The Science of Salt: A Systematic Review of Clinical Salt Studies 2013 to 2014

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The authors provided a systematic review of the clinical and population health impact of increased dietary salt intake during 1 year. Randomized controlled trials or cohort studies or meta-analyses on the effect of sodium intake were examined from Medline searches between June 2013 to May 2014. Quality indicators were used to select studies that were relevant to clinical and public health. A total of 213 studies were reviewed, of which 11 (n=186,357) were eligible. These studies confirmed a causal relationship between increasing dietary salt and increased blood pressure and an association between several adverse health outcomes and increased dietary salt. A new association between salt intake and renal cell cancer was published. No study that met inclusion criteria found harm from lowering dietary salt. The findings of this systematic review are consistent with previous data relating increased dietary salt to increased blood pressure and adverse health outcomes. *J Clin Hypertens (Greenwich)*. 2015;17:401–411. © 2015 Wiley Periodicals, Inc.

In 2010, increased blood pressure (BP) caused an estimated 18% of all global deaths and 7% of global disability-adjusted life years lost. Habitual excess salt consumption, in turn, is attributed to about one third of hypertension cases[1] and is a key determinant of increased BP.[2,3] Increased dietary salt also contributes to a range of other adverse health outcomes such as gastric cancer and osteoporosis.[4] In view of this and the cost-effectiveness of population strategies to reduce salt, the World Health Organization (WHO) has identified salt reduction as a high priority intervention.[5] A 30% reduction in mean population salt intake by 2025 has been included as one of the targets of the "25 by 25" United Nations/WHO initiative for the control of noncommunicable diseases.[5]

BACKGROUND

Despite the large body of research and evidence supporting salt reduction, several studies have been published in recent years that challenge the benefits of reducing dietary salt.[6,7] This has generated much media attention and has resulted in some health organizations, policy makers, and consumers to question recommended salt reduction targets. In response, international health and scientific organizations including the Pan American Health Organization/WHO Technical Advisory Group have requested regular scientific updates. While reviews of the science have been published, there were previously no ongoing processes to keep the science related to dietary salt up-to-date and accessible.

AIMS

The aim of this review is to update recent evidence on the impact of dietary salt on public health using the existing *Science of Salt* search methodology. The *Science of Salt* utilizes "quality" criteria to ensure that studies are relevant to clinical and population health and to ensure that low-quality or irrelevant research designs do not skew review findings.

METHODS

Search Strategy and Selection Criteria

This review used the existing automated search strategy (Table I) set up for the weekly *Science of Salt* eNewsletter publication. This undertakes weekly Medline via Ovid searches to identify studies on dietary sodium according to quality criteria. The criteria were adapted from the systematic reviews conducted to develop WHO dietary salt recommendations. Studies were included from searches conducted between June 2013 to May 2014.

Inclusion/Exclusion Criteria

For the purposes of this review, inclusion criteria were any randomized controlled trials (RCTs) or cohort studies in nonacutely ill adults that examined sodium intake (excluding studies with participants who had type II diabetes, chronic kidney disease, or chronic heart failure) and were published in English. Specifically, RCTs evaluating the association between sodium intake and BP, or any substantive adverse health outcome, were included if the following criteria were met: there was a minimum intervention period of 4 weeks; the

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TABLE I. Included Studies (N=11)

Author	Country	Outcome	Population	Intervention/Follow-Up	Measurement Method	Results	Comments
Surrogate markers (2 randomized controlled trials [RCTs], 1 systematic review, 2 cohort [total of 5 studies])							
Dickinson and colleagues[30]	Australia	Endothelial function, endothelin-1	25 overweight or obese normotensive participants	6 weeks of "low" sodium 6 g salt (sodium 2400 mg)/24 h and 6 weeks of "usual" sodium 9 g salt (sodium 3600 mg)/24 h. 12-week crossover	24-h urinary sodium excretion; flow-mediated dilatation (FMD)	Endothelin-1 decreased by 14% after 6 weeks ($P<.05$) and this was associated with 45% increase in FMD (from 3.5 to 5.6; $P<.001$)	No changes to blood pressure (BP) between RCC cases and subcohort members. FMD not a hard outcome
Jablonkski (2013)	United States	Systolic BP (SBP), urinary marinobufagenin (MBG), and arterial stiffness	11 participants with SBP within 130–159 mm Hg and diastolic BP (DBP) <99 mm Hg	5 weeks on a low-sodium diet with 4.4±0.5 g salt (sodium 1760±200 mg)/24 h and 5 weeks on a normal-sodium diet with 8.2±0.5 g salt (sodium 3280±200 mg)/24 h. 10-week intervention	24-h urinary sodium excretion; urine and plasma MBG excretion; aortic pulse wave velocity	urinary MBG excretion, SBP, DBP, and aortic pulse wave velocity were lower during the low- vs normal-sodium intake (25.4 vs 30.7 pmol/kg per day; 127 mm Hg vs 138 mm Hg and 77 mm Hg vs 81 mm Hg; and 700 cm/s vs 843 cm/s; $P<.05$)	
Aburto and colleagues[32]	Australia, Belgium, Finland, France, Germany, the Netherlands, Norway, New Zealand, Sweden, United Kingdom, United States, Japan, Scotland, Taiwan. One cohort study included participants from 40 countries.	Cholesterol: total, low- and high-density lipoprotein; triglycerides; urinary nor/adrenaline; plasma nor/adrenaline; urinary protein excretion protein:creatinine ratio; creatinine clearance; serum creatinine; glomerular filtration rate	5508 participants	Decreased sodium intake	Sodium intake was estimated to equal 24-h urinary sodium excretion	Reduced sodium intake had no significant adverse effect on total cholesterol, low- and high-density lipoprotein cholesterol, or triglyceride levels (mean difference 0.02 mmol/L, 0.03 mmol/L, −0.01 mmol/L, and 0.04 mmol/L, respectively). No effect of reduced sodium intake on urinary nor/adrenaline (mean difference −13.10 pg/mL and 17.13 pg/mL, respectively). No effect of reduced sodium on catecholamine levels (adrenaline 6.90 pg/mL, noradrenaline 8.23 pg/mL); nonsignificantly lower urinary protein excretion with reduced sodium intake (−76.61 μmol/L); lower urinary protein excretion with lower sodium intake; beneficial effect of lower sodium intake on renal function	
Larsen and colleagues[26]	Denmark	Body weight, waist circumference, body fat, and fat free mass (FFM)	215 participants	Changes in body weight, waist circumference, body fat, and FFM were calculated after 6 years of follow-up	24-h urinary sodium excretion	Increase in body fat of 0.24 kg ($P=.015$, confidence interval, 0.05–0.43) per 6 g of salt (sodium 2400 mg)/24 h; decrease in FFM of −0.21 kg ($P=.041$, confidence interval,	

