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Understanding the science that supports population-wide salt reduction programs

Jacqui Webster PhD[1] | Temo Waqanivalu MBBS, MPH[2] | JoAnne Arcand PhD, RD[3] | Kathy Trieu MPH[1] | Francesco P. Cappuccio MD, DSc[4] | Lawrence J. Appel MD, MPH[5] | Mark Woodward BSc, MSc, PhD[1,6,7] | Norm R. C. Campbell MD[8] | Rachael McLean BA, MBChB, MPH, PhD, FNZCPHM[9]

[1]The George Institute for Global Health, University of Sydney, Sydney, New South Wales, Australia

[2]The World Health Organization, Geneva, Switzerland

[3]Faculty of Health Sciences, University of Ontario Institute of Technology, Oshawa, Ontario, Canada

[4]Warwick Medical School, University of Warwick, Coventry, UK

[5]Welch Center for Prevention, Epidemiology and Clinical Research, Johns Hopkins University, Baltimore, MD, USA

[6]University of Oxford, Oxford, UK

[7]Department of Epidemiology, Johns Hopkins University, Baltimore, Maryland, USA

[8]Department of Medicine, Physiology and Pharmacology and Community Health Sciences, O'Brien Institute for Public Health and Libin Cardiovascular Institute of Alberta, University of Calgary, Calgary, Alberta, Canada

[9]Departments of Preventive & Social Medicine, University of Otago, Dunedin, New Zealand

Correspondence
Jacqui Webster, PhD, The George Institute for Global Health, University of Sydney, Sydney, New South Wales, Australia.
Email: jwebster@georgeinstitute.org.au

1 | BACKGROUND

Independent systematic reviews of the totality of the evidence by governments and international agencies throughout the world uniformly conclude that population-wide interventions to reduce salt are beneficial for health. However, some scientists continue to produce and cite studies with paradoxical findings that conflict with the evidence base used to develop national and World Health Organization (WHO) guidelines on salt reduction.[1–5] While conflicting studies are not uncommon in any area of research,[6] in the case of salt, such studies attract widespread attention in the media; misinform program leaders, clinicians, and the general public; and impede program implementation. Such impediments to progress have occurred despite the fact that the designs and methods of studies with paradoxical findings have been criticized by international experts who highlight the fact that the results are not valid.[7-9]

To address this problem, a consortium of national and international health and scientific organizations is leading a program of work through its Standards for Salt Research group. The objective of this consortium is to develop a clear set of processes and criteria to which new scientific projects relating to salt should adhere, in order to achieve at least a minimum quality of research in the field.[10] While general criteria for judging the scientific evidence for studies are available,[11] they do not address the complexity inherent in accurately assessing salt intake and its relationship with health outcomes. The new Standards for Salt Research will help to ensure that only robust scientific studies are used when national and international recommendations relating to salt reduction are reviewed.

In the meantime, the objective of this paper is to provide an overview of the main arguments used against reducing salt and to counter these arguments with evidence in support of reducing population-wide salt intake. This work updates previous similar reviews that have explained some of the controversies.[12–14] The intent of this paper is to assist policy makers, program implementers, and clinicians in understanding the science in support of salt reduction and provide them with tools to counter arguments against population-wide salt reduction.

1.1 | Main arguments used against and counterarguments to support salt reduction

1. *Can we make recommendations about salt without consensus on the science?* Salt is an unsettled and hot topic for investigation and so it would be premature to make recommendations in the absence of trial data.

Response: *There is consensus about the need to reduce population salt intake from the organizations that have systematically and independently examined the totality of the evidence*. Public health policy recommendations need to be based on critical appraisals of the totality of the evidence by expert scientific groups overseen by governmental or nongovernmental health and scientific organizations. As in most areas of public health, the evidence base is incomplete, as it is lacking in definitive randomized controlled trials (RCTs) for cardiovascular disease (CVD) outcomes, due to practical and ethical considerations. Nevertheless, multiple independent review processes in different countries[15–19] have all concluded that typical dietary salt intake is too high, that it creates serious health problems, and that consequently salt intake should be reduced. The current WHO recommendation is that salt (sodium chloride) intake should be <5 g/d* for adults, with lower levels in children based on their lower caloric needs.[20]

The evidence supporting the need to reduce salt and the impact of reducing salt on health is increasing.[21–23] However, every year there are a few controversial studies that get most of the media coverage and cause some people to question current recommendations. These studies are usually linked to a small group of individuals, several with ties to commercial interests.[14] Such studies are not appropriately designed to assess the association between salt intake and disease as outlined below.

2. *What are the estimated potential benefits of salt reduction on the burden of disease and death?* Some estimates of the potential benefits of salt reduction in terms of burden of disease and deaths are much lower than initially thought.

