Understanding the science that supports population-wide salt reduction programs

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Background

Independent systematic reviews of the totality of the evidence by governments and international agencies throughout the world uniformly conclude that population-wide interventions to reduce salt are beneficial for health. However, some scientists continue to produce and cite studies with paradoxical findings that conflict with the evidence-base used to develop national and World Health Organization (WHO) guidelines on salt reduction.[1-5] Whilst conflicting studies are not uncommon in any area of research,[6] in the case of salt, such studies attract widespread attention in the media; mis-inform program leaders, clinicians, and the general public; and impede program implementation. Such impediments to progress have occurred despite the fact that the designs and methods of studies with paradoxical findings have been criticised by international experts who highlight the fact that the results are not valid.[7-9]

To address this problem, a consortium of national and international health and scientific organizations is leading a program of work through its Standards for Salt Research group. The objective of this consortium is to develop a clear set of processes and criteria that new scientific projects relating to salt should adhere to, so as to achieve at least a minimum quality of research in the field.[10] Whilst general criteria for judging the scientific evidence for studies are available,[11] they do not address the complexity inherent in accurately assessing salt intake and its relationship with health outcomes. The new Standards for Salt Research will help to ensure that only robust scientific studies are used when national and international recommendations relating to salt reduction are reviewed.

In the meantime, the objective of this paper is to provide an overview of the main arguments used against reducing salt and to counter these arguments with evidence in support of reducing population-wide salt intake. This work updates previous similar reviews which have

explained some of the controversies.[12-14] The intent of this paper is to assist policy makers, program implementers and clinicians in understanding the science in support of salt reduction and provide them with tools to counter arguments against population-wide salt reduction.

Main arguments used against and counter-arguments to support salt reduction

Can we make recommendations about salt without consensus on the science? *Salt is an unsettled and hot topic for investigation and so it would be premature to make recommendations in the absence of trial data.*

RESPONSE: There is consensus about the need to reduce population salt intake from the organisations that have systematically and independently examined the totality of the evidence. Public health policy recommendations need to be based on critical appraisals of the totality of the evidence by expert scientific groups overseen by governmental or non-governmental health and scientific organizations. As in most areas of public health, the evidence base is incomplete, as it is lacking in definitive randomized controlled trials for cardiovascular disease outcomes, due to practical and ethical considerations. Nevertheless, multiple independent review processes in different countries [15-19] have all concluded that typical dietary salt intake is too high, that it creates serious health problems and consequently salt intake should be reduced. The current WHO recommendation is that salt (sodium chloride) intake should be less than 5 g/day[*] for adults, with lower levels in children based on their lower caloric needs.[20]

[*] 5 grams of salt corresponds to 2000 mg or 85 mmol of sodium

The evidence supporting the need to reduce salt and the impact of reducing salt on health is increasing.[21-23] However, every year there are a few controversial studies that get most of the media coverage and cause some people to question current recommendations. These studies are usually linked to a small group of individuals, several with ties to commercial interests.[14] Such studies are not appropriately designed to assess the association between salt intake and disease as outlined below.

What are the estimated potential benefits of salt reduction on the burden of disease and death? *Some estimates of the potential benefits of salt reduction in terms of burden of disease and deaths are much lower than initially thought.*

RESPONSE: Reducing salt intake would save millions of lives a year globally. High dietary salt is associated with wide ranging health problems including hypertension, stroke, cardiovascular disease, bone demineralization, kidney stones, gastric cancer and kidney disease.[24-29] The greatest health risk is the increase in blood pressure caused by excess salt intake. Although the magnitude of change in blood pressure from modest changes in dietary salt are relatively small in individuals, on a population scale[21], a reduction in salt explains between one fifth [30] and one third[19] of cases of hypertension. The Global Burden of Disease study[31] estimated that increased dietary salt is the 2nd leading behavioural risk for death and the 3rd leading behavioural risk for disability globally, such that 4.129 million deaths and over 83 million disability adjusted life years (DALYs) lost could be attributed to high dietary sodium consumption in 2015. Health economic analyses find reducing dietary salt to be cost

saving or highly cost effective in different analyses.[32,33] Such evidence has provided the rationale for the WHO and the World Economic Forum to identify population-wide sodium reduction as a "best-buy" intervention for public health.[34]

Does reducing salt reduce blood pressure long term? *Most evidence only shows that reducing salt reduces blood pressure in the short term (< 6 months) only. Should we be cautious in extrapolating from short-term studies of a few months or weeks to what might be expected in the long-term?*