TABLE I. Included Studies (N=11) (Continued)

Author	Country	Outcome	Population	Intervention/Follow-Up	Measurement Method	Results	Comments
						−0.40 to −0.001) per 6 g of salt (sodium 2400 mg)/24 h. No significant associations between 24-h urinary sodium and change in body weight or waist circumference	
Jain and colleagues[25]	United States	Total-body percentage fat (TBPF)	2782 participants	Association of urinary sodium-to-potassium ratio with obesity; multiethnic cohort Dallas Heart study: race classified into African American (49.8%), white (30.8%), and Hispanic (17.2%) and other (2.2%); 12% diabetes mellitus and 36% hypertension	Ratio of sodium-to-potassium intake estimated from spot urine; TBPF measured by dual-energy x-ray absorptiometry; fasting venous blood	TBFP was 32%±10%; urinary sodium to potassium was 4.2±2.6; TBPF increased by 0.75% (95% confidence interval, 0.25–1.25; *P*=.003) and 0.43%(95% confidence interval, 0.15–0.72; *P*=.003) in unadjusted and adjusted models, respectively, for every 3-unit increase in urinary sodium to potassium ratio	
Blood pressure (1 RCT, 2 COCHRANE, and 1 systematic review [total of 4 studies])							
Diaz and colleagues[33]	United States	Visit-to-visit (VVV) BP variability	1820 overweight participants with high-normal DBP	TOHP II: Education and counselling on (1) weight loss, (2) sodium reduction, (3) combined weight loss, and sodium reduction vs (4) usual care. 36-month follow-up	24-h urinary sodium excretion	VVV of SBP was not significantly different among the 3 intervention groups vs usual care (7.2, 7.1, 6.9, and 6.9 mm Hg respectively). Similarly, maintained sodium reduction throughout follow-up did not have an effect on VVV	The aim of the TOPH II trial was not to test VVV, rather the adherence to and effects of the sodium reduction intervention among overweight adults
He and colleagues[34]	Multinational	BP	3230 participants (34 RCTs)	Decreased sodium intake in participants with normal and elevated BP	24-h urinary sodium excretion	Elevated BP: sodium reduction 4.4 g of salt (sodium 1760 mg)/24 h and reduction of 5.39 mm Hg SBP and 2.82 mm Hg DBP. Normal BP: sodium reduction 4.4 g salt (sodium 1760 mg)/24 h and BP reduction of 2.42 mm Hg SBP and 1.00 mm Hg DBP	
Aburto and colleagues[32]	Australia, Belgium, Finland, France, Germany, the Netherlands, Norway, New Zealand, Sweden, United Kingdom, United States, Japan, Scotland, and Taiwan. One cohort study included participants from 40 countries	BP	5508 participants	Decreased sodium intake	Sodium intake was estimated to equal 24-h urinary sodium excretion	Sodium intake of <5 g of salt (sodium <2000 mg) vs >5 g of salt (sodium >2000 mg)/24 h reduced SBP by 3.39 mm Hg and DBP by 1.54 mm Hg	

TABLE I. Included Studies (N=11) (Continued)