Response: *Reducing salt intake would save millions of lives a year globally*. High dietary salt is associated with wide-ranging health problems including hypertension, stroke, CVD, bone demineralization, kidney stones, gastric cancer, and kidney disease.[24–29] The greatest health risk is the increase in blood pressure (BP) caused by excess salt intake. Although the magnitude of change in BP from modest changes in dietary salt are relatively small in individuals, on a population scale,[21] a reduction in salt explains between one fifth[30] and one third[19] of cases of hypertension. The Global Burden of Disease Study[31] estimated that increased dietary salt is the second leading behavioral risk for death and the third leading behavioral risk for disability globally, such that 4.129 million deaths and more than 83 million disability-adjusted life years lost could be attributed to high dietary sodium consumption in 2015. Health economic analyses have found that reducing dietary salt is cost saving or highly cost effective in different investigations.[32,33] Such evidence has provided the rationale for the WHO and the World Economic Forum to identify population-wide sodium reduction as a "best-buy" intervention for public health.[34]

3. *Does reducing salt reduce BP long term?* Most evidence shows that reducing salt reduces BP only in the short term (<6 months). *Should we be cautious in extrapolating from short-term studies of a few months or weeks to what might be expected in the long term?*

Response: *A large body of evidence supports the fact that reducing dietary salt has a long-term effect on BP.* In a wide variety of animal studies, BP continues to increase if salt intake is increased, and this is not attenuated over time.[35–37] In human epidemiological studies, habitually high dietary salt intake is associated with high BP and increasing BP with age.[38–40] BP would not continue to rise with age if changes in BP were only for a short time after exposure.[37] In long-term population intervention studies that reduced dietary salt and lasted for decades, decreases in BP have matched or exceeded reductions predicted from results of shorter-term clinical trials.[41,42] In clinical trials of reducing dietary salt, BP reduces in proportion to reductions in dietary salt.[43–48] Many trials lasting 4 weeks or longer have shown reductions in BP.[45] Several high-quality randomized clinical trials that reduced dietary salt have demonstrated reductions in BP up to 18 months with no attenuation in reduction of BP.[44,49] Most longer-term trials have not been able to sustain reductions in dietary salt among participants and have been challenged regarding confounding with other cointerventions.[44,50] Nevertheless, in the sodium reduction arm of the Trials of Hypertension Prevention (TOHP) 2 study,[50] systolic BP was still reduced in the intervention arm compared with control after 3 years. In conclusion, well-designed meta-analyses of salt reduction trials clearly demonstrate that salt reduction will have a long-term impact on BP.[9]

4. *What is the evidence that lowering BP in nonhypertensive persons will reduce CVD mortality?* Some studies suggest that lowering BP increases mortality and cardiovascular events (other than stroke) in people without hypertension.

Response: *Lowering BP will reduce CVD mortality, including in persons without hypertension.* The extensive evidence from epidemiology and higher-quality analyses of randomized clinical trials shows a direct relationship between BP and CVD.[48,49,51–54] This relationship between BP and CVD is evident at SBP values beginning at ≈115 mm Hg,[55] a finding that suggests that nonhypertensive persons will also benefit from reductions in BP. The long-term follow-up from the TOHP studies, which showed that reduced sodium was associated with reduced CVD, were all performed in prehypertensive patients.[56] Reductions in CVD are related to the extent to which BP is reduced as well as to the absolute cardiovascular risk of the study population.[51–54,57]

The controversy arises from retrospective nonrandomized analyses of studies that include individuals who are already sick. Some such studies have found a U- or J-shaped curve that can be explained by reverse causality (whereby BP may be low because of preclinical or prevalent diseases such as myocardial infarction or heart failure, which then lead to increased risk of premature death).[1–3,58] Studies where aggressive BP-lowering therapy is used in populations susceptible to clinical hypotension may also cause cardiovascular and renal disease.[59] A recent study that suggested a relationship between reduced BP and increased CVD events included patients with diabetes, and therefore treatment and other factors were likely to have influenced the results.[60] Such studies do not provide evidence to counter support for population-wide salt reduction strategies.[7,8,61–63] An overview of some of the main weaknesses in these studies is provided below.

*5 g of salt corresponds to 2000 mg or 85 mmol of sodium.

5. *Why are there no randomized clinical trials proving that salt reduction reduces CVD?* These must be performed to provide robust data proving that salt reduction reduces CVD before we implement interventions.

