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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Salt Reduction to Prevent Hypertension and Cardiovascular Disease

JACC State-of-the-Art Review

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ABSTRACT

There is strong evidence for a causal relationship between salt intake and blood pressure. Randomized trials demonstrate that salt reduction lowers blood pressure in both individuals who are hypertensive and those who are normotensive, additively to antihypertensive treatments. Methodologically robust studies with accurate salt intake assessment have shown that a lower salt intake is associated with a reduced risk of cardiovascular disease, all-cause mortality, and other conditions, such as kidney disease, stomach cancer, and osteoporosis. Multiple complex and interconnected physiological mechanisms are implicated, including fluid homeostasis, hormonal and inflammatory mechanisms, as well as more novel pathways such as the immune response and the gut microbiome. High salt intake is a top dietary risk factor. Salt reduction programs are cost-effective and should be implemented or accelerated in all countries. This review provides an update on the evidence relating salt to health, with a particular focus on blood pressure and cardiovascular disease, as well as the potential mechanisms. (J Am Coll Cardiol 2020;75:632–47) © 2020 by the American College of Cardiology Foundation.

The human body needs a very small amount of salt from the diet to maintain fluid balance and cellular homeostasis. For several million years, the only source of salt for human ancestors was that naturally found in foods, and salt intake was below 0.5 g/day (1). Following the discovery of its preservative properties some 5,000 years ago, salt gradually became the most taxed and traded commodity in the world (1). At the present time, although refrigeration technologies obviate the need for salt as a preservative, the current salt intake averages ≈10 g/day in most countries (2,3), representing a >20 times increase in a short period of time in the evolutionary timescale. The repercussions on our health are multiple, as human physiology has not adapted to excrete these large amounts of salt. Via several complex and interconnected pathways, our current high salt intake leads to key target organ damages, resulting in cardiovascular and other chronic diseases (**Central Illustration**). Worldwide, ≈70 million disability-adjusted life-years and 3 million deaths in 2017 were attributed to high salt intake, making it one of the top 3 dietary risk factors (4).

In this paper, we review the evidence relating salt to health, with a particular focus on blood pressure (BP) and cardiovascular disease (CVD). We also briefly discuss the pathophysiological mechanisms. Finally, we provide a brief update on salt-reduction programs in different parts of the world.

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HIGHLIGHTS

- Our current high salt intake is among the top 3 dietary risk factors worldwide.
- Population-wide reduction in salt intake lowers population BP and alleviates the burden of CVD and other chronic diseases.
- Paradoxical findings from methodologically flawed studies should not be used to refute the strong evidence on the benefits of salt reduction.
- Worldwide salt-reduction efforts should be reinforced to save millions of people dying unnecessarily from stroke and heart disease each year.

ABBREVIATIONS AND ACRONYMS

BP = blood pressure

CKD = chronic kidney disease

CVD = cardiovascular disease

HICs = high-income countries

LMICs = low- and middle-income countries

RAAS = renin-angiotensin-aldosterone system

SALT AND SODIUM

The terms salt and sodium (1 g sodium = 2.5 g salt) are often used interchangeably. However, on a weight basis, salt comprises 40% sodium and 60% chloride. Salt is the major source of sodium in the diet (≈90%). In the United States and Canada, the term "sodium" is usually used in the scientific publications and on food labels, whereas "salt" is used in most other countries. Throughout this review, we use "salt" for simplicity.

CAUSAL RELATIONSHIP BETWEEN SALT INTAKE AND BP

A vast and diverse body of evidence has consistently shown a causal relationship between salt intake and BP (5). Here, we review the observational and interventional evidence linking salt to BP, the underlying physiological mechanisms, and the effect of salt reduction in relation to antihypertensive therapy.

OBSERVATIONAL EPIDEMIOLOGICAL STUDIES. The methodological challenge posed by salt intake assessment has long been a major limitation in epidemiological studies. In response, the INTERSALT (International Study of Sodium, Potassium, and Blood Pressure) was conducted, using standardized methods to collect 24-h urine and to measure BP in 10,079 adults from 32 countries (6). INTERSALT demonstrated a direct association between salt intake as measured by 24-h urinary sodium and BP. This finding was confirmed by multiple other large epidemiological studies (7,8) and natural experiments at population level (9,10). INTERSALT also revealed an association between salt intake and BP rise with age, suggesting that, in addition to a short-term decrease in BP, salt reduction could slow down the rise in BP with aging.

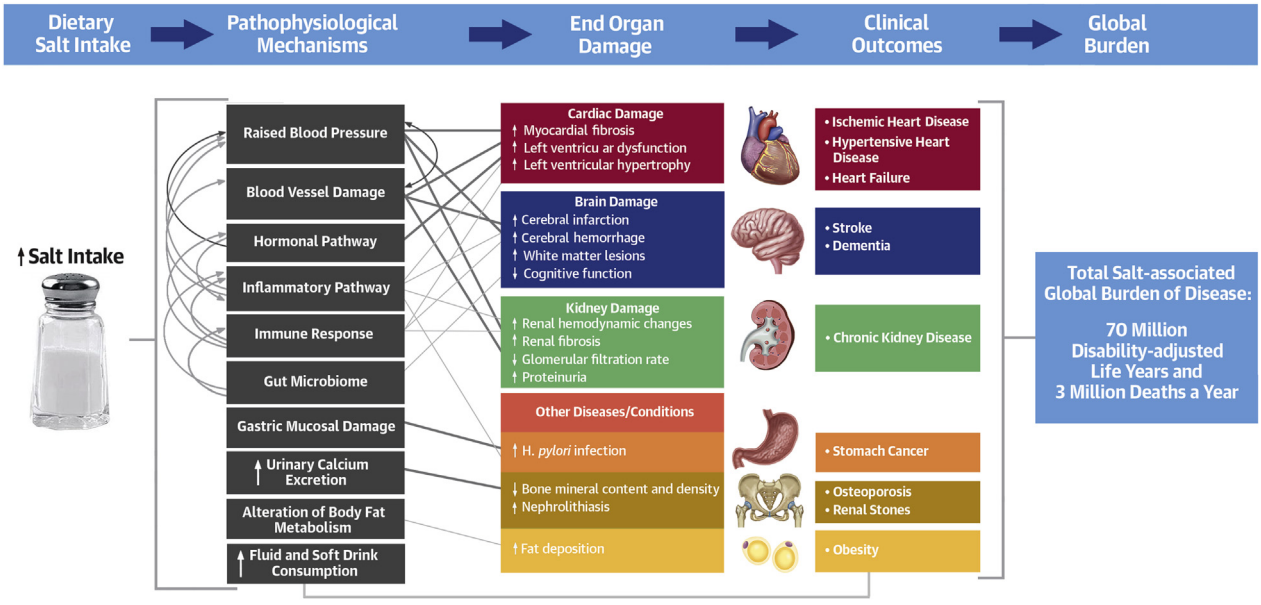
RANDOMIZED TRIALS. There have been several meta-analyses of randomized salt-reduction trials and their results are summarized in Figure 1. Almost all meta-analyses have shown significant falls in BP (11–23) although the extent of the BP fall varied, which is largely due to different inclusion criteria.