Author	Country	Outcome	Population	Intervention/Follow-Up	Measurement Method	Results	Comments
Rees and colleagues[35]	Multinational	Cardiovascular disease risk	18,175 participants/clusters in 44 RCTs (11 on BP and sodium: 6406 participants)	Dietary advice vs no advice or minimal advice	24-h urinary sodium excretion	BP reduced by 2.61 mm Hg SBP and 1.45 mm Hg DBP. 24-h urinary sodium excretion reduced by 2.3 g salt (sodium 940 mg) after 3–36 months. Serum cholesterol reduced; mean high-density lipoprotein cholesterol and triglyceride unchanged	
Substantive patient outcomes (3 cohort and 1 systematic review [total of 4 studies])							
Deckers (2014)	The Netherlands	Renal cell cancer (RCC)	120,852 participants 55–69 years from The Netherlands Cohort Study (485 RCC cases included in case-cohort analysis)	Follow-up of 17.3 years	Food frequency questionnaire to assess sodium, potassium, and fluid intake; observed incidence of RCC cases	Sodium intake increased RCC risk (*P* trend=0.03). High-sodium and low-fluid intake increase RCC risk (*P* interaction=.02). Potassium intake and RCC risk was not associated	Exposure was only assessed at baseline. Food frequency questionnaire shows weak estimate of sodium intake
Cook and colleagues[27]	United States	Cardiovascular disease or cardiovascular disease death	2275 participants (30–54 years) from the Trials of Hypertension Prevention (TOHP) I and II who were not in sodium-reduction intervention arm	Follow-up of 10 years after end of TOHP I and 5 years after the end of TOHP II	24-h urinary sodium excretion; review of medical records on notification of primary end point	There was a 17% increase in risk of cardiovascular disease per 2.5 g of salt (sodium 1000 mg)/24 h (*P*<.054)	Residual confounding of other healthy lifestyle behaviors
He and colleagues[28]	United Kingdom	BP, stroke, and ischemic heart disease	31,672 participants from the Health Survey for England from 2003 to 2011	Follow-up of 9 years during the implementation of United Kingdom's National Salt Reduction Program	24-h urinary sodium excretion in a random sample of 1589 participants 19–64 years; review of national statistics on deaths from ischemic heart disease and cardiovascular disease	Stroke mortality decreased by 42% (*P*<.001); ischemic heart disease decreased by 40% (*P*<.001); BP decreased by 3.0±0.33/1.4±0.20 mm Hg (*P*<.001); salt intake decreased by 1.4 g of salt (sodium 560 mg)/24 h (*P*<.001)	Does not quantify salt reduction contribution to stroke, and ischemic heart disease mortality "likely to play and important role"
Aburto and colleagues[32]	Australia, Belgium, Finland, France, Germany, the Netherlands, Norway, New Zealand, Sweden, United Kingdom, United States, Japan, Scotland, Taiwan. One cohort study included participants from 40 countries	All-cause mortality; cardiovascular disease; stroke; coronary heart disease	5508 participants	Decreased sodium intake	Sodium intake was estimated to equal 24-h urinary sodium excretion	Sodium intake was associated with an increased risk of stroke, stroke mortality, and coronary heart disease mortality (risk ratio: 1.24, 1.63, and 1.32, respectively)	

intervention was composed of at least one group receiving decreased sodium intake compared with a control group; there was a difference of at least 2.3 g of salt (sodium 920 mg) per 24 hours between the intervention and the control; and sodium intake was measured by 24-hour urinary excretion. RCTs were excluded if additional cointerventions were part of the study (including nondrug interventions, antihypertensives, or other drugs), thus preventing the independent assessment of the effects of reducing dietary salt. Cohort studies evaluating the association between sodium intake and any substantive adverse health outcome were included if they were prospective in design for at least 1 year or more and measured sodium intake in any way. Substantive adverse health outcomes of interest were all-cause mortality, cardiovascular disease (CVD), stroke, coronary heart disease (CHD), kidney disease, bone disease, and cancer. Surrogate markers such as endothelium-dependent dilation, urinary marinobufagenin (MBG) excretion, aortic pulse wave velocity (aPWV), plasma and urinary nitrate/nitrite, osteoporosis, renal stones, weight gain and obesity, and heart rate were assessed.

Data Extraction and Quality Assessment

Two reviewers (CJ and TSR) independently evaluated and excluded articles at the title/abstract review stage. Full-text articles whose abstracts met the inclusion criteria were then reviewed. An Excel data extraction template was developed, tested, and then refined and populated articles that met the final inclusion criteria. For the RCTs, methodological quality was assessed using the Cochrane Risk of Bias Assessment Tool. Discrepancies in article inclusion, data extraction, and bias assessment were solved by team consensus.

RESULTS

A total of 5534 studies were identified, of which 213 were selected for full review (Figure). Of these, 202 were excluded for the following reasons: 181 studies were cross-sectional or other; five RCTs and two non-RCTs included unhealthy populations (two populations with heart failure,[8,9] two involving patients with kidney disease,[10,11] two involving hypertensive patients,[12,13] and one involving participants with type II diabetes[14]). Seven cohort studies did not investigate an outcome of interest: five measured BP[15–19] (one study measured environmental influences, such as sharing current residence, on sodium intake[20] and one study investigated sex differences in salt sensitivity[21]). Additionally, seven RCTs were excluded (three did not investigate either BP or an outcome of interest nor did they measure sodium intake using 24-hour urinary sodium excretion, three study interventions were for <4 weeks' duration,[22–24] and one study did not investigate BP or an outcome of interest).

The 11 studies included in the final review are summarized in Table II. They include two RCTs on measures of surrogate markers including urinary MBG excretion and aPWV, flow-mediated dilatation (FMD), pulse wave velocity (PWV), plasma and urinary nitrate/nitrite, asymmetric dimethylarginine (ADMA), renin, aldosterone, and endothelin-1 and vascular adhesion molecules; one RCT on BP; five cohort studies including two studies on measures of surrogate markers including obesity[25] and change in weight[26]; three studies on substantive patient outcomes including CVD and/or mortality,[27] stroke and ischemic heart disease (IHD) mortality,[28] and renal cell cancer (RCC)[29]; and one systematic review and two Cochrane reviews including studies on all-cause mortality, CVD, stroke, chronic heart failure, changes in blood lipids, catecholamine levels and renal function, BP, and CVD risk assessed as BP.

