe, and Australia/New Zealand ranged from 3.4 to 3.8 g/day. Intakes were lower (< 3.3 g/day), but more uncertain, in sub-Saharan Africa and Latin America. Between 1990 and 2010, there was a suggestion of slight increases in overall sodium intakes. These regional variations are consistent with reports from the PURE study involving 18 countries which used 24-h formula-derived estimates from fasting morning urine specimens, which was published after this systematic review.[21]

In addition to regional variations in mean sodium intake, there are important variations in the degree to which intake is from discretionary and non-discretionary sodium, which has implications for developing approaches to reduce sodium intake, especially whether priority should be given to a population vs. individual-level interventional approach. The proportion of sodium intake from discretionary sources in North America and Europe is about 10–25%, compared to about 70% in China, other parts of Asia and Africa. Therefore, in countries with high non-discretionary use, reducing sodium in processed or pre-packaged foods through reformulation is more important, whereas in countries with high discretionary use, reducing salt during cooking and added at table appear to be the most relevant priority targets. Thus, knowledge of the main sources of high sodium intake is a mandatory step in developing country-specific approaches to reducing high sodium intake.

Socioeconomic variation in sodium intake

Studies in several countries have found that those with lower levels of education or living in disadvantaged areas have higher salt intakes,

and exhibit less change during the course of national salt reduction campaigns.[22,23]

Effect of reducing sodium intake on blood pressure

Evidence of an association between sodium intake and blood pressure comes from numerous lines of evidence, including observational research and results of clinical trials reporting a reduction in blood pressure following lowering of sodium intake. In these studies, there is evidence of variations in the associations among different subgroups of people, with a stronger association in older age groups, people with hypertension and those consuming low potassium diets.

Clinical trials

Over 40 clinical trials have evaluated the effects of reducing sodium intake on blood pressure, and other biomarkers. Of these, most (> 95%) were short-term trials (< 6 months).[24,25]

Of short-term trials, the findings from the DASH trial have exerted greatest influence on current guidelines, and demonstrated short-term reductions in blood pressure (30 days) with reductions of sodium intake to under 1.5 g/day.[26] In the DASH trial, all foods were provided to participants, and was therefore conducted in a highly controlled environment which cannot be replicated in routine daily life. Such low intake levels have not been achieved after routine clinician recommendations, or even with intensive counselling interventions in RCTs. Whereas the short-term nature of the clinical intervention is known, the long-term effect of this diet on blood pressure and outcomes has not been established in RCTs.

The TOHP-II trial is the largest clinical trial ($n = 2382$) evaluating the effectiveness of a counselling/educational intervention to reduce sodium reduction and thus blood pressure, with a mean duration of follow-up of 36 months.[27] The trial was a 2×2 factorial that also evaluated a behavioural change intervention for weight loss. At 18 months, a mean sodium of 3.1 g/day (3.2 g/day at 36 months) was achieved in the intervention group (vs.) compared to mean intake of 3.9 g/day (4.0 g/day at 36 months) in the control group. The difference in systolic blood pressure between sodium intake groups was 2.9 mmHg at 6 months, 2.0 mmHg at 18 months, and 1.2 mmHg at 36 months, with a reduction in the incidence of hypertension which also diminished over time, with a risk ratio of 0.61 ($P = 0.04$) at 6 months, 0.88 ($P = 0.28$) at 18 months, and 0.82 ($P = 0.05$) at study end.[28] This trial suggests that a 0.8 g/day difference in sodium intake lowered blood pressure by 2 mm Hg. While this may have been the case, repetitive urine collections were variable in TOPH II, imprecisely documented, and the goal in TOPH II was not to provide a long-term study of cardiovascular events as the outcome. Finally, the circaseptan (7 day) variability in daily sodium excretion was unknown at the time of TOPH II.[12]