Response: *Pooled data from RCTs with long-term follow-up for CVD suggest that salt reduction reduces CVD.*[64] *The reasons few RCTs have been designed and conducted specifically to examine whether salt reduction reduces CVD is because adequately designed and appropriately powered trials would be too expensive, impractical, or potentially unethical, given the high quality of evidence documenting the benefits of salt reduction.* This is the same in many other fields of public health (eg, tobacco control, obesity reduction, actions to reduce climate change, air pollution, physical inactivity, and excessive alcohol consumption). Because of the high content of salt in the food supply, long-term RCTs of salt reduction have found it hard to sustain reduced dietary salt for more than 3 years in free-living patients.[44,65] The alternative approach of asking patients to increase dietary salt would be unethical due to the evidence that eating too much salt harms health. In most clinical trials, the relatively small number of people who have a CVD event precludes the establishment of any relationship between salt intake and CVD. However, studies that have pooled the data from RCTs of salt reduction, or salt replacers, using meta-analyses, have demonstrated a reduction in cardiovascular events with reduced dietary sodium.[64,66]

The existing evidence is strong enough to support the implementation of strategies to reduce salt intake. Meta-analyses of cohort studies of salt intake in healthy populations, or where filters were used to exclude low-quality research, have also shown that salt intake is associated with CVD.[21,67] Long-term experience with salt reduction in Finland, Japan, and the United Kingdom has shown an association between salt reduction and reduced BP and CVD at the population level.[41,68] Long-term follow-up of individuals in the TOHP trials, which carefully assessed usual salt intake through repeat 24-hour urine collections, found that salt intake <2300 mg/d was associated with reduced CVD.[56,69]

6. *Aren't low levels of sodium consumption associated with increased CVD events and mortality?* Some studies show that low levels of sodium (<3000 mg sodium or 7.5 g salt/d) are associated with increased mortality, especially in nonhypertensive persons. The most recent study quoted is the Prospective Urban Rural Epidemiology (PURE) study.

Response: *It is important to emphasize that consumption of* <3 *of sodium a day is not considered low sodium consumption*[70] *and that such levels are not associated with increased CVD events and mortality*. Population salt intake for communities with diets that do not have added salt are nearly all below 1 g of sodium (2.5 g of salt) per day.[71–73] So, although sodium is required for proper bodily function, the minimum physiological amount required is <1 g of sodium per day.[70] Very few populations are currently consuming such low amounts, but in the few remaining hunter-gatherer populations where they do, BP does not rise with age and hypertension and CVD are uncommon.[37,74,75] Reliable vital statistics are unavailable in these isolated populations, but mortality appears to be related to infectious diseases and other problems of economically developing regions that are unrelated to salt intake.

While some of the studies that suggest lower amounts of dietary salt are associated with increased CVD events and mortality are based on very large numbers of participants, the methodologies are seriously flawed. Hence, their findings should be interpreted with caution and are not appropriate to guide policy. Systematic reviews of cohort studies that have criteria to exclude lower-quality studies, as well as systematic reviews of RCTs, have found that CVD is reduced (not increased) with lower intakes of dietary sodium.[21–23,51,67]

Some of the common methodological problems have been addressed extensively in previous reviews[7,63] and are summarized as follows:

- Measurement error: The most accurate technique to estimate usual dietary salt intake is the collection of multiple, high-quality 24-hour urine samples. A single urine sample is often used to estimate usual intake; however, this is also less accurate because of large day-to-day variation in dietary intake and because excretion varies widely even with a fixed salt intake.[76,77] Several of the studies showing a J-shaped relationship between salt intake and health outcomes rely on a single spot urine assessment to estimate each person's long-term usual sodium intake.[1,2] Single spot urine sodium samples cannot accurately assess an individual's usual salt intake, because sodium intake varies meal to meal and day to day and is also impacted by seasonal food availability.[78–80] Other studies have had a large proportion of 24-hour urine collections that were incomplete, leading to inaccurate estimates of salt intake that would impact the results.[4] Incomplete 24-hour urine collections have lower sodium levels and do not reflect true intake.[81,82] Other studies have used food surveys that may also not reliably estimate salt intake.[83] In contrast, a follow-up study of participants in the TOHP study used multiple 24-hour sodium measurements and documented that people with lower sodium intakes have a lower risk of CVD and total mortality. More recent analysis has shown that this relationship is still present after a median of 24 years of follow-up, with no evidence of a J-shaped curve.[56,69]
- Reverse causality: In observational studies, persons consuming the least salt may be more likely to have the highest risk of cardiovascular events and death because they were already ill when they entered the study–the problem known as "reverse causation."[7,84] These people are likely to consume fewer calories and therefore eat less salt because they are ill, rather than being ill as a result of eating less salt. For example, in the PURE study, older age, having diabetes, and having a history of CVD were more common among patients with lower estimated sodium intakes than those with higher intakes.[63]
- Confounding factors: Residual confounding cannot be excluded in observational studies, even when multiple factors are controlled for in the analysis.[7,84] Specifically, studies often do not assess or control for factors that may address the health outcome of interest.

Such factors may include chronic kidney disease, family history of CVD, and levels of or changes in nutrient or calorie intake (which might be related to age, physical activity, or chronic disease status). RCTs, such as TOHP,[49] control for confounding factors through randomization at baseline and therefore provide a higher standard of evidence than observational studies.

