Sodium and health—concordance and controversy

Nancy Cook and colleagues describe the sources of agreement and disagreement about the health effects of sodium and how they might be resolved

Despite many decades of research and studies in both animals and humans, disagreements about the effects of salt (sodium chloride) on health remain. Sodium is essential to health and resides in the extracellular fluid, regulating plasma volume as well as cellular transport. It serves many physiological functions, including nutrient absorption and maintaining fluid balance.

Humans can obtain sufficient sodium from the low amounts present in many foods, including fresh meat, fish, and vegetables, but most of the sodium we now consume is added in food processing or at the table. Salt has been used as a preservative for centuries and is now added for flavouring during food preparation. It can also alter the texture of meats, such as in brining, which can produce a juicier product while increasing the sodium content. Sodium phosphates or sodium glutamate are also used to enhance flavour or other characteristics, but in this article we focus on sodium chloride, the most common form.

In most of the world's populations, sodium intake greatly exceeds the minimal physiological need. Although small amounts of sodium are necessary for health, too much may cause health problems. For example, because sodium affects fluid regulation, a high sodium intake may increase blood pressure through volume expansion. However, there is some debate about how far salt intake should be reduced. Current mean population sodium intake is about 3600 mg/day in the US,[1] and the estimated global average is 3660-4000 mg/day,[2 3] with a wide range across countries.[4] Recent guidelines in the US, Canada, and the UK call for lowering sodium consumption below 2300-2400 mg/day,[5-7] but some organisations go even lower. The American Heart Association recommends no more than 2300 mg/day but suggests an ideal limit of 1500 mg per day for most adults,[8] especially those with high blood pressure. The World Health Organization calls for <2000 mg/day.[9] Others conclude that the optimal range is much higher.[10 11] If true, there would be little need to reduce current consumption in most countries except at the highest levels.

Measuring sodium intake

Measuring sodium consumption is difficult, and all methods have limitations (table 1).[6] Feeding studies, in which participants consume only foods that have been precisely prepared in a research kitchen, can directly control consumption, but such procedures are only possible in short term studies, such as randomised controlled trials. Long term observational studies instead often rely on estimation of nutrient intake through food frequency questionnaires, dietary records, or 24 hour recall. These methods are prone to bias, and it can also be difficult to estimate the sodium content of the foods consumed, particularly any added during cooking or at the table.

A more objective measure of sodium intake can be obtained from urine collections. The most accurate measure is 24 hour urine collection. Balance studies conducted under controlled conditions and measuring all sodium intake as well as output from urine, faeces, and sweat suggest that over 90% of the sodium consumed is excreted in the urine over 24 hours,[12] making it a close estimate of actual sodium intake. Since collection of 24 hour urine can be challenging for participants, many studies use simpler but less accurate measures. Some studies collect an overnight or 8 hour urine specimen, but spot samples are more commonly used. Results from spot samples can be converted to an estimate of 24 hour excretion using equations such as the Kawasaki equation,[13] which was developed in an Asian population. Bland-Altman plots suggest that high values are underestimated and low values are overestimated by spot samples compared with the 24 hour urine collections.[14 15]

Even 24 hour urine can vary from day to day along with variations in diet. The sodium excretion in the urine not only depends on intake but also on an internal fluctuating balance with sodium stores in the bones and the skin, and therefore may deviate substantially from intake.[16 17] Balance studies under controlled conditions suggest that single 24 hour collections are not adequate to detect a 3 g difference in sodium intake (1200 mg/day).[18] Repeated measurements of 24 hour sodium excretion improve precision, and three to seven samples are recommended to estimate an individual's usual sodium intake, though less precise measures may be adequate for population averages.

Sodium and blood pressure

Several cross sectional observational analyses have found a direct linear relation between sodium intake and blood pressure. One of the largest was INTERSALT, an international study of electrolytes and blood pressure in over 10 000 participants across 52 centres that was first published in 1988.[19] The maximally adjusted within-centre analysis showed a significant association of sodium, as measured in 24 hour urinary excretions, with systolic but not diastolic pressure. Of note was the low blood pressure in four isolated populations with very low sodium excretions, much less than 1000 mg/day. Though this shows that very low levels are physiologically possible, the relation of sodium with blood pressure may be confounded by other factors in these isolated populations. The positive association of sodium with blood pressure has been replicated in other observational studies, including the recent PURE study.[20]

