Sodium Reduction: How Big Might the Risks and Benefits Be?

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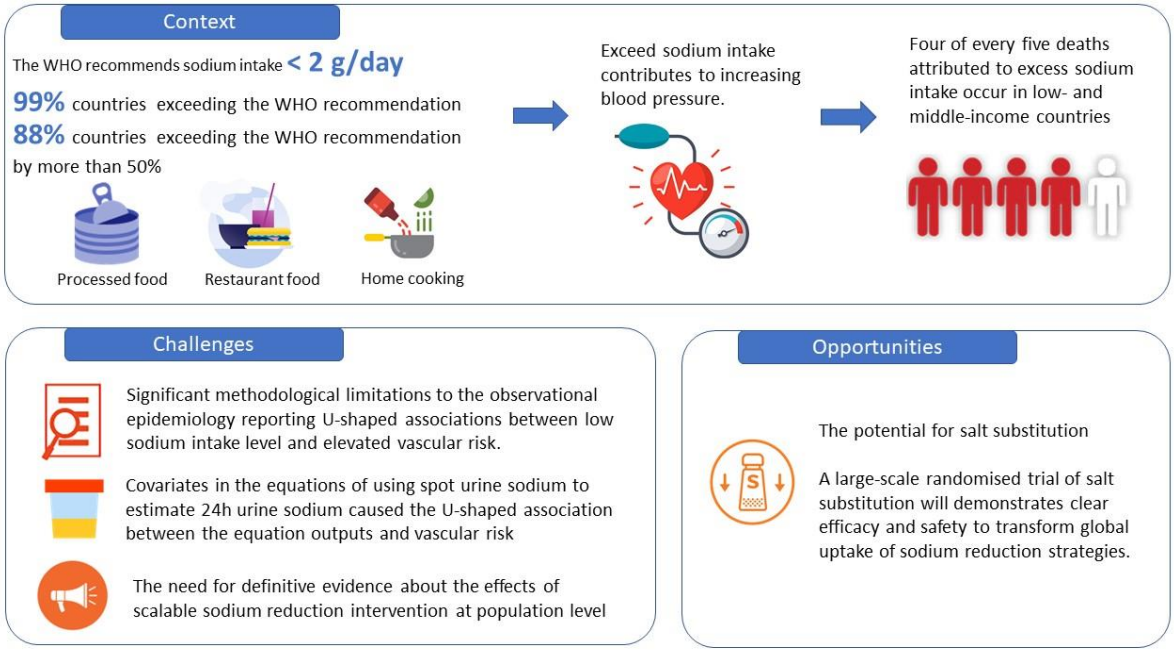
Abstract

Cardiovascular diseases are the leading cause of death worldwide and raised blood pressure is the leading risk for these conditions. Excess sodium intake clearly elevates blood pressure though the association of sodium intake with cardiovascular outcomes has been disputed. Nonetheless, it was estimated that in 2017 excess dietary sodium caused between 1.4 and 5.4 million deaths. Key underlying assumptions for those estimates were that the association between sodium intake and cardiovascular disease is direct and linear, and that a daily consumption level of 2.0g of sodium minimized risk. Recent data indicating that reported U-shaped associations of sodium with risk are the result of confounding provide strong support for the first assumption. Cardiovascular risks may, however, continue to decline below intake levels of 2.0g per day. Further, because excess sodium intake appears to drive a progressive rise in blood pressure with age, the magnitude of the disease burden avoidable by sodium reduction may have been under-estimated. Regardless, health benefits will only be achieved if safe, effective and scalable interventions can be defined and none have been identified to date. Salt substitution, which switches regular salt for a reduced-sodium, added-potassium alternative offers a significant opportunity. Falls in blood pressure with salt substitution are comparable to single-drug therapy and salt substitutes are low cost, simple to use, well -tolerated and could be applied community-wide. Data that prove clinical benefits and exclude risks will be required to support widespread use. An ongoing large-scale randomised trial of the effects of salt substitution on stroke, major cardiovascular events and death will complete soon and define the role of salt substitutes in public health.

