Circulation Research Compendium on Hypertension

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Giuseppe Mancia, Guest Editor

Sodium Intake and Cardiovascular Health

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Abstract: Sodium is an essential nutrient. Increasing sodium intake is associated with increasing blood pressure, whereas low sodium intake results in increased renin and aldosterone levels. Randomized controlled trials have reported reductions in blood pressure with reductions in sodium intake, to levels of sodium intake <1.5 g/d, and form the evidentiary basis for current population-wide guidelines recommending low sodium intake. Although low sodium intake (<2.0 g/d) has been achieved in short-term feeding clinical trials, sustained low sodium intake has not been achieved by any of the longer term clinical trials (>6-month duration). It is assumed that the blood pressure-lowering effects of reducing sodium intake to low levels will result in large reductions in cardiovascular disease globally. However, current evidence from prospective cohort studies suggests a J-shaped association between sodium intake and cardiovascular events, based on studies from >300 000 people, and suggests that the lowest risk of cardiovascular events and death occurs in populations consuming an average sodium intake range (3–5 g/d). The increased risk of cardiovascular events associated with higher sodium intake (>5 g/d) is most prominent in those with hypertension. A major deficit in the field is the absence of large randomized controlled trials to provide definitive evidence on optimal sodium intake for preventing cardiovascular events. Pending such trials, current evidence would suggest a recommendation for moderate sodium intake in the general population (3–5 g/d), with targeting the lower end of the moderate range among those with hypertension. (*Circ Res.* 2015;116:1046–1057. DOI: 10.1161/CIRCRESAHA.116.303771.)

Key Words: cardiovascular diseases ■ prevention and control ■ sodium chloride

Sodium is an essential nutrient, required for normal physiological function.¹ Total body sodium is tightly regulated to maintain extracellular sodium concentrations within a narrow range, which involves the engagement of multiple physiological mechanisms.¹ Salt (sodium chloride) is the main source of sodium intake, accounting for ≈95% of daily intake with the vast majority (>85%) being excreted by the kidneys.

There is a positive association between increasing sodium intake and blood pressure (BP) in populations.² Because hypertension is a leading risk factor for cardiovascular disease (CVD) globally,^{3,4} reducing sodium intake in populations has emerged as a proposed target for cardiovascular prevention.⁵ Evidence from clinical trials showing that sodium restriction reduces BP⁶ has prompted a proposal for a dramatic reduction

Original received October 22, 2014; revision received December 30, 2014; accepted December 30, 2014. In January 2015, the average time from submission to first decision for all original research papers submitted to *Circulation Research* was 14.7 days.

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DOI: 10.1161/CIRCRESAHA.116.303771

Nonstandard Abbreviations and Acronyms

BP	blood pressure
CVD	cardiovascular disease
HR	hazard ratio
INTERSALT	International Study of Salt and Blood Pressure
INTERMAP	International Study of Macro/Micronutrients and Blood Pressure
ONTARGET	Ongoing Telmisartan Alone and in combination with Ramipril Global End point Trial
PREVEND	Prevention of Renal and Vascular End-stage Disease
PURE	Population Urban Rural Epidemiology
RAAS	renin–aldosterone–angiotensin system
RR	relative risk
TOHP	Trial of Hypertension Prevention
TRANSCEND	Telmisartan Randomized Assessment Study in ACE intolerant subject with cardiovascular Disease
UMOD	uromodulin-associated kidney disease

of sodium intake in the entire population, from a current mean intake of ≈ 4 g/d,⁷ to <2 g/d (ie, more than half current intake).⁵ Most of the world's population ($\approx 95\%$) consume between 3 and 6 g/d of sodium,^{7,8} which means that most people will require a major change to their diet, to achieve this current guideline target. However, evidence linking sodium intake with cardiovascular risk has been inconsistent and resulted in considerable controversy about optimal sodium intake for cardiovascular health.

In this article, we will review the evidence linking sodium intake and cardiovascular health. We begin with a historical review of salt intake and health, and then summarize sodium intakes around the world, review of different methods of measuring sodium intake, summary of evidence linking sodium intake to BP, detailed review of evidence linking sodium intake to CVD, and propose how current evidence should be reflected in guideline recommendations for sodium intake in populations.

History of Sodium and Health

It is contended that paleolithic humans consumed <1 g of sodium/d, and that current mean sodium intake (4 g/d) in a human population is a relatively recent phenomenon (within the past 5000 years).⁹ However, there are several unproven assumptions that underlie the contention of low sodium intake in paleolithic humans, including assuming no fish or shellfish intake, seawater not used in food preparation, and no salt preservation of foods. In truth, the contention is speculative, and the true sodium intake in paleolithic humans is unknown. Among small cohorts of hunter-gatherer population (eg, Yononami Indians in the International Study of Salt and Blood Pressure [INTERSALT] study^{10,13,14}), very low sodium intakes seem common. However, capturing sodium intake, using 24-hour urinary collections, is extremely challenging in such populations.

Access to salt has been a pivotal ingredient in the transition from hunter-gatherer to settled communities, as it was needed to maintain livestock on farms and used in preservation of perishable foods, necessary to survive winter months.¹¹

Recognition of the importance of salt to human survival has resulted in its figurative importance in many societies and religions. Salt became an early trading commodity. The word salary is derived from the Latin *salarium*, which was money paid to Roman Army soldiers to purchase salt. Its symbolic importance as being vital to human health was also used in politics. In 1930, Mahatma Gandhi led $>100\,000$ people on Salt Satyagraha in which protesters made their own salt from the sea, in defiance of the salt tax imposed by the British Empire. When asked why he chose salt as the focus of the action, he stated, “next to air and water, salt is perhaps the greatest necessity of life.”

The idea that salt intake could be a threat to humans has only emerged in the past 5 decades, and coincident with the transition of salt intake from discretionary to nondiscretionary sources in North America and Europe. This transition has resulted in less individual-level control of the level of sodium intake, and it is proposed that physiologically regulated salt intake (salt-thirst) has been replaced by a salt-preference related to intake because of chronic excess in sodium intake from nondiscretionary sources.¹²

Global Sodium Intake

The INTERSALT study provided estimates of sodium intakes from 52 population samples in 32 countries ($n=10\,079$) based on data from 24-hour urinary collections.^{10,13,14} A subset of 8% of the study sample collected a second 24-hour urinary specimen 3 to 6 weeks later to estimate within-individual variability of sodium excretion. At the time, INTERSALT collected the most extensive set of standardized data on 24-hour urinary sodium excretion patterns around the world. Among the 52 population samples included in INTERSALT, 24-hour sodium excretion ranged from 0.46 g/d (Yanomami Indians, Brazil) to 5.6 g/d (North China). Three other remote population groups had mean 24-hour urinary sodium excretion of ≤ 1.2 g/d: Xingu Indians of Brazil, Papua New Guinea Highlanders, and the Luo in rural Kenya. Highest mean urinary sodium excretion was recorded in Tianjin, Northern China: 6.0 g/d in men and 5.4 g/d in women.^{10,13,14}

Several years later, the International Study of Macro/Micronutrients and Blood Pressure (INTERMAP) study conducted an in-depth nutritional study of 4680 men and women from 17 population samples in 4 countries: Japan (4 samples), China (3 samples), United Kingdom (2 samples), and United States (8 samples). Participants completed two 24-hour dietary recalls (on consecutive days) and 1 timed 24-hour urine collection (started with the first dietary recall).¹⁵ As in INTERSALT, the highest mean values of urinary sodium excretion were found in China, up to as high as 6.9 g/d in men and 5.8 g/d in women in the Beijing sample, Northern China. Sodium excretion in Southern China (Guangxi) was much lower: 3.5 g/d in men and 2.9 g/d in women. In the United States, mean sodium excretion for the 8 population samples were all in the range 4.1 to 4.4 g/d for men and 3.0 to 3.5 g/d for women. For the 4 Japanese samples, mean 24-hour urinary sodium excretion was in the range of 4.5 to 5.1 g/d in men and 3.7 to 4.6 g/d in women. Mean sodium excretion in the 2 UK samples were 3.7 g/d in men and 2.9 g/d in women.^{16,17}