RESPONSE: A large body of evidence supports the fact that reducing dietary salt has a long-term effect on blood pressure. In a wide variety of animal studies, blood pressure continues to increase if salt intake is increased, and this is not attenuated over time.[35-37] In human epidemiological studies, habitually high dietary salt is associated with high blood pressure, and increasing blood pressure with age.[38-40] Blood pressure would not continue to rise with age if changes in blood pressure were only for a short time after exposure.[37] In long term population intervention studies that reduced dietary salt and lasted for decades, decreases in blood pressure have matched or exceeded reductions predicted from results of shorter-term clinical trials.[41,42] In clinical trials of reducing dietary salt, blood pressure reduces in proportion to reductions in dietary salt.[43-48] Many trials lasting 4 weeks or longer have shown reductions in blood pressure.[45] Several high quality randomized clinical trials that reduced dietary salt have demonstrated reductions in blood pressure up to 18 months with no attenuation in reduction in blood pressure.[44,49] Most longer-term trials have not been able to sustain reductions in dietary salt among participants and have been challenged regarding confounding with other co- interventions. [44,50] Nevertheless in the sodium

reduction arm of the Trials of Hypertension Prevention (TOHP) 2 study, systolic blood pressure was still reduced in the intervention arm compared to control after 3 years.[50] In conclusion, well designed meta-analyses of salt reduction trials clearly demonstrate that salt reduction will have a long term impact on blood pressure.[9]

What is the evidence that lowering blood pressure in non-hypertensive people will reduce CVD mortality? *Some studies suggest that lowering blood pressure increases mortality and CV events (other than stroke) in people without hypertension.*

RESPONSE: Lowering blood pressure will reduce CVD mortality, including people without hypertension. The extensive evidence from epidemiology and from higher quality analysis of randomized clinical trials shows a direct relationship between blood pressure and cardiovascular diseases [48,49,51-54]. This relationship between blood pressure and CVD is evident at SBP beginning at ~ 115 mmHg[55], a finding which suggests that non-hypertensive people will also benefit from reductions in blood pressure. The long term follow up from the TOHP studies that showed reduced sodium was associated with reduced CVD, were all done in pre-hypertensives.[56] Reductions in cardiovascular disease are related to the extent to which blood pressure is reduced as well as to the absolute cardiovascular risk of the study population.[51-54,57]

The controversy arises from retrospective non-randomized analyses of studies which include people who are already sick. Some such studies have found a U or J shaped curve which can be explained by reverse causality (whereby blood pressure may be low because of pre-

clinical or prevalent diseases such as myocardial infarction or heart failure which then lead to increased risk of premature death).[1-3,58] Studies where aggressive blood pressure lowering therapy is used in populations susceptible to clinical hypotension may also cause cardiovascular and renal disease.[59] A recent study that suggested a relationship between reduced blood pressure and increased CVD events included people with diabetes and so treatment and other factors are likely to have influenced the results.[60] Such studies do not provide evidence to counter support for population wide salt reduction strategies.[7,8,61-63] An overview of some of the main weaknesses in these studies is provided below.

Why are there no randomized clinical trials proving that salt reduction reduces CVD?

These must be done to provide robust data proving that salt reduction reduces CVD before we implement interventions.

RESPONSE: Pooled data from randomized controlled trials with long-term follow-up for CVD suggests that salt reduction reduces CVD.[64] The reasons few RCTs have been designed and conducted specifically to examine whether salt reduction reduces CVD is because adequately designed and appropriately powered trials would be too expensive, impractical or potentially unethical, given the high quality of evidence documenting the benefits of salt reduction. This is the same in many other fields of public health (e.g. tobacco control, obesity reduction, actions to reduce climate change, air pollution, physical inactivity, and excessive alcohol consumption). Because of high content of salt in the food supply, long term RCTs of salt reduction have found it hard to sustain reduced dietary salt for more than 3 years in free-living subjects.[44,65] The alternative approach of asking subjects to increase dietary salt would be unethical due to the evidence that eating too much salt will

harm health. In most clinical trials, the relatively small number of people that have a CVD event precludes the establishment of any relationship between salt intake and CVD. However, studies that have pooled the data from RCTs of salt reduction, or salt replacers, using meta analyses, have demonstrated a reduction in cardiovascular events with reduced dietary sodium.[64,66]

The existing evidence is strong enough to support the implementation of strategies to reduce salt intake. Meta-analyses of cohort studies of salt intake in healthy populations, or where filters were used to exclude low quality research, have also shown that salt intake is associated with CVD.[21,67] Long term experience with salt reduction in Finland, in Japan and the United Kingdom has associated salt reduction with reduced blood pressure and cardiovascular disease at the population level.[41,68] Long term follow up of individuals in the TOHP trials that carefully assessed usual salt intake through repeat 24 hour urine collections found that salt intake below 2300 mg/day was associated with reduced cardiovascular disease.[56,69]