7. *Why can't untimed collections (eg, spot samples) such as those used in the PURE study and others, which show a J-shaped curve, accurately reflect the usual long-term salt intake of individuals?*

Response: *Spot urine samples are an unreliable measure of individual salt intake and should not be used as the basis for correlating salt intake with health outcomes, such as BP or CVD.*[78,85–87] There is ongoing research to examine the potential for use of spot urine samples from a large sample of the population to estimate mean population salt intake.[88] However, spot urine samples do not provide an accurate assessment of an individual's intake. The reasons are as follows:

- Salt intake varies from day to day and from meal to meal.[4,79–83] Therefore, the sodium content of a spot urine sample reflects what was just eaten rather than usual salt intake over an extended period in an individual.[8,80]
- Other factors affect spot urine sodium excretion concentration and include state of hydration, posture, renal function, diurnal variation, and other regulatory functions.[89,90]
- The equations used to calculate 24-hour salt intake from spot urine samples include several variables strongly associated with disease outcomes (age, sex, and urine creatinine concentration), which means that the estimate is not independent of other potential confounding factors.
- The correlation between spot urine samples and 24-hour urine estimates of salt intake varies from one population to another and so the equations cannot be applied without validation studies.[91] For example, in the main PURE study, the correlation was relatively high at around 0.7; however, the correlation in the PURE China population was <0.3.[92,93] Also, validation studies show differences of 8000 to 9000 mg sodium per day in spot and 24-hour urine samples from the same individuals even when both are from the same collection day.[92,93]
- Bland-Altman plots of spot urine vs 24-hour urine plot show bias at high and low intakes. Spot urine overestimates at low intake and underestimates at high intake, which means that risk is exaggerated at low intake and underestimated at high intake. Therefore, spot urine samples do not reflect individual intakes well across their range.

2 | DISCUSSION

Public health policy regarding nutritional exposures and chronic disease outcomes (including CVD and cancer), where diseases develop over decades, is seldom based solely on evidence from RCTs.[94] Although RCTs are widely regarded as the best evidence to test the effects of a medical therapy, they are often impractical in the context of long-term public health interventions on outcomes that may have multifactorial influences over time. They may also be unethical, particularly if there is already a substantial body of evidence from epidemiological studies and/or intervention studies using intermediate end points, such as BP in the case of salt reduction.[94] To delay implementation of public health policy, in the absence of RCT data providing "direct" evidence, may convey considerable harm to the population, especially if such RCT evidence is unlikely to be forthcoming.[95] For this reason, authoritative bodies have developed tools for systematically appraising the totality of scientific evidence (including experimental, epidemiological, and RCT evidence) in order to develop recommendations aimed at individuals and populations.[96] Despite this, vested interests (including the food industry) may exaggerate any uncertainties that this situation offers in order to prevent or delay government action or regulation.[12,13,97]

The evidence regarding the harms of diets high in salt is sufficient to justify recommendations from the WHO and other governmental and health-related organizations to reduce population salt intake.[16,20,61] For example, there is a "substantial amount of evidence" of a dose-response relationship that dietary salt and salted foods are positively associated with stomach cancer,[28] leading the World Cancer Research Fund and WHO to conclude that dietary salt and salted foods are a probable cause of this cancer.[20,96] There is a much larger body of evidence that supports an association between high intake of dietary salt and elevated BP[45] and CVDs, such as myocardial infarction and stroke.[21] On the other hand, the premise that reducing salt intake in populations could cause harm is not supported by a strict application of the criteria used to demonstrate cause and effect.[8]

The WHO target to implement population-level interventions to lower dietary salt intake by 30% by 2025 was agreed on by its 194 member states in 2013.[98] The WHO and regional offices have developed a number of different tools to support member states to achieve this target.[99,100] A 2014 review highlighted the fact that 75 countries already had national programs in place to reduce population salt intake.[101] There is growing evidence of the efficacy of such programs.[102] Evaluations of the more established interventions have also shown that population-level reductions in salt intake have been associated with declines in CVD rates in those populations.[42,103]

The recent publication of paradoxical studies with low-quality methodology should not delay implementation of public health interventions. The attention given to such studies in comparison to the critique of them[8,63,104,105] is completely unwarranted. The call for further research[106] is also not a reason to delay such implementation. There are numerous examples where the conduct of further research has not added to knowledge but merely delayed implementation of policies based on findings that would have been apparent if systematic synthesis of existing study results had been available or undertaken.

To document contemporary evidence on the science of salt, the World Hypertension League and other organizations support a regular (every few months) updated review. Over the past 3 years (2013–2015), having screened for inclusion based on minimum methodologic criteria set a priori, this approach found 14 studies that supported and no studies that countered the evidence for the beneficial impact of salt reduction on disease.[22,23,107]

International organizations have published a statement of concern about the impact of research studies that do not meet quality criteria (including the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial [ONTARGET], the Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease [TRANSCEND], Diabetes REduction Assessment with ramipril and rosiglitazone Medication [EpiDREAM], and PURE).[10] An international expert group (the TRUE consortium) has been established and will soon be publishing the criteria that need to be met in order for studies of salt reduction to be reliable.