In a recent meta-analysis of cross-sectional studies from 187 countries,⁷ mean global intake was estimated at 3.95 g/d. Intakes were highest in East Asia, Central Asia, and Eastern Europe (mean >4.2 g/d) and in Central Europe and Middle East/North Africa (3.9–4.2 g/d). Mean intakes in North America, Western Europe, and Australia/New Zealand ranged from 3.4 to 3.8 g/d. Between 1990 and 2010, there was a suggestion of slight increases in overall sodium intakes. Other reviews have reported generally stable levels of intake in population in North America and Europe for several decades, but there are examples of large (eg, Finland) and small (eg, United Kingdom) reductions in sodium intake among individual countries.

More recently, the Prospective Urban Rural Epidemiological (PURE) Study⁸ has reported on the largest study to measure global variations in sodium intake. PURE is a large-scale epidemiological cohort study that has enrolled 155 875 individuals (35–70 years) residing in 628 urban and rural communities in 18 low-, middle-, and high-income countries around the world (Bangladesh, India, Pakistan, Zimbabwe, Argentina, Brazil, Chile, Malaysia, Poland, South Africa, Turkey, Palestine, China, Colombia, Iran, Canada, Sweden, and United Arab Emirates).¹⁸ In PURE, urinary estimates of sodium and potassium intake were measured in >100 000 individuals. Mean ($\pm$ SD) excretion was 4.93 ± 1.72 g for sodium and highest in China (mean intake, 5.6 g/d). Overall, 43.5% of the PURE population had sodium excretion >5 g/d, 45.9% between 3 and 5 g/d, and 10.5% <3 g/d (3.3% had an excretion <2.3 g/d and 0.6% <1.5 g/d). Sodium excretion was higher in rural than in urban areas ($P < 0.001$). The higher estimate for sodium intake, reported in the PURE study, compared with the global burden of disease meta-analysis is likely related to differences in populations between studies.⁷

Variations in Sources of Sodium Intake

Sodium intake is embedded within an overall dietary pattern. Sodium intake may be from discretionary salt use (added to cooking or at the table, under an individual's control) or nondiscretionary when salt is invested in processed or preprepared foods.¹⁹ In the INTERMAP study, regional variations in sources of sodium intake were reported. In China, most (76%) dietary sodium was from salt added in home cooking and lower in Southern than Northern populations. In Japan, most (63%) dietary sodium came from soy sauce, commercially processed fish/seafood, salted soups, and preserved vegetables. Processed foods, including breads/cereals/grains, were main sources of sodium intake in the United Kingdom (95%) and the United States (71%).²⁰ Among processed foods, key sources of excess sodium intake are breads, salted meats, canned goods, cereals, pastries, and fast foods. It is proposed that the food industry has been responsible for a gradual increase in sodium intake in populations. However, ecological data would argue against this contention, as mean sodium intake in North America, for example, has remained stable, despite a marked increase in sodium intake from nondiscretionary sources.²¹ Moreover, regions in the world that consume the highest proportion of nondiscretionary salt foods (eg, North America, Western Europe) are not the regions with the highest sodium intake.

Measuring Sodium Intake

Methods of Measuring Sodium Intake

There are 2 main approaches to estimating sodium intake, namely measuring urinary sodium excretion and estimating sodium intake from dietary questionnaires. Repeated 24-hour urinary sodium excretion is the reference standard for sodium intake estimation, on the premise that the majority (90%–95%) of sodium ingested is excreted in the urine. It has been assumed that sodium intake and urinary excretion track closely, during a 24- or 48-hour period. However, recent evidence from a small study ($n=10$) has raised the possibility of nonrenal endogenous clocks that generate weekly and monthly infradian rhythmicity of sodium storage that is independent of daily sodium intake.^{22,23} One implication of this study is that multiple measures of 24-hour urine are required to measure sodium intake accurately in individuals, and large samples size are required to estimate sodium intake in group/populations, ideally with repeated measures. Moreover, it means that variations in accumulation and excretion of sodium, in addition to total sodium intake, may be important determinants of the association between sodium intake and cardiovascular health and requires further investigation. A major limitation of 24-hour urine collection is the high frequency of incomplete sample collection, which results in either biased estimates or exclusion of participants (eg, those engaged in manual labor or those who have to travel for work) which limits generalizability. Although repeated 24-hour urine collections are feasible in small clinical trials for a few hundred people, they are impractical in large international epidemiological studies involving thousands of individuals, especially in low- and middle-income countries.

To overcome these limitations of 24-hour urine collections, several formula-derived estimates have been developed, and some validated against 24-hour urinary collections, which include the Kawasaki formula, Tanaka formula, INTERSALT formula, and Mege formula.²⁴ For random samples (nonfasting), the Tanaka and INTERSALT formulae seem to be associated with least biased estimates, based on a study performed in a young North American population.²⁴ When using a fasting urine sample, the Kawasaki formula-derived estimates produce the least biased estimates of sodium intake (intraclass correlation of 0.71 for Kawasaki formula estimated 24-hour sodium excretion compared with actual 24-hour urinary collections), based on an international validation study in 11 countries.²⁵ In other settings, for example, when using a nonfasting sample, that Kawasaki formula is associated with more biased estimates than other formula which were developed for use of spot random samples.²⁴ Therefore, the type of sample collected (time and fasting status), population included, and formula used are important considerations.

An alternative to urinary methods to estimate sodium consumption is dietary questionnaires, either food frequency questionnaires or based on 24-hour dietary recall, ideally repeated multiple times. 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 measure overall diet quality. However, limitations include

recall bias, variations of sodium content of common food items (eg, 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 addition, regional variations in the sodium content of certain food items may undermine the validity of international studies, making these methods particularly unsuitable for large international studies.²⁶ In general, dietary questionnaires underestimate sodium intake, compared to 24-hour urinary collections.²⁶

An underappreciated aspect of measuring sodium intake is the purpose of the study and sources of errors in different types of studies. In small studies where the goal is to measure changes within individuals at different time points, the main source of variation is within subject circadian and day to day variability. In such circumstances (as in a small randomized controlled trial of sodium reduction for BP change), it is appropriate to use prolonged (eg, 24- or 72-hour sample collections) on several different days or weeks to obtain individual-level precision in estimating sodium intake. By contrast, when the goal is to compare large populations (eg, one country versus another or a rural versus urban area, or across quintiles or deciles in a large cohort study), the chief source of variation is the between-subject variability. In such circumstances, estimating the population mean (and reducing the SE of the mean value) in a group is chiefly accomplished by including a large number of individuals in the sample. Similarly, when one is comparing the levels of sodium intake with clinical outcomes (eg, mortality), estimates of sodium intake are represented at a group level. Recognizing the difference between individual-level estimation and group-level estimation is crucial in distinguishing which method one is most appropriate for a specific purpose. A convenient, simple measure of sodium intake is essential for large population studies, for example, to compare mean levels across countries or to detect associations as such studies need to accrue several thousands of events to be reliable, which in turn needs methods that can be used in large sample sizes of diverse populations.