Acute and large reductions in salt intake are known for triggering compensatory mechanisms, such as increases in plasma renin activity and angiotensin II, stimulation of the sympathetic nervous system, and reduction in plasma volume, which increases plasma lipid concentration. Such acute metabolic studies are irrelevant to the public health recommendation of modest reduction in salt intake over a long period of time. Despite this, Graudal et al. (23) included these very short-term salt-reduction trials in their series of meta-analyses and drew the erroneous conclusion that salt reduction has very little effect on BP in individuals who are normotensive, and implied potential harm on health, challenging the current salt-reduction policy. However, meta-analyses excluding very short salt restriction trials demonstrate that modest salt reduction causes decreases in BP of clinical and public health significance in both hypertensive and normotensive individuals, does not have adverse effect on blood lipids or catecholamine, and increases only slightly plasma renin activity and aldosterone (21,22).

For a given reduction in salt intake, the falls in BP are larger in individuals who are hypertensive, black, and older compared with individuals who are normotensive, white, and young, respectively. This could, at least partially, be attributable to differences in the renin-angiotensin-aldosterone system (RAAS) response (24,25). From a public health perspective, whole-of-population salt reduction, even by a small amount, lowers population BP, as demonstrated by countries where salt intake has been successfully reduced, for example, Finland and the United Kingdom (9,10).

A dose-response relationship between salt intake and BP has also been demonstrated (22,26–28) perhaps most compellingly by 2 well-controlled trials where participants were assigned different levels of salt intake: 11.2, 6.4, and 2.9 g/day in one (27); and 8, 6, 4 g/day in the other (28). Both trials demonstrated that BP changes with salt intake, so that the lower the salt intake, the lower the BP. This effect occurred in a stepwise fashion, regardless of the order in which salt

CENTRAL ILLUSTRATION Salt and Health



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Biological pathways whereby excess salt intake leads to organ damage and chronic diseases. GBD = Global Burden of Disease; RAAS = renin-angiotensin-aldosterone system; TMAO = trimethylamine N-oxide.

intake was altered and the participants' diet (27,28). This concurs with epidemiological studies (6) and experiments in chimpanzees (29). These findings suggest that while reducing salt to the World Health Organization-recommended intake of 5 g/day will bring health gains, a further reduction to 3 g/day will be more beneficial. The U.K. National Institute for Health and Care Excellence has recommended 3 g/day as the long-term population salt intake target (30). In the United States, 4 g/day has been recommended for >50% of the population including blacks, individuals >50 years old, and those with hypertension, diabetes, or chronic kidney disease (CKD) (31).

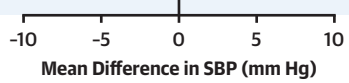
PHYSIOLOGICAL MECHANISMS. Multiple mechanisms relate dietary salt intake to BP, and many are yet to be elucidated (32). The primacy of the kidney-fluid volume system has been demonstrated, most notably in kidney cross-transplantation experiments (33,34).

Excess salt intake suppresses the RAAS, which in turn reduces sodium reabsorption and thereby facilitates its excretion (35). The RAAS relies on the kidney, whose function deteriorates with age. Sodium balance is then maintained by raising the fractional excretion of sodium, which is done by increasing plasma atrial natriuretic peptide and raising BP (36). As the kidney's functional deterioration and structural changes progress, the RAAS is increasingly impaired, leading to sodium and water retention (37) and increased vasculature resistance (38). As a result, smaller increases in salt intake induce greater rises in BP.

Plasma sodium also plays an important role in influencing BP through extracellular fluid volume. Changes in salt intake cause parallel changes in plasma sodium in both individuals who are normotensive and those who are hypertensive (39,40). A rise in plasma sodium is immediately buffered by the increased osmolality in the extracellular space, which moves fluid from the intracellular to the extracellular compartment. The small increase in plasma sodium also stimulates the thirst center, leading to water intake and secretion of arginine vasopressin, resulting in water retention (41). These mechanisms restore plasma sodium to its previous level, but also increase