3 | CONCLUSIONS

Current recommendations to reduce population sodium intake[20] are based on sound scientific evidence. The recent publication of a few paradoxical studies of questionable scientific merit should not delay implementation of salt reduction initiatives worldwide. Governments and health organization should continue to implement programs to reduce salt in line with the WHO Global Action Plan for the prevention and control of noncommunicable diseases.[108]

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REFERENCES

1. Mente A, O'Donnell M, Rangarajan S, et al. Associations of urinary sodium excretion with cardiovascular events in individuals with and without hypertension: a pooled analysis of data from four studies. *Lancet*. 2016;388:465-475.
2. O'Donnell MJ, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA*. 2011;306:2229-2238.
3. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371:612-623.
4. Alderman MH, Madhavan S, Cohen H, Sealey JE, Laragh JH. Low urinary sodium is associated with greater risk of myocardial infarction among treated hypertensive men. *Hypertension*. 1995;25:1144-1152.
5. Graudal N, Jurgens 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.
6. Hill AB. The environment and disease: association or causation? 1965. *J R Soc Med*. 2015;108:32-37.
7. Cobb LK, Anderson CA, Elliott P, et al. Methodological issues in cohort studies that relate sodium intake to cardiovascular disease outcomes: a science advisory from the American Heart Association. *Circulation*. 2014;129:1173-1186.
8. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary sodium and cardiovascular disease risk-measurement matters. *N Engl J Med*. 2016;375:580-586.
9. Cappuccio FP. Pro: reducing salt intake at population level: is it really a public health priority? *Nephrol Dial Transplant*. 2016;31:1392-1396.
10. Campbell NR, Appel LJ, Cappuccio FP, et al. A call for quality research on salt intake and health: from the World Hypertension League and supporting organizations. *J Clin Hypertens (Greenwich)*. 2014;16:469-471.
11. Prictor M, Hill S. Cochrane Consumers and Communication Review Group: leading the field on health communication evidence. *J Evid Based Med*. 2013;6:216-220.
12. Cappuccio FP, Capewell S, He FJ, MacGregor GA. Salt: the dying echoes of the food industry. *Am J Hypertens*. 2014;27:279-281.
13. Cappuccio FP, Capewell S. Facts, issues, and controversies in salt reduction for the prevention of cardiovascular disease. *Funct Food Rev*. 2015;7:41-46.
14. Appel LJ, Angell SY, Cobb LK, et al. Population-wide sodium reduction: the bumpy road from evidence to policy. *Ann Epidemiol*. 2012;22:417-425.
15. Campbell NR, Lackland DT, Niebylski ML. 2014 dietary salt fact sheet of the World Hypertension League, International Society of Hypertension, Pan American Health Organization technical advisory group on cardiovascular disease prevention through dietary salt reduction, the World Health Organization collaborating centre on population salt reduction, and World Action on Salt & Health. *J Clin Hypertens (Greenwich)*. 2015;17:7-9.
16. Scientific Advisory Committee on Nutrition. *Salt and Health*. Norwich, UK: The Stationery Office; 2003.
17. Appel LJ, Brands MW, Daniels SR, et al. Dietary approaches to prevent and treat hypertension: a scientific statement from the American Heart Association. *Hypertension*. 2006;47:296-308.
18. Dickinson BD, Havas S. Council on Science and Public Health American Medical Association. Reducing the population burden of cardiovascular disease by reducing sodium intake: a report of the Council on Science and Public Health. *Arch Intern Med*. 2007;167:1460-1468.
19. Institute of Medicine of the National Academies. *Sodium Intake in Populations: Assessment of Evidence*. Washington, DC: National Academies Press; 2013.
20. World Health Organization. *WHO Guideline: Sodium Intake for Adults and Children*. Geneva, Switzerland: WHO Press; 2012.
21. 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.
22. Johnson C, Raj TS, Trudeau L, et al. The science of salt: a systematic review of clinical salt studies 2013 to 2014. *J Clin Hypertens (Greenwich)*. 2015;17:401-411.
23. Johnson C, Raj TS, Trieu K, et al. The science of salt: a systematic review of quality clinical salt outcome studies June 2014 to May 2015. *J Clin Hypertens (Greenwich)*. 2016;18:832-839.