Aren't low levels of sodium consumption associated with increased CVD events and mortality? *Some studies show that low levels of sodium (less than 3000mg sodium or 7.5g salt per day) are associated with increased mortality especially in non-hypertensives. The most recent study quoted is the PURE Study.*

RESPONSE: It is important to emphasize that consumption of less than 3 grams of sodium a day is not low sodium consumption[70] and that such levels are not associated

with increased CVD events and mortality. Population salt intake for communities with diets that do not have added salt are nearly all below 1 gram of sodium (2.5 grams of salt)/day.[71-73] So although sodium is required for proper bodily function, the minimum physiological amount required is less than 1g of sodium per day.[70] Very few populations are currently consuming such low amounts but in the few remaining hunter-gatherer populations where they do, blood pressure does not rise with age and hypertension and cardiovascular disease are uncommon.[37,74,75] Reliable vital statistics are unavailable in these isolated populations, but mortality appears to be related to infectious diseases and other problems of economically developing regions that are unrelated to salt intake.

Whilst some of the studies suggesting lower amounts of dietary salt are associated with increased CVD events and mortality are based on very large numbers of participants, the methodologies are seriously flawed. Hence their findings should be interpreted with caution and are not appropriate to guide policy. Systematic reviews of cohort studies that have criteria to exclude lower quality studies, as well as a systematic reviews of randomized controlled trials, have found that cardiovascular disease is reduced (not increased) with lower intakes of dietary sodium. [21-23,51,67]

Some of the common methodological problems have been addressed extensively in previous reviews [7,63] and are summarised as follows:

- **Measurement Error**: The most accurate technique to estimate usual dietary salt intake is the collection of multiple, high quality 24 hour urines. A single urine is often used to estimate usual intake; however, this is also less accurate because of large day-

to-day variation in dietary intake and because even on a fixed salt intake, excretion varies widely.[76,77]

Several of the studies showing a J-shaped relationship between salt intake and health outcomes rely on a single spot urine assessment to estimate each person's long-term usual sodium intake.[1,2] Single spot urine sodium samples cannot accurately assess an individual's usual salt intake, because sodium intake varies meal to meal, day to day and is also impacted by seasonal food availability.[78-80] Other studies have had a large proportion of 24-hr urines that were incomplete, leading to inaccurate estimates of salt intake which would impact the results.[4] Incomplete 24 hr urines will have lower sodium levels and do not reflect true intake.[81,82] Other studies have used food surveys that may also not reliably estimate salt intake.[83] In contrast, a follow-up study of participants in the TOHP study, used multiple 24-hour sodium measurements, and documented that people with lower sodium intakes have a lower risk of cardiovascular disease and total mortality. More recent analysis has shown this relationship is still present after a median of 24 years of follow up, with no evidence of a J-Shaped curve.[56,69]

- **Reverse Causality**: In observational studies, subjects consuming the least salt may be more likely to have the highest risk of cardiovascular events and death because they were already ill when they entered the study – the problem known as 'reverse causation'.[7,84] These people are likely to be consuming fewer calories and therefore eating less salt because they are ill, rather than being ill as a result of eating less salt. For example, in the PURE study, older age, having diabetes, and having a history of CVD were more common amongst those with lower estimated sodium intakes than those with higher intakes.[63]

- **Confounding factors**: Residual confounding cannot be excluded in observational studies, even when multiple factors are controlled for in the analysis.[7,84] Specifically, studies often do not assess or control for factors that may address the health outcome of interest. Such factors may include chronic kidney disease, family history of cardiovascular disease, and levels of or changes in nutrient or calorie intake (which might be related to age, physical activity or chronic disease status). Randomised controlled trials, such as TOHP[49], control for confounding factors through randomisation at baseline and therefore provide a higher standard of evidence than observational studies.

Why can't untimed collections (e.g. spot samples) like those used in the PURE study and others which show a J-shaped curve accurately reflect the usual long term salt intake of individuals?