The TONE trial evaluated a similar intervention to TOHP-II in older adults (60–80 years) with controlled hypertension ($n = 975$). Ninety days after introduction of the intervention, systolic blood pressure was reduced by 3.4 mmHg. Withdrawal of antihypertensive therapy began at 90 days, and the proportion of patients requiring antihypertensive therapy was lower in the sodium intervention group compared to control (24% vs. 38%).[29] These data suggest that despite sustained maintenance of most of the difference in sodium intake between intervention and control, the differences in blood pressure were attenuated over time, and large trials with extended duration of follow-up are needed to assess the long-term antihypertensive effect of sodium reduction in this sodium intake range. In each of these clinical trials, the control group did not include a control intervention (e.g. dietary counselling that did not include advice on salt intake), which means that they were unable to determine the effects of sodium reduction, independent of other dietary changes (e.g. increase in fruit/vegetable intake). An educational intervention targeting school children in a cluster RCT in China (28 schools, 832 family members) reported a reduction in sodium intake (0.8 g/day in adults with mean intake of sodium 4.7 g/day), and, while blood pressure increased in both the intervention and control groups during follow-up, the increase was significantly less in the intervention group.[30]

There have been several meta-analyses of clinical trials evaluating sodium reduction for blood pressure reduction.[31,32] In a recent meta-analysis of 34 blood pressure clinical trials ($n = 3230$), a reduction in sodium intake (1.76 g/day difference in mean change between intervention and control) was associated with a mean 4.2/2.1 mmHg reduction in blood pressure. Among participants with hypertension, the blood pressure reduction was greater (-4.06/2.26 mmHg) compared to those without hypertension (-1.38/0.58 mmHg).[19] Duration of follow-up may be an important determinant of treatment effect, which was explored in another meta-analysis of blood pressure trials that included 36 trials.[24,25] In trials of < 3 months, 3–6 months and more than 6 month's duration, blood pressure reductions were 4.07/1.67 mmHg, 1.91/1.33 mmHg and 0.88 mmHg/0.45 mmHg, respectively. These data demonstrate the challenges faced by counselling interventions in maintaining adherence to reduced sodium intake from moderate to low intake levels over time, even when dietary counselling is relatively intense, and raise a suspicion that the blood pressure lowering effects of moderate sodium reduction may diminish over time, based on findings from the largest long-term trial included in the review (TOHP trial).

A number of clinical trials have evaluated use of salt substitutes (low-sodium salt) usually involving a reduction of the proportion of NaCl proportion in total salt to about 45–65%, and replacing it with KCl or $MgSO_2$. This is especially applicable in populations with high discretionary salt use (e.g. China). A meta-analysis of these clinical trials (5 clinical trials, $n = 1974$) reported a reduction in blood pressure (-4.9/1.5 mmHg) with use of salt substitutes, ranging from 6 months to 2 years. A recent large cluster RCT in China (China Rural Health Initiative-Sodium Reduction Study) randomized 120 villages to either intervention (health education and access to salt substitution, with 30 of the 60 intervention villages also receiving a price subsidy as salt substitute is more expensive than regular salt) or control.[33] Among 1295 participants in the intervention villages (1063 with urine assessment), there was a 0.3 g lower sodium intake ($P = 0.03$) on follow-up compared to control (1272 participants, 1001 with urine assessments). There was no significant difference in change in blood pressure (-1.0/0.8 mmHg, $P = 0.39$ and 0.34, respectively). A large cluster RCT of 600 villages with over 21 000 participants is being undertaken in China designed to evaluate the effects of salt substitution on stroke risk in individuals at high risk of stroke, over 5-year's follow-up (SSaSS trial). Findings from the SSaSS trial may have important implications for population-level approach to prevention of stroke in

communities with high discretionary sodium intake. However, as this trial evaluated salt substitution in a region with high sodium intake, it will be unable to determine the effect of lowering sodium intake from moderate to low intake levels, and unable to determine the independent effect of sodium reduction from increased potassium intake on stroke risk.

Effects of sodium intake on cardiovascular biomarkers

The level of sodium intake affects the renin-angiotensin-aldosterone system (RAAS), with low sodium intake resulting in activation in RAAS shown in short-term studies.[34,35] Activation of the sympathetic nervous system with an impairment of reflex homeostatic control has been reported.[28,24] However, the clinical relevance of this observation is uncertain, since some effective antihypertensive therapies that lower blood pressure and CVD also increase renin levels and sympathetic nerve activity levels, and it is unclear whether these effects persist during long-term low-sodium intake. It does however demonstrate that sodium intake exerts endocrine feedback effects at sodium intakes below 3 g/day. Sodium intake also appears to exact effects on immune and inflammatory biomarkers, whose relevance remains unclear. Moreover, in prospective cohort studies, the magnitude of association between sodium intake and cardiovascular outcomes is only modestly attenuated after adjustment for blood pressure, suggesting that the potential adverse effects on cardiovascular outcome are only partly attributable to changes in blood pressure. These data suggest that the effects of changes in sodium intake on health are complex, and could be mediated through a number of different physiologic mechanisms, including, but not isolated to, blood pressure.