KEY MESSAGES

- Reducing sodium intake is generally agreed to reduce blood pressure, at least in people with hypertension
- Controversy remains over the effects of sodium on other health outcomes, including cardiovascular disease and mortality
- Some observational studies suggest a U-shaped or J-shaped curve, while others show a linear association with cardiovascular events and total mortality
- More work needs to be done to explain the discrepancy in results, which could be due to heterogeneity across studies, bias, measurement error, or unexplained physiological effects

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Table 1 | Measures to assess sodium intake

Method	Description	Advantages	Disadvantages
Diet			
Feeding studies	All food provided prepared in a research kitchen with precise measurement of sodium content	Accurate measure of actual sodium consumed	Only possible under controlled and short term conditions
24 hour recall	Questions on what the participant ate in the previous 24 hours	Easy to administer in large populations	Prone to recall bias; does not capture day-to-day variability
Food records	Detailed records of all foods consumed over, for example, a period of three days	Can capture all foods consumed over several days	Difficult to administer in large cohorts; prone to observation bias
Food frequency questionnaire	Questionnaire asking about average consumption of specific foods over a longer period (such as past year)	Easy to assess in populations; captures long term patterns	Limited ability to capture major sources of sodium in processed foods, eating out, or added at table
Urine			
Spot urine	Collection of a sample from a single urine excretion	Easy to collect	Measures sodium concentration; needs to be converted to intake
Overnight urine	Timed collection of all urine excreted overnight or over an 8 hour period, for example	Estimates excretion rather than concentration	Overnight sodium excretion levels may be greater than during the daytime; captures intake only on the previous day
24 hour urine	Collection of all urine excreted over a 24 hour period	Accurately captures over 90% of sodium intake in the previous 24 hours	Challenging for participants; captures intake only in previous 24 hours; may be incomplete
Multiple 24 hour urines	Multiple collection of all urine excreted over a 24 hour period, ideally non-sequential	Accurate average of sodium intake over a long term period of time	Challenging for participants; may be incomplete though errors may average out

More direct evidence of a causal relation between sodium levels and blood pressure comes from the many randomised trials that have compared sodium interventions. The DASH (Dietary Approaches to Stop Hypertension)-Sodium trial[21] was a feeding study with randomisation to DASH or control diets with high, medium, and low sodium intake (roughly 3300, 2400, and 1500 mg/day on average) for 30 days. Eligible participants were aged 22 years or older, had blood pressure of 120-159/80-95 mm Hg, and were not taking anti-hypertensive medication. It found a graded reduction in blood pressure with lower sodium versions of both diets, with a stronger effect among those with hypertension at baseline

In a meta-analysis of 47 sodium reduction trials recently conducted for the 2019 version of the US *Dietary Reference Intakes for Sodium and Potassium*[6] an average 42 mmol decrease in 24 hour sodium excretion was associated with a mean reduction in blood pressure of 3.3/2/2 mm Hg in adults. While some of the effect could be due to changes in other nutrients in trials using a lifestyle intervention, crossover studies providing foods or using salt supplements gave similar estimates of effect.

The meta-analysis reported a significant dose-response relation between the size of the sodium reduction and the blood pressure response, although there was sizeable heterogeneity across trials, primarily related to baseline blood pressure. The effect was stronger among people with blood pressure ≥140/90 mm Hg (−4.0 mm Hg systolic, −2.7 mm Hg diastolic) but was still present in those with lower blood pressure (−1.3 mm Hg

systolic, −0.7 mm Hg diastolic). In addition, a meta-analysis of three trials of hypertension prevention[11] suggested a 20% lower incidence of hypertension among those in a sodium reduction intervention. Overall, there seems to be a consensus that reducing sodium has beneficial effects on blood pressure, at least among those with above average pressure.[22 23]

Sodium and cardiovascular disease

Because of the overall dose dependent effect of sodium on blood pressure and the known relation between blood pressure and cardiovascular disease, many have used modelling to estimate the effect of lowering sodium on cardiovascular disease from these relations. For example, mortality benefits were found using three different approaches: a coronary heart disease policy model, estimates based on trials of hypertension treatment, and more direct estimates based on data on both blood pressure and cardiovascular disease from the Trials of Hypertension Prevention (TOHP).[24] Substantial benefits were seen even if sodium reduction was confined to those with hypertension.