RESPONSE: Spot urine samples are an unreliable measure of individual salt intake and should not be used as the basis for correlating salt intake with health outcomes, such as blood pressure or CVD.[78,85-87] There is ongoing research to examine the potential for use of spot urine samples from a large sample of the population to estimate mean population salt intake.[88] However, spot urines do not provide an accurate assessment of an individual's intakes. The reasons are as follows:

a) Salt intake varies from day to day and from meal to meal.[4,79-83] So the sodium content of a spot urine reflects what was just eaten rather than usual salt intake over an extended period of time in an individual.[8,80]

b) Other factors affect spot urine sodium excretion concentration and include state of hydration, posture, renal function, diurnal variation and other regulatory functions.[89,90]

c) The equations used to calculate 24 hr salt intake from spot urine samples include several variables strongly associated with disease outcomes (age, gender, and urine creatinine concentration) which means that the estimate is not independent of other potential confounding factors.

d) The correlation between spot urine samples and 24 hr urine estimates of salt intake varies from one population to another and so the equations can't be applied without validation studies.[91] For example, in the main PURE stud,y the correlation was relatively high at around 0.7, however the correlation in the PURE China population was much less than 0.3.[92,93] Also validation studies show differences of up to 8-9000 mg sodium/day in spot and 24 hr urine samples from the same individuals even when both are from the same collection day.[92,93]

e) Bland Altman plots of spot urine vs 24 hr urine plot show bias at high and low intakes. Spot urine overestimates at low intake and underestimates at high intake, which means that risk is exaggerated at low intake and underestimated at high intake. Therefore spot urine samples are not reflecting individual intakes well across their range.

Discussion:

Public health policy regarding nutritional exposures and chronic disease outcomes (including cardiovascular disease and cancer) where diseases develop over decades, is seldom based solely on evidence from randomized controlled trials.[94] Although randomized controlled

trials are widely regarded as the best evidence to test the effects of a medical therapy, they are often impractical in the context of long-term public health interventions on outcomes that may have multifactorial influences over time, and may be unethical, particularly if there is already a substantial body of evidence from epidemiological studies, and/or intervention studies using intermediate endpoints, such as blood pressure in the case of salt reduction.[94] To delay implementation of public health policy, in the absence of RCT data providing 'direct' evidence, may convey considerable harm to the population, especially if such RCT evidence is unlikely to be forthcoming.[95] For this reason, authoritative bodies have developed tools for systematically appraising the totality of scientific evidence (including experimental, epidemiological and RCT evidence) in order to develop recommendations aimed at individuals and populations.[96] Despite this, vested interests (including the food industry) may exaggerate any uncertainties that this situation offers in order to prevent or delay government action or regulation.[12,13,97]

The evidence regarding the harms of diets high in salt is sufficient to justify recommendations from the WHO and other governmental and health related organisations to reduce population salt intake.[16,20,61] For example there is a "substantial amount of evidence" of a dose-response relationship that dietary salt and salted foods are positively associated with stomach cancer,[28] leading the World Cancer Research Fund and WHO to conclude that dietary salt and salted foods are a probable cause of this cancer.[20,96] There is a much larger body of evidence supporting an association between high intakes of dietary salt and elevated blood pressure[45] and cardiovascular diseases such as myocardial infarction and stroke,[21] On the other hand, the premise that reducing salt intake in populations could cause harm is not supported by a strict application of the criteria used to demonstrate cause and effect.[8]

The WHO target to implement population level interventions to lower dietary salt intake by 30% by 2025 was agreed by its 194 member states in 2013.[98] The WHO and regional offices have developed a number of different tools to support member states to achieve this target.[99,100] A 2014 review highlighted the fact that 75 countries already had national programs in place to reduce population salt intake.[101] There is growing evidence of the efficacy of such programs.[102] Evaluations of the more established interventions have also shown that population level reductions in salt intake have been associated with declines in CVD rates in those populations.[42,103]

The recent publication of a paradoxical studies with low quality methodology should not delay implementation of public health interventions. The attention given to such studies in comparison to the critique of them [8,63,104,105] is completely unwarranted. The call for further research[106] is also not a reason to delay such implementation. There are numerous examples where the conduct of further research has not added to knowledge but merely delayed implementation of policies based on findings that would have been apparent if systematic synthesis of existing study results had been available or undertaken.

To document contemporary evidence on the science of salt, the World Hypertension League (WHL) and other organizations support a regular (every few months) updated review. Over the last 3 years (2013-2015), having screened for inclusion based on minimum methodologic criteria set *a priori*, this approach found 14 studies supporting and no studies that countered the evidence for the beneficial impact of salt reduction on disease.[22,23,107]

International organizations have published a statement of concern about the impact of research studies that don't meet these quality criteria (such as ONTARGET, TRANSCEND, EPIDREAM and PURE) on dietary salt.[10] An international expert group (The TRUE consortium) has been established and will soon be publishing the criteria that need to be met in order for studies of salt reduction to be reliable.

In conclusion, current recommendations to reduce population sodium intake[20] are based on sound scientific evidence. The recent publication of a few paradoxical studies of questionable scientific merit should not delay implementation of salt reduction initiatives worldwide. Governments and health organization should continue to implement programs to reduce salt in line with the WHO Global Action Plan for the prevention and control of non-communicable diseases.[108]

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