

## Nutrition in cardiovascular disease

# Salt intake and cardiovascular disease: why are the data inconsistent?

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Effective population-based interventions are required to reduce the global burden of cardiovascular disease (CVD). Reducing salt intake has emerged as a leading target, with many guidelines recommending sodium intakes of 2.3 g/day or lower. These guideline thresholds are based largely on clinical trials reporting a reduction in blood pressure with low, compared with moderate, intake. However, no large-scale randomized trials have been conducted to determine the effect of low sodium intake on CV events. Prospective cohort studies evaluating the association between sodium intake and CV outcomes have been inconsistent and a number of recent studies have reported an association between low sodium intake (in the range recommended by current guidelines) and an increased risk of CV death. In the largest of these studies, a J-shaped association between sodium intake and CV death and heart failure was found. Despite a large body of research in this area, there are divergent interpretations of these data, with some advocating a re-evaluation of the current guideline recommendations. In this article, we explore potential reasons for the differing interpretations of existing evidence on the association between sodium intake and CVD. Similar to other areas in prevention, the controversy is likely to remain unresolved until large-scale definitive randomized controlled trials are conducted to determine the effect of low sodium intake (compared to moderate intake) on CVD incidence.

**Keywords** Salt • Sodium • Cardiovascular • Prevention • Population health

## Introduction

Population-based interventions to reduce the risk of cardiovascular disease (CVD) should target a common risk factor, which is modifiable through simple effective interventions and may be implemented in a range of settings and populations.<sup>1</sup> Reducing excess sodium intake presents a compelling target for population-based prevention of CVD, given its association with blood pressure and that interventions to reduce sodium intake may be targeted at individual, community, societal, and policy levels.<sup>2</sup>

In 2003, the World Health Organization (WHO) recommended that adults ingest <2.0 g/day of sodium (which corresponds to 5 g of salt/day), based on an assessment of the best available evidence.<sup>3</sup> At that time, some epidemiological studies reported an association between higher levels of sodium intake and CV events,<sup>4–6</sup> and clinical trials had demonstrated that reduced sodium intake to low levels was associated with a reduction in blood pressure which formed the basis for guideline thresholds.<sup>7–10</sup> Since then, however, there have been a number of studies that have

questioned whether the recommended target of sodium intake is optimal, with some recent studies reporting that intakes of under 3 g/day may be associated with an increased risk of CV death.<sup>11–16</sup> These recent studies, and the absence of a definitive randomized controlled trial indicating that reducing sodium intake to low levels will reduce CVD, have re-ignited the controversy surrounding the optimal target for sodium intake.<sup>17,18</sup> Despite a large number of studies evaluating the association between sodium intake and blood pressure and CVD, there are few areas in CVD prevention that evoke more diverse opinions.

In this article, we explore potential reasons for the differing interpretations of existing evidence on the association between sodium intake and CVD, such as differences in methods of measurement, population characteristics, study designs, and outcome measures. In addition, reduction in sodium intake may have differing effects on other dietary factors known to affect CV risk, which may vary by population. We also contend that there may be a J-shaped association between sodium intake and CVD, which is the principal reason for different findings between studies.

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Finally, we present some approaches that are required to clarify the uncertainty, and discuss what further research is required to determine the optimal sodium intake range.

## Variations in methods of measuring sodium intake

There are two main approaches to estimate sodium intake, namely measuring urinary excretion or dietary intake.<sup>19</sup> For either method, it is optimal to complete repeated measurements to capture 'usual' intake of sodium.

**Urinary Methods:** 24 h urinary sodium excretion is the reference standard for sodium intake estimation, on the premise that the vast majority (90–95%) of sodium ingested is excreted in the urine. Limitations of this approach are incomplete collection of urine for <24 h, under-estimation of sodium intake in populations with increased sodium excreted in sweat, and impracticality of collecting 24 h collections in sufficiently large numbers of individuals so that a large number of CVD events occur over a reasonable follow-up period (e.g. 5 or 10 years), which will allow careful characterization of the strength and nature of any relationship between sodium intake and CVD incidence. A more convenient urinary method is estimated urinary sodium excretion from early fasting morning urine, which has been shown to be a valid group estimate compared with 24 h urine.<sup>20</sup>

**Dietary Methods:** Dietary assessment may be measured using 24 h dietary recall, food diaries, or food frequency questionnaire. Dietary methods are more convenient than urinary methods, can be more easily administered repeatedly, and have the advantage of also identifying the key sources of excess sodium in the diet and measuring overall diet quality. However, limitations include recall bias, variations of sodium content of common food items (e.g. sodium content of a slice of bread may vary considerably), lack of information on sodium added at the table or cooking, and imprecision with estimating portion size. In general, dietary methods of assessment underestimate sodium intake, compared with 24 h urinary measures.