Effect of reducing sodium intake on cardiovascular disease

Clinical trials

No RCTs have been undertaken to determine specifically whether low compared to moderate sodium intake reduces the incidence of CV events or death (compared to moderate intake). Meta-analyses of those blood pressure trials that reported CV events do not report a significant reduction in CVD with lowering sodium intake, but these trials are underpowered to detect moderate risk reductions. An extended observational follow-up of the TOHP I and II trials reported on the risk of death and CV events (composite of myocardial infarction, stroke, coronary revascularization or cardiovascular death) during 10–15 years after completion of the trials, which reported a reduction (OR 0.75; 99% CI 0.59–0.99) on adjusted analyses, but not in unadjusted analyses. However, there were very high rates of loss to follow-up for CV outcomes, as this was opportunistic rather than planned extended observation follow-up. For all-cause mortality (100% follow-up), there was complete determination of outcome, and no significant association. In summary, no individual trial, or combination of all longer-term trials, is sufficiently powered to detect whether moderate risk reduction in CVD associated with reducing sodium intake. While there are also no large RCTs demonstrating a reduction in CVD with reducing high sodium intake (>5 g/day), the consistency of findings from blood pressure trials and observational studies provide evidence that reducing high sodium intake will reduce blood pressure and CVD, in the absence of harm, especially in people with hypertension.

A small cluster RCT ($n = 1981$) conducted in five kitchens of veteran's retirement homes in Taiwan, in which participants increased potassium consumption and reduced sodium consumption through use of potassium-enriched salt, found a reduction in cardiovascular mortality (HR 0.59; 95% CI 0.37–0.95) in those assigned to the higher potassium group.[25] The trial, which utilized cluster randomization, was analysed using individual-level (inappropriately), rather than cluster-level data. Moreover, in that trial, sodium intake was estimated to be reduced from 5.2 g/day to 3.8 g/day, with a proportionately larger effect on potassium intake than sodium intake. Thus, it is necessary to await the findings of the SSaSS trial to ascertain the effectiveness of sodium reduction through salt substitution intervention in the setting of high levels of discretionary salt use.

Prospective cohort studies

Among individual studies which have included a defined group with high sodium intake (>5g/day), most report an overall increased risk of CV events in these groups.[36] However, in many prospective cohort studies, urinary samples were collected for a variety of purposes, and not specifically to measure sodium intake. Meta-analyses of prospective cohort studies have generally compared the lowest quintile of sodium intake with highest quintiles.[37] In the most recent of these meta-analyses, there was a significant association between highest sodium intake quintile and stroke (RR 1.24; 95% CI 1.08–1.43) and fatal coronary events (RR 1.32; 1.13–1.53), but not all-cause mortality (RR 1.06; 0.94–1.20) or all CVD mortality (1.12; 0.93–1.34). In another meta-analysis[38] that compared high (>5 g/day) sodium intake to moderate (2.7–5 g/day) sodium intake, there was an increased risk of all-cause mortality (HR 1.16; 1.03–1.30), CVD (HR 1.12; 1.02–1.24), stroke (HR 1.18; 1.05–1.33), and heart disease (HR 1.17; 1.08–1.27). In that meta-analysis,[39] a comparison of low sodium intake (< 2.7 g/day) with moderate/usual intake (2.7–5 g/day) intake found that moderate sodium intake was associated with a lower risk of all-cause mortality (0.91; 0.82–0.99) and all CVD mortality (HR 0.90; 0.82–0.99), compared to low intake (< 2.7 g/day). Following these meta-analyses, the PURE study, the largest international study ($n = 101\,945$, 3.7 years follow-up) to evaluate the association between sodium intake (based on formula-derived 24-h sodium excretion from a fasting urine sample) reported a J-shaped association between sodium excretion and CVD incidence and mortality, consistent with findings from the most recent meta-analysis.[40] In contrast to the earlier studies that were included in the meta-analysis, the PURE study had greater representation from LMICs and so are probably most relevant to informing policy in LMICs. One study, which analysed an extended follow-up of the control group ($n = 2275$) in the TOHP trial, reported a linear association between sodium intake and CVD, but the proportion of the population with low sodium intake was small ($n = 235$) with wide confidence intervals in the lower intake range.[41]