FIGURE 1 Effects of Salt Reduction on BP

Study	No. of Studies	No. of Participants	Mean Difference	95% CI
Both Normotensives and Hypertensives				
Grobbee, 1986 (12)	13	584	-3.6	[-5.56; -1.64]
Hooper (at 6 to 12 months), 2002 (13)	7	NR	-2.5	[-5.00; 0.00]
Hooper (at 13 to 60 months), 2002 (13)	4	NR	-1.1	[-1.80; -0.40]
Hooper (at >60 months), 2002 (13)	1	NR	-3.8	[-7.90; 0.30]
Geleijnse, 2003 (14)	40	NR	-2.54	[-3.16; -1.92]
Normotensives				
Midgley, 1996 (15)	28	2035	-1.6	[-2.41; -0.79]
Cutler, 1997 (16)	12	NR	-1.9	[-2.62; -1.18]
Graudal, 1998 (17)	56	2581	-1.2	[-1.80; -0.60]
He, 2002 (18)	17	734	-2.03	[-2.56; -1.50]
Jürgens (W), 2004 (19)	57	NR	-1.27	[-1.76; -0.78]
Graudal (A), 2011 (20)	3	393	-1.27	[-3.07; 0.53]
Graudal (B), 2011 (20)	7	506	-4.02	[-7.37; -0.67]
Graudal (W), 2011 (20)	71	7299	-1.27	[-1.88; -0.66]
Aburto, 2013 (21)	7	3067	-1.38	[-2.74; -0.02]
He, 2013 (22)	12	2240	-2.42	[-3.55; -1.29]
Graudal (W), 2017 (23)	89	8569	-1.09	[-1.62; -0.56]
Graudal (B), 2017 (23)	7	506	-4.02	[-7.36; -0.68]
Graudal (A), 2017 (23)	3	393	-0.72	[-3.85; 2.41]
Hypertensives				
Midgley, 1996 (15)	28	966	-5.9	[-7.77; -4.03]
Cutler, 1997 (16)	22	NR	-4.83	[-5.87; -3.79]
Graudal, 1998 (17)	58	2161	-3.9	[-4.80; -3.00]
He, 2002 (18)	11	2220	-4.96	[-5.75; -4.17]
Jürgens (W), 2004 (19)	58	NR	-4.18	[-5.08; -3.28]
Graudal (A), 2011 (20)	9	674	-6.44	[-8.85; -4.03]
Graudal (B), 2011 (20)	8	477	-10.21	[-16.98; -3.44]
Graudal (W), 2011 (20)	76	4903	-5.48	[-6.53; -4.43]
He, 2013 (22)	22	990	-5.39	[-6.62; -4.16]
Aburto, 2013 (21)	24	2273	-4.06	[-5.16; -2.96]
Graudal (W), 2017 (23)	84	5925	-5.51	[-6.45; -4.57]
Graudal (B), 2017 (23)	8	619	-6.64	[-9.00; -4.28]
Graudal (A), 2017 (23)	9	501	-7.75	[-11.43; -4.07]



Forest plot of the results from published meta-analyses of randomized trials on the effect of salt reduction on systolic blood pressure (SBP) in adults. A = Asians; B = blacks; CI = confidence interval; NR = not reported; W = whites.

extracellular fluid volume, which stimulates other compensatory mechanisms involved in the autoregulatory effect on resistance vessels, as first suggested by Coleman and Guyton (42) and Manning et al. (43). Plasma sodium may also affect BP directly, that is, independently of and additively to its effect on extracellular volume (40,44). Small changes in plasma sodium affects the hypothalamus (45), the local renin-angiotensin system (40,46), the heart and vasculature (47), inflammatory mechanisms (48), and the immune response (48), all of which influence BP.

SALT REDUCTION AND ANTIHYPERTENSIVE THERAPY. Salt reduction is additive to other nonpharmacological and pharmacological interventions in lowering BP. The DASH (Dietary Approaches to Stop Hypertension)-Sodium trial demonstrates that a combination of lower salt intake and the DASH diet (rich in fruits, vegetables, and low-fat dairy products)

has a greater effect on lowering BP. Compared with the participants on the control diet (i.e., the usual American diet), those assigned to the DASH diet had significantly lower BP at any given salt intake level (i.e., at 8, 6, or 4 g/day), so that the greatest reductions in BP were achieved when combining the DASH diet to a low salt intake (28). In the TONE (Trial of Nonpharmacologic Interventions in the Elderly) (49), salt reduction combined with weight loss was more effective than either intervention alone in maintaining BP control after withdrawal of antihypertensive therapy in individuals who are older, obese, and hypertensive. Similarly, the TOHP II (Trial of Hypertension Prevention) (50) showed that combining salt and weight reduction had a greater effect on reducing hypertension incidence in people who are overweight with high-normal BP. However, this effect was seen only during the first 6 months and was not sustained over the following 30 months, as participants failed to maintain their lower salt intake and body weight (50).

RAAS blockers increase the effectiveness of salt reduction in lowering BP because BP falls would be offset by the reactive increases in plasma renin activity and angiotensin II when salt intake is reduced. A randomized double-blind trial in individuals who are hypertensive on captopril showed that reducing salt intake by 5.8 g/day over a month resulted in further lowering BP by 13/9 mm Hg (**Figure 2**) (51). These BP reductions were greater than those obtained in individuals with untreated hypertension in other similar salt-reduction trials (27,52). Due to their low plasma renin activity, black patients who are hypertensive are usually considered poor responders to RAAS blockers and better responders to diuretics. However, the opposite was found in a randomized crossover trial, where black patients who are hypertensive on a lower-salt diet exhibited a better BP response to an angiotensin-converting enzyme inhibitor than to a diuretic (53). This suggests that salt reduction may restore BP response to RAAS blockers, even in black individuals who are hypertensive. The TONE study demonstrated that, over a 28-month follow-up after antihypertensive medication withdrawal in elderly individuals who are hypertensive, a 2.4 g/day reduction in salt intake resulted in a significant decrease in the occurrence of high BP, medication resumption, and CVD events by 32% (54).

High salt intake contributes to the development of resistant hypertension. In a randomized crossover trial of 12 patients with resistant hypertension (average BP of 146/84 mm Hg while taking 3 or more antihypertensive drugs), reducing salt intake from 14.8 to 2.7 g/day for a week produced a 23/9 mm Hg decrease in their office BP and similarly large falls in 24-h ambulatory, day-time, and night-time BP (55). In dialysis patients, resistant hypertension is highly prevalent and its treatment includes lowering both dietary salt intake and dialysate sodium concentration (56).

RELATIONSHIP BETWEEN SALT INTAKE AND CVD

Raised BP is a major cause of CVD. Reducing salt intake lowers BP, and thus reduces CVD risk. There is also evidence from animal experiments and epidemiological studies that salt reduction has a direct effect, independent of, and additive to its effect on BP, for example, a direct effect on reducing the risk of stroke, improving left ventricular function, or potentiating regression of left ventricular hypertrophy (5). Therefore, the total effect of salt reduction on CVD would be larger than that predicted from BP falls alone. In this section, we review the evidence on salt and CVD and discuss recent controversial findings from cohort studies.

COHORT STUDIES AND NATURAL EXPERIMENTS. Over 30 cohort studies have reported the relationship between salt intake and the risk of CVD and/or mortality, and meta-analyses pooling their results show a direct linear association between them (21,57,58). However, a few recent cohort and ecological studies from the same research group have stirred controversy and confusion, as the investigators reported J- or U-shaped associations, that is, both low and high salt intakes being associated with an increased risk (59,60). This prompted a working group from several health organizations, including the World Heart Federation, to suggest salt reduction should be confined to countries where salt intake exceeds 12.5 g/day (61), which essentially puts into question salt-reduction efforts for the vast majority of the world. These J- or U-shaped findings should not have been used to challenge the current public health policies due to their severe methodological limitations (62–64).