Between-study differences in the methods of measuring sodium intake make between-study comparisons difficult. For example, dietary methods may underestimate sodium intake compared with urinary methods, and, therefore, studies employing dietary methods may observe lower absolute thresholds of sodium intake associated with CV risk. One approach is to confine analysis to studies that used reference standard (24 h urinary collections) to estimate sodium intake. Of eight prospective cohort studies,<sup>5,12–14,21–24</sup> two reported a positive association, two reported no association, and four reported an inverse association between sodium intake and some CV events. All of these studies were conducted in Europe, Australia or the USA.

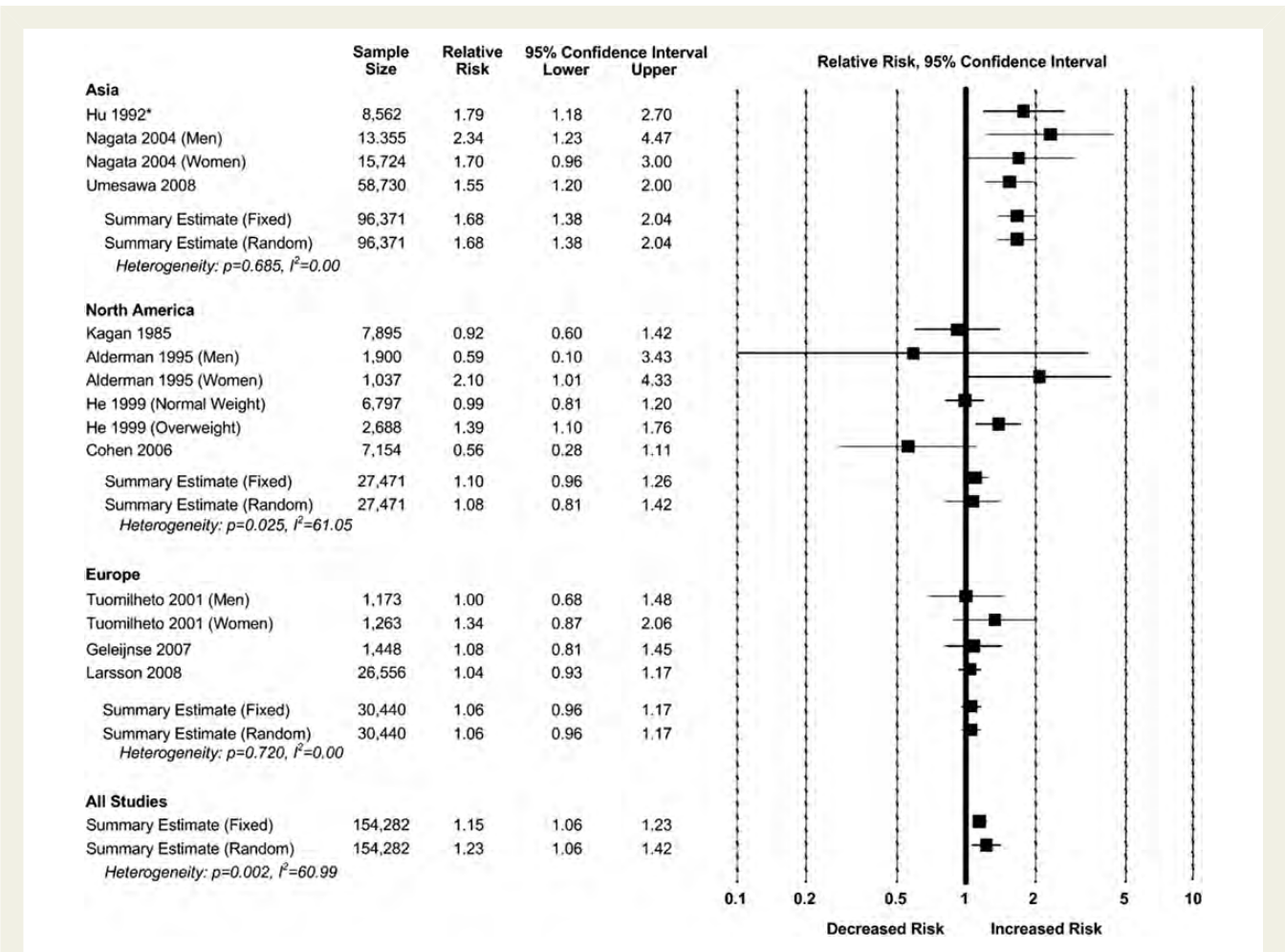
Differences in the methods of measurement also present problems for implementation and monitoring of guideline recommendations. For example, guideline thresholds are primarily based on estimates from clinical trials (examining the effects of a sodium-lowering diet on blood-pressure lowering) which used 24 h urinary estimates of sodium intake. However, most population-based surveys of sodium intake in communities have used dietary recall methods. In studies that compared 24 h urinary sodium to