Observational studies, even when conducted with methodological rigour and analysed to optimally adjust for measured confounders, have inherent limitations, including residual confounding and reverse

causation.[42] In the CRIC cohort, repeated 24-h urine collections were used to estimate sodium excretion wherein sodium was strongly related to CVD events, for sodium intakes over 4.5 g/day.[43] In another meta-analysis of observational studies that employed the Kawasaki formula and created two groups based on presence or absence of hypertension, a direct relationship between sodium excretion and CVD was noted in the hypertensive group for high vs. moderate sodium excretion but an inverse relationship was noted for both the hypertensive and normotensive groups.[9] While the totality of evidence from observational studies raise caution about the safety of reducing sodium intake to very low levels, and none report a significantly lower risk of CVD for low vs. moderate sodium intake, definitive evidence can only come from large RCTs.

There are no prospective RCTs with hard major adverse cardiac events (MACE) cardiovascular endpoints. TOPH II and TONE were never conceived as such. Admittedly, an individual-level RCT with sodium reduction as the only variable would be exceedingly difficult in free-living individuals for reasons made clear above.

What factors modify the association between sodium intake and CVD?

Hypertension

Clinical trials and observational studies have generally reported a greater blood pressure lowering effect of sodium reduction among individuals with hypertension. Two prospective cohort studies have reported an effect-modification of hypertension for CVD. In the PREVEND study, ($n = 7543$),[44] an association between high sodium intake and CVD was confined to participants with baseline hypertension. In the PURE cohort,[45] a significant interaction between baseline hypertension and sodium intake ($P = 0.02$) was found, with the increased risk of CVD associated with high sodium intake only found in those with hypertension. However, the increased risk of CVD and mortality at sodium intake below 3 g/day was seen in those with and without hypertension.

Diabetes mellitus

There is no convincing evidence that the presence of diabetes mellitus modifies the association between sodium intake and clinical outcomes, although reports of an increased CV risk with low sodium intake have been prominent in patients with diabetes.

Obesity

Two studies reported an increased risk of higher sodium intake among participants with increased BMI (but not in the entire cohort).[39,46]

Other dietary factors

Many dietary factors (e.g. fruit, vegetable and meat intake) and dietary patterns (e.g. prudent diet, Mediterranean diet) have been associated with differing risk of CVD.[45,47]

Overall diet quality appears to be an important modifying effect, supported by evidence from the DASH-Sodium trial, which reported a greater blood pressure lowering effect among those with a healthy CV diet, compared to a less healthy one.

In this regards, potassium intake may modify the association between sodium intake, blood pressure and CVD.[48] Epidemiological studies have also reported that increased potassium intake is associated with reduced risk of CVD, particularly for stroke.[49,50] While the effect of dietary sodium is likely to be the same regardless of source, certain sources may provide other nutrients and micro-nutrients with consequences for CVD, creating potential for confounding. For example, in some regions, high sodium intake may be primarily from processed foods and food types such as fried foods, especially in high-moderate income countries. In other regions, the main sources of high sodium intake may include salted fish and vegetables, which, independently, do not increase CV risk.

Cardiovascular disease

The blood pressure lowering effects of reducing sodium intake appear similar in populations with and without CVD, although most studies have been in populations without CVD. The relative association between sodium intake and CVD also appears to be similar, although rates of events are higher in populations with prior CVD.[51,52] Patients with heart failure represent a unique population, where the effects of low sodium intake require further study (and are dealt with in another section). The PREVEND study reported pro-BNP to be an effect-modifier of the association between sodium intake and CVD.

Genetic determinants of salt sensitivity

Some individuals are more sensitive to the hypertensive effects of increased sodium intake, termed 'salt sensitivity'.[53] About 30–50% of persons with hypertension are thought to be salt-sensitive. An intensive area of research seeks to identify genetic polymorphisms that are associated with both hypertension and 'salt sensitivity'.[54] The clinical relevance of salt sensitivity is uncertain, as definition and identification of salt sensitive populations lack clarity, although people who develop hypertension appear to have a greater increase in blood pressure for a given increase in sodium intake compared to those who do not develop hypertension.