The included RCTs and cohort studies were conducted in the United States, Australia, the United Kingdom, Denmark, and the Netherlands and systematic reviews were multinational including Australia, Belgium, Finland, France, Germany, the Netherlands, Norway, New Zealand, Sweden, the United Kingdom, the United States, and Japan.

Surrogate Markers

Four studies assessed the relationship between salt intake and surrogate markers. In a 12-week single-blind randomized controlled crossover study undertaken in Australia, Dickinson and colleagues[30] recruited a sample of 25 overweight/obese participants to examine the effects of a reduction of 3 g of salt (sodium 1200 mg) per 24 hours from a usual 9 g of salt (sodium 3600 mg) per 24 hours on measures of vascular function and explored mechanisms of effect in overweight and obese adults. Participants were randomized to a 6-week diet with reduced 6 g of salt (sodium 2400 mg) per 24 hours and then crossed over to 6 weeks on their usual salt diet of 9 g salt (sodium 3600 mg) per 24 hours. FMD, 24-hour BP, augmentation index, PWV, plasma and urinary nitrate/nitrite, ADMA, renin, aldosterone, and endothelin-1 and vascular adhesion molecules were measured after 2 days and 6 weeks. Adherence to the diets was determined from two 24-hour urinary excretions for measurement of sodium, potassium, creatinine, and nitrate/nitrite. The study showed that a diet of 9 g of salt (sodium 3600 mg) per 24 hours impairs FMD and increases endothelin-1 and that these effects were reversed by salt reduction of approximately 3 g of salt (sodium 1200 mg) per 24 hours. Endothelin-1 decreased by 14% after 6 weeks, which was associated with a 45% increase in FMD. The renin-angiotensin-aldosterone system was not altered by this change in salt intake. The authors say this study demonstrates a reduction in dietary salt intake of 3 g of salt (sodium 1200 mg) per 24 hours improves endothelial function in normotensive overweight and obese patients. There were no statistically significant changes in BP between the diets, which were consistent with the hypothesis that salt reduction has beneficial effects on endothelial function independently of BP. Additionally, there was
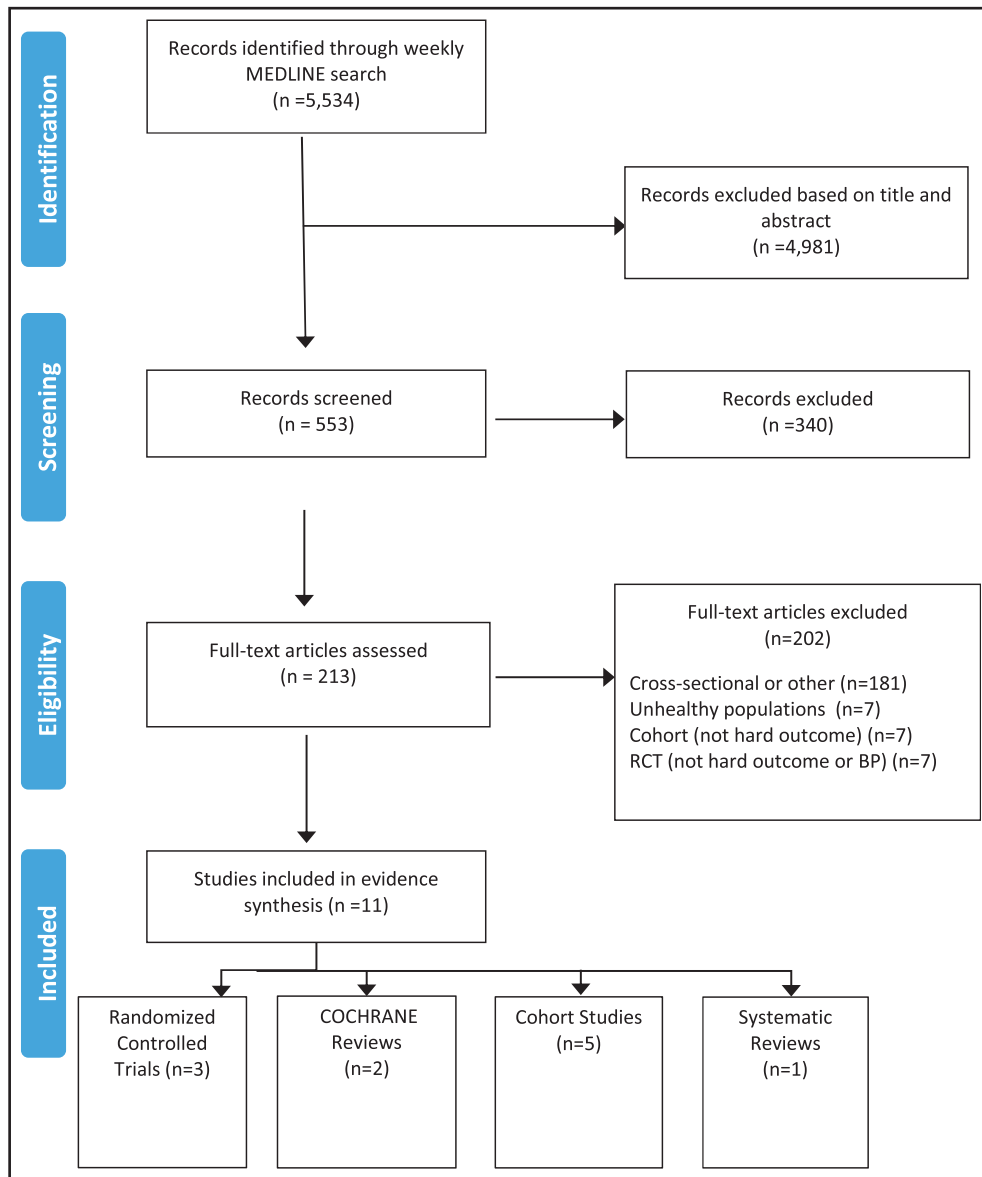
FIGURE. Included/excluded studies. RCT indicates randomized controlled trial.