24 h dietary recall, correlations were poor to moderate.<sup>25</sup> At present, there is no reliable method of standardizing between methods, or estimating comparable levels of sodium based upon urinary and dietary methods of estimating sodium intake. To this end, future studies should ensure that both dietary and urinary methods of sodium intake are measured.

## Variations in population characteristics

### Geographical region and range of sodium intake

A 2009 meta-analysis<sup>26</sup> of 13 prospective cohort studies reported a significant association between increased sodium intake and CV events and stroke. In that meta-analysis, which compared highest vs. lowest quantiles of sodium intake among studies, a 2 g/day increase in sodium intake (5 g of salt) was associated with an increased risk of stroke (RR 1.23; 1.06–1.43) and composite of all CV events (RR 1.14; 0.99–1.32). However, for both outcomes, there was statistically significant heterogeneity ( $I^2 = 61$  and 80%, *Figures 1* and *2*), with less than half of individual studies reporting either no association or an inverse association. One potential source of heterogeneity was differing ranges of sodium intake of populations included among studies, in that an association between sodium intake and CV disease appeared to be positive in populations with high intakes (e.g. >4.5 g/day of sodium) but not in those with moderate or low intakes.<sup>27</sup> However, differences in the methods of sodium intake measurement (24 h urine, food frequency, 24 h dietary recall), and inconsistent reporting of mean intake, precludes a precise exploration of whether this was the only source of heterogeneity. An alternative indirect method is to look at region/country where the study was conducted, as some regions are known to have high sodium intake. *Figures 1* and *2* show the same studies included in the meta-analysis by Strazzullo et al.,<sup>26</sup> but categorized by region (Asia, North America, and Europe). For stroke, much of the heterogeneity appears to be explained by region, with all studies in Asia reporting an association between increased intake and risk of stroke (RR 1.68; 1.38–2.04;  $I^2 = 0\%$ ) but there is no significant association for studies in Europe (RR 1.04; 0.93–1.17;  $I^2 = 0\%$ ) or North America (RR 1.08; 0.81–1.42;  $I^2 = 61\%$ ), although heterogeneity remained for studies in North America. Studies in Asia were conducted in Japan and Taiwan, meaning that populations from many other parts of Asia (China, South Asia, Southeast Asia, and the Middle-east) are not represented in this analysis. Based on what is known about estimates of sodium intake, it is reasonable to suggest that most of the association between sodium intake and CVD comes from regions known to have high intake, and no association, or an inconsistent association, in studies conducted in countries with moderate intake levels.<sup>27</sup> For the composite outcome of all CVD (inconsistent definitions among studies), only one study was conducted in Asia which reported a significant association (*Figure 2*), and there was no significant association for studies in Europe and North America. Since that meta-analysis, other prospective cohort studies have been published.<sup>12–15,28–30</sup>



**Figure 1** Prospective cohort studies evaluating the association between sodium intake and stroke categorized by region (Asia, North America, and Europe) included in meta-analysis by Strazzullo et al. Comparison between highest and lowest quantiles of sodium intake.

Of these, five were conducted in Europe/Australia/USA, of which two reported a positive association, two reported an inverse association and one reported a J-shaped association between sodium intake and some CV events or all-cause mortality and one conducted in Japan which reported a positive association. Only one study<sup>15</sup> was conducted in an international population, and reported a J-shaped association with CV death and hospital admission for congestive heart failure (Figure 3).