Few sodium reduction trials have directly examined cardiovascular disease, but there have been follow-up studies of trials of sodium reduction and blood pressure. A 9-12 year follow-up of the TOHP trials found a 25% reduction in cardiovascular disease among people with "high normal" blood pressure (80-89 mm Hg diastolic) who had been randomised to a sodium reduction intervention.[25] In a meta-analysis of five randomised comparisons in people with prehypertension or hypertension, there was an 18% reduction in cardiovascular disease.[6] Another

meta-analysis found similar results for cardiovascular disease but no reduction in all-cause mortality, though estimates were imprecise.[26]

Trials of health outcomes in healthy normotensive individuals have not been done. Natural experiments across populations—eg, in Finland and the UK—associate a reduction in sodium intake with lower population blood pressure and cardiovascular mortality,[27 28] though this may be influenced by other concurrent changes such as reduced smoking rates, statin use, accessibility and availability of medical care, and medical interventions and procedures.

Results from observational cohort studies have been more mixed. TOHP[29] and some other studies have found a direct linear association between baseline sodium excretion and incidence of cardiovascular disease (fig 1, top). However, several others—including studies of high risk cohorts,[30] prospective cohort studies of genetic risk,[31] and population samples such as the PURE study (fig 1, bottom)—have found a U-shaped or J-shaped curve, with higher risk of cardiovascular disease, including heart failure, and all-cause mortality at both the high and the low ends of intake.

Meta-analyses of observational studies have produced similarly diverse results, with conclusions supporting[32] and opposing[33] sodium lowering below the recommended level of 2300 mg/day. Studies of Western populations have few participants with a low sodium intake, however,[34] making it difficult to calculate incidence among this group. In studies using multiple sodium excretion measures there are fewer participants in this range owing to more precise estimates of intake.
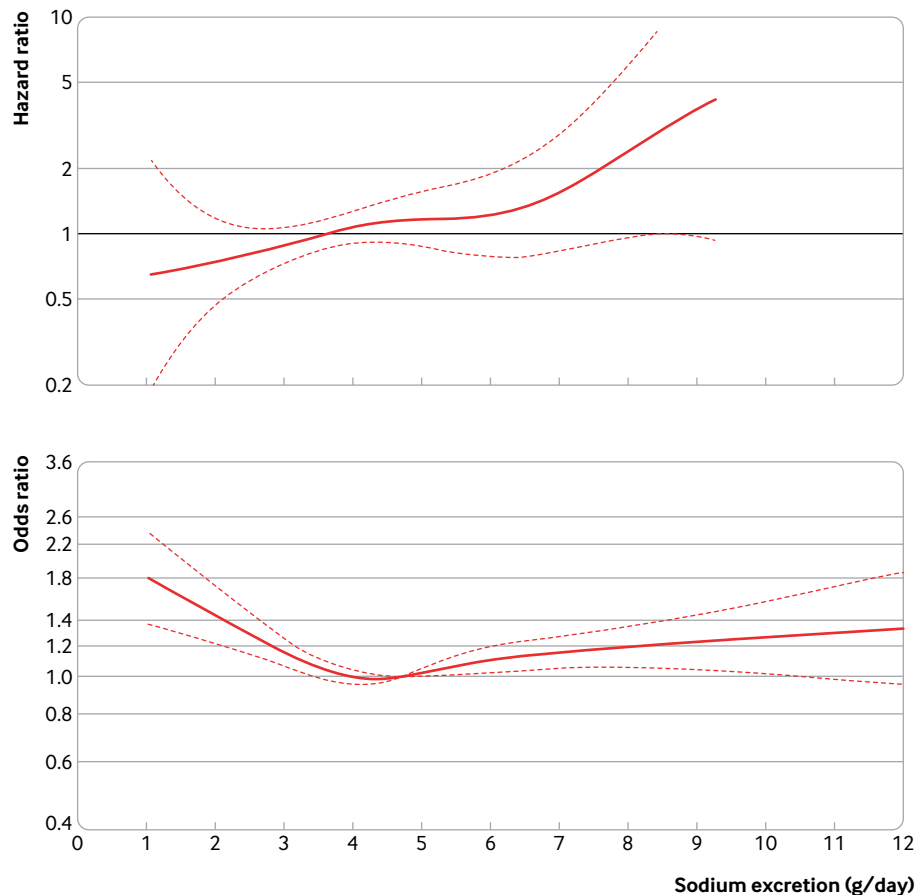
Fig 1 | Association of sodium excretion with cardiovascular disease in the Trials of Hypertension Prevention (top)[29] and PURE study (bottom).[11] Reproduced with permission

Why are the results different?

There has been much discussion about why the results from different types of sodium reduction study produce varying results. In particular, if there is a dose-response relation between sodium and blood pressure, why do some studies find a higher risk of CVD at low sodium levels? Suggested explanations have included heterogeneity across study populations, measurement error, confounding, reverse causation, or adverse biological effects at low levels (box 1).