Keywords: Salt; Review; Cardiovascular diseases; Salt substitutes

Introduction

Cardiovascular diseases are a leading cause of disease burden responsible for about 18 million deaths, a third of all mortality, worldwide [1, 2]. High blood pressure is a major contributor to cardiovascular diseases and blood pressure levels above 115mmHg systolic are estimated to cause between 9.4 and 11.5 million deaths each year [3]. Dietary sodium intake is a strong determinant of blood pressure levels[4] and recent data from the Global Burden of Disease study estimated that in 2017 between 1.4 and 5.4 million deaths were attributable to excess dietary sodium consumption [5]. Despite the large effects of excess dietary sodium consumption on global disease burden there are no proven, scalable and widely implemented methods for the reduction of dietary sodium intake. In higher-income countries, as high as 75% of sodium are added by industry to packaged and restaurant foods, and the populations of some Asian and developing countries still use more than 70% of sodium for the preparation and consumption of food in the home.[6] In this paper, we review the evidence of studies relating salt reduction to hypertension and cardiovascular diseases, dispel doubts on the low-salt diet and recommend salt substitutes as a potential strategy to scale up sodium reduction intervention. Key points of this review are summarised in Figure 1.



How much sodium are we designed for?

Hundreds of thousands of years of hominid evolution in a salt-poor environment resulted in the selection of sodium-conserving traits that persist to this day. Anthropological studies of dietary patterns suggest that daily sodium intake from a hunter-gatherer diet is less than 1.0g [7]. The first evidence of a salt manufacturing facility dates from just 6,000 years ago but it is only in the last hundred years that sodium has been produced at scale, worldwide. As such, there has been no opportunity for human physiology to adapt to the current salt rich environment and our preference for salty foods, and our physiology designed for sodium retention, now represent a significant disadvantage.

The primary consequence of over-exposure to sodium is chronic elevation of blood pressure which occurs universally in populations exposed to excess dietary intake and drives marked elevations in vascular risks[8]. These effects are well-illustrated by studies of unacculturated populations like the Kalahari Bushmen and the Amazonian Yanomami. They had been living in isolated tribes in the Amazon rainforest. In their traditional setting, these populations consume only naturally occurring sodium at very low levels with adult blood pressure distributions that exhibit no rise with age and an

almost complete absence of clinical hypertension [7]. Upon migration to urban settings and exposure to foods containing added sodium, there is a rapid rise in blood pressure, hypertension and the risk of cardiovascular diseases [9].

What are recommended dietary intake levels?

The WHO recommends that dietary sodium intake for adults should be less than 2 grams per day (equivalent to 5 grams of salt) [10]. Directly comparable advice is provided by most national and international guidelines for the management of hypertension. However, these recommendations are a pragmatic compromise that recognise the limited feasibility of reducing sodium intake from current very high levels. Physiological, observational and experimental data suggest that sodium intake of 0.5-1.0 grams per day is the level of consumption for which humans are optimally adapted. The neurohormones of the renin angiotensin aldosterone system switch from a pattern driving sodium retention to sodium excretion at this level and there are clear long-term beneficial effects on blood pressure from reducing daily dietary sodium intake below 2.0g. The Dietary Approaches to Stop Hypertension (DASH) trial, for example, showed a fall in blood pressure with a reduction in salt intake from 3.3 g to 2.5 g per day but an additional marked decline amongst participants who reduced their sodium intake further from 2.5 g to 1.5 g per day [11]. A recent meta-analysis of 133 studies also indicated a dose-response relation between sodium reduction and lowering systolic blood pressure. In these analyses, each 50 mmol reduction in 24 hour urinary sodium was associated with a 1.10 mm Hg decrease in systolic blood pressure and a 0.33 mm Hg decrease in diastolic blood pressure.[12]

How much sodium do we eat?

Average adult sodium intake worldwide is far above WHO recommendations and evolutionary norms. Global average intake is estimated to be a least 4g/day [13], and possibly higher [2], with mean levels in 181 of 187 countries for which estimates have been made (constituting 99% of the world adult population), exceeding the World Health Organization recommendation. For 119 countries (88% of the world's adult population) the national intake of sodium was estimated to exceed the WHO recommendation by more than 50 per cent. Average national sodium intake levels are highest in Central Asia, East Asia and Eastern Europe where mean intake is more than double the WHO target and perhaps five to ten times evolutionary norms. Intake estimates are consistently higher for men than for women and greater at higher levels of body mass index due to greater food consumption. Lower levels of sodium intake are observed at older ages in both men and women and this likely reflects lesser intake of food at older ages [14].