A limitation of current evidence is that all but one prospective cohort study, evaluating the association between sodium intake and CV events, has been conducted in a single country or region. This indicates substantial gaps in our knowledge of the association between sodium intake and CVD, with no information currently available from several regions of the world, such as Africa, South America, India, and Russia.

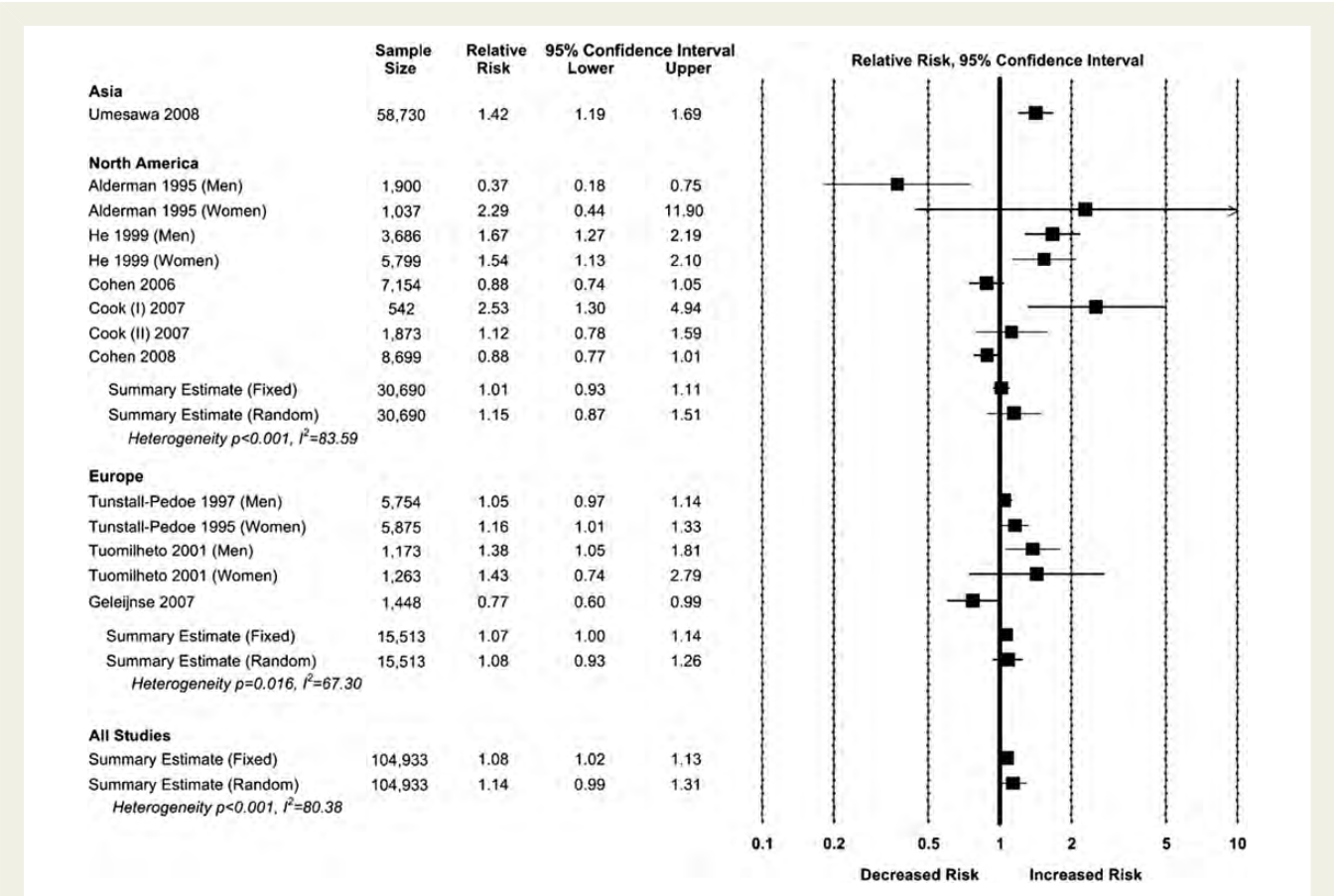
**Cardiovascular risk**

Patients with established CVD are expected to be most susceptible to the effects of extremes of sodium intake (and consequently the most to benefit if low sodium intake reduces CVD). While most studies evaluating the association between