A major limitation is the inclusion of participants with CVD or at high risk of CVD. Sick individuals eat less food and thus less salt, or they had been advised to reduce salt intake due to their illness. This leads to reverse causality, meaning that the association seen between a lower salt intake and higher CVD risk is explained by these individuals' underlying diseases rather than their salt intake.

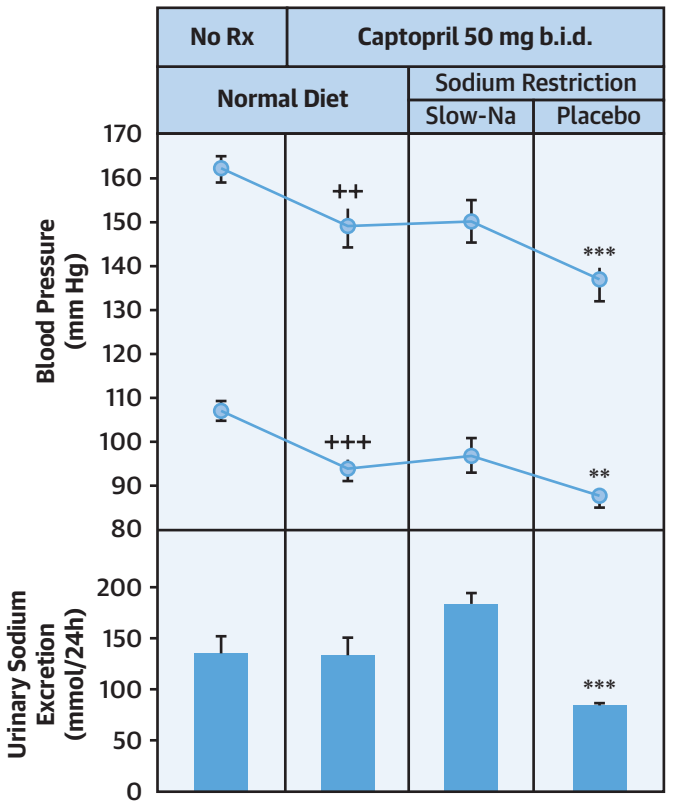
Another major limitation is the use of biased methods to assess individuals' usual salt intake, such as single spot urine samples. This is problematic in

several ways. First, spot urinary sodium concentration varies depending on fluid consumption, time of the day, duration and volume of collection, participant's posture, the time and amount of salt consumed in the last meal, as well as neural hormonal systems associated with cardiovascular outcomes (e.g., RAAS). It is therefore possible that spot urinary sodium concentration reflects cardiovascular risk related to the control mechanisms for sodium excretion. Second, various formulas have been used to estimate salt intake from spot urine. All the formulas are based on age, sex, height, weight, and urinary creatinine concentration. Most of these parameters are associated with both salt intake and health outcomes and therefore could confound the relationship between them (65). Third, a single measurement is not sufficient to reflect an individual's usual salt intake even if using the most accurate method of 24-h urine collection, because there are large day-to-day variations in salt consumption as well as salt excretion (66,67). Multiple nonconsecutive 24-h urine collections are necessary when investigating the association with health outcomes (64). It has been shown that the use of multiyear 24-h urine collections versus a single baseline 24-h urine increases CVD and renal risk by up to 85% (68).

Recent analyses, using TOHP follow-up data, provided insights into how the shape of the relationship between salt intake and health outcomes can be distorted by the use of unreliable intake assessment methods. When measured with multiple nonconsecutive 24-h urinary sodium excretions, the relationship between salt intake and CVD events (69) and all-cause mortality was direct and linear, down to a level of 3 g/day (65) (**Figure 3**). However, when estimating salt intake by applying the formulas developed for spot urine samples on sodium concentrations, the relationship appeared J- or U-shaped (65,70). Using the average of multiple collections versus single baseline samples also made a difference, as using the single estimated salt intake flattened the relationship, likely due to imprecise measurements leading to regression dilution bias. Importantly, when keeping sodium concentration constant in the formulas, the estimated salt intake appeared to be inversely related to mortality at intakes below 10 g/day (65), suggesting that the formulas per se, at least partially, explain the increased mortality risk seen with lower salt intakes in some cohort studies.