Universal high levels of sodium intake are driven by the joint effects of genetic traits that give us a taste preference for sodium containing foods, and a food environment that provides easy access to sodium. Salt is a low-cost seasoning that was widely employed by low-income communities for preservation prior to the availability of refrigeration and continues to be used as a low cost means of enhancing the palatability of staple food products. In parallel, the global food industry adds very large quantities of sodium during food processing, alongside fat and sugar, to maximise product sales and profitability.

Could low sodium intake be harmful?

There are compelling arguments supporting sodium consumption of 0.5-1.0 grams per day as optimal physiological intake but there have been concerns raised about possible adverse health effects of reducing sodium intake below the global mean consumption level [15, 16]. These concerns derive primarily from prospective observational studies, some of which report U-shaped associations of sodium intake and cardiovascular disease [17-19]. While it is possible that both low and high sodium intake levels may be harmful the mechanism for such effects is uncertain.[20] In particular, the beneficial effects of sodium on blood pressure are constant across all consumption levels, and with

blood pressure the primary mediator of the health effects of sodium, lower sodium intake would be anticipated to be protective at all but the very lowest levels of consumption. There are significant methodological limitations to the observational epidemiology reporting U-shaped associations and there have been longstanding concerns that the elevated vascular risk at low consumption levels may be a consequence of reverse causation - individuals reporting low sodium intake levels are frequently patients with a history of disease who have been advised to reduce sodium. Amongst these individuals it may be their increased risk consequent upon concomitant disease that drives adverse cardiovascular outcomes, not their low sodium intake level. It is now clear that inappropriate measures of exposure to sodium are also causing serious confounding of the associations in some studies [15, 16].

Is the use of spot urine samples confusing the epidemiology?

Spot urine samples are much easier to collect than 24-hour urine samples and, therefore, have been used in several cohort studies as a proxy for measured 24-hour intake based upon gold-standard 24-hour urine collections. While using estimating equations based upon spot urine samples may be a reasonable strategy for calculating the mean sodium intake of a population (for which the approach was developed), the equations provide a poor measure of individual sodium intake and are inappropriate for studies exploring the role of sodium in disease causation [21, 22]. The key issue regarding the use of sodium intake levels derived from estimating equations to assess casual relationships is that the equations include multiple other variables that are separately associated with disease risk. This is true for all the widely used estimating equations [23-25]. which variously include age, sex, body weight and creatinine concentration. Each of these covariates has an independent, and in some cases non-linear, association with adverse health outcomes. The very widely cited Prospective Urban Rural Epidemiology study [16], which has generated much of the debate concerning possible adverse effects of low sodium levels on health outcomes used these approaches and the conclusions are almost certainly seriously flawed as a consequence.

The problem with using daily sodium intake levels estimated from equations has been directly illustrated by recent secondary analyses of the Trials Of Hypertension Prevention (TOHP) studies. The Trials Of Hypertension Prevention studies collected baseline 24-hour urine samples and then did long-term follow-up of participants for deaths and cardiovascular events beyond the initial trial intervention period. Estimates of the association between sodium excretion and mortality based upon directly measured sodium excretion using the 24-hour urine samples showed clear positive and linear associations with death and vascular events. By contrast, when the same associations were examined using estimates of sodium excretion based upon baseline spot urine concentrations and estimating equations, the relationships became U-shaped with increased risks observed at low as well as high levels of estimated sodium intake. Further exploration of this phenomenon revealed that it was the covariates in the equations, not the spot sodium concentration values, that caused the U-shaped association between the equation outputs and vascular risk [26].

How large is the potential benefit achievable with sodium reduction

The magnitude of the disease burden attributable to excess sodium intake is large but may be a significant under-estimate. The reasons for this are two-fold. First, chronic exposure to excess sodium intake appears to drive a progressive rise in blood pressure with age [27] and this effect is incompletely captured in the current modelling. Second, the level of sodium intake at which risk is assumed to be minimized (2.0 grams per day) may be too high. If lower levels of sodium intake do attenuate the rise in blood pressure with age, and if reduction in sodium intake to 0.5 or 1.0 grams per day results in additional benefit, then the attributable disease burden, as well as the potentially avoidable disease burden might be even greater than reported. Four of every five deaths attributed to excess sodium intake occur in low- and middle-income countries [28].