Sodium Intake and CVD

What Factors Underlie an Association Between Sodium Intake and CVD?

Sodium Intake, Kidney and Renin–Angiotensin–Aldosterone System

Sodium is the most important extracellular cation in the body, producing an osmotic pressure that maintains water in the extracellular space.¹ To maintain a constant extracellular volume, sodium intake and excretion need to balance. The kidney is central to maintaining sodium levels and may reabsorb sodium throughout the nephron (primarily in the proximal tubule). The principal regulator of renal sodium reabsorption is aldosterone. Aldosterone secretion is stimulated by angiotensin II, for which the rate-limiting step for production is controlled by renin. Renin secretion requires sympathetic nervous system activation by carotid baroreceptors, direct effect of pressure in the afferent arteriole, and concentration of sodium delivered to the distal tubule. Atrial natriuretic peptide is also involved in sodium regulation, released

by the atrium of the heart in response to increased plasma volume. Volume status and serum sodium concentration govern renin production and consequently sodium excretion and reabsorption. In most people with normal renal function and BP, the kidney is capable of dealing with wide variations in sodium intake, without producing increases in BP. However, in some individuals, moderate changes (eg, 1–2 g/d) in sodium intake can exert a substantial effect on BP, a concept called salt sensitivity.²⁷

A physiological consequence of low sodium intake is activation of the rennin–angiotensin–aldosterone system (RAAS). A recent Cochrane review²⁸ of 167 studies evaluating the effect of sodium restriction on renin–aldosterone–angiotensin activity, catecholamine, and lipids reported an increase in renin and aldosterone and catecholamine activity and adverse effects on lipid profile. Another recent meta-analysis that excluded short-term follow-up studies reported activation of RAAS but no adverse effect on lipids.²⁹ In the Cochrane meta-analysis, most studies were small (usually <50 participants), and median duration of follow-up was 28 days in those with hypertension (mean age, 51 years), and only 17 days in those without hypertension (mean age, 27 years). Therefore, the sustained effects of long-term low sodium intake on these biomarkers of cardiovascular risk, in an older (more representative) population, have not been adequately studied.

Sodium Intake and BP

Current guidelines are based on the evidence linking sodium intake and BP.^{5,30} The proposed mechanisms through which increased sodium intake produces hypertension are incompletely understood and may involve a variety of pathways rather than a simple causative model.¹

Observational Studies

INTERSALT¹³ reported center-level and individual-level association between sodium excretion and BP. At a center-level (primary hypothesis), they reported a weak but statistically significant association between mean sodium intake and BP ($P=0.0446$) among 52 centers. However, there were 4 outlier centers, which were heterogeneous from other sites and included those centers of Brazilian tribes, Papua New Guinea, and Kenya. When these sites were excluded, there was no significant association between sodium intake and BP among the other 48 centers ($P=0.33$). The Scottish Health Study ($n=7354$), another large study published at the same time, reported a null association between sodium intake and BP. Since these studies, several other cohort studies have reported a generally positive association between sodium intake and BP, but none were sufficiently large to define the pattern of association, especially at low levels of sodium intake. Recently, the PURE study⁸ has reported on the association between sodium intake and BP in >100 000 individuals from 18 countries. In the PURE study, for each 1-g increase in mean sodium intake, systolic BP increased by 2.63, 1.72, and 0.71 mmHg for sodium intakes of >5, 3 to 5, and <3 g/d, respectively (Figure 1) Based on these findings, the anticipated reduction in BP, associated with sodium reduction, would be expected to be dependent on baseline level of intake of sodium and seems greatest in those consuming high

Figure 1. A and B, Forest plot for change in blood pressure per 1 g/d increase in sodium excretion (Mente et al⁶). Change in blood pressure per 1 g/d increase in sodium excretion by subgroups, sodium intake range, hypertension, and age subgroups. Multivariable estimates of age, sex, geographic region, body mass index, educational level, and alcohol intake and adjusted for regression dilution bias. CI indicates confidence interval.

sodium diets (>5 g/d). The association between sodium and BP was positive in all regions of the world and was strongest in those with hypertension, those who consumed low potassium diets (Figure 2), and in older adults. Therefore, there is a nonlinear positive association between increasing sodium intake and BP, with modest effects in nonhypertensive and younger individuals.

Clinical Trials

A large number of clinical trials, mostly short term (<6 months), evaluating the effect of sodium reduction on BP, have been completed.⁶ The most prominent clinical trials, on which sodium guidelines are primarily based, include the dietary approaches to stop hypertension (DASH)³¹ and Trial of Hypertension Prevention (TOHP) trials, both of which were conducted in North America. The TOHP-II trial is the largest clinical trial (n=2382) to evaluate the effect of longer term sodium reduction on BP, with a mean duration of follow-up of 36 months.³² The trial was a 2×2 factorial that also evaluated weight loss. The target sodium intake in the intervention group was <1.8 g/d. At 6 months, sodium intake was 2.5 g/d in the intervention group and 3.7 g/d in the control group and by 36 months it was 3.1 and 4.1 g/d, respectively. The difference in systolic BP between sodium intake groups was 2.9 mm Hg at 6 months and 1.2 mm Hg at 36 months, suggesting a diminution in BP-lowering effect. In addition, the effect of reducing sodium intake on incidence of hypertension also diminished over time, risk ratio of 0.61 (P=0.04) at 6 months, 0.88 (P=0.28) at 18 months to 0.82 (P=0.05) at study end. This suggests that even in controlled clinical trials, it is difficult to make sustainable

changes in sodium consumption in populations who already consume moderate levels of sodium to achieve current low sodium intake recommendations.

Figure 2. Association between sodium intake and blood pressure (BP) by potassium intake groups (Population Urban Rural Epidemiology [PURE] Study). Mean systolic and diastolic BP according to sodium and potassium excretion. Adjustment was made for age, sex, geographic region, body mass index, educational level, and alcohol intake. The P value for interaction is for testing the joint effect of the 2 electrolytes on BP.

The Dietary Approaches to Stop Hypertension Sodium trial³¹ (n=412) was randomized crossover clinical trial, a feeding study that compared moderate (mean, 3.3 g/d), low (mean, 2.5 g/d), and very low sodium (mean, 1.5 g/d) intake for 30 days in a factorial design (DASH diet emphasizing fruits, vegetables, and low-fat dairy products or control diet which was low in those foods and higher in fat, cholesterol, red meat, and sugars). All foods for the participants were provided by the study during the 30 days of the study. Compared with moderate intake, reductions to low and very low sodium intake levels reduced systolic BP by 2.1 mmHg ($P<0.001$) and 4.6 mmHg ($P<0.001$) in the control diet group and by 1.3 mmHg ($P=0.03$) and 1.7 mmHg ($P<0.01$) in the dietary approaches to stop hypertension diet group. There was a significant interaction between sodium intake groups and dietary groups.

There have been several meta-analyses of clinical trials evaluating sodium reduction for BP reduction.^{6,28,29,33} In the most recent meta-analyses of 34 BP clinical trials (n=3230), a reduction in sodium intake (≈ 1.76 g/d) was associated with a mean 4.2/2.1 mmHg reduction in BP. Among participants with hypertension, the BP reduction was greater compared with those without hypertension.³³ Duration of follow-up may be an important determinant of treatment effect, which was explored in another meta-analysis of BP trials, including 36 trials.⁶ In trials of <3 months, 3 to 6 months and >6 months of duration, BP reductions were 4.07/1.67, 1.91/1.33, and 0.88/0.45 mmHg, respectively. One potential reason for this observation may be that adherence with low sodium intake may not be sustained over time. However, results from the TOPH-II trial, which had the largest sample size, would suggest that the antihypertensive effects of reductions in sodium intake may attenuate over time, as detailed above.³²

Biomarkers

There have been inconsistent reports about the association between sodium intake and other cardiovascular biomarkers, including validated inflammatory biomarkers of cardiovascular risk (C-reactive protein and interleukin-6), markers of cardiac injury/strain (Troponin T, brain natriuretic peptide/pro-brain natriuretic peptide) and of salt sensitivity (uromodulin).^{34–37} In each of these studies, the duration of dietary change in sodium intake was short, and longer term effects on these cardiovascular biomarkers are not known.