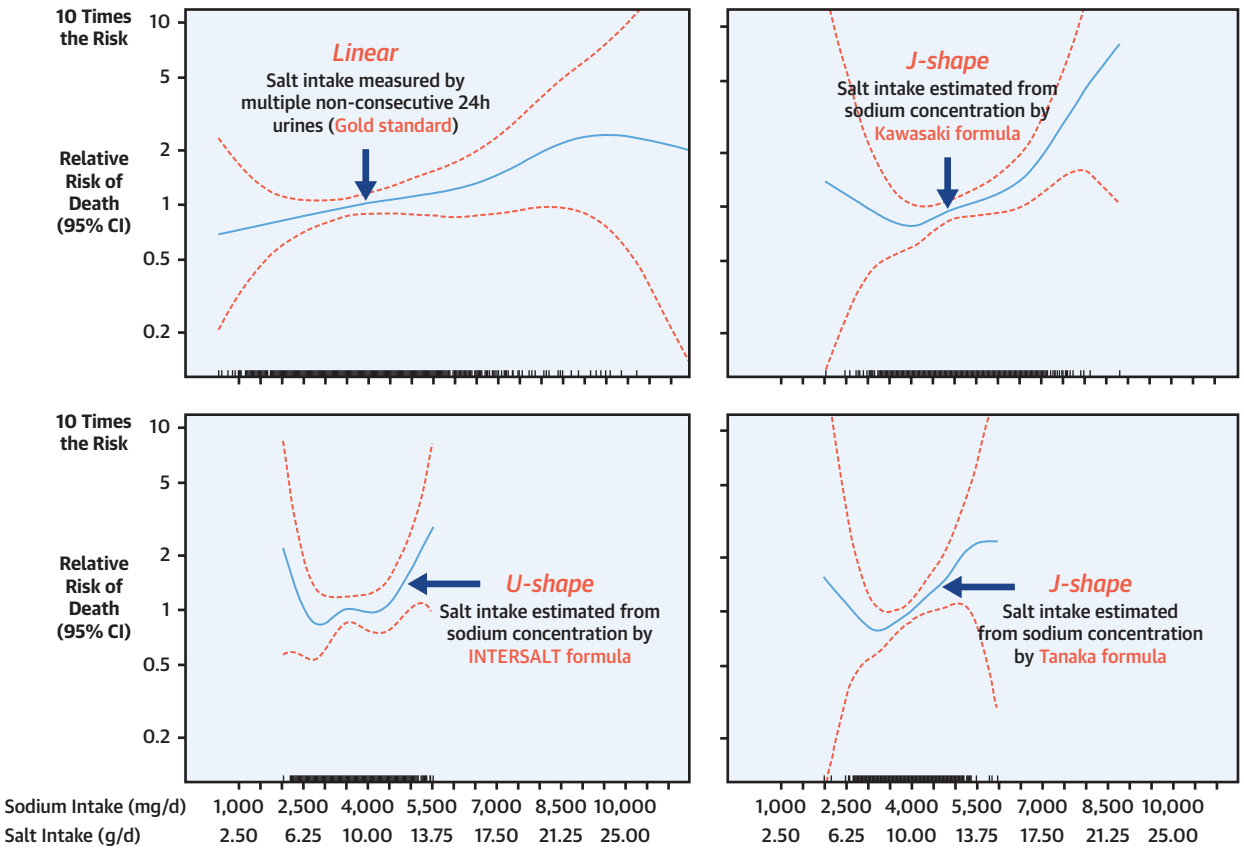
Further evidence on the public health benefits of reducing salt intake comes from natural experiments, for example, those in Finland and the United Kingdom. In Finland in the late 1970s, a salt-reduction program combining salt-awareness campaigns, collaboration with food industry, and adoption of salt-labelling legislation, resulted in a salt reduction from ≈14 g/day in 1972 to ≈9 g/day in 2002 (10), leading to a 10-mm Hg decrease in both systolic and diastolic BP and a 75% to 80% reduction in CVD mortality (10), despite increases in obesity and alcohol consumption during that time. The United Kingdom's salt-reduction program, by setting voluntary, incrementally lower salt-reduction targets for >85 food categories, led to a 15% reduction in salt intake (as measured by 24-h urinary sodium), that is, from 9.5 g/day in 2003 to 8.1 g/day in 2011 (9). This caused a 2.7-mm Hg fall in population systolic BP and a significant reduction in mortality from stroke and ischemic heart disease (**Figure 4**) (9).

FIGURE 2 Salt and BP in Individuals Who Are Hypertensive and Receiving Captopril



Average 24-h urinary sodium and blood pressure (BP) in individuals who are hypertensive after 1 month's observation without any treatment (No Rx), after 1 month's treatment with captopril, and at the end of each month of randomized double-blind crossover trial of slow sodium versus placebo while on a reduced salt intake. **$p < 0.01$, ***$p < 0.001$, comparing measurements on slow sodium with placebo. $^{++}p < 0.01$, $^{+++}P < 0.001$, comparing no treatment with captopril. Adapted from MacGregor et al. (51). b.i.d. = twice daily.

FIGURE 3 Salt and Mortality



Relationship between average estimates of 24-h urinary sodium excretion and all-cause mortality in the TOHP (Trials of the Hypertension Prevention) (N = 2,974), adjusted for age, sex, race/ethnicity, clinic, treatment assignment, education status, baseline weight, alcohol use, smoking, exercise, and family history of cardiovascular disease. Rug plot indicates distribution of sodium excretion, adapted from He et al. (65). CI = confidence interval; INTERSALT = International Study of Sodium, Potassium, and Blood Pressure.

OUTCOME TRIALS. Long-term randomized trials on the effect of salt reduction on CVD are extremely scarce because they are difficult to carry out, owing to ethical concerns over subjecting participants to high salt intakes as well as to multiple methodological challenges, such as compliance with lower salt intake over many years in food environments where highly salted processed foods are widespread, cross-contamination between study groups, and the large sample size that would be required to achieve sufficient statistical power.

Nevertheless, in 6 publications from the same research group, based on similar randomized trials in patients with severe heart failure, it was reported that not only did salt reduction have no benefits, but also, it could increase mortality or rehospitalization (71). However, the patients were receiving multiple treatments (including aggressive diuretic treatments, combined with angiotensin-converting enzyme inhibitors), were on the verge of salt and water depletion, and their diuretic doses were not adjusted on randomization to different salt intakes. It is therefore not surprising that a lower salt intake worsened clinical outcomes. Several other issues were also identified in the publications, culminating in the retraction of the meta-analysis of these studies, along with some of the individual trials, after investigation by the BMJ Publishing Ethics Committee (71). In patients with heart failure, despite a paucity of high-quality studies (72), it is evident that a high salt intake causes salt and water retention, thus exacerbating the symptoms and progression of the disease. A lower salt intake plays an important role in the management of heart failure (73).

Setting aside the problematic trials, the only interventional evidence we are left with on CVD is the long-term follow-up of participants who previously took part in salt-reduction trials (74,75). Pooling their results showed that salt reduction has a significant beneficial effect, with a 2.5 g/day reduction being associated with a 20% reduction in CVD events (**Figure 5**) (54,74,76–80). These findings provide further evidence in favor of salt reduction as a preventive public health measure against CVD.