no nonobese control group, and this affects the generalizability of the results.

Jablonski and colleagues[31] conducted a randomized placebo-controlled crossover study in the United States on a sample of 11 middle-aged/older adults to investigate whether dietary sodium restriction would reduce urinary MBG as well as systolic BP (SBP) and aPWV (the gold standard measure of large elastic artery stiffness), hypothesizing that production of the natriuretic hormone MBG is increased in salt-sensitive hypertension and contributes to the rise in SBP during sodium loading. Authors randomized participants to 5 weeks on a low-sodium diet with 4.4±0.5 g of salt (sodium 1760±200 mg) per 24 hours and 5 weeks on a normal-sodium diet with 8.2±0.5 g of salt (sodium 3280±200 mg) per 24 hours. Results showed that urinary MBG excretion (weekly measurements; 25.4±1.8 pmol/kg/d vs 30.7±2.1 pmol/kg/d), SBP (127±3 mm Hg vs 138±5 mm Hg), and aPWV (700±40 cm/s vs 843±36 cm/s) were lower during the low- vs normal-sodium condition ($P<.05$, for all). Additionally, urinary MBG excretion was associated with SBP and sodium excretion, as assessed from all urine collections, and this association was found to be stronger in the diet with 4.4±0.5 g of salt (sodium 1760 ± 200 mg) per 24 hours but not stronger in the higher-salt diet. The authors concluded that dietary sodium restriction reduces urinary MBG excretion and that MBG excretion is positively associated with SBP and aortic stiffness.

TABLE II. Weekly Medline (Ovid) Search Strategy Years: 1946 – Present

Step	Search
1	exp Sodium Glutamate
2	(monosodium glutamate or msg).tw.
3	(salt or sodium).tw.
4	1 or 2 or 3
5	exp Diet
6	(diet* or food or intake).tw.
7	5 or 6
8	4 and 7
9	exp Sodium, Dietary
10	exp Diet, Sodium-Restricted
11	8 or 9 or 10
12	limit 11 to English language
13	limit 12 to year="2013–Current"
14	limit 13 to humans

Weekly Medline (Ovid) Search Strategy on dietary sodium is a modified version of the search strategy developed by a Cochrane librarian to support the development of the Canadian Hypertension Education Program recommendations regarding dietary sodium.

In a systematic review of the effect of lower sodium intake on health, Aburto and colleagues[32] reviewed several estimates of effect of reduced sodium on surrogate markers such as total cholesterol, low- and high-density lipoprotein cholesterol, and triglyceride levels. The review showed that reduced sodium intake had no significant effect on total cholesterol (mean difference, 0.02 mmol/L; 95% confidence interval [CI], −0.03 mmol/L to 0.07 mmol/L), low-density lipoprotein cholesterol (0.03 mmol/L, −0.02 mmol/L to 0.08 mmol/L), high-density lipoprotein cholesterol (−0.01 mmol/L, −0.03 mmol/L to 0.00 mmol/L), or triglyceride levels (0.04 mmol/L, −0.04 mmol/L to 0.09 mmol/L). Additionally, one RCT reporting urinary adrenaline (epinephrine) and two RCTs reporting urinary noradrenaline (norepinephrine) detected no effect of reduced sodium intake on these (mean differences, adrenaline −13.10 pg/mL, −29.24 pg/mL to 3.04 pg/mL; noradrenaline 17.13 pg/mL, −34.06 pg/mL to 68.33 pg/mL). Four RCTs reporting plasma adrenaline and seven RCTs reporting plasma noradrenaline also detected no effect of reduced sodium on catecholamine levels (adrenaline 6.90 pg/mL, −2.17 pg/mL to 15.96 pg/mL; noradrenaline 8.23 pg/mL, −27.84 pg/mL to 44.29 pg/mL). A meta-analysis of three comparisons of renal function indicators showed a nonsignificant lower urinary protein excretion with reduced sodium intake (−76.61 μmol/L, −0.97 μmol/L to −154.2 μmol/L). Four additional RCTs (one using urinary protein excretion and three using urinary albumin excretion) also reported results consistent with a beneficial effect of lower sodium intake on renal function.