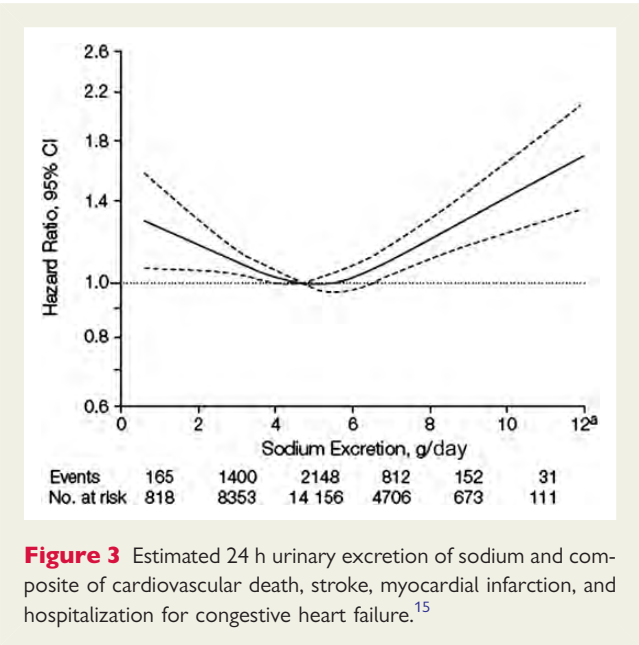
sodium intake and CV events have been conducted in primary prevention populations, the most convincing evidence of a J-shaped association between sodium intake and CV events comes from two prospective cohorts in patients at increased CV risk (included participants with established CV disease or diabetes mellitus).<sup>13,15</sup> Within clinical trials,<sup>31</sup> the only trials reporting an increased mortality with low sodium intake included patients with established congestive heart failure,<sup>32</sup> while extended follow-up of some trials in primary prevention populations suggest a potential benefit of low sodium intake<sup>33</sup> (although loss to follow-up was 23% in extended observational follow-up of the TOPH trials)<sup>24</sup> (Figure 3). Baseline CV risk, therefore, may be an important determinant of the association between sodium intake and CV disease, which is important because it is the high-risk populations that are most likely to receive recommendations on sodium intake. In addition, studies of low-risk populations, especially small studies, have a low number of events and hence reduced power, so the estimates may be less reliable.

**Dietary patterns**

Sodium intake is embedded as part of an entire pattern of consumption of other dietary factors which may complicate, and



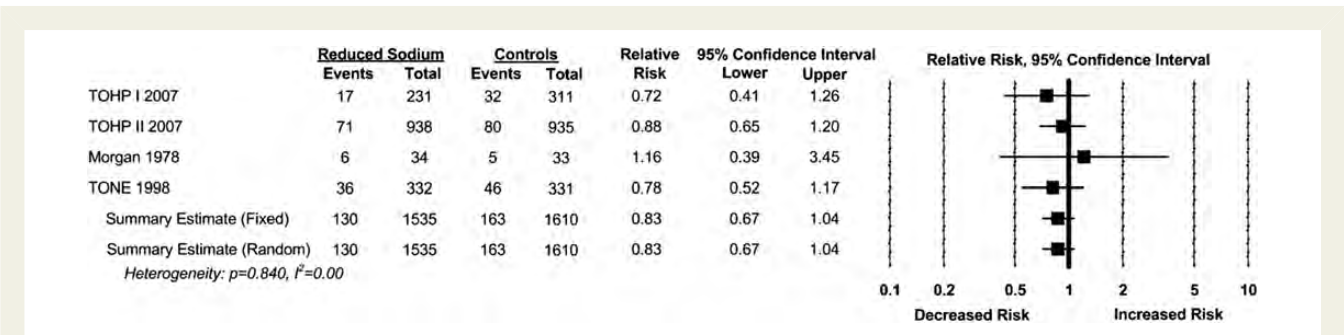
**Figure 2** Prospective cohort studies evaluating the association between sodium intake and composite of CV events categorized by region (Asia, North America, and Europe) included in meta-analysis by Strazzullo *et al.* Comparison between highest and lowest quantiles of sodium intake.