OTHER HARMFUL EFFECTS OF SALT ON HEALTH

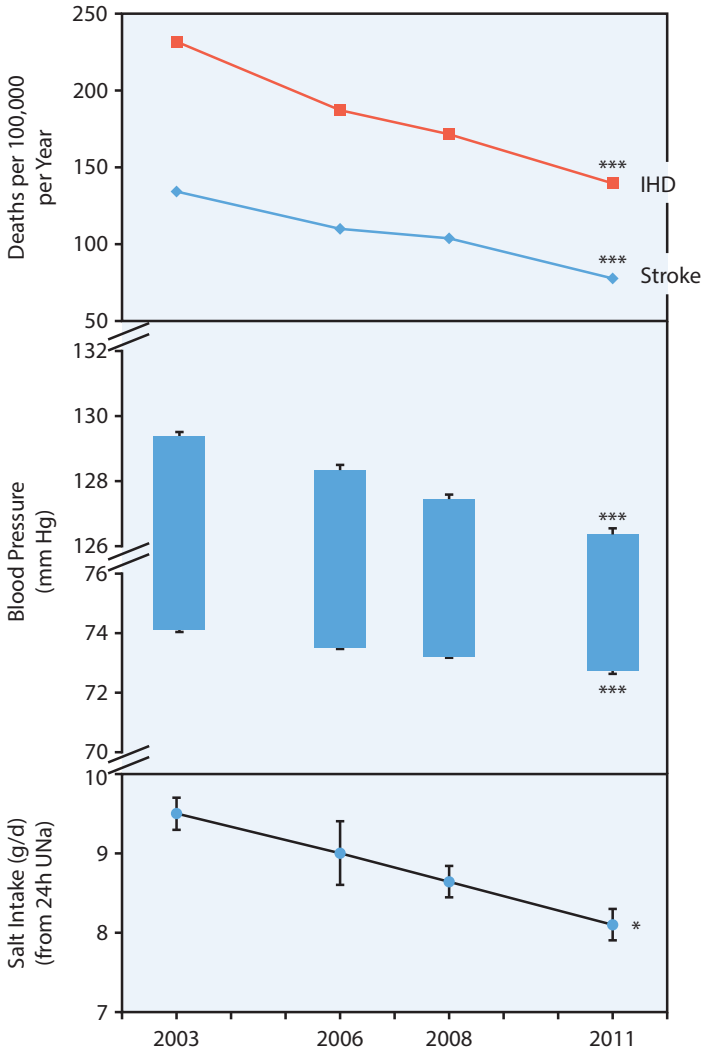
There is clear evidence that a high salt intake is associated with many other health conditions including kidney disease, renal stones, osteoporosis, stomach cancer, and obesity (5). There is also emerging evidence for an association with dementia (81).

KIDNEY DISEASE. Many risk factors for CKD progression have been linked to salt intake, such as BP, proteinuria, oxidative stress, and endothelial dysfunction (82). The relationship between salt intake and urinary albumin excretion is direct and dose-dependent (83). Randomized trials demonstrated that modest reductions in salt intake significantly reduced 24-h urinary albumin and protein excretion in individuals with hypertension (84,85), diabetes (86), and CKD (87). The antiproteinuric effects of angiotensin-converting enzyme inhibitor or angiotensin receptor blocker were attenuated or abolished when salt intake was increased in patients with proteinuria or diabetes (88,89). There are also studies showing that a lower salt intake could slow down CKD progression (90).

STOMACH CANCER. Stomach cancer has been linked to salt intake (91) and the consumption of highly salted foods (92). Salt intake is closely associated with *Helicobacter pylori* infection, a risk factor for stomach cancer (93,94).

RENAL STONES AND OSTEOPOROSIS. A high salt intake increases the risk of renal stones by increasing urinary calcium excretion, as calcium is the major component of most urinary stones (95). An increase in salt intake leads to a negative calcium balance, which stimulates compensatory mechanisms to increase intestinal calcium absorption and, at the same time, also mobilize calcium from the bone. Cohort studies have shown that the loss of hip bone density in postmenopausal women was related to baseline salt intake and this association was as strong as that related to calcium intake (96).

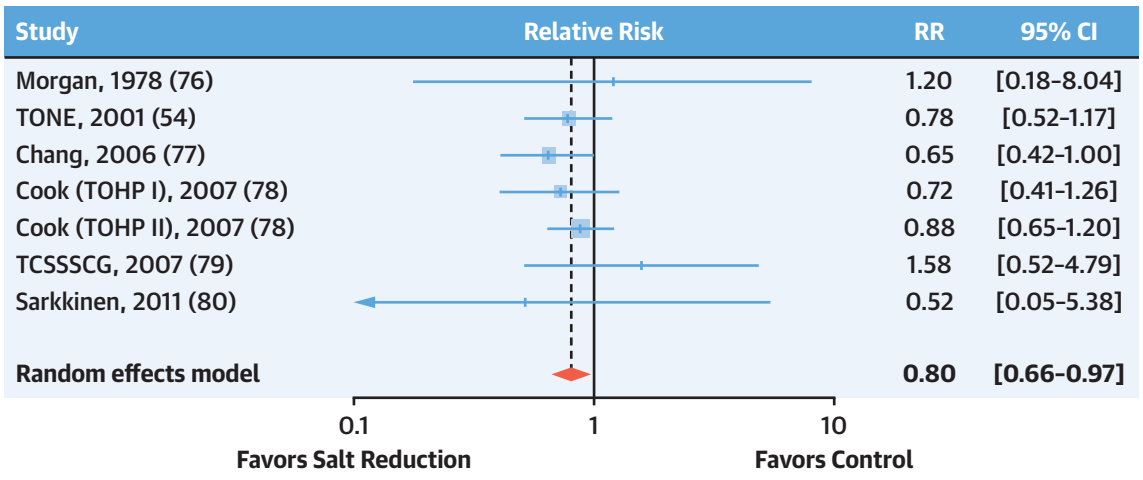
FIGURE 4 Salt, BP, and CVD in England 2003 to 2011



Changes in salt intake as measured by 24-h urinary sodium (UNa) excretion, blood pressure (BP), stroke, and ischemic heart disease (IHD) mortality in England from 2003 to 2011. *$p < 0.05$, ***$p < 0.001$ for trend. CVD = cardiovascular disease.

OVERWEIGHT AND OBESITY. High salt intake is associated with an increased risk of overweight and obesity through increasing sugar-sweetened beverage consumption (97,98). There is also evidence suggesting a direct link between salt intake and overweight and/or obesity, independent of total calorie or sugar-sweetened beverage consumption (99). Animal experiments indicated that salt intake may have a direct effect on body fat metabolism (100). Innovative work on long-term sodium homeostasis suggests

FIGURE 5 Salt and CVD



Forest plot of trials on the effect of salt reduction on cardiovascular disease. RR = relative risk; TCSSSCG = The China Salt Substitute Study Collaborative Group; TONE = Trial of Nonpharmacologic Interventions in the Elderly; other abbreviations as in Figures 3 and 4.

energy-intense mechanisms whereby high salt intake could lead to muscle mass catabolism, which would only be preventable by increasing food (and thus calorie) intake (101,102).

BRAIN DISEASES AND DISORDERS. A few studies in both animals and humans have suggested a link between high salt intake and cognitive impairment and Alzheimer disease, either through the effect of salt on BP, or through some BP-independent mechanisms (81,103–105). It has also been reported in randomized trials that lowering dietary salt intake reduced the risk of headache (106,107).