Sodium Intake and Cardiovascular Events

Given the competing effects of restricting sodium intake on physiological parameters expected to reduce CVD (ie, lowering BP) and increasing CVD (eg, activation of RAAS), the key question is whether changes in sodium intake result in changes in cardiovascular events and mortality. The evidence-base to answer this question comes primarily from observational research studies, as no large and long-term randomized controlled trial has been completed to determine the effects of reducing sodium intake on CVD.

Prospective Cohort Studies

A large number of prospective cohort studies have been completed that have included $>300\,000$ participants.^{38,39} However, findings from these studies have been variable, with some

reporting a positive association between sodium intake and cardiovascular events, some reported a null association, and some reporting an inverse or J-shaped association.⁴⁰ Some differences among these studies, which may account for differences in findings and conclusions, include differences in sample size, differences in mean intake of sodium, differences in outcome measures, and differences in population, such as geographical region and baseline cardiovascular risk of population included.

Sodium Intake Level

The most obvious source of heterogeneity between studies is the mean sodium intake and range of sodium intake included in the population. In addition, many studies, including meta-analyses, did not explore whether the relationship was linear or nonlinear, which is especially important for evaluation of the association between an essential nutrient and health (Figure 1A).

Meta-Analyses of Prospective Cohort Studies

High sodium intake (>5 g/d) versus moderate (3–5 g/d) or low sodium intake (<3 g/d): Among individual studies which have included a category for high sodium intake (>5 g/d), most report an overall increased risk of cardiovascular events with high sodium intake.⁴¹ Meta-analyses of prospective cohort studies have generally compared lowest quantile of sodium intake with highest quantiles.^{6,38} In a recent meta-analyses, there was a significant association between highest quantile (compared to lowest quantile) and stroke (RR, 1.24; 95% confidence interval, 1.08–1.43) and fatal coronary events (RR, 1.32; 95% CI, 1.13–1.53), but not for all-cause mortality (RR, 1.06; 95% CI, 0.94–1.20) or all CVD (RR, 1.12; 95% CI, 0.93–1.34).⁶ In another meta-analysis³⁹ that included the same study pool, but compared high (>5 g/d) sodium intake to moderate (2.7–5 g/d) sodium intake, an increased risk of all-cause mortality (hazard ratio [HR], 1.16; 95% CI, 1.03–1.30), CVD (HR, 1.12; 95% CI, 1.02–1.24), stroke (HR, 1.18; 95% CI, 1.05–1.33), and heart disease (HR, 1.17; 95% CI, 1.08–1.27) was observed. Therefore, meta-analytic summaries that compare moderate with high sodium intake have reported more consistent increases in cardiovascular risk and mortality than those comparing low with high sodium intake groups.

Moderate (3–5 g/d) versus low sodium intake (<3 g/d): One meta-analysis³⁹ completed a comparison of low sodium intake (<2.7 g/d) with moderate/usual intake (2.7–5 g/d) intake. In that analysis, usual sodium intake was associated with a lower risk of all-cause mortality (HR, 0.91; 95% CI 0.82–0.99) and all CVD (HR, 0.90; 95% CI, 0.82–0.99), compared with low intake.

Large International Cohort Studies

Few individual studies have been sufficiently large, with inclusion of diverse populations, to determine the pattern of association across low, moderate, and high sodium intakes. To date, there have only been 2 large international cohort studies evaluating the association between sodium intake and CVD and mortality.

Population at high cardiovascular risk: The Ongoing Telmisartan Alone and in combination with Ramipril Global End point Trial (ONTARGET)/Telmisartan Randomized Assessment Study in ACE intolerant subject with cardiovascular Disease (TRANSCEND; n=28880) study included a population at high cardiovascular risk⁴²; 16.4% of the cohort

Figure 3. A, Relationship of risk and nutrient intake, showing the location of the 3 principal dietary reference intakes.⁵⁹ B, Estimated 24-hour urinary excretion of sodium and composite of cardiovascular (CV) death, stroke, myocardial infarction and hospitalization for congestive heart failure (secondary prevention cohort); Ongoing Telmisartan Alone and in combination with Ramipril Global End point Trial [ONTARGET]/Telmisartan Randomized Assessment Study in ACE Intolerant subject with cardiovascular Disease [TRANSCEND].⁴² X-axis is level of sodium intake and Y-axis is hazard ratio for risk of composite outcome. C, Estimated 24-hour urinary excretion of sodium and composite of CV death, stroke, myocardial infarction and hospitalization for congestive heart failure (primary prevention cohort), Population Urban Rural Epidemiology [PURE] study.⁴³ X-axis is level of sodium intake and Y-axis is hazard ratio for risk of composite outcome. CI indicates confidence interval; EAR, estimated average requirement; RDA, recommended dietary allowance; and UL, tolerable upper intake level.

experienced a major vascular event or died during 5 years of follow-up. In that study, a J-shaped association between sodium intake and cardiovascular mortality was found, with those

at high cardiovascular risk, with an increased risk in the group consuming <3 g/d of sodium and >6 g/d (Figure 3B).

Population at average cardiovascular risk: The PURE prospective cohort study (n=101 745) included a population at average cardiovascular risk⁴³; 3.3% of the cohort experienced a major vascular event or died during 3.7 years of follow-up. Compared with sodium excretion (intake) of 4 to 5.99 g/d, both higher baseline sodium excretion (>7 g/d) and low sodium excretions (<3 g/d) were associated with higher risk of the composite outcome (Figure 3C).

Both studies conducted extensive analyses to control for confounders, reverse causality, and potential biases, but the J-shaped association between sodium intake and cardiovascular outcomes remained despite all such analyses. Sodium intakes between 3.0 and 6.0 g/d were associated with the lowest risk of CVD in both studies compared with levels that were higher or lower.

Regional Variations

In 1 systematic review of prospective cohort studies, we reported variations in magnitude of association by region, whereby studies from Asia reporting a significant association, but no significant association for studies in Europe or North America.⁴⁰ However, this observation may be mostly because of differences in mean levels of sodium intake among studies, with higher mean intakes in studies from Asia compared with North America and Europe. In both the ONTARGET/TRANSEND and the PURE cohorts,^{42,43} we did not find evidence of significant heterogeneity in those participants from Asia compared with other regions. Before the PURE study, there were no studies from many regions of the world, including India, Africa, and South America. Extended follow-up of the PURE study will enable a more complete evaluation of whether there are regional variations in pattern and magnitude of association between sodium intake and clinical outcomes.

Population Characteristics

Several factors are proposed to modify the association between sodium intake and CVD and mortality. The most obvious is the presence or absence of hypertension, which is proposed to be the key effect of increased sodium intake. In the PURE cohort,⁴³ we reported a significant interaction between baseline hypertension and sodium intake ($P=0.02$). Among those without hypertension, we found no association between high sodium intake and cardiovascular events and mortality and found that the increased risk of clinical outcomes occurred at sodium intake levels >6 g/d among those with hypertension. The association between low sodium intake (<3 g/d) and increased cardiovascular and mortality was not affected by baseline hypertension. Another recently published cohort study (Prevention of Renal and Vascular End-stage Disease [PREVEND] study; n=7543)⁴⁴ reported an association between high sodium intake and CVD that was confined to participants with baseline hypertension and in those with baseline pro-brain natriuretic peptide levels above the median (P interaction: $P=0.0002$). Other studies have not reported a significant modifying effect of prior hypertension, but these studies have been much smaller than PURE study.