National interventions to reduce sodium intake

A recent systematic review examined 39 state and community level interventions, which included nutrition education programmes, public education campaigns, changes to the food environment, other 'novel' approaches and multifaceted approaches.[55] It concluded that there was some evidence of effectiveness but most studies had methodological limitations and more robust evaluations were needed.

The WHO has published guidelines on approaches to develop, implement, and monitor sodium intake, and integrate them with approaches to eliminate iodine deficiency. However, such programs have been adopted or implemented[56] mainly in higher income counties. Interventions can be divided into those seeking to change individual choices, such as consumer education and front of pack labelling, and those limiting the choices that are available, such as reformulation or changes to cooking methods in institutional settings (e.g. schools, workplaces). The latter can be further divided into those that are voluntary and those that are imposed through legislation.

In some of these countries, reductions in mean sodium intake have been reported, which was most apparent in countries with a relatively higher mean intake of sodium (>4 g/day), but less evidence is available in countries with mean intake in the moderate range.[57] However, a separate meta-analysis completed by the GBD did not report reductions in sodium intake in any region from 1990 to 2010. In most regions of Africa and Asia (with exception of China), no public health strategy has been developed to reduce sodium intake. In China, where mean intake of sodium is high (4.8 g/day), there is evidence of a reduction in mean sodium intake over time (from 6.7 g/day to 4.8 g/day from 1991 to 2009), which has been largely due to reduction in discretionary salt intake. However, the reduction in discretionary intake has been countered by a recent increase in consumption of processed foods and non-discretionary salt intake. This is not unique to China and reflects the increasing globalization of the food industry. This has led to pressure for reformulation to reduce sodium content which can, as noted above, be voluntary or imposed through legislation or regulation. Unsurprisingly, the food industry argues for voluntary agreements and for a major role in developing standards, although even in high-income countries progress has been mixed unless there is a credible threat of regulation.[58,59] There is now extensive evidence from other areas of public health that voluntary approaches more generally are often ineffective, with industry emphasizing measures that impose least costs on it rather than those that work, and committing to measures that it is already implementing.[60,61]

Consequently, some countries have implemented legislative intervention to reduce sodium intake, including mandatory salt targets (e.g. Paraguay), taxation on high salt foods (e.g. Portugal), regulations to ensure front of pack labelling (e.g. Ecuador, Indonesia) and standards for salt in procurement policies (e.g. Argentina, Latvia). Other LMIC are developing approaches to inform strategies to reduce sodium intake.[62]

Summary and recommendations

Research to address knowledge gaps

Measuring sodium intake?

- There is a need to identify simple methods to objectively measure sodium intake that are valid and reliable and applicable in diverse populations. The absence of such measures is an obstacle to implementing strategies to reduce sodium intake, and evaluating different sodium intake targets for cardiovascular prevention.
- There is a need to complete studies to identify key sources of high sodium intake, discretionary and non-discretionary, in different regions of the world with distinct dietary patterns, particularly in LMICs. It is necessary to develop simple screening methods to identify populations consuming high sodium intake, which can be administered by healthcare workers and self-assessed.

Feasibility of long-term low sodium intake?

- Despite recommendations for population-wide low sodium intake, it has not been shown that sustained low sodium intake is feasible in free living individuals. Examples of reducing sodium intake from high to moderate intake levels have been reported in countries (e.g. Finland, Japan). We recommend studies to identify simple/generalizable interventions to reduce sodium intake to low intake levels, which would enable studies to assess the feasibility and effectiveness of such sodium intake targets in the long-term (e.g. over 2 years).
- We note the particular paucity of studies of from LMIC in different regions of the world (e.g. Africa, Latin America, India, or SE Asia) and we recommend that such studies should be conducted in each region given the marked variations in diet and cooking methods in these regions. Such studies can also document whether the reductions in sodium will also lead to similar reductions in blood pressure, in populations consuming different diets. In addition, such studies should identify regional and local barriers to sodium intake reduction.

Long-term low sodium intake reduce the risk of cardiovascular disease and death?