24. Wang XQ, Terry PD, Yan H. Review of salt consumption and stomach cancer risk: epidemiological and biological evidence. *World J Gastroenterol*. 2009;15:2204-2213.
25. He FJ, MacGregor GA. A comprehensive review on salt and health and current experience of worldwide salt reduction programmes. *J Hum Hypertens*. 2009;23:363-384.
26. McMahon EJ, Campbell KL, Bauer JD, Mudge DW. Altered dietary salt intake for people with chronic kidney disease. *Cochrane Database Syst Rev*. 2015;2:CD010070.
27. Cappuccio FP, Kalaitzidis R, Duneclift S, Eastwood JB. Unravelling the links between calcium excretion, salt intake, hypertension, kidney stones and bone metabolism. *J Nephrol*. 2000;13:169-177.
28. D'Elia L, Rossi G, Ippolito R, Cappuccio FP, Strazzullo P. Habitual salt intake and risk of gastric cancer: a meta-analysis of prospective studies. *Clin Nutr*. 2012;31:489-498.
29. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ*. 2009;339:b4567.
30. Committee on Public Health Priorities to Reduce and Control Hypertension in the US. Population Institute of Medicine of the National Academies. A population-based policy and systems change approach to prevent and control hypertension. Washington, DC: National Academies Press; 2010.
31. Institute for Health Metrics and Evaluation (IHME). GBD compare data visualization; 2016. http://www.healthdata.org/gbd/data-visualizations. Accessed December 19, 2016.
32. Asaria P, Chisholm D, Mathers C, Ezzati M, Beaglehole R. Chronic disease prevention: health effects and financial costs of strategies to reduce salt intake and control tobacco use. *Lancet*. 2007;370:2044-2053.
33. Wang G, Labarthe D. The cost-effectiveness of interventions designed to reduce sodium intake. *J Hypertens*. 2011;29:1693-1699.
34. World Heath Organization and World Economic Forum. From burden to best buy: reducing the economic impact of non-communicable diseases in low- and middle-income countries; 2011. http://www.who.int/nmh/publications/best_buys_summary.pdf. Accessed January 11, 2017.
35. Elliott P, Walker LL, Little MP, et al. Change in salt intake affects blood pressure of chimpanzees: implications for human populations. *Circulation*. 2007;116:1563-1568.
36. Van Vliet BN, Montani JP. The time course of salt-induced hypertension, and why it matters. *Int J Obes (Lond)*. 2008;32 (suppl 6):S35-S47.
37. Meneton P, Jeunemaitre X, de Wardener HE, MacGregor GA. Links between dietary salt intake, renal salt handling, blood pressure, and cardiovascular diseases. *Physiol Rev*. 2005;85:679-715.
38. Kagan A, Popper JS, Rhoads GG, Yano K. Dietary and other risk factors for stroke in Hawaiian Japanese men. *Stroke*. 1985;16:390-396.
39. 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.
40. Yamori Y, Liu L, Ikeda K, et al. Different associations of blood pressure with 24-hour urinary sodium excretion among pre- and postmenopausal women. WHO Cardiovascular Diseases and Alimentary Comparison (WHO-CARDIAC) Study. *J Hypertens*. 2001;19(3 pt 2):535-538.
41. Karppanen H, Mervaala E. Sodium intake and hypertension. *Prog Cardiovasc Dis*. 2006;49:59-75.
42. He FJ, Pombo-Rodrigues S, Macgregor GA. Salt reduction in England from 2003 to 2011: its relationship to blood pressure, stroke and ischaemic heart disease mortality. *BMJ Open*. 2014;4:e004549.
43. Sacks FM, Svetkey LP, Vollmer WM, et al. 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.
44. Law MR, Frost CD, Wald NJ. By how much does dietary salt reduction lower blood pressure? III–Analysis of data from trials of salt reduction. *BMJ*. 1991;302:819-824.
45. 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.
46. He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. *Cochrane Database Syst Rev*. 2004;3: CD004937.
47. He FJ, MacGregor GA. Effect of modest salt reduction on blood pressure: a meta-analysis of randomized trials. Implications for public health. *J Hum Hypertens*. 2002;16:761-770.
48. He FJ, MacGregor GA. How far should salt intake be reduced? *Hypertension*. 2003;42:1093-1099.
49. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. Results of the Trials of Hypertension Prevention, Phase I. *JAMA*. 1992;267:1213-1220.
50. 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;157:657-667.
51. Czernichow S, Zanchetti A, Turnbull F, et al. The effects of blood pressure reduction and of different blood pressure-lowering regimens on major cardiovascular events according to baseline blood pressure: meta-analysis of randomized trials. *J Hypertens*. 2011;29: 4-16.
52. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 2. Effects at different baseline and achieved blood pressure levels–overview and meta-analyses of randomized trials. *J Hypertens*. 2014;32:2296-2304.
53. Thomopoulos C, Parati G, Zanchetti A. Effects of blood pressure lowering on outcome incidence in hypertension: 3. Effects in patients at different levels of cardiovascular risk–overview and meta-analyses of randomized trials. *J Hypertens*. 2014;32:2305-2314.
54. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. *Lancet*. 2016;387:957-967.
55. Lewington S, Clarke R, Qizilbash N, Peto R, Collins R; Prospective Studies C. Age-specific relevance of usual blood pressure to vascular mortality: a meta-analysis of individual data for one million adults in 61 prospective studies. *Lancet*. 2002;360:1903-1913.
56. Cook NR, Appel LJ, Whelton PK. Sodium intake and all-cause mortality over 20 years in the trials of hypertension prevention. *J Am Coll Cardiol*. 2016;68:1609-1617.
57. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. *JAMA*. 2015;313:603-615.
58. Dorresteijn JA, van der Graaf Y, Spiering W, et al. Relation between blood pressure and vascular events and mortality in patients with manifest vascular disease: J-curve revisited. *Hypertension*. 2012;59:14-21.
59. Yusuf S, Teo KK, Pogue J, et al. Telmisartan, ramipril, or both in patients at high risk for vascular events. *N Engl J Med*. 2008;358: 1547-1559.
60. Brunstrom M, Carlberg B. Effect of antihypertensive treatment at different blood pressure levels in patients with diabetes mellitus: systematic review and meta-analyses. *BMJ*. 2016;352:i717.
61. Dietary Guidelines Advisory Committee. Part D. Chapter 6: cross-cutting topics of public health importance. *Scientific Report of the 2015 Dietary Guidelines Advisory Committee*. United States: The Dietary Guidelines Adivsory Committee; 2015.
62. Elijovich F, Weinberger MH, Anderson CA, et al. Salt sensitivity of blood pressure: a scientific statement from the american heart association. *Hypertension*. 2016;68:e7-e46.