Baseline CVD: Although the absolute risk of cardiovascular events and mortality, associated with both high and low sodium intake (versus moderate intake), is more marked in those with prior CVD,^{42,45,46} no study have reported a significant interaction by pre-existing clinical CVD.

Body mass index: One study (NHANES-1 [National Health and Nutrition Examination Survey]) reported an increased risk of higher sodium intake among participants with increased body mass index (but not in entire overall cohort).⁴⁷ However, this finding has not been replicated in other cohort studies, although numerous studies have evaluated the role of body mass index as an effect modifier.

Other dietary factors: Many dietary factors (eg, fruit, vegetable, and meat intake) and dietary patterns (eg, prudent diet, Mediterranean diet) have been associated with differing risk of CVD.^{48,49} A key factor is potassium intake that may modify the association between sodium intake, BP, and CVD, of which the most prominent is potassium intake.^{50,51} Epidemiological studies have also reported that increased potassium intake is associated with reduced risk of CVD, most notably for stroke.⁵² In both the PURE and the ONTARGET/TRANSCEND studies, we did not find evidence of an interaction between sodium intake and potassium intake for cardiovascular events. However, the lowest risk of cardiovascular events occurred in the group of individuals with moderate sodium intake and high potassium intake. In PURE, we did observe an interaction between sodium intake and potassium intake for the association with BP (Figure 2).⁸ Variations in sources of sodium intake are an important confounding variable in studies linking sodium intake and health outcomes. For example, in some regions, high sodium intake may be primarily from processed foods and food types that are known to be independently associated with CVD, such as fried foods, especially in high-moderate income countries. In other regions, key sources of high sodium intake may include salted fish and vegetables, which, independently, do not increase cardiovascular risk. For example, in a Japanese study,¹⁹ a traditional dietary pattern with the highest sodium intake (and BP) was counterintuitively associated with the lowest risk of cardiovascular disease, attributed to the diet also being rich in fish and vegetables.

Genetic determinants of salt sensitivity: It is established that some individuals are more sensitive to the hypertensive effects of increased sodium intake, termed salt sensitivity,⁵³ a concept that seems at odds with the current population-based approach to sodium reduction. Although there is clear evidence that some populations are more prone to the hypertensive effects of sodium intake, there is no clear working clinical definition for salt sensitivity and has not emerged from research into clinical practice. About 30% to 50% of people with hypertension and a smaller percentage of individuals with normal BP are thought to be salt-sensitive.⁵³ In some studies, salt sensitivity is defined by the BP response of participants to saline infusions. An intensive area of research is identification of genetic polymorphisms that are associated with both hypertension and salt sensitivity. In some cases, these polymorphisms have also been associated with an increased risk of cardiovascular events (eg, uromodulin).³⁵ Candidate genes associated with BP have been identified in large genome-wide studies.⁵⁴ Although genome-wide

association study has not been conducted for salt sensitivity, potential candidates include⁵⁵ (1) gene-expressing proteins that increase renal sodium transport (eg, angiotensin I-converting enzyme); (2) gene-expressing proteins that decrease renal sodium transportation; (3) G-protein-coupled receptor kinase-4; and (4) activation of the renal sodium cotransporter, Na-K-Cl cotransporter-4 (eg, uromodulin). In particular, recent studies suggest that uromodulin (Tamm-Horsfall protein) may be a key determinant of salt sensitivity.³⁵ Genome-wide association study has identified common variants in the promoter of the UMOD gene, which encodes uromodulin, causes susceptibility to hypertension and uromodulin overexpression in transgenic mice leads to salt sensitivity hypertension. The mechanism through which uromodulin is linked with hypertension is because of activation of the renal sodium cotransporter Na-K-Cl cotransporter-4. Of potential therapeutic importance, pharmacological inhibition of Na-K-Cl cotransporter-4 effectively reduces BP in hypertensive patients who are homozygous for UMOD promoter risk variants.

Types of Cardiovascular Outcomes

For the association between high sodium intake (versus low or moderate) with clinical outcomes, stroke and cardiovascular death are the outcomes most consistently reported with increased risk. Stroke is the cardiovascular outcome most sensitive to the effects of increasing BP. Because stroke is more common in Asia, than Europe or North America, this may also contribute to the suggested regional variations in association between sodium intake and CVD. Many studies have reported that the association between high sodium intake and cardiovascular death is independent of BP, which suggest that some of the effects may be mediated through mechanisms other than BP.

For the association between low sodium intake (versus moderate) and clinical outcomes, cardiovascular death and hospitalization for heart failure are the outcome most consistently reported with increased risk. In the ONTARGET/TRANSCEND cohort study, the increased risk of CVD with low sodium intake (<3 g/d) was specific for cardiovascular death and hospitalization for congestive heart failure, whereas high sodium intake (>6 g/d) was associated with an increased risk of all cardiovascular event and non-cardiovascular mortality. A U-shaped association between sodium intake and heart failure was also reported in the European Prospective Investigation of Cancer-Norfolk, which included an inception cohort of participants without cardiovascular (n=19857), and followed up for 12.9 years.⁵⁶ An important potential confounder in the association between sodium intake and congestive heart failure is use of diuretics.

Randomized Controlled Trials

No randomized controlled trials have been undertaken to specifically determine whether low sodium intake reduces the incidence of cardiovascular events or death (compared with moderate intake), and none are underway.¹ Meta-analyses of BP trials, that reported cardiovascular events, do not report a significant reduction in CVD with lowering sodium intake, but these trials are underpowered to detect moderate risk reductions (eg, <25% RR reduction, which would require a difference in sodium intake of ≈ 3 or 4 g/d and which has never been

accomplished in long-term trials of sodium intake). An extended observational follow-up of the TOHP I and II trials reported on the risk of death and cardiovascular events (composite of myocardial infarction, stroke, coronary revascularization or cardiovascular death) during 10 to 15 years after completion of the trials. However, loss to follow-up for determination of cardiovascular outcomes in that study was 23%, which makes interpretation of cardiovascular outcomes findings difficult. For all-cause mortality, where there was complete determination of outcome, there was no significant association (2.3% in intervention group and 2.6% in control group; adjusted odds ratio, 0.80; 95% confidence interval, 0.51–1.26). For cardiovascular disease outcomes, there was no significant difference on univariate analyses (7.5% in intervention group versus 9.0% in control group; $P=0.19$, which is the standard approach to analyses of RCTs) but was reported to be significantly reduced in the low sodium group, after adjustment for covariates (odds ratio, 0.75; 95% confidence interval, 0.57–0.99). The magnitude of risk reduction (25% RR reduction) in CVD exceeds the anticipated benefit expected from a small difference in sodium intake and systolic BP observed in final follow-up of the intervention period in these trials.

A small cluster randomized controlled trial ($n=1981$) conducted in 5 kitchens of veteran's retirement homes in Taiwan, in which participants increased potassium consumption and reduced sodium consumption through use of potassium-enriched salt, found a reduction in cardiovascular mortality (HR, 0.59; 95% confidence interval, 0.37–0.95) in those assigned to the higher potassium group.⁵⁷ Moreover, in that trial, sodium intake was estimated to be reduced from 5.2 to 3.8 g/d, but with a proportionately larger effect on potassium intake than sodium intake. Therefore, this trial evaluated a reduction of sodium intake from high to moderate levels, but confounded by the increase in potassium intake, which may have also explained the reduction in cardiovascular risk. However, this trial provides a model for the conduct of larger and longer trials to evaluate whether sodium reduction will actually reduce CVD and other important clinical events.