MECHANISMS FOR THE HARMFUL EFFECTS OF SALT ON CARDIOVASCULAR AND OTHER ORGANS

Salt damages target organs mainly via raised BP, but also via hormonal and inflammatory mechanisms, as well as more novel pathways, such as the immune response and the gut microbiome. All pathways are interconnected, but are discussed here separately for clarity.

DAMAGE VIA RAISED BP. The pressure load that comes with raised BP causes damage to multiple organs and tissues. In the vasculature, this leads to endothelial dysfunction, generalized atherosclerosis, arteriosclerotic stenosis, as well as to the remodeling of small and large arteries and aortic aneurysm. In the heart, this leads to left ventricular hypertrophy, atrial fibrillation, coronary microangiopathy, coronary heart disease, and heart failure. In the brain, raised BP increases the risk of acute hypertensive encephalopathy, stroke, intracerebral hemorrhage, lacunar infarction, focal or diffuse white matter lesions, and vascular dementia. In the kidney, it leads to albuminuria, proteinuria, reduced glomerular filtration rate, chronic renal insufficiency, and renal failure (108,109).

DAMAGE VIA THE HORMONAL SYSTEM. High aldosterone levels could mediate the effect of salt on left ventricular hypertrophy. Studies have shown an association between left ventricular hypertrophy and urinary excretion of sodium and aldosterone, as well as plasma aldosterone, in patients with hypertension or primary aldosteronism and in the general population (110–114). The hypothesis of an interplay between salt and aldosterone is supported by robust evidence from animal studies (115,116). Aldosterone affects the redox potential of different cell types, and exposure to high concentrations of salt amplifies this effect (117). Changes in the intracellular redox state leads to the activation of mineralocorticoid receptors, on which the salt-aldosterone interplay may depend (118). Ultimately, this results in an increased production of reactive oxygen species that causes cellular and tissue injury (119).

DAMAGE VIA INFLAMMATION AND OXIDATIVE STRESS. The role of inflammatory mechanisms in mediating the damage of salt on the kidney (120,121) and the endothelium (122,123) is increasingly

recognized. In patients with CKD who are not diabetic, a high salt intake may promote a proinflammatory and profibrotic state (124,125). In animal studies, a high salt intake decreased nitric oxide production (126) and salt loading was found to increase the production of oxygen-free radicals, enhance the expression of pro-oxidant enzymes (127), and cause renal hemodynamic changes while only minimally increasing BP (120,128,129). In humans, a high salt intake is associated with albuminuria while salt restriction reduces it, and this was shown to occur independently of BP (83,84,130–132).

Salt may also damage the endothelium through oxidative stress, as the administration of antioxidants has been shown to reverse that damage (122,133). Salt could suppress the activity of the superoxide dismutase, an enzyme that scavenges the superoxide radicals (123). In living endothelial cells incubated in vitro, salt increased their stiffness and reduced the release of nitric oxide (134,135). In healthy adults, a high salt intake impaired flow-mediated dilation (136) and increased arterial stiffness (137), whereas salt reduction had the opposite effects (138). The suppressive effect of salt on endothelial function has been demonstrated to be independent of BP (133,139,140). Endothelial dysfunction, an important initial event in atherogenesis and impaired production of the vasodilator nitric oxide, results in endothelial injury and progression to CVD (141).

DAMAGE VIA THE IMMUNE RESPONSE. A high salt intake can undermine the course and balance of the immune response by promoting the development of macrophage and T cells with proinflammatory functions (142,143). It induces pathogenic interleukin 17, which produces CD4+ T-helper 17 cells (142,144), which in turn contribute to the development of autoimmune disease (145) and inflammatory renal diseases (142,145,146), such as glomerulonephritis. Interleukin 17 also acts on smooth muscle cells and adventitial fibroblasts, thereby decreasing bioavailable nitric oxide, impairing vasodilation, and increasing vascular stiffness, resulting in endothelial dysfunction and elevations in systematic vascular resistance (48).

Salt damages bones by increasing urinary calcium excretion (due to their linked reabsorptive pathways) (147,148), thus increasing parathyroid hormone secretion, which in turn increases bone remodeling (147). Bone loss can also be regarded as an inflammatory condition, as T-helper cells 17 (induced by salt) are associated with inflammatory bone loss through their production of proinflammatory cytokines (149), whereas regulatory T cells (impaired by salt) are associated with bone protective functions through their production of anti-inflammatory factors (150).