Areas of agreement

Overall there is general agreement that reducing sodium intake reduces blood pressure, especially in people with hypertension. The effects are smaller among people with lower levels (130-139 mm Hg systolic or 80-89 mm Hg diastolic) of hypertension, but sodium reduction still slows down progression of hypertension and reduces risk of blood pressure related disease in this group. People with normal blood pressure (<120/80 mm Hg) have least benefit from sodium reduction. Genetic factors may modify the effect of sodium on blood pressure, such that some individuals are less affected by sodium and thus maintain low blood pressure despite consuming levels associated with raised blood pressure.

High sodium intake is generally agreed to be deleterious. Even in studies that found a U-shaped or J-shaped curve, mortality from cardiovascular disease increased at the highest levels (≥5000 mg/day). One study found this association only in people with hypertension, with no link in people with normal blood pressure,[42] again suggesting some influence of sodium sensitivity. There is controversy surrounding whether advice on sodium reduction should be restricted to people with hypertension or applied population-wide. Proponents of a population approach argue that prevalence of hypertension is high in older adults and that a population strategy could prevent the rise in blood pressure with age.

Areas of controversy

The biggest controversy is how low to go in sodium recommendations (box 1). Should the recommended level be ≤2300 mg/day as suggested by several international guide-lines,[5-7] nearer the current average sodium intake levels (3600 mg/day), or <5000 mg/day? The difference depends on whether the J-shaped curve truly exists. Data on sodium and blood pressure indicate at least some improvement with sodium lowering. Why this would not consistently translate into lowered risk of cardiovascular disease is not clear. Even the PURE study found a direct cross sectional relation between sodium and blood pressure,[20] but a J-shaped curve emerged when looking at subsequent cardiovascular disease.[11] Some studies even show an increase in stroke at low sodium levels, despite the fact that blood pressure is a strong risk factor for stroke.[43] Others show the increase mainly in heart failure.[30] Human populations can also survive at extremely low levels of sodium, as shown by the isolated communities in INTERSALT.[19]

J-shaped curves have been observed and disputed in many other areas of research, including blood pressure interventions and obesity.[44 45] Some have found that such curves can be explained by examining trajectories[46] which examine trends just

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Box 1: Possible explanations for discrepant results on relation between sodium and cardiovascular disease in cohort studies

Random variation
Chance alone may result in different outcomes from different population samples even if the samples originate from the same background population.

Measurement error
Epidemiological studies often use cheap and practical methods (eg, spot urine measurements) rather than potentially laborious and expensive but more accurate methods (eg, 24 hour urine measurements). Such simple measurements may result in individual errors, which may reduce the possibility of detecting a relation if random. A recent study[15] found that error could even change the shape of the dose-response curve. If systematically distributed, the error could lead to sick people being placed into groups with low sodium intake and falsely ascribe higher mortality to the low sodium intake. A limitation of this study was that the formulas were applied on 24 hour urine samples although designed for fasting morning spot urines.

Confounding
Heterogeneity in overall sodium intake could explain some of the differences across studies. Within studies, many factors may influence the outcome such as sex, age, energy intake, smoking, blood pressure, social status, and comorbidities. Adjustment for these factors may attenuate[35] or amplify[11 36 37] the association between sodium intake and outcome. Despite such within study adjustments, there may still be unexplained differences across studies (residual confounding).

Reverse causation
Reverse causation occurs when the probability of the exposure is causally influenced by the outcome being studied.[38] People with hypertension or cardiovascular disease may be advised to lower their sodium intake, for example. This would reduce their apparent intake while only altering one aspect of their cardiovascular risk. People with other diseases may have a lower sodium intake simply because they eat less owing to a decreased appetite. Thus, people with a high mortality risk could accumulate in the low sodium group. Similarly, overweight individuals with high food intake with diabetes and hypertension could accumulate in the high sodium intake group.

Effects on lipids and the renin-angiotensin-aldosterone system
Moderate reductions in sodium down to about 2000 mg do not activate the sympathetic nervous system or increase lipids in serum, and only have a small effect on the renin-angiotensin-aldosterone (RAAS) system.[39] However, larger reductions to levels below 2000 mg lead to significant activation of the sympathetic nervous system and RAAS, and a significant increase in serum lipids.[22] There is a disagreement about whether such effects would have a sizeable impact on health outcomes, such as cardiovascular events and mortality. In addition, recent research suggests that sodium intake may be regulated by a neurohormonal system to achieve a physiological optimum, rather than a physiological minimum.[40] This could explain the relatively narrow sodium intake range of the of the world's populations.