Other Cardiovascular-Related Outcomes

A systematic review of the association between sodium intake and chronic kidney disease found an increased risk of adverse renal effects with high sodium intake, but not association between moderate intake (compared to low intake).⁵⁸

What Is Normal Sodium Intake?

Despite considerable clinical research, the range of sodium intake, that is considered normal or adequate, is disputed. It is not just the inconsistency in the data, but lack of agreement on the basis for how a normal range of sodium intake should be established that has led to controversy in this field. Moreover, there is an emphasis on identifying an optimal range for the entire population, rather than a recognition that sodium intake requirements may differ in subpopulation (eg, the old versus the young or hypertensive versus nonhypertensive).

The framework for developing guidelines on daily recommended intake for nutrients differs from recommendations for medicinal products in several ways. Unlike investigational

medications, where research is needed to prove efficacy, one begins with the knowledge that essential nutrients are beneficial to health.⁵⁹ The question is not whether sodium is beneficial but rather, within what range of intake is there most benefit and lowest harm. Therefore, a recommended intake needs to include a range of intake, with an upper and lower limit. The current sodium intake recommendations that do not include a lower recommended limit are therefore inconsistent with such an approach.

The process for setting a daily recommended intake range requires identification of the estimated average requirement, which is the daily value of a nutrient that is estimated to meet the nutrient requirement of half the healthy individuals in a life stage and sex group, the recommended daily allowance, the no observed adverse effect level, the tolerable upper intake level, and the lowest observed adverse effect level.⁶⁰ Accordingly, observational studies assume greater importance in setting nutritional guidelines than for recommendations for medicinal products. A fundamental question is which outcomes should be considered in defining a range, to define what constitutes the limits for lower and upper limits of intake, beyond which intakes are associated with harm. Depending on the approach, therefore, a recommendation on sodium intake may vary. For example, if one takes BP as the sole criterion, then recommending sodium intake <2.0 g/d may be appropriate (although as shown by Mente et al,⁸ the effects on BP are small at sodium intakes <3 g/d). Alternatively, if one selects cardiovascular events as the sole criterion outcome, then intake between 3 and 6 g/d would seem optimal. Another approach, advocated by Heaney,⁵⁹ is to use set-point or least adaptation theory, based on the premise that physiological systems function at a status that ensures conditions are optimal for physiology. This approach explores the consequence of varying sodium intakes on a range of physiological systems known to regulate sodium, and deems normal intake as the sweet-spot where compensatory, or adaptive, processes are least engaged. Based on the critical importance of RAAS, balanced against blood pressure reductions, on maintaining sodium status, studies by Brunner et al⁶¹ and others⁶² would argue that optimal sodium intake is between 3 and 5 g/d, as this is the intake range with least activation of RAAS, balanced against blood pressure reductions, and this seems to coincide with the optimal range based on clinical outcomes.

Guideline Recommendations and Evolving Evidence

Most international guideline recommends intakes varying from <2.4 to <1.5 g/d. Since the introduction of international guidelines in the early 2000s, there have been 4 main observations that challenge the appropriateness of these recommendations for all people. First, as detailed above, several prospective cohort studies have reported an increased risk of cardiovascular events in people consuming low sodium intake (<3 g/d), compared with moderate intake. Second, an assumed linear association between BP and CVD may not be correct, for BP <130 systolic.^{63–65} In addition, the mechanism of BP lowering seems important. In particular, drugs that inhibit the RAAS (note extreme Na reductions <3 g/d increases renin and aldosterone levels) seem to reduce the risk of CVD,

independent of BP lowering.⁶⁶ Third, the feasibility of reducing sodium intake levels to <2.0 g/d in the entire population is questionable, as this level of sodium intake has not been achieved in any country despite population-level interventions or even in the intervention arm of the largest and longest study (TOHP-II, where the mean sodium intake in the intervention group was 3.1 g/d at the end of follow-up).

Anticipated Gains from Reducing Sodium Intake

In a recent modeling study, Mozaffarian et al⁶⁷ reported that an estimated 1.65 million deaths annually are attributable to increased sodium intake, based on the contention that sodium intake >2 g/d is considered excess and a linear assumption both between sodium intake and BP and between BP and CVD. Recent evidence would suggest that both of these assumptions may be incorrect, and the reported estimates are a likely exaggeration of the true effect. In that study, it has been reported that an estimate 512 901 were attributable to sodium intake >4 g/d. Therefore, targeting a feasible sodium intake range of 3 to 4 g/d, which is a target where there is consistent evidence of benefit and no suggestion of harm, one can anticipate a much more modest impact of avoidance of ≈500 000 deaths per year.

Future Research

Large randomized controlled trials showing a reduction in clinically important cardiovascular 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 recommendations on essential nutrients, in comparison with medications, the feasibility of randomized controlled trials is more challenging. Some believe that recommendations should be based exclusively on blood pressure trials; others think that findings from large epidemiological studies should also inform guidelines, whereas others argue that the only way to truly resolve the controversy is to complete a large-scale randomized controlled trial comparing low to moderate sodium intake and cardiovascular outcomes. Additional research is also required to more fully appreciate the effects of sustained low sodium intake on physiological parameters of cardiovascular risk.

Interpreting Current Evidence

Optimal Intake for Cardiovascular Health

Based on current evidence, we would consider that a range of 3 to 5 g/d of sodium to be optimal for cardiovascular health. At this range, one achieves BP benefits of lowering sodium intake without activation of RAAS, and epidemiological studies report the lowest rate of cardiovascular events.

Sources of Funding

No funding was received for the current article. We have received funding from the Heart and Stroke Foundation of Ontario for Population Urban Rural Epidemiology-Salt Study of association of sodium intake and cardiovascular events and mortality.

Disclosures

None.