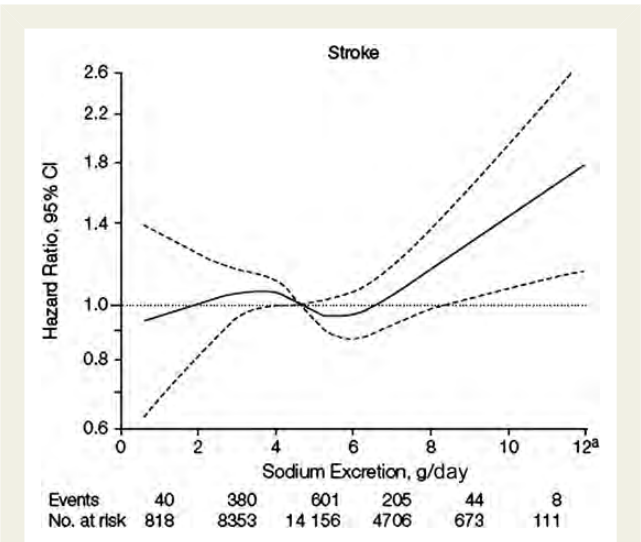
**Figure 3** Estimated 24 h urinary excretion of sodium and composite of cardiovascular death, stroke, myocardial infarction, and hospitalization for congestive heart failure.<sup>15</sup>

confound, the association between sodium intake and CVD in a number of ways, especially in high-moderate income countries where some 80% of dietary sodium intake is from non-discretionary sources.<sup>19</sup> First, dietary patterns (and sources of sodium intake) differ by region, country, and communities within countries. Dietary factors (e.g. fruit and vegetable intake) and dietary patterns (e.g. prudent diet, Mediterranean diet) have been associated with marked changes in the risk of CVD.<sup>34–36</sup> Therefore, some diets may be high in sodium content but also high in other cardioprotective factors (e.g. salted fish and vegetables), while other diets may be high in sodium content and low in cardioprotective factors (e.g. fast foods, some processed foods), which might contribute to between-study differences in findings. In one Japanese study, a traditional dietary pattern with the highest sodium intake (and blood pressure) was associated with the lowest risk of CV disease, attributed to the diet also being rich in fish and vegetables.<sup>37</sup> Second, the ‘knock-on’ effect of lowering sodium intake on other dietary factors may differ by dietary pattern and region. In most clinical trials, evaluating the effect of sodium re-





**Figure 4** Extended Follow-up clinical trials evaluating reduction in sodium intake from moderate to low levels (Note: Data for 2 trials, and overall summary estimate, differs from that reported by He et al, following independent data abstraction).



**Figure 5** Estimated 24 h urinary excretion of sodium and stroke.<sup>15</sup>

duction on blood pressure, the sodium reduction intervention was carefully implemented within a balanced dietary regimen. However, in the real world, the effect of an ‘isolated’ recommendation on sodium restriction on other dietary factors is less predictable and more inconsistent, and may have unintended adverse effects on the diet.<sup>38</sup> Third, there is evidence that some dietary factors may modify the association between sodium intake, blood pressure, and CVD, of which the most prominent is potassium intake.<sup>39</sup> In this regard, there is some indirect evidence to suggest that the blood pressure lowering effect of sodium restriction is dependent on whether the dietary reduction is embedded within a multi-component intervention.

Epidemiological studies have also reported that increased potassium intake is associated with reduced risk of CVD, most notably for stroke,<sup>40,41</sup> but also that the association between sodium intake and CVD may be mitigated by increased potassium intake. In the ONTARGET/TRANSCEND study,<sup>15</sup> we observed that the lowest rate of CV events occurred in the group with moderate

sodium intake and high potassium intake. The relationship between sodium and potassium intake also complicates interpretation of some studies, which target both electrolytes. One study,<sup>42</sup> often referenced as robust evidence to support sodium restriction, replaced sodium with potassium and reported a reduction in CV events.<sup>43</sup> In that trial, relative increases in objective measures of potassium intake were greater than reductions in sodium intake, and makes it impossible to determine whether the reported benefits were attributed to sodium reduction or potassium supplementation. Potassium intake is also a surrogate for a healthy CV diet,<sup>44</sup> as many of the foods associated with reduced CV risk are rich in potassium, especially fruits and vegetables.