Pre-existing illness
People with heart disease and hypertension are usually treated with diuretics or drugs that block RAAS. All these treatments can provoke hyponatraemia, especially in patients with heart failure, which could be amplified by a low sodium intake. As hyponatraemia is associated with increased mortality,[41] this effect might contribute to the increased mortality observed in low sodium intake groups.

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before the outcome, indicating possible reverse causation (box 1), or through genetic analyses such as mendelian randomisation.[47]

How to resolve the controversy
Some researchers argue that the existing sodium reduction trials on blood pressure, in conjunction with other types of studies, offer sufficient evidence to support public policy.[48] Others argue that existing trials on blood pressure, hormones, and lipids and observational studies on health outcomes offer sufficient evidence to reject the present public policy.[49] Some have called for definitive large scale randomised trials of sodium intake and cardiovascular disease to resolve the controversy.[50] It is not clear, however, what the ideal long term sodium intervention would be. Unlike other nutrients, sodium generally needs to be removed from the diet and it cannot be given in a supplement pill. Long term lifestyle interventions are difficult, especially if follow-up must be at least five years, making studies complex and expensive.

Recently, a diverse group of sodium researchers tried to achieve consensus on a recommendation for a randomised sodium trial.[51] They considered various controlled environments, such as the veterans' home setting used in a trial in Taiwan.[52] Their suggestion was a trial within prison populations. This offers the advantage that sodium intake could be controlled through cluster randomisation of kitchen practices. Disadvantages include practicality, such as whether long term follow-up can be achieved and prevalence of pre-existing conditions, as well as ethical concerns about experimenting on people in prison.[53]

While difficult, there are other possible approaches. The Salt Substitute and Stroke Study (SSaSS) is a large cluster randomised controlled trial being conducted in China.[54] It has randomised participants with a history of stroke or increased risk of stroke in 600 villages in China to either usual care or a salt substitute that is low in sodium and high in potassium. Outcomes include stroke, major vascular events, and total mortality. The trial is due to end in 2020

and should provide more evidence on the role of sodium, at least among people at high risk. If successful, this study design could be used in a more representative population sample.

Smaller sodium trials in progress include the Sodium Intake in Chronic Kidney Disease (STICK) trial in 105 participants with chronic kidney disease (ClinicalTrials.gov Identifier: NCT02458248) and the SODIUM_HF trial in around 1000 patients with heart failure (ClinicalTrials.gov Identifier: NCT02012179), though data from these high risk patients may not generalise to the wider population.

Other possible trial designs include those that are internet based, though the feasibility of achieving a sufficient separation in sodium intake is unclear. One web based trial in patients with chronic kidney disease achieved a short term but not long term reduction in sodium excretion.[55] However, as with all nutritional evidence, long term randomised trials are unlikely to be possible because of practical issues. Long term observational follow-up

studies with multiple 24 hour urinary excretion measures could, however, help resolve the shape of the sodium-cardiovascular disease curve.[56]

It is also possible that more information can be determined from genetic studies. For example, a mendelian randomisation design could be used to assess causal associations, as has been done to investigate the effects of alcohol consumption on cardiovascular disease.[57] A mendelian randomisation study using the UK Biobank dataset has identified a causal association between the sodium/potassium (Na/K) ratio and blood pressure.[58] Although this study identified inverse observational associations between Na/K ratio derived from spot urine samples and cardiovascular events, there was not enough power to conduct mendelian randomisation for these events. Pazoki et al[59] used mendelian randomisation, functional assessment, co-localisation, genetic risk score, and pathway analyses and found a shared genetic component between urinary sodium and potassium expression and several cardiovascular traits. Loci for sodium and potassium expression were associated with anthropometric traits and dietary habits such as salt added to food and alcohol consumption. Their sodium genetic risk score was associated with the annual rise in blood pressure, and mendelian analysis suggested urinary sodium was positively related to diastolic blood pressure and coronary heart disease. Pathway analysis implied that sodium had various effects that may act through different mechanisms to affect both behaviour and thermoregulation. Further work along these lines could help determine whether effects of sodium come from associated behaviours or a direct effect on the vasculature and other tissues.

Several other uncertainties remain. Are there comorbidities or demographic and genetic differences that make some people more sensitive to the effects of salt? Should sodium requirements be tailored to body size? We need to know more about sodium's long term effects on blood vessels and other body systems as well as its relation to other cations such as potassium. These interact, but joint recommendations for public health need to be determined. Scientists should commit to examining unbiased evidence and conducting further studies to reduce the need to rely on imperfect existing data.

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