Larsen and colleagues[26] undertook a longitudinal study in Denmark among 215 adults to examine the association between dietary salt and subsequent changes in weight, waist circumference, and body composition. Neither the crude nor the adjusted models in the analyses showed any statistically significant associations between sodium excretion and change in body weight or waist circumference. The study found that there was a significant increase in body fat of 0.24 kg (P=.015; CI, 0.05–0.43) per 6 g of salt (sodium 2400 mg) per 24 hours during the 6-year period as well as a significant association with fat free mass of −0.21 kg (P=.041; CI, −0.40 to −0.01).

Jain and colleagues[25] conducted a cohort study in the United States among a sample of 2782 multiethnic participants to evaluate the association between the ratio of dietary sodium-to-potassium intake and obesity. The investigators collected health-related data, fasting venous blood, early-morning first-void urine sample, and total-body percentage fat (TBPF), which was measured by dual-energy x-ray absorptiometry. An independent direct association between urinary sodium-to-potassium ratio and TBPF was revealed whereby TBPF increased by 0.75% (95% CI, 0.25–1.25; P=.003), respectively, for every three-unit increase in the urinary sodium-to-potassium ratio. The association was present even after adjustment for BP, diabetes, and serum glucose and triglyceride concentrations.

Blood Pressure

Four studies assessed the relationship between salt intake and BP. Diaz and colleagues[33] conducted an RCT investigating the effects of weight loss and salt reduction on visit-to-visit (VVV) BP variability. VVV of BP was defined as the standard deviation of BP across six follow-up visits. The authors state that VVV of BP is associated with CVD events including stroke, CHD, and mortality. The study was a secondary analysis of Trials of Hypertension Prevention (TOHP) II and participants were randomly assigned to one of four treatment groups: weight loss alone (10.5 g of salt [sodium 4232 mg] per 24 hours), sodium reduction alone (10.6 g of salt [sodium 4278 mg] per 24 hours), combined weight loss and sodium reduction (10.2 g of salt [sodium 4117 mg] per 24 hours), or usual care (10.9 g of salt [sodium 4393 mg] per 24 hours) for 36 months. The results of this study found that there were no significant differences in VVV of SBP or diastolic BP (DBP) for participants in any of the active intervention groups compared with participants in the usual care group over a 36-month follow-up period (weight loss 7.2+3.1 mm Hg, sodium reduction 7.1+3.0 mm Hg, or combined 6.9+2.9 mm Hg, usual care group 6.9+2.9 mm Hg). It was also found that participants who maintained a reduced sodium intake throughout follow-up did not have lower VVV of SBP compared with those who did not reduce their sodium intake (0.1+0.3 mm Hg). The findings suggest that weight loss and sodium reduction may not be effective interventions for lowering VVV of BP in individuals with high-normal DBP.

A Cochrane systematic review and meta-analysis of randomized trials conducted by He and colleagues[34] aimed to examine the effects of longer-term modest salt reduction on blood pressure, hormones, and lipids. The authors reviewed data from 34 trials of salt reduction over at least 4 weeks. The studies included 3230 participants. The results found that among hypertensive participants there was a reduction in urinary sodium of 4.4 g of salt (sodium 1760 mg) per 24 hours and a reduction in BP of 5.39 mm Hg systolic and 2.82 mm Hg diastolic. Among normotensive participants there was a reduction in urinary sodium of 4.4 g of salt (sodium 1760 mg) per 24 hours and a reduction in BP of 2.42 mm Hg systolic and 1.00 mm Hg diastolic. The authors conclude that a reduction in salt intake lowers BP both in individuals with elevated BP and in those with normal BP.

Rees and colleagues[35] conducted a Cochrane systematic review to assess the effectiveness of providing dietary advice on sustained improved diets of healthy adults. The authors reviewed 18,175 participants or clusters that included 6406 participants from 11 studies on BP and salt intake. The results showed that serum cholesterol was reduced, mean high-density lipoprotein cholesterol and triglyceride were unchanged, BP was reduced by 2.61 mm Hg systolic and 1.45 mm Hg diastolic, and 24-hour urinary sodium excretion was reduced by 2.3 g of salt (sodium 940 mg) after 3 to 36 months. The authors conclude that dietary advice appears to be effective in bringing about modest beneficial changes in diet and cardiovascular risk factors over approximately 12 months, but longer-term effects were not known. Additionally, the authors found that advice to reduce salt intake from 3 to 36 months of follow-up was associated with a reduction in BP of 2.61 mm Hg systolic and 1.45 mm Hg diastolic.

Substantive Adverse Health Outcomes

Four studies examined the relationship between salt intake and adverse health outcomes. In a cohort study investigating whether sodium, potassium, and fluid intake were associated with RCC, Deckers and colleagues[29] recruited 120,852 participants aged 55 to 69 years from the Netherlands Cohort Study (NLCS) to complete a baseline questionnaire on dietary habits and lifestyle. After 17.3 years of follow-up, 485 RCC cases and 4438 subcohort members were available for analyses. The results indicated that higher sodium intake was associated with increased RCC risk whereas fluid and potassium intake was not. Significant increases were observed in RCC risk per increment of 1 g of salt (sodium 400 mg) per 24 hours (hazard ratio, 1.07; 95% CI, 1.00–1.15). Furthermore, there was a significant increase in risk across sodium intake quintiles (P trend=.03), with a hazard ratio of 1.40 (95% CI, 0.99–1.97) in the highest quintile compared with the lowest. The authors state that high sodium intake increased RCC risk, and for high sodium and low fluid intake combined, the RCC risk additionally increased (P interaction=.02).

