Population Dietary Salt Reduction and the Risk of Cardiovascular Disease: A Commentary on Recent Evidence

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Raised blood pressure (BP) is the leading cause of death and disability in adults worldwide, mainly due to cardiovascular disease (CVD). The risk of CVD increases progressively with increasing BP. However, the majority of CVD deaths and morbidity attributable to BP occur at a level around or below 140/90 mm Hg, because there are so many individuals in the population with BP below these levels. Based on recommendations from clinical guidelines, the majority of these individuals would not be treated with drugs. Furthermore, there is a graded relationship between BP and CVD down to at least 115/75 mm Hg. Therefore, a population-approach through nonpharmacological measures (diet and lifestyle) is the most feasible option to prevent BP-related adverse outcomes and is recommended by the World Health Organization[1] and adopted under a United Nations resolution of the 66th World Health Assembly in 2013.[2]

High salt intake is associated with high BP and a moderate reduction in salt consumption causes a significant reduction in BP.[3] Furthermore, in well-conducted cohort studies[4,5] and in few intervention trials,[6] lower salt consumption is associated with reduced cardiovascular events.

A recent publication in *The Lancet*[7] has reported that low salt intake is associated with a high risk of CVD. The paper methodology suffers from flaws that have been repeatedly addressed in the medical literature in recent years and that are ignored.[8]

First, the study reported in *The Lancet* used a morning spot urine sample to estimate usual salt intake. The use of sodium concentrations from a single morning urine fasting sample extrapolated to 24-hour urinary sodium excretion using the Kawasaki formula is an inappropriate method for estimating salt intake in individuals.[9–11] The authors' reference to their validation,[12] critiqued at the time of its publication,[13] neglects the presence of a significant bias when estimating individuals' sodium excretion, as shown in the Bland-Altman plots, results superimposable to other validations.[9–11] They also do not mention that a similar validation in the Chinese cohort of the Prospective Urban Rural Epidemiology (PURE) study presents the results with less confidence.[14] The authors insist on the concept (uncritically repeated in the editorial)[15] that the method could be useful to assess group means. However, they use data on individuals when assessing risk prediction in a cohort study design. This is misleading as it has been long established that several 24-hour urine collections are needed to approximate an individual's salt intake with a high degree of confidence (ie, within 10%) and without bias.[16–18] In contrast, cohort studies that use the method of repeated 24-hour urine collections to assess salt intake show beyond doubt a linear graded relationship between sodium excretion and cardiovascular outcomes with no increase at lower sodium intakes.[4,5]

Second, the present study is a republication of previous data from the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE Intolerant Subjects With Cardiovascular Disease (TRANSCEND)[19] and from the PURE study,[20] with the addition of EpiDREAM (study of screenees from the DREAM trial). Not surprising, the results in this "larger" sample are confirmatory of their previous results. There are several considerations to make. The authors split a continuously distributed biological variable in the population (BP) in a biological meaningless dichotomy of "hypertension" and "normotension." By doing that, they reduced the statistical power of detecting relationships, particularly when studying trends. Similarly, in randomized controlled trials, salt reduction was shown not to impact cardiovascular events when dichotomized into hypertensive and normotensive categories[21] but had a statistically significant impact on cardiovascular events in the studies overall.[6]

An important point is the consistent use of sick populations and patient groups to study the implications of a moderate reduction in salt consumption in the general population. The ONTARGET/TRANSCEND study selected 28,800 participants from a high-risk population to undergo randomized clinical trials of antihypertensive treatments. Patients were old (66.5±7.2 years, with patients 2.4 years older in the low sodium group), 71% were men of white European background (but the low sodium group included 54% women), all with significant previous disease (48% with myocardial infarctions, 21% cerebral vascular accidents, 70% hypertension, and 37% diabetes), and all highly medicated with β-blockers (57%), diuretics

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(29%), calcium channel blockers (35%), or blockers of the renin-angiotensin system (≈75%). More interesting, the proportion of patients taking diuretics was higher in both the low (41%) and the high (43%) sodium groups (see Table I in O'Donnell and colleagues).[19] The reported higher cardiovascular mortality in the low sodium group was, in fact, only detected in the composite outcome of total cardiovascular death (see Table II in O'Donnell and colleagues).[19] This was exclusively accounted for by excess heart failure in this group, but not excess myocardial infarction, stroke, or noncardiovascular death. Taken together, the results suggest that the overrepresentation in the low sodium group of patients at high risk for heart failure, who are more likely to take diuretics and are at higher risk of death, explains the high mortality rates detected in that group (reverse causality). Similar attention should be given to the PURE study, an ongoing epidemiological cohort study that has enrolled more than 156,000 individuals in 17 countries. This sodium study reported on only 102,000 participants (65% of the original cohort) who were able to provide a urine sample. Compared with the overall original cohort, the sodium cohort had fewer participants from India (5% vs 18%) and more from China (42% vs 30%), with unbalanced distribution across sodium groups (see Table I in O'Donnell and colleagues).[20] The low sodium group was 2.8 years older, had fewer men (29.6% vs 58.1%), fewer participants of Asian ancestry (33.8% vs 73.0%), more with a history of CVD (9.2% vs 7.1%) and diabetes (10.6% vs 8.4%), and a greater proportion of people taking regular medications, suggesting the presence of self-selected sicker participants in the low sodium group. These imbalances are likely the result of self-selection bias and incorrect assessment of sodium intake. Studies with more stringent quality features have been able to avoid such biases and have obtained more reliable results.[5] Finally, EpiDREAM screened people at high risk for type 2 diabetes, with the majority being of non-European ethnicity and over 70% being obese women, and with a high proportion of treated individuals.[22] None of these studies' results can be generalized to inform current public health strategies for a moderate reduction in sodium consumption in populations or to be considered of good quality to support a causal relationship between low sodium intake and increased cardiovascular mortality.[23]

In conclusion, the evidence supporting global actions for a moderate reduction in salt consumption to prevent CVD is strong and the recent study from the *The Lancet*[7] should not overturn the concerted public health action to reduce salt intake globally.

Conflict of Interests: Dr Cappuccio is an unpaid member of Consensus Action on Salt and Health (CASH), World Action on Salt and Health (WASH), the UK National Forum, advisor to the World Health Organization, and trustee of the Student Heart Health Trust, a Registered Charity. Dr Campbell is a volunteer member of WASH and receives a consulting fee from the Novartis Foundation for assisting in hypertension control programs in low- and middle-income countries.

References

1. World Health Organization. *Guideline: Sodium Intake for Adults and Children*. Geneva: World Health Organization; 2012:1–46.
2. Sixty-Sixth World Health Assembly follow-up to the political declaration of the high-level meeting of the General Assembly on the Prevention and Control of Non-communicable Diseases. http://apps.who.int/gb/ebwha/pdf_files/WHA66/A66_R10-en.pdf. Accessed September 9, 2016.
3. Aburto NJ, Ziolkovska A, Hooper L, et al. Effect of lower sodium intake on health: systematic review and meta-analyses. *Br Med J*. 2013;346:f1326.
4. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. *Circulation*. 2014;129:981–989.
5. Mills KT, Chen J, Yang W, et al. Sodium excretion and the risk of cardiovascular disease in patients with chronic kidney disease. *JAMA*. 2016;315:2200–2210.
6. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. *Lancet*. 2011;378:380–382.
7. 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.
8. 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.
9. Cogswell ME, Wang C-Y, Chen T-C, et al. Validity of predictive equations for 24-h urinary sodium excretion in adults aged 18-39 y. *Am J Clin Nutr*. 2013;98:1502–1513.
10. Wang C-Y, Cogswell ME, Loria CM, et al. Urinary excretion of sodium, potassium, and chloride, but not iodine, varies by timing of collection in a 24-hour calibration study. *J Nutr*. 2013;143:1276–1282.
11. Ji C, Venezia A, Miller MA, et al. Comparisons of spot vs 24-h urine samples for estimating population salt intake: validation study in two independent samples of adults in Britain and Italy. *Nutr Metab Cardiovasc Dis*. 2014;24:140–147.
12. 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;32:1005–1015.
13. 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.
14. 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(2):e0149655.
15. O'Brien E. Salt – too much or too little? *Lancet*. 2016;388:439–440.
16. Liu K, Dyer AR, Cooper RS, et al. Can overnight urine replace 24-hour urine collection to assess salt intake? *Hypertension*. 1979;1:529–536.
17. Siani A, Iacoviello L, Giorgione N, et al. Comparison of variability of urinary sodium, potassium, and calcium in free-living men. *Hypertension*. 1989;13:38–42.
18. 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.
19. O'Donnell M, Yusuf S, Mente A, et al. Urinary sodium and potassium excretion and risk of cardiovascular events. *JAMA*. 2011;306:2229–2238.
20. O'Donnell M, Mente A, Rangarajan S, et al. PURE Investigators Urinary sodium and potassium excretion, mortality, and cardiovascular events. *N Engl J Med*. 2014;371:612–623.
21. Taylor RS, Ashton KