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VIEWPOINT
Epidemiology and prevention

Salt reduction to prevent hypertension: the reasons of the controversy

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There is a causal relationship between dietary salt intake and blood pressure. A reduction in salt intake from the current world average of ∼10 g/day to the WHO recommended level of <5 g/day, lowers blood pressure and reduces the risk of cardiovascular disease and all-cause mortality. However, a few cohort studies have claimed that there is a J-shaped relationship between salt intake and cardiovascular risk, i.e. both high and low salt intakes are associated with an increased risk. These cohort studies have several methodological problems, including reverse causality, and inaccurate and biased estimation of salt intake, e.g. from a single spot urine sample with formulas. Recent studies have shown that the formulas used to estimate salt intake from spot urine cause a spurious J-curve. Research with inappropriate methodology should not be used to refute the robust evidence on the enormous benefits of population-wide reduction in salt intake. Several countries, e.g. Finland, the UK, have successfully reduced salt intake, which has resulted in falls in population blood pressure and deaths from stroke and ischaemic heart disease. Every country should develop and implement a coherent, workable strategy to reduce salt intake. Even a modest reduction in salt intake across the whole population will lead to a major improvement in public health, along with huge cost-savings to the healthcare service.

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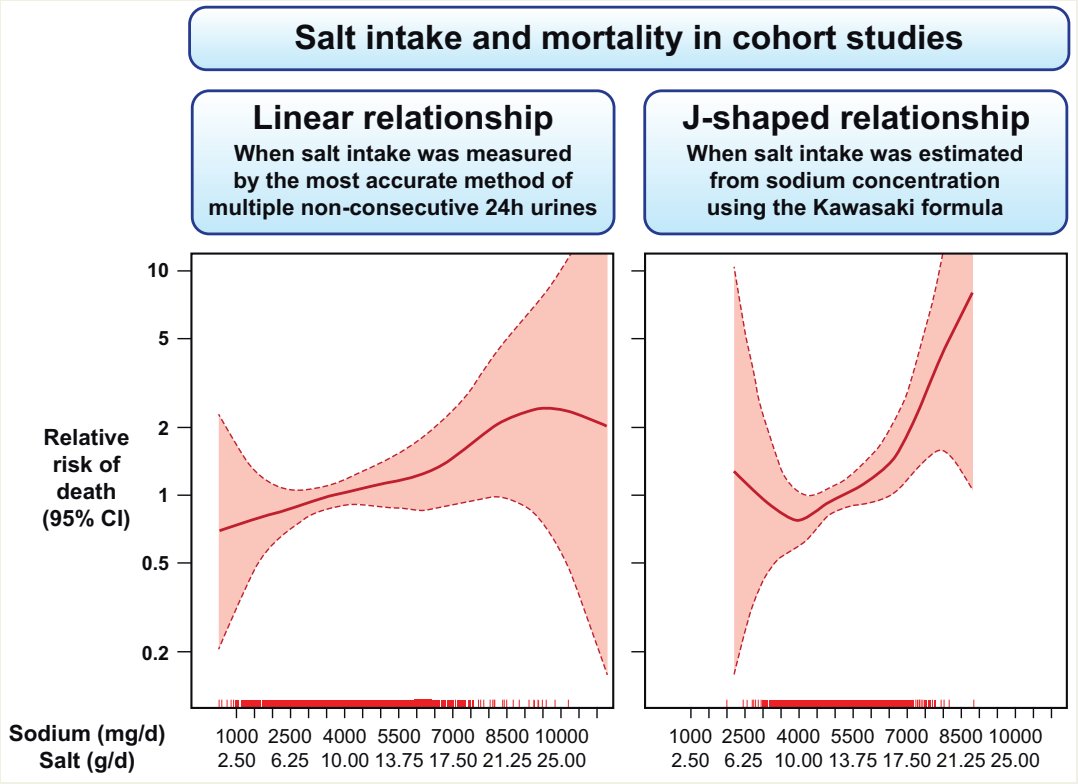
Graphical Abstract



Salt intake and risk of death: inaccurate estimate of salt intake alters the linear relationship. Spline plot of all-cause mortality (log scales) against salt intake in the follow-up study of Trials of Hypertension Prevention. Data from 2974 participants who were not in the salt reduction group, followed up for 23–26 years post-trial, adjusted for age, sex, race/ethnicity, clinic, treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, and family history of cardiovascular disease. Rug plots indicate the distribution of estimated salt intake.

Keywords Salt intake • 24-h urinary sodium • Spot urine • Cardiovascular disease • Cohort studies

Introduction

There is a large and diverse body of evidence demonstrating that high salt intake results in increased blood pressure (BP), which is the major cause of cardiovascular disease (CVD) and the single biggest cause of deaths (≈10.8 million deaths per year) worldwide.[1] Randomized controlled trials demonstrate that a reduction in salt intake lowers BP in both hypertensive and normotensive individuals, in men and women, in all age groups and all ethnic groups.[2] Methodologically robust cohort studies and meta-analysis of randomized controlled trials have demonstrated that a lower salt intake is associated with a reduced risk of CVD and all-cause mortality.[3] Countries where salt intake has been reduced have observed falls in population BP and CVD mortality.[4] Hence, hypertension guidelines and population dietary policies, developed using comprehensive evidence-based reviews by major governmental and non-governmental organizations, almost without exception, recommend reducing salt intake to below 5–6 g/day.[3]

However, several analyses of cohort studies have claimed that there is a 'J-shaped' association of salt intake with CVD events and all-cause mortality, i.e. both high and low salt intakes are related to an increased risk[5] and the ideal salt intake is around 10 g/day, which is the current world average. This implies that many countries should not reduce salt intake, and some countries, e.g. the UK with an average intake of around 8 g/day, should increase salt consumption, in spite of the fact that the reduction from 9.5 to 8.1 g/day (from 2003 to 2011) had resulted in a decrease in CVD mortality.[4] The J-shaped findings have caused substantial controversy,[6] casting doubt on the current public health policies. These cohort studies, however, have many methodological problems, particularly biased estimation of salt intake, reverse causation, and residual confounding. Major health and scientific organizations have expressed concern that research with inappropriate methodology is a major cause of the salt reduction controversy and even taken the unusual step of developing a consortium to define minimum standards for clinical and population research on dietary salt.[7]

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In this article, we briefly outline the methodological issues in cohort studies causing controversy between salt intake and health outcomes.

Inaccurate and biased estimation of salt intake

Most of the cohort studies showing J-curves have estimated an individual's usual salt intake from a single spot urine sample at one-time point and then associated this estimated salt intake with CVD outcomes during many years of follow-up. This is problematic in several ways.

First, spot urinary sodium concentration does not reflect daily salt intake, being influenced by several factors such as fluid consumption, time of the day, duration and volume of the collection, individual's posture, and the amount of salt in the last meal consumed, as well as neurohormonal systems associated with CVD outcome (e.g. the renin-angiotensin-aldosterone system, the sympathetic nervous system). Spot urinary sodium concentration could reflect CVD risk related to the control mechanisms for sodium excretion.

Second, to estimate daily salt intake (24-h urinary sodium excretion, 24 h UNa) from spot urinary sodium concentration, complex formulas have been developed. To date, there are more than five different formulas, e.g. the Kawasaki, Tanaka, and INTERSALT equations.[8] All formulas include age, weight, height, and urinary creatinine concentration, although the equations vary across formulas and some have sex-specific equations. The most commonly used is the Kawasaki formula shown below[9]:

$$\text{24h UNa (mmol/day)} = 16.3 \times \sqrt{\frac{\text{Spot Na [mmol/L]}}{\text{Spot Cr [mg/dL]} \times 10}} \times \text{Predicted 24h urinary Cr [mg/day]},$$

where predicted 24-h urinary creatinine (Cr) for females is as follows: Creatinine (mg/day) = [−4.72 × age (years)] + [8.58 × weight (kg)]+[5.09 × height (cm)] - 74.5; and for males is as follows: Creatinine (mg/day) = [-12.63 × age (years)] + [15.12 × weight (kg)] + [7.39 × height (cm)] - 79.9.

Comparisons of the measured 24-h urinary sodium excretion (i.e. 24-h urine volume × sodium concentration) with that estimated from spot urine using formulas, demonstrate that estimates of individuals' salt intake from spot urine by all formulas are inaccurate, unreliable, not reproducible, and systematically biased, with overestimation at lower levels and underestimation at higher levels of salt consumption.[10] Such a systematic bias can create an artefactual appearance of increased CVD risk at low levels of salt intake.

Third, the use of formula-estimated salt intake is particularly problematic when calculating the salt-CVD association because the salt intake has been estimated from a formula using age, weight, and creatinine, all of which themselves are potent predictors of CVD risk. Recent studies have demonstrated that the Kawasaki and other commonly used formulas for estimating 24-h urinary sodium, cause a spurious J-shaped association with outcome.[8] An analysis of the Trials of Hypertension Prevention (2974 participants who were not in the salt reduction group, followed up for 23–26 years post-trial) demonstrated that when salt intake was measured with multiple non-consecutive 24-h urinary sodium excretions, its association with mortality was direct and linear, down to a level of 3 g/day. However, when the Kawasaki and other formulas were used to estimate salt intake, the linear relationship with mortality changed to J-shaped (*Graphical abstract*).[8] Furthermore, if urinary sodium concentration was kept constant, but the individual data of age, weight, height, and creatinine were entered into the equations, there was an inverse association between the estimated salt intake and the risk of deaths at intakes below 10 g/day.[8] In other words, the variables used in the formulas, independent of salt intake, are, at least, partially responsible for the increased risk with lower salt intakes seen in some cohort studies.

Fourth, a single measurement of urinary sodium, irrespective of spot or 24-h urine, does not reflect an individual's usual salt intake, because salt consumed changes from meal to meal, day to day, and has seasonal and other sources of variation in most free-living societies. Additionally, sodium excretion is affected by some medications, e.g. diuretics, in the short term. Some high potent diuretics alter sodium excretion kinetics within the 24-h time frame (i.e. an increase in excretion hours after ingestion with sodium retention later in the day when natriuretic effects have dissipated) and will therefore impact spot urine sample estimates of salt intake.

Fifth, salt intake measured at baseline, regardless of single or multiple 24-hour urine collections, does not capture the changes in salt intake during many years' follow-up. A study by Olde Engberink *et al.*[11] showed a significant misclassification of individuals by salt intake group (thirds) when a single baseline 24-h urine collection was used, compared with an average of multiple measurements across years. With one 24-h urinary sodium excretion, its relationship with CVD events and mortality appeared to be J-shaped. However, when multiple 24-hour urinary sodium excretions were used, there was a direct linear association.[11] Furthermore, the risk of CVD and deaths (highest vs. lowest tertile of salt intake) increased by up to 85% with the use of multiple 24-h urinary sodium excretions across years instead of a single baseline measurement.[11] These findings clearly demonstrate the importance of accurately measuring individuals' long-term salt intake in cohort studies.

Finally, even with the most accurate method of multiple 24-h urine collections, incomplete collection of urine samples is very common in almost all population-based studies. A recent paper showed that different criteria used to exclude potential incomplete 24-h urine samples, altered the relationship between salt intake and BP.[12]

Reverse causation

Another major issue with the cohort studies showing J-shaped curves is the inclusion of individuals who are ill or at an increased risk of CVD, e.g. with kidney disease, diabetes. Since illness can lead participants to change their diets, or participants had been advised to change their diets, sick individuals often eat less food and less salt, and are also more likely to suffer and die from CVD during the follow-up period. This leads to reverse causality, i.e. the association between a lower salt intake and higher risk of CVD is explained by these individuals' underlying conditions, rather than their salt intake.

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Other methodological issues in cohort studies

Several other factors could also alter the association between salt intake and health outcome, e.g. inadequate follow-up with a large proportion of the participants dropped out, residual confounding due to imbalance among salt intake groups or incomplete adjustment of confounding factors as described in an American Heart Association Science Advisory.[13]

Problems with ecological studies

Some researchers have attempted to investigate the relationship between salt intake and health outcome in ecological studies, which are well-known for being notoriously unreliable for studying aetiology. For instance, a recent ecological analysis by Messerli *et al.*[14] claims that salt intake is correlated positively with life expectancy and inversely with all-cause mortality. Among the 181 countries included, 30 had salt intake below 5 g/day and most of these countries with low salt intakes are in Africa, where malnutrition is highly prevalent and infectious diseases are the major cause of deaths. Despite Messerli *et al.*'s attempt to adjust for confounding factors, it is impossible to do so in such hugely diverse populations worldwide. Additionally, very few countries had reliable data of population salt intake at the time of data collection (i.e. in 1990 and 2010), and almost all salt intakes were derived, using a Bayesian hierarchical model, from some localized studies that collected urine samples or dietary survey data, which are unreliable in estimating salt intake, particularly as the amount of salt discretionarily added by the consumers cannot be quantified in dietary surveys. The inaccurate estimations of salt intake would have caused further major biases in the association of salt with outcome. Publication of such research undermines scientific integrity and can damage scientists', clinicians', and public faith in research and in health, scientific, and clinical organizations.

Conclusions

The J-shaped or inverse association between salt intake and CVD or mortality claimed by some observational epidemiological studies is mainly due to their methodological problems, particularly the inaccurate and biased estimation of salt intake from spot urine with formulas. For more than a decade, many national and international health and scientific organizations have recommended against using spot urine samples to estimate an individual's salt intake, especially in relation to health outcome, because of the likelihood of producing spurious findings.[7] This likelihood is now a proven reality.

The totality of the evidence from various types of studies with sound methodology, particularly accurate measurements of salt intake, has demonstrated a strong, positive association of salt intake with BP and a direct linear association with CVD and all-cause mortality, down to a salt intake of <5 g/day, i.e. the target set by the World Health Organisation. The recent Global Burden of Disease analysis has estimated that salt intake is responsible for ≈1.8 million deaths and ≈44 million disability-adjusted life-years in 2019.[1]

Worldwide action to reduce salt intake is vital and should not be diverted by controversial studies with methodological issues. Various salt reduction initiatives have started in more than 70 countries. Several developed countries, e.g. the UK, have implemented a successful salt reduction programme, predominately by setting incrementally lower salt targets for processed food, which has led to a decrease in population salt intake and falls in population BP and CVD mortality.[4] In many developing countries, where most of the salt in the diet is added by the consumers, innovative, scalable, and sustainable strategies are needed. Replacing the usual salt with low-sodium high-potassium salt substitutes, and salt reduction education through a schoolchildren-to-adults approach,[15] have shown promising results. Every country should adopt a coherent, workable strategy. A reduction in salt intake, even by a small amount, across the whole population will result in a major improvement in public health and huge cost-savings to the healthcare service.

Conflict of interest: F.J.H. is an unpaid member of Action on Salt and World Action on Salt and Health (WASH). N.R.C.C. is an unpaid consultant/advisor on dietary sodium and hypertension control to numerous governmental and non-governmental organizations. N.R.C.C. chairs the International Consortium for Quality Research on Dietary Sodium/Salt (TRUE) and is a member of WASH, which are unpaid voluntary positions. M.W. is a consultant to Amgen, Freeline, and Kyowa Kirin. G.A.M. is the unpaid Chair of WASH and Action on Salt, Sugar and Health. Both F.J.H. and G.A.M. are partially funded by the National Institute for Health Research (NIHR) (16/136/77) using UK aid from the UK Government to support global health research. The views expressed in this publication are those of the authors and not necessarily those of the NIHR or the UK government.

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