The need for definitive evidence about the effects of sodium reduction

The recently reported data explaining the reasons for observed non-linear associations with disease outcomes in conjunction with a wealth of data describing beneficial effects on blood pressure make a compelling case for the implementation of sodium reduction strategies.[26, 29] Indeed, the WHO advocates dietary sodium reduction as a highly cost-effective measure to decrease blood pressure levels and reduce the risk of cardiovascular diseases.[30] However, the widespread promulgation of confounded data from projects such as the Prospective Urban Rural Epidemiology study and the confusion that it has caused, means that there is no strong likelihood that sodium reduction initiatives will be widely implemented.[15] In addition, there is currently no proved efficacious and safe method for reducing sodium intake that could be implemented at scale.

While sodium intake can be reduced in carefully controlled research settings, and amongst a subset of highly motivated patients in the clinical setting, there is little evidence that potentially scalable sodium reduction initiatives based upon education and social marketing will be effective. Likewise, programs targeting sodium levels in processed foods have showed limited success and there are few data describing the effects of such initiatives on clinical outcomes.[31] The challenges with achieving substantial changes in sodium intake using these methods have made it difficult to generate robust evidence about the effects of sodium reduction on clinical and safety parameters. One intervention, salt substitution, may provide a solution to this problem.

The potential for salt substitution

Salt substitutes replace regular salt (sodium chloride), the main source of dietary sodium for most populations, with a reduced-sodium, added potassium salt alternate. Salt substitutes can achieve significant reductions in sodium intake and blood pressure and effects are maximised amongst individuals for whom most dietary sodium derives from salt added as seasoning or during food preparation at home. These are typically the most disadvantaged in our societies and salt substitution may have a particular role in enhancing equity of access to effective cardiovascular disease prevention.

Salt substitutes vary in composition, but all have a reduced sodium chloride content that is substituted with potassium chloride and/or magnesium sulphate and other minerals. There are more than 30 companies around the world that manufacture salt substitutes which are marketed in many different countries. There is a wealth of evidence from randomised trials describing beneficial effects on blood pressure with studies completed in in China [32, 33], Finland [34], Brazil [35] and Taiwan [36]. Meta-analysis of the trial data showed a reduction in blood pressure of 7.8/4.0mmHg [37, 38] with one larger study also suggesting protection against clinical events [36]. Salt substitutes are recommended by many guidelines for the treatment of hypertension but despite excellent acceptability amongst patients [39-41], uptake is very limited. This is because salt substitutes are not widely available and because there are concerns about possible risks of hyperkalaemia amongst patients with seriously impaired kidney function. Trials of salt substitutes completed to date have identified no increase in the risk of adverse outcomes but the quality of the safety data is limited [42].

World Health Organization (WHO) recommended salt iodisation as an effective means of improving iodine status at population level. Currently, fortification of salt with iodine is voluntary. There is no guidance on fortification of potassium‐based salts with iodine. Adding iodine in salt substitute may optimise public gains of using salt substitutes, especially for iodine deficient area. But the concentration of iodine in salt substitute needs to be tailored to local conditions.

The need for a large-scale randomised trial of salt substitution

Adequately-powered, high-quality, large scale, randomized controlled trials drive practice change, health policy updates and financial reimbursement practices around the world. There is significant

potential for a definitive trial of sodium reduction that demonstrates clear efficacy and safety to transform global uptake of sodium reduction strategies. The ongoing Salt Substitute and Stroke Study (SSaSS) has been designed with this objective and will complete shortly. The trial has enrolled 20,996 patients at elevated risk of cardiovascular disease across 600 rural villages in five Northern Chinese provinces. The intervention is a salt substitute and the primary outcome is stroke. The effects of the salt substitute compared to usual salt will also be assessed for the secondary outcomes of major cardiovascular events and total mortality [43].

What does the future hold?

There is little doubt that current levels of sodium consumption are far above evolutionary norms for all but a tiny fraction of the world's population. It is also very likely that this is causing much premature death and disability, with a disproportionate adverse impact amongst low-income and disadvantaged communities. The magnitude of the disease burden is probably towards the upper end of current estimates and may exceed even current worst-case projections. It seems unlikely, however, that any action will be forthcoming unless there is clear evidence that sodium reduction can safely and effectively reduce the risk of serious disease outcomes. Only with clear evidence from a trial like the ongoing Salt Substitute and Stroke Study will it be possible to overcome the concerns raised by poor quality epidemiology and the commercial interests of the food industry. If a large trial does show a clear benefit then there is the potential for unprecedented health gains, at very low cost, for many of the most disadvantaged populations in the world. Given the decades over which this debate has rumbled on, it is a travesty that such data are not already available.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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