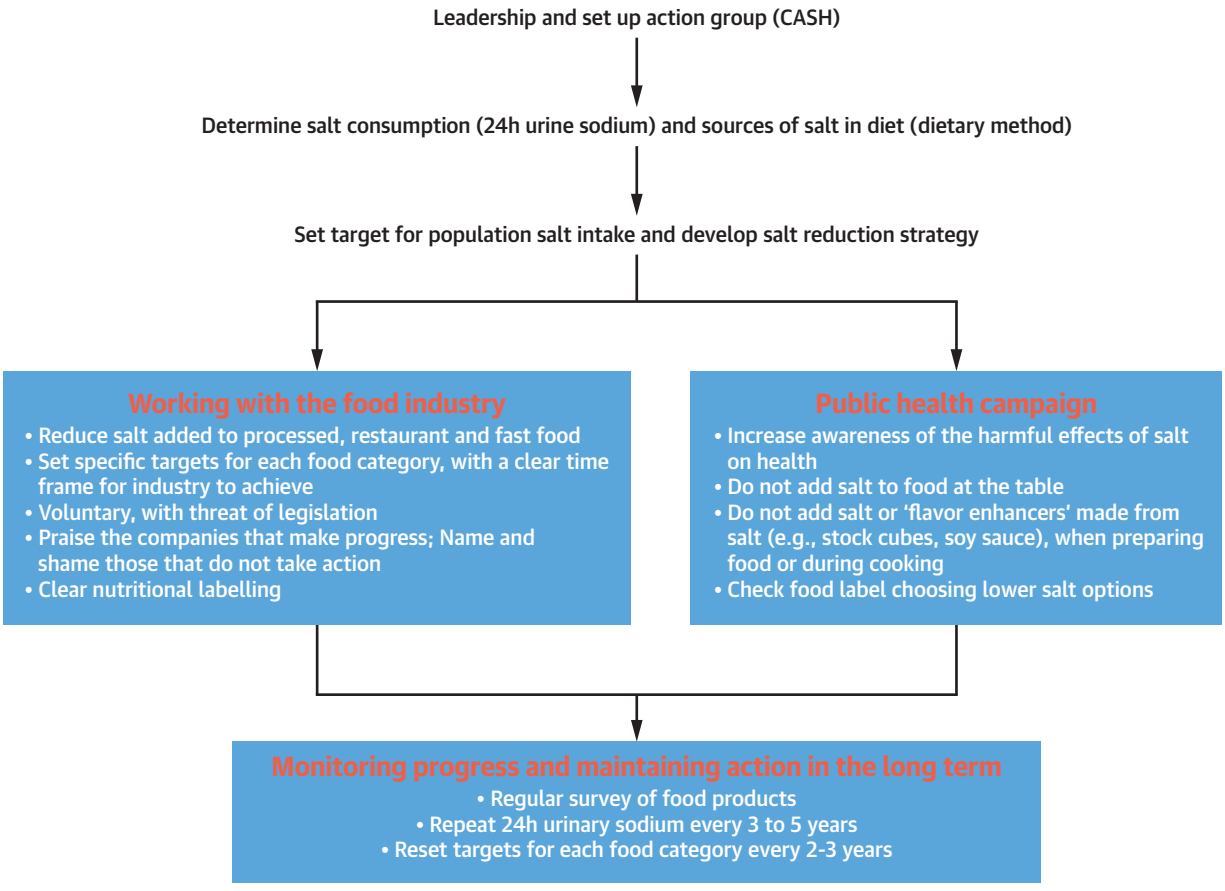
DAMAGE VIA THE GUT MICROBIOME. The gut microbiome has been recently proposed as a key moderator of the effect of salt on intermediate mechanisms (e.g., inflammation) and health outcomes (81,151). This hypothesis concurs with the traditional use of salt as an antiseptic and food preserver to inhibit bacterial proliferation (152). Indeed, it has been reported that a high salt intake changed gut bacteria composition and increased T-helper 17 cells and BP in both animals and humans (151,153). In animal studies, a high salt intake increased plasma trimethylamine N-oxide (154), a putative microbiome-dependent promoter for CVD (155). Metabolomics profiling has identified increasing number of microbiota-dependent metabolites associated with salt intake (156–161), although most of the evidence is limited to animal studies or small-scale human experiments of short-term changes in salt intake.

Animal studies have shown that feeding rodents with a high-salt diet over the long term may impair cognitive function, especially in domains related to spatial memory, possibly through oxidative stress and gut microbiome-dependent inflammation (81,103,104,162). The mediation role of gut microbiome in the relationship between high salt intake and chronic diseases such as Alzheimer's disease, dementia, and CVD warrants further investigation.

COST-EFFECTIVENESS OF POPULATION SALT REDUCTION

Numerous cost-effectiveness analyses from both high-income countries (HICs) and low- and middle-income countries (LMICs) have shown that population-wide salt reduction is highly cost-effective and cost-saving in reducing CVD and premature deaths (30,163–166). The United Kingdom's salt-reduction program has prevented ≈9,000 CVD deaths per year and saved the health care service ≈£1.5 billion per annum (30). In the United States, a 3-g/day reduction in salt intake could prevent ≈146,000 new CVD cases and >40,000 deaths per year. The health impact of achieving this reduction would be on par with that from reductions in tobacco use or obesity, saving 194,000 to 392,000 quality-adjusted life-years and $10 to $24 billion in health care costs annually (163). Similarly, in LMICs, salt reduction is estimated to be more, or at least as, cost-effective as tobacco control in preventing CVD (164).

FIGURE 6 U.K. Salt Reduction Model



An action framework of reducing salt intake in the population in the United Kingdom. CASH = Consensus Action on Salt and Health.

GLOBAL ACTION TO REDUCE POPULATION SALT INTAKE

In HICs, ≈80% of the salt in the diet is from processed, restaurant, and fast foods (167). The strategy must be centered on persuading all food manufacturers and retailers to reduce the amount of salt they add to their products, in a gradual and sustained manner. This can be done by setting food categories-specific salt targets to be incrementally lowered with a clear time frame for the industry to achieve, combined with an independent and transparent monitoring program (**Figure 6**). This model was pioneered by the United Kingdom. By getting all companies to work toward the same targets, the United Kingdom has achieved a 20% to 50% reduction in the salt content of many food products over a decade (168,169), leading to concurrent falls in population salt intake, BP, and CVD mortality (9). Whereas many countries such as Canada, Australia, and the United States, have followed the U.K. model of setting voluntary salt targets (170,171), South Africa and several other countries went a step further by setting mandatory salt targets (172), which is a far more effective approach.

In most LMICs, salt reduction is lagging despite very high salt intake levels (173) and these countries bearing >80% of the global salt-related disease burden (174). In these settings, most of the salt comes from that added by the consumer during cooking or in sauces (175). Therefore, salt-awareness education is needed to encourage individuals to reduce the amount of salt they use for food preparations at home. Behavior change is extremely difficult, but new promising approaches are under development (77,176,177). A study in northern China suggested that children could play a key role in helping the whole family to reduce salt intake (176). Another promising

strategy is to replace regular salt with salt substitutes, which are made with less sodium and more potassium, and have been shown to reduce BP and CVD mortality (77).

CONCLUSIONS

Population salt reduction is among the most cost-effective, feasible, and affordable strategies to prevent CVD, the leading cause of death and disability worldwide. Salt reduction is crucial and should not be diverted by controversial and methodologically flawed studies. Future research should instead focus on how to best achieve population salt reduction, looking at improving food supply in HICs, and for innovative, scalable, and sustainable strategies in LMICs. By implementing multifaceted programs, several HICs have successfully reduced their populations' salt intake, whereas major challenges remain to achieve the World Health Organization's target in all countries. Various salt-reduction initiatives have started in >70 countries (comprising consumer education, reformulation, target setting, labelling improvement, taxation of highly salted foods). However, progress has been slow, mainly due to the food industry's fierce opposition. Achieving and sustaining salt reduction, even by a modest amount, will have enormous benefits worldwide; meeting the World Health Organization's recommended level could prevent ≈1.65 million CVD-related deaths each year, with major cost-savings for individuals, their families, and health services.

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