Cook and colleagues[27] conducted a reanalysis of a cohort study that investigated the relationship between sodium intake and CVD among 1855 prehypertensive individuals aged between 30 and 54 years from 1987 to 1990 and 1191 participants from 1990 to 1995 from phases 1 and 2 of the TOHP. TOHP I evaluated the effects of four supplement and three lifestyle interventions, including weight loss and sodium reduction interventions, on BP whereas TOHP II evaluated the effects of sodium reduction and weight loss on BP over a longer 3- to 4-year follow-up period. There were 193 CVD deaths during the extended observational follow-up for CVD in 2000, 10 years after the end of TOHP I, and 5 years after the end of TOHP II. In this reanalysis, results showed that median sodium excretion was 9 g of salt (sodium 3600 mg) per 24 hours, with 1.4% of participants consuming <3.75 g of salt (sodium <1500 mg) per 24 hours and 10% of participants consuming <5.75 g of salt (sodium <2300 mg) per 24 hours, consistent with current dietary guidelines. The findings showed that risk of CVD for participants whose sodium intake was <5.75 g of salt (sodium <2300 mg) per 24 hours was 32% lower compared with those who had sodium intakes from 9 g of salt to <12 g (sodium 3600–<4800 mg) per 24 hours. There was a linear 17% increase in risk per 2.5-g increase in salt (sodium 1000 mg) per 24 hours. The authors concluded that the study findings were consistent with overall health benefits of reducing sodium intake to between 3.75 g and 5.75 g of salt (sodium 1500–2300 mg) per 24 hours.

A cohort study was conducted in England by He and colleagues[28] to determine the relationship between the reduction in population salt intake and fall in BP and mortality from stroke and IHD during 2003 to 2011. Authors analyzed the Health Survey for England data from 2003 (n=9183), 2006 (n=8762), 2008 (n=8974), and 2011 (n=4753) for participants aged 16 years and older. In all surveys, participants underwent BP measurement, anthropometric measures, 24-hour dietary recall surveys, and 24-hour urinary sodium excretion. Stroke and IHD mortality rates were calculated as the number of stroke or IHD deaths divided by the population. The study found that from 2003 to 2011 there was a decrease in mortality from stroke by 42% and from IHD by 40%. Similarly, there was a fall in BP of 3.0±0.33/1.4±0.20 mm Hg, a decrease in cholesterol of 0.4±0.02 mmol/L, a reduction in smoking prevalence from 19% to 14%, an increase in fruit and vegetable consumption of 0.2±0.05 portions per day, and an increase in body mass index (BMI) of 0.5±0.09 kg/m². After adjusting for age, sex, ethnic group, education, household income, alcohol consumption, fruit and vegetable intake, and BMI in participants not treated for hypertension, there was a fall in BP of 2.7±0.34/1.1±0.23 mm Hg. Salt intake, as measured by 24-hour urinary sodium, decreased by 1.4 g of salt

(sodium 560 mg) per 24 hours between 2003 and 2011 (salt intake was 9.5 g of salt (sodium 3800 mg) per 24 hours in 2003, 9 g (sodium 3600 mg) per 24 hours in 2005, 8.64 g (sodium 3456 mg) per 24 hours in 2008, and 8.1 g (sodium 3240 mg) per 24 hours in 2011). The authors conclude that the reduction in salt intake was likely to be an important contributor to the fall in BP between 2003 and 2011 in England and, as a result, the decrease in salt intake could have played an important role in the reduction of stroke and IHD mortality during this period.

Aburto and colleagues[32] conducted a systematic review and meta-analysis to assess the effect of lower sodium intake on BP, all-cause mortality, CVD, stroke, CHD, and potential adverse effects such as changes in blood lipids, catecholamine levels, and renal function in adults and on BP, blood lipids, and catecholamine levels in children. Inclusion and exclusion criteria were similar to the methods used in this review. However, in order to assess studies in children, exclusion criteria were changed to include duration of more than 3 weeks, any controlled design, any difference in sodium intake between intervention and control, and any method of measuring intake. Thirty-six RCTs were included in the meta-analyses in adults, which found that a reduction in sodium intake significantly reduced resting SBP by 3.39 mm Hg and resting DBP by 1.54 mm Hg. When sodium intake was <5 g of salt (sodium 2000 mg) per 24 hours, compared with >5 g of salt (sodium 2000 mg) per 24 hours, SBP was decreased by 3.47 mm Hg and DBP by 1.81 mm Hg. Data from RCTs on cardiovascular outcomes lacked sufficient power to detect a relationship between sodium intake and the outcomes of interest. Results from 10 cohort studies in a meta-analyses found that increased sodium intake was associated with an increased risk of stroke, stroke mortality, and CHD mortality (risk ratio, 1.24, 1.63, and 1.32, respectively). Ten studies in children were included in the review: six randomized controlled trials, three non-RCTs, and one cohort study. The findings suggest that a reduction in sodium intake in children would significantly reduce SBP by 0.84 mm Hg and DBP by 0.87 mm Hg. None of the studies that reached the inclusion criteria for this review reported the effect of lower sodium intake on blood lipids, catecholamine levels, or side effects in children. The meta-analysis concluded at the evidence suggests most people would likely benefit from reducing sodium intake.