63. Cappuccio FP, Campbell NR. Population dietary salt reduction and the risk of cardiovascular disease: a commentary on recent evidence. *J Clin Hypertens (Greenwich)*. 2017;19:4-5. doi:10.1111/jch.12917.
64. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet*. 2011;378:380-382.
65. Hooper L, Bartlett C, Davey Smith G, Ebrahim S. Systematic review of long term effects of advice to reduce dietary salt in adults. *BMJ*. 2002;325:628.
66. Adler AJ, Taylor F, Martin N, Gottlieb S, Taylor RS, Ebrahim S. Reduced dietary salt for the prevention of cardiovascular disease. *Cochrane Database Syst Rev*. 2014;12:CD009217.
67. Poggio R, Gutierrez L, Matta MG, Elorriaga N, Irazola V, Rubinstein A. Daily sodium consumption and CVD mortality in the general population: systematic review and meta-analysis of prospective studies. *Public Health Nutr*. 2015;18:695-704.
68. He FJ, Brinsden HC, MacGregor GA. Salt reduction in the United Kingdom: a successful experiment in public health. *J Hum Hypertens*. 2014;28:345-352.
69. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. *Circulation*. 2014;129:981-989.
70. Campbell NR, Correa-Rotter R, Cappuccio FP, et al. Proposed nomenclature for salt intake and for reductions in dietary salt. *J Clin Hypertens (Greenwich)*. 2015;17:247-251.
71. Eaton SB, Konner M. Paleolithic nutrition. A consideration of its nature and current implications. *N Engl J Med*. 1985;312:283-289.
72. Michell AR. Physiological basis of nutritional requirement for sodium. *The Clinical Biology of Sodium: The Physiology and Pathophysiology of Sodium in Mammals*. New York: Elsevier Science Ltd; 1995: 105-122.
73. 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;297:319-328.
74. Blackburn H, Prineas R. Diet and hypertension: anthropology, epidemiology, and public health implications. *Prog Biochem Pharmacol*. 1983;19:31-79.
75. Gleibermann L. Blood pressure and dietary salt in human populations. *Ecol Food Nutr*. 1973;2:143-156.
76. Weaver CM, Martin BR, McCabe GP, et al. Individual variation in urinary sodium excretion among adolescent girls on a fixed intake. *J Hypertens*. 2016;34:1290-1297.
77. Rakova N, Juttner K, Dahlmann A, et al. Long-term space flight simulation reveals infradian rhythmicity in human Na(+) balance. *Cell Metab*. 2013;17:125-131.
78. Lerchl K, Rakova N, Dahlmann A, et al. Agreement between 24-hour salt ingestion and sodium excretion in a controlled environment. *Hypertension*. 2015;66:850-857.
79. Cogswell ME, Maalouf J, Elliott P, Loria CM, Patel S, Bowman BA. Use of urine biomarkers to assess sodium intake: challenges and opportunities. *Annu Rev Nutr*. 2015;35:349-387.
80. Cogswell ME, Elliott P, Wang CY, Rhodes DG, Pfeiffer CM, Loria CM. Assessing U.S. sodium intake through dietary data and urine biomarkers. *Adv Nutr*. 2013;4:560-562.
81. John KA, Cogswell ME, Campbell NR, et al. Accuracy and usefulness of select methods for assessing complete collection of 24-hour urine: a systematic review. *J Clin Hypertens (Greenwich)*. 2016;18:456-467.
82. Wielgosz A, Robinson C, Mao Y, et al. The impact of using different methods to assess completeness of 24-hour urine collection on estimating dietary sodium. *J Clin Hypertens (Greenwich)*. 2016;18:581-584.
83. McLean RM. Measuring population sodium intake: a review of methods. *Nutrients*. 2014;6:4651-4662.
84. 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.
85. Campbell N. 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;32:2499-2500.
86. He FJ, Ivkovic V, Jelakovic B, Morris J, MacGregor GA. Estimation of sodium excretion should be made as simple as possible, but not simpler: misleading papers and editorial on spot urines. *J Hypertens*. 2015;33:884-886.