Salt sensitivity

Salt sensitivity describes the observation that certain populations, or individuals, may be at increased risk of the CV risk associated with sodium intake. Clinical data show marked heterogeneity in blood pressure change in response to sodium reduction.<sup>45,46</sup> Ethnicity, hypertensive status, and obesity have been reported to modify the association between sodium intake and CVD (or blood pressure) in some studies but there have not been consistent observations in studies. Genetic underpinnings for salt sensitivity, and their direct association with specific genetic polymorphisms for hypertension,<sup>47</sup> remain to be determined, but may be of importance in explaining inter-regional differences in the association between sodium intake and CV risk.

Variations in outcome measures

Blood pressure

Meta-analysis of clinical trials and observational studies have reported a generally consistent association between reduced sodium intake and lowering of blood pressure in both primary and secondary prevention populations.<sup>10,48</sup> The INTERSALT study,<sup>49</sup> a cross-sectional study ( $n = 10\,079$ ) from 52 centres around the world, was the first large study to report an association between sodium intake and blood pressure. In that study, sodium intake was estimated from 24 h urine excretion, and ranged from 0.2 mmol/24 h (Yanomamo Indians, Brazil) to 242 mmol/24 h (North China). Overall, there was a significant association

between increasing sodium intake and increasing blood pressure. Even in recent prospective studies reporting an inverse or J-shaped association between low sodium intake and increased CV risk, a positive association between sodium intake and blood pressure has been shown.<sup>12,15</sup> The assumption that underlies most guidelines is that reductions in blood pressure, due to sodium reduction, will translate into reductions in CVD.<sup>2,3</sup> However, the results of some recent randomized controlled trials have challenged whether reducing blood pressure in patients with mild hypertension results in subsequent reduction of CVD.<sup>50–52</sup> In addition, different classes of antihypertensive are associated with differing risk reduction for CV events, and some of the benefit of certain antihypertensive classes appears to be independent of blood pressure lowering. In particular, drugs that inhibit the RAAS reduce the risk of CVD, independent of blood pressure lowering.<sup>53</sup> In contrast, low sodium intake reduces blood pressure but increases RAAS activity.<sup>54</sup> Therefore, the proposed model that reduced sodium intake results in reduced blood pressure, which in turn, results in the reduction in CV disease is overly simplistic and is likely dependent on the mechanism through which blood pressure is reduced and the baseline blood pressure of the population. In addition, the association between high sodium intake and increased CV risk is only partly explained by blood pressure, and other mechanisms proposed to mediate the association, such as fluid balance, may also contribute to the observed increase in CV risk with high intake.

## Cardiovascular outcomes

Sodium intake may have differing effects on individual CV outcomes, namely CV death, myocardial infarction, stroke, and congestive heart failure.<sup>15</sup> This makes between-study comparisons difficult, as there is inter-study variation in the outcome that is reported (and studies may be subject to reporting bias). The most consistent outcome reported in studies is CV death, and for this outcome, a J-shaped association exists, based on the totality of data.<sup>11,15,55,56</sup> For myocardial infarction, only one study has reported an inverse association<sup>22</sup> and no study has reported an inverse association for stroke. In the ONTARGET/TRANSCEND cohort,<sup>15</sup> we observed a J-shaped association for CV death and congestive heart failure but not for myocardial infarction or stroke. Therefore, some of the differences between study findings may relate to what outcomes were measured and selected, and may contribute to the heterogeneity reported in meta-analyses of these studies (Figure 2). However, epidemiological associations can never be free of confounding despite extensive adjustments, but, for the time being, at levels of sodium intake below around 4–5 g/day, there is no consistent positive relationship between sodium intake and any CVD event.<sup>27</sup>

## What is the safe lower threshold for sodium intake?

A minimal level of sodium intake is a necessary requirement for normal physiological processes. With very few exceptions for specific populations,<sup>57</sup> guidelines do not report a lower recommended intake. This approach is based on the assumption that there is no

unsafe lower limit or, that it is not possible to ingest sodium levels that are associated with harm.<sup>58</sup> It is proposed by some that humans require about 0.5 g/day (or less),<sup>44</sup> based largely on studies in Yanomamo Indians who consumed <0.5 g/day and had very low prevalence of hypertension<sup>59</sup> (although life expectancy in this tribe was very low; mean of about 40 years, and increased renin activity is reported in this population<sup>60</sup>). In contrast, other studies report that adverse effects on some physiological parameters occur when intake levels fall below about 2.0 g/day, such as activation of RAAS, increased catecholamines, dyslipidaemia, and dysglycaemia. Therefore, some of the controversy relates to differing interpretations of what is an adequate intake of sodium for normal physiological function. Establishing a safe lower threshold for sodium intake, associated with low CV risk, remains an unanswered question, and a priority to resolve. It is expected that minimum daily sodium requirements may differ by population characteristics (e.g. background diet, level of exercise) and climate.

## Study design and level of evidence

Large randomized controlled trials showing a reduction in clinically important CV events are required to test interventions that are proposed to be effective, especially where uncertainty exists about whether the benefits outweigh harm or expense. For some recommendations (e.g. smoking cessation), large randomized controlled trials are not required because of the overwhelming observational evidence and very large excess risks (e.g. smoking 20 or more cigarettes per day increases the risk of lung cancer 20-fold and increases the risk of vascular events by 2.5–3-fold) to support benefit and the absence of evidence to suggest harm. Many believe that the epidemiological data is sufficient to advocate a public health policy for sodium reduction in the entire population, across all levels of intake. However, as summarized earlier, the association between sodium intake and CVD is unclear in populations consuming moderate-low intake (<4–5 g/day). While it may be appropriate to recommend reducing sodium intake in populations whose average consumption is over 5 g/day (either in individuals with high intake or in populations with high intake), whether further reducing intake from moderate (where most Western populations reside) to lower levels (<3 g/day) results in more benefit than harm is uncertain. While most randomized controlled trials have reported a benefit in surrogate outcome (blood pressure) by reducing sodium intake from moderate to low levels, most prospective cohort studies in countries with moderate sodium intake have either reported no association or an inverse association between reduced intake and CV death. Some of the controversy relates to differing opinions on whether ‘best evidence’ comes from clinical trials of surrogate outcomes (BP) or prospective cohort studies of CV outcomes. Since original guidelines were developed, a new body of evidence has established clinical uncertainty about the benefits of low sodium intake. This uncertainty is reflected in differing opinions and interpretations of the evidence.<sup>27,61</sup> At present, no high-quality trial has been completed indicating that low sodium intake reduces CVD incidence.

## Other observations contributing to uncertainty

Given that CVD is the major cause of death globally,<sup>1</sup> it appears inconsistent that some of the countries with the highest sodium intake (e.g. Japan, Finland) have been those with the highest life expectancy. In countries such as the USA, there have been marked reductions in stroke rates over the last 25 years although the levels of sodium intake appear to have remained constant (perhaps due to the difficulties in implementing a society wide strategy).<sup>62</sup>

## Other considerations

There are many determinants of elevated blood pressure. In addition to higher sodium intake, a low level of potassium intake, low levels of fruit and vegetable intake, obesity, and lack of physical activity have major effects on blood pressure. It is likely that a strategy that tries to influence multiple factors that influence blood pressure is more likely to be effective than a strategy focused solely on sodium intake.

## Conclusions and future directions

### (1) High sodium intake

- (a) *What is Known?* There is strong and convincing evidence of an association between high sodium intake (>5 g/day) and CVD, and no evidence that reducing sodium from high intakes to moderate intakes causes harm.
- (b) *What Should be Done?* Efforts to reduce sodium intake should target people who consume high sodium or be tailored to the average levels of sodium intake in the population. For example, in countries such as those with moderate sodium intake, avoidance of high intake should be a goal. In contrast, in countries with high average intake (e.g. China) this should be complemented with population-based strategies to reduce sodium intake in the population as a whole, by targeting key sources of excess sodium in the diet (e.g. processed food and fast food outlets). Recommendations on sodium reduction should be embedded within general recommendations on healthy dietary patterns, such as increased consumption of fruits and vegetables etc.

### (2) Moderate sodium intake

- (a) *What is Known?* There is no convincing evidence that moderate intake sodium (3–5 g/day) is associated with an increased risk of CVD compared with lower levels of sodium consumption. While there is convincing evidence (from studies in high-risk individuals) that reducing sodium intake from moderate to lower levels has a modest effect on blood pressure from clinical trials, there is also evidence that low intake may be associated with an increased risk of CV death and hospitalization for heart failure from prospective cohort studies.
- (b) *What Should be Done?* The only definitive way of clarifying the uncertainty is to conduct a large-scale randomized controlled trial evaluating the effect of reducing sodium

intake from moderate to low levels on CVD outcomes. While there are logistical difficulties to undertaking such trials, the challenge of getting entire populations to consume low sodium diets is monumentally greater.

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