DISCUSSION

This systematic review of studies published on salt during the past 12 months found 11 studies that associated increased dietary salt intake with adverse health outcomes. A meta-analysis of RCTs did not have statistical power to assess increased dietary salt intake with substantive adverse outcomes. Findings from a meta-analysis of cohort studies in healthy populations was consistent with higher dietary salt being associated

with higher CVD rates and increased risk of all stroke, fatal stroke, and fatal CHD events. The meta-analysis of cohort studies included studies with salt intake reduced to 5 g (sodium 2000 mg) per 24 hours. Examination of reductions of 1.4 g of salt (sodium 560 mg) per 24 hours in England were also consistent with expected reduced CVD and reduced BP, but, as is the case with observational studies of this nature, there were multiple confounding factors. The association with reduced cardiovascular events was also seen in one cohort study at levels of sodium intake of 3.75 to 5.75 g of salt (sodium 1500–2300 mg) per 24 hours. It is of note that the systematic review also identified a study that associated increased dietary salt with RCC.

Two meta-analyses examined RCTs of salt reduction with changes in BP as an outcome. The meta-analyses confirm decreases in BP with reduced dietary salt in a variety of settings including an impact on children, people with normal BP as well as hypertension, and people who eat a diet with <5 g of salt (sodium 2000 mg) per 24 hours. Two RCTs that assessed the impact of salt consumption on BP were also identified. One was a re-analysis of a previously published study while the other should be included in subsequent meta-analyses.[13]

Studies of the impact of dietary salt on surrogate endpoints showed that reduced dietary salt improved flow-mediated vasodilation and aortic stiffness. Several of the studies examining surrogate endpoints also examined BP and should be incorporated into future meta-analyses on the impact of salt on BP. Hence, the findings of this updated systematic review of studies that are relevant to clinical and population efforts are in support of current recommendations to reduce dietary salt and, specifically, the recommendations of the WHO, World Hypertension League, and International Society of Hypertension.[36]

It is notable that this systematic review did not identify studies that showed increases in adverse outcomes associated with lower dietary salt. This review applied a priori criteria to ensure that the included studies met minimum methodological standards, that the intervention had an impact on dietary salt, and that the studies were of a duration that had relevance to public health and clinical medicine. Low-quality research methods have been identified as a critical factor in generating controversy over the impact of changing dietary salt on health.[37] It is notable that reviews that included poor-quality clinical designs (short duration, ineffective reduction in salt intake) and flawed assessments of intake and that included cohort studies in people with disease have resulted in conflicting conclusions on dietary salt.[1,38]

The standards applied in this review should not be interpreted as being optimum for the conduct of clinical studies on dietary salt. The majority of the studies assessed salt intake based on a single day's urine collection despite day-to-day variability, meaning that multiple days of assessment are required to have a

higher degree of accuracy. Further, studies should apply criteria for ensuring that 24-hour urine collections were complete. Lastly, in cohort studies, we allowed any assessment of salt intake, which means that studies using inaccurate assessments of salt intake may have been included. The lack of ability to accurately classify an individual's salt intake is likely to result in underestimates of the impact of dietary salt on health and favor the null hypothesis. Where salt intake is estimated using a formula that includes parameters which predict outcomes (age, sex, creatinine), confounding may occur. Further, the impact of salt on BP may not be fully assessed using the criteria applied in this review, including studies as short as 4 weeks; optimally, studies should be much longer. Animal studies find irreversible, epigenetic, and long-term changes in BP associated with salt ingestion that short (4-week) studies of salt reduction would be unlikely to detect.[39,40] Studies are markedly limited by the challenges of substantively reducing dietary salt over long periods of time in the research setting, making large-scale RCTs challenging at best. Nearly all of the methodological limitations favor the null hypothesis or even reverse causality. The World Hypertension League is leading an effort to develop recommended standards for the conduct of such research to improve reliability of findings.[41]

The fact that this is a systematic review of the literature for a single year is another potential limitation. Past evidence linking high dietary salt to gastric cancer (systematic review), kidney stones, osteoporosis, asthma, and other outcomes were not covered in this year's literature review. In addition, cohort studies conducted in people with chronic disease in which there is a high risk of the studies being influenced by reverse causality (where more severe disease results in lower food intake [and salt intake] resulting in false associations between low food [and salt] intake and increased adverse outcomes) were excluded. However, the inclusion of recent comprehensive systematic reviews on the impact of high dietary salt on cardiovascular patient outcomes, BP, and some surrogate markers and means it represents much of the relevant research.

The review found insufficient statistical power in RCTs to assess the impact of high dietary salt on substantive adverse patient outcomes. The challenges of conducting large, long-duration, randomized trials of salt reduction are substantive. A large RCT of a salt replacer (partial replacement of sodium with potassium) on substantive patient outcomes is currently being conducted with results expected in 2017 to 2018.[42]

CONCLUSIONS

A variety of modeling studies have estimated the impact of changes in BP related to recommended changes in dietary salt (and, in some, the association of increased dietary salt to gastric cancer). About one third hypertension cases have been attributed to increased dietary salt.[1] In a recent updated analyses of the Global Burden of Disease Study, 1.65 million

deaths in 2010 were attributed to dietary salt in excess of 5 g of salt (sodium 2000 mg) per 24 hours.[43] The data in this updated systematic review are consistent with the data that were used in these modeling studies and outline the substantive impact that increased dietary salt is estimated to have based on best available evidence. The systematic review also extends the health concerns of increased dietary salt to RCC, which will require further study.

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