87. Dougher CE, Rifkin DE, Anderson CA, et al. Spot urine sodium measurements do not accurately estimate dietary sodium intake in chronic kidney disease. *Am J Clin Nutr*. 2016;104:298-305.
88. Huang L, Crino M, Wu JH, et al. Reliable quantification of the potential for equations based on spot urine samples to estimate population salt intake: protocol for a systematic review and meta-analysis. *JMIR Res Protoc*. 2016;5:e190.
89. Panel on Dietary Reference Intakes for Electrolytes and Water-Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. *Dietary Reference Intakes for Water, Potassium, Sodium, Chloride and Sulfate*. Scientific evaluation of dietary reference. Washington, DC: National Academies Press; 2005.
90. Sterns RH. Disorders of plasma sodium–causes, consequences, and correction. *N Engl J Med*. 2015;372:55-65.
91. Wang CY, Carriquiry AL, Chen TC, et al. Estimating the population distribution of usual 24-hour sodium excretion from timed urine void specimens using a statistical approach accounting for correlated measurement errors. *J Nutr*. 2015;145:1017-1024.
92. 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.
93. Peng Y, Li W, Wang Y, et al. Validation and assessment of three methods to estimate 24-h urinary sodium excretion from spot urine samples in Chinese adults. *PLoS One*. 2016;11:e0149655.
94. Mann JI. Evidence-based nutrition: does it differ from evidence-based medicine? *Ann Med*. 2010;42:475-486.
95. Strazzullo P. Benefit assessment of dietary salt reduction: while the doctors study, should more people die? *J Hypertens*. 2011;29:829-831.
96. World Cancer Research Fund. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: A Global Perspective*. Washington: American Institute for Cancer Research; 2007.
97. Kearns CE, Schmidt LA, Glantz SA. Sugar industry and coronary heart disease research: a historical analysis of internal industry documents. *JAMA Intern Med*. 2016;176:1680-1685.
98. The World Health Organization. A comprehensive global monitoring framework including indicators and a set of voluntary global targets for the prevention and control of noncommunicable diseases. Second WHO discussion paper. Geneva. 08.01.2013 2012.
99. World Health Organization. SHAKE the salt habit. The SHAKE technical package for salt reduction; 2016. http://www.who.int/dietphysicalactivity/publications/shake-salt-habit/en/. Accessed January 11, 2017.
100. Pan American Health Organization. Salt-smart Americas: a guide for country level action; 2013. http://www.paho.org/hq/index.php?option=com_docman&task=doc_download&gid=21554&Itemid=270&lang=en. Accessed January 11, 2017.
101. Trieu K, Neal B, Hawkes C, et al. Salt reduction initiatives around the world - a systematic review of progress towards the global target. *PLoS One*. 2015;10:e0130247.
102. McLaren L, Sumar N, Barberio AM, et al. Population-level interventions in government jurisdictions for dietary sodium reduction. *Cochrane Database Syst Rev*. 2016;9:CD010166.
103. Tuomilehto J, Jousilahti P, Rastenyte D, et al. Urinary sodium excretion and cardiovascular mortality in Finland: a prospective study. *Lancet*. 2001;357:848-851.
104. Cappuccio FP. Sodium and cardiovascular disease. *Lancet*. 2016;388:2112.

105. Campbell NR, Cappuccio FP. Dietary salt and blood pressure: verdict is clear so why any debate? *Hypertens J*. 2016;2:57-69.
106. Oparil S. Low sodium intake—cardiovascular health benefit or risk? *N Engl J Med*. 2014;371:677-679.
107. Arcand J, Webster J, Johnson C, et al. Announcing "up to date in the science of sodium." *J Clin Hypertens (Greenwich)*. 2016;18:85-88.
108. World Health Organization. Global action plan for the prevention and control of noncommunicable diseases 2013-2020; 2013. http://www.who.int/nmh/events/ncd_action_plan/en/. Accessed January 11, 2017.

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