- We support the conduct of definitive RCTs, comparing low sodium intake (< 2.4 g/day) to moderate intake (2.4–5 g/day) on cardiovascular events and mortality. Currently, there is insufficient information to reliably answer this question, as there are competing lines of evidence from blood pressure trials (which report a reduction in blood pressure) and epidemiologic studies of association between sodium intake and cardiovascular events (some of which report a higher risk associated with low sodium intake).

Practical recommendations based on current evidence

A. Population-level

Measuring sodium intake (population)

- Measure sodium intake in the population (average intake and distribution), to determine current and future (monitoring) sodium intake. Measuring and monitoring of sodium intake using formula-derived estimates of 24-h sodium excretion from morning fasting urines are reasonable, and ensure standardized measurement in different regions. Employ dietary assessments to determine key sources of sodium intake.

Sodium intake target (population)

- Sodium is an essential nutrient, and is a dietary requirement for all humans, and should be included in a healthy balanced diet. Excess sodium intake is an important determinant of hypertension and CV risk.
- For population-wide recommendation of sodium intake, lowering sodium intake from high intakes (> 5 g/day) to moderate intakes (3–5 g/day) is associated with lower blood pressure and lower CVD in observational studies. Although there are no RCTs demonstrating a reduction in CVD with lowering sodium intake from high to moderate levels, the consistency in data from observational studies (reporting a lower CV risk in populations consuming moderate intake compared to high sodium intake) and clinical trials (reporting a reduction in blood pressure) support reducing high sodium intake in all populations.
  - In populations with high mean sodium intake (e.g. China), a population-wide approach to sodium reduction is probably appropriate, with a target of reducing mean sodium intake by 30% (WHO).
  - In countries/populations where mean intake is moderate (e.g. 3–5 g/day, a targeted approach of reducing salt in those consuming high salt intake is appropriate, especially among those with hypertension.

- Reducing mean sodium intake from moderate intake to below 3 g/day is expected to reduce blood pressure, but the effects on CVD and mortality are uncertain, especially in populations who do not have hypertension.
- Recommendations on diet should be included within an overall recommendation for healthy dietary pattern, rich in fruit and vegetables (e.g. Mediterranean diet) and other lifestyle recommendations.

Reducing sodium intake (intervention in populations)

- Existing interventions to reduce high sodium intake in populations appear reasonable, including educational interventions in public institution settings (e.g. School Edu-Salt), food reformulation, consumer education, front of pack labelling, and intervention in public institution settings. Such interventions are expected to reduce sodium intake from high to moderate intake ranges, based on prior ecological research studies, and community-level education intervention trials. Educational interventions should target overall dietary pattern but are not a substitute for population level measures. Educational interventions should be informed by research studies of local dietary patterns, and dietary sources of high sodium.
- Current evidence supports the safety of low-sodium salt substitutes, although a large ongoing clinical trial to determine its effectiveness in reducing stroke risk is pending (SSaSS Trial).

B Individual-level

Measuring sodium intake (individual)

- Practical measurement of sodium intake requires dietary assessment, as there is no practical objective measurement of sodium intake.
- Screening of individuals, especially those with hypertension, for high sodium intake factors (e.g. adding salt in cooking, adding salt in table, excess consumption of processes foods high in salt content) is a practical approach to identifying individuals consuming high sodium diets.

Sodium intake target (individual)

- Sodium is an essential nutrient, and is a dietary requirement for all humans, and should be included in a healthy balanced diet. Excess sodium intake is an important determinant of hypertension and CV risk.
- As there is no practical method to objectively and accurately measure sodium intake in individuals, we recommend avoiding a numeric target in individual counselling. Rather, individuals should be screened for their consumption of food patterns. Food items known to be associated with high sodium content should be reduced, or substituted, and reductions/substitutions recommended. Such an approach requires knowledge of main sources of high sodium intake (discretionary vs. non-discretionary) and high sodium food items that are consumed commonly in the setting in question.

Reducing sodium intake target (intervention in individuals)

- Individual-level counselling/educational interventions that have been shown to reduce sodium intake in clinical trials are impractical for primary care settings, although these have targeted reducing sodium intake from moderate to low sodium intake levels.
- Family and community-level interventions have been shown to reduce high sodium intake, although the available evidence suffers from methodological limitations.
- Current evidence supports the safety of low-sodium salt substitutes, although a large ongoing clinical trial to determine its effectiveness in reducing stroke risk is pending (SSaSS Trial).

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