References

- Kotchen TA, Cowley AW Jr, Frohlich ED. Salt in health and disease—a delicate balance. *N Engl J Med*. 2013;368:1229–1237. doi: 10.1056/NEJMra1212606.
- Frost CD, Law MR, Wald NJ. By how much does dietary salt reduction lower blood pressure? II—Analysis of observational data within populations. *BMJ*. 1991;302:815–818.
- O'Donnell MJ, Xavier D, Liu L, et al; INTERSTROKE Investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet*. 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3.
- Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L; INTERHEART Study Investigators. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. *Lancet*. 2004;364:937–952. doi: 10.1016/S0140-6736(04)17018-9.
- World Health Organisation. *Diet, Nutrition and the prevention of chronic diseases. Report of the Joint WHO/FAO Expert Consultation*. Geneva: World Health Organisation;2003 (WHO Technical Report Series, No 916).
- Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ*. 2013;346:f1326.
- Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, Engell RE, Lim SS, Danaei G, Mozaffarian D. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ Open*. 2013;3:e003733.
- Mente A, O'Donnell MJ, Rangarajan S, et al; PURE Investigators. Association of urinary sodium and potassium excretion with blood pressure. *N Engl J Med*. 2014;371:601–611. doi: 10.1056/NEJMoa1311989.
- Frassetto LA, Schloetter M, Mietus-Synder M, Morris RC Jr, Sebastian A. Metabolic and physiologic improvements from consuming a paleolithic, hunter-gatherer type diet. *Eur J Clin Nutr*. 2009;63:947–955. doi: 10.1038/ejcn.2009.4.
- Elliott P, Stamler J, Nichols R, Dyer AR, Stamler R, Kesteloot H, Marmot M. Intersalt revisited: further analyses of 24 hour sodium excretion and blood pressure within and across populations. Intersalt Cooperative Research Group. *BMJ*. 1996;312:1249–1253.
- DeSanto NG, Bisaccia C, Cirillo M, DeSanto RM, DeSanto LS, DeSanto D, Papalia T, Capasso G, De Napoli N. A contribution to the history of common salt. *Kidney Int Suppl*. 1997;59:S127–S134.
- MacGregor GA, He FJ. World action on salt. *Lancet*. 2008;371:471. doi: 10.1016/S0140-6736(08)60228-7.
- Intersalt. An international study of electrolyte excretion and blood pressure. Results for 24 hour urinary sodium and potassium excretion. Intersalt Cooperative Research Group. *BMJ*. 1988;297:319–28.
- INTERSALT Study: an international co-operative study on the relation of blood pressure to electrolyte excretion in populations. I. Design and methods. The INTERSALT Co-operative Research Group. *J Hypertens*. 1986;4:781–787.
- Stamler J, Elliott P, Dennis B, Dyer AR, Kesteloot H, Liu K, Ueshima H, Zhou BF; INTERMAP Research Group. INTERMAP: background, aims, design, methods, and descriptive statistics (nondiary). *J Hum Hypertens*. 2003;17:591–608. doi: 10.1038/sj.jhh.1001603.
- Zhou BF, Stamler J, Dennis B, Moag-Stahlberg A, Okuda N, Robertson C, Zhao L, Chan Q, Elliott P; INTERMAP Research Group. Nutrient intakes of middle-aged men and women in China, Japan, United Kingdom, and United States in the late 1990s: the INTERMAP study. *J Hum Hypertens*. 2003;17:623–630. doi: 10.1038/sj.jhh.1001605.
- Dennis B, Stamler J, Buzzard M, Conway R, Elliott P, Moag-Stahlberg A, Okayama A, Okuda N, Robertson C, Robinson F, Schakel S, Stevens M, Van Heel N, Zhao L, Zhou BF; INTERMAP Research Group. INTERMAP: the dietary data—process and quality control. *J Hum Hypertens*. 2003;17:609–622. doi: 10.1038/sj.jhh.1001604.
- Yusuf S, Islam S, Chow CK, et al; Prospective Urban Rural Epidemiology (PURE) Study Investigators. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. *Lancet*. 2011;378:1231–1243. doi: 10.1016/S0140-6736(11)61215-4.

19. Shimazu T, Kuriyama S, Hozawa A, Ohmori K, Sato Y, Nakaya N, Nishio Y, Tsubono Y, Tsuji I. Dietary patterns and cardiovascular disease mortality in Japan: a prospective cohort study. *Int J Epidemiol*. 2007;36:600–609. doi: 10.1093/ije/dym005.
20. Anderson CA, Appel LJ, Okuda N, Brown IJ, Chan Q, Zhao L, Ueshima H, Kesteloot H, Miura K, Curb JD, Yoshita K, Elliott P, Yamamoto ME, Stamler J. Dietary sources of sodium in China, Japan, the United Kingdom, and the United States, women and men aged 40 to 59 years: the INTERMAP study. *J Am Diet Assoc*. 2010;110:736–745. doi: 10.1016/j.jada.2010.02.007.
21. Bernstein AM, Willett WC. Trends in 24-h urinary sodium excretion in the United States, 1957–2003: a systematic review. *Am J Clin Nutr*. 2010;92:1172–1180. doi: 10.3945/ajcn.2010.29367.
22. Titze J. Sodium balance is not just a renal affair. *Curr Opin Nephrol Hypertens*. 2014;23:101–105. doi: 10.1097/01.mnh.0000441151.55320.c3.
23. Rakova N, Jüttner K, Dahmann A, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. *Cell Metab*. 2013;17:125–131. doi: 10.1016/j.cmet.2012.11.013.
24. Cogswell ME, Wang CY, Chen TC, Pfeiffer CM, Elliott P, Gillespie CD, Carriquiry AL, Sempos CT, Liu K, Perrine CG, Swanson CA, Caldwell KL, Loria CM. Validity of predictive equations for 24-h urinary sodium excretion in adults aged 18–39 y. *Am J Clin Nutr*. 2013;98:1502–1513. doi: 10.3945/ajcn.113.059436.
25. Mente A, O'Donnell MJ, Dagenais G, et al. Validation and comparison of three formulae to estimate sodium and potassium excretion from a single morning fasting urine compared to 24-h measures in 11 countries. *J Hypertens*. 2014;32:1005–1014; discussion 1015. doi: 10.1097/HJH.0000000000000122.
26. Espeland MA, Kumanyika S, Wilson AC, Reboussin DM, Easter L, Self M, Robertson J, Brown WM, McFarlane M; TONE Cooperative Research Group. Statistical issues in analyzing 24-hour dietary recall and 24-hour urine collection data for sodium and potassium intakes. *Am J Epidemiol*. 2001;153:996–1006.
27. Coffman TM. The inextricable role of the kidney in hypertension. *J Clin Invest*. 2014;124:2341–2347. doi: 10.1172/JCI72274.
28. Graudal NA, Hubeck-Graudal T, Jurgens G. Effects of low sodium diet versus high sodium diet on blood pressure, renin, aldosterone, catecholamines, cholesterol, and triglyceride. *Cochrane Database Syst Rev*. 2011;CD004022.
29. He FJ, Li J, Macgregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev*. 2013;4:CD004937. doi: 10.1002/14651858.CD004937.pub2.
30. Whelton PK, Appel LJ, Sacco RL, et al. Sodium, blood pressure, and cardiovascular disease: further evidence supporting the American Heart Association sodium reduction recommendations. *Circulation*. 2012;126:2880–2889. doi: 10.1161/CIR.0b013e318279acbf.
31. Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER 3rd, Simons-Morton DG, Karanja N, Lin PH; DASH-Sodium Collaborative Research Group. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344:3–10. doi: 10.1056/NEJM200101043440101.
32. TOHP Investigators. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. The Trials of Hypertension Prevention, phase II. The Trials of Hypertension Prevention Collaborative Research Group. *Arch Intern Med* 1997;157:657–67.
33. He FJ, Li J, Macgregor GA. Effect of longer term modest salt reduction on blood pressure: Cochrane systematic review and meta-analysis of randomised trials. *BMJ*. 2013;346:f1325.
34. Oudot C, Lajoix AD, Jover B, Rugale C. Dietary sodium restriction prevents kidney damage in high fructose-fed rats. *Kidney Int*. 2013;83:674–683. doi: 10.1038/ki.2012.478.
35. Trudu M, Janas S, Lanzani C, et al; Swiss Kidney Project on Genes in Hypertension (SKIPOGH) team. Common noncoding UMOD gene variants induce salt-sensitive hypertension and kidney damage by increasing uromodulin expression. *Nat Med*. 2013;19:1655–1660. doi: 10.1038/nm.3384.
36. Damgaard M, Goetze JP, Norsk P, Gadsbøll N. Altered sodium intake affects plasma concentrations of BNP but not proBNP in healthy individuals and patients with compensated heart failure. *Eur Heart J*. 2007;28:2726–2731. doi: 10.1093/eurheartj/ehm396.
37. Yilmaz R, Akoglu H, Altun B, Yildirim T, Arici M, Erdem Y. Dietary salt intake is related to inflammation and albuminuria in primary hypertensive patients. *Eur J Clin Nutr*. 2012;66:1214–1218. doi: 10.1038/ejcn.2012.110.
38. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ*. 2009;339:b4567.
39. Graudal N, Jürgens G, Baslund B, Alderman MH. Compared with usual sodium intake, low- and excessive-sodium diets are associated with increased mortality: a meta-analysis. *Am J Hypertens*. 2014;27:1129–1137. doi: 10.1093/ajh/hpu028.
40. O'Donnell MJ, Mente A, Smyth A, Yusuf S. Salt intake and cardiovascular disease: why are the data inconsistent? *Eur Heart J*. 2013;34:1034–1040. doi: 10.1093/eurheartj/ehs409.
41. Alderman MH, Cohen HW. Dietary sodium intake and cardiovascular mortality: controversy resolved? *Curr Hypertens Rep*. 2012;14:193–201. doi: 10.1007/s11906-012-0275-6.
42. O'Donnell MJ, Yusuf S, Mente A, Gao P, Mann JF, Teo K, McQueen M, Sleight P, Sharma AM, Dans A, Probstfield J, Schmedier RE. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA*. 2011;306:2229–2238. doi: 10.1001/jama.2011.1729.
43. O'Donnell M, Mente A, Rangarajan S, et al; PURE Investigators. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371:612–623. doi: 10.1056/NEJMoa1311889.
44. Joosten MM, Gansevoort RT, Mukamal KJ, Lambers Heerspink HJ, Geleijnse JM, Feskens EJ, Navis G, Bakker SJ; PREVENT Study Group. Sodium excretion and risk of developing coronary heart disease. *Circulation*. 2014;129:1121–1128. doi: 10.1161/CIRCULATIONAHA.113.004290.
45. Thomas MC, Moran J, Forsblom C, Harjutsalo V, Thorn L, Ahola A, Wadén J, Tolonen N, Saraheimo M, Gordin D, Groop PH; FinnDiane Study Group. The association between dietary sodium intake, ESRD, and all-cause mortality in patients with type 1 diabetes. *Diabetes Care*. 2011;34:861–866. doi: 10.2337/dc10-1722.
46. Ekinci EI, Clarke S, Thomas MC, Moran JL, Cheong K, MacIsaac RJ, Jerums G. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care*. 2011;34:703–709. doi: 10.2337/dc10-1723.
47. He J, Ogden LG, Vupputuri S, Bazzano LA, Loria C, Whelton PK. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. *JAMA*. 1999;282:2027–2034.
48. Iqbal R, Anand S, Ounpuu S, Islam S, Zhang X, Rangarajan S, Chifamba J, Al-Hinai A, Keltai M, Yusuf S; INTERHEART Study Investigators. Dietary patterns and the risk of acute myocardial infarction in 52 countries: results of the INTERHEART study. *Circulation*. 2008;118:1929–1937. doi: 10.1161/CIRCULATIONAHA.107.738716.
49. Mente A, de Koning L, Shannon HS, Anand SS. A systematic review of the evidence supporting a causal link between dietary factors and coronary heart disease. *Arch Intern Med*. 2009;169:659–669. doi: 10.1001/archinternmed.2009.38.
50. Morris RC Jr, Schmidlin O, Frassetto LA, Sebastian A. Relationship and interaction between sodium and potassium. *J Am Coll Nutr*. 2006;25:262S–270S.
51. Cook NR, Obarzanek E, Cutler JA, Buring JE, Rexrode KM, Kumanyika SK, Appel LJ, Whelton PK; Trials of Hypertension Prevention Collaborative Research Group. Joint effects of sodium and potassium intake on subsequent cardiovascular disease: the Trials of Hypertension Prevention follow-up study. *Arch Intern Med*. 2009;169:32–40. doi: 10.1001/archinternmed.2008.523.
52. Aburto NJ, Hanson S, Gutierrez H, Hooper L, Elliott P, Cappuccio FP. Effect of increased potassium intake on cardiovascular risk factors and disease: systematic review and meta-analyses. *BMJ*. 2013;346:f1378.
53. Felder RA, White MJ, Williams SM, Jose PA. Diagnostic tools for hypertension and salt sensitivity testing. *Curr Opin Nephrol Hypertens*. 2013;22:65–76. doi: 10.1097/MNH.0b013e3182835b3693.
54. Ehret GB, Munroe PB, Rice KM, et al. Genetic variants in novel pathways influence blood pressure and cardiovascular disease risk. *Nature*. 2011;478:103–9.
55. Felder RA, White MJ, Williams SM, Jose PA. Diagnostic tools for hypertension and salt sensitivity testing. *Curr Opin Nephrol Hypertens*. 2013;22:65–76. doi: 10.1097/MNH.0b013e3182835b3693.
56. Pfister R, Michels G, Sharp SJ, Luben R, Wareham NJ, Khaw KT. Estimated urinary sodium excretion and risk of heart failure in men and women in the EPIC-Norfolk study. *Eur J Heart Fail* 2014;16:394–402.
57. Chang HY, Hu YW, Yue CS, Wen YW, Yeh WT, Hsu LS, Tsai SY, Pan WH. Effect of potassium-enriched salt on cardiovascular mortality and medical expenses of elderly men. *Am J Clin Nutr*. 2006;83:1289–1296.

58. Smyth A, O'Donnell MJ, Yusuf S, Clase CM, Teo KK, Canavan M, Reddan DN, Mann JF. Sodium intake and renal outcomes: a systematic review. *Am J Hypertens*. 2014;27:1277–1284. doi: 10.1093/ajh/hpt294.
59. Heaney RP. Sodium: how and how not to set a nutrient intake recommendation. *Am J Hypertens*. 2013;26:1194–1197. doi: 10.1093/ajh/hpt130.
60. Institute of Medicine. *Dietary Reference Intakes*. Washington, DC: Institute of Medicine, National Academies Press;2006.
61. Brunner HR, Laragh JH, Baer L, Newton MA, Goodwin FT, Krakoff LR, Bard RH, Bühler FR. Essential hypertension: renin and aldosterone, heart attack and stroke. *N Engl J Med*. 1972;286:441–449. doi: 10.1056/NEJM197203022860901.
62. McCarron DA. Physiology, not policy, drives sodium intake. *Am J Hypertens*. 2013;26:1191–1193. doi: 10.1093/ajh/hpt151.
63. Yusuf S, Diener HC, Sacco RL, et al; PROfESS Study Group. Telmisartan to prevent recurrent stroke and cardiovascular events. *N Engl J Med*. 2008;359:1225–1237. doi: 10.1056/NEJMoa0804593.
64. Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med* 2010;362:1575–85.
65. Lithell H, Hansson L, Skoog I, Elmfeldt D, Hofman A, Olofsson B, Trenkwalder P, Zanchetti A; SCOPE Study Group. The Study on Cognition and Prognosis in the Elderly (SCOPE): principal results of a randomized double-blind intervention trial. *J Hypertens*. 2003;21:875–886. doi: 10.1097/01.hjh.0000059028.82022.89.
66. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145–153. doi: 10.1056/NEJM200001203420301.
67. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, Lim S, Danaei G, Ezzati M, Powles J; Global Burden of Diseases Nutrition and Chronic Diseases Expert Group. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371:624–634. doi: 10.1056/NEJMoa1304127.

Circulation Research

JOURNAL OF THE AMERICAN HEART ASSOCIATION

Sodium Intake and Cardiovascular Health Martin O'Donnell, Andrew Mente and Salim Yusuf

Circ Res. 2015;116:1046-1057

doi: 10.1161/CIRCRESAHA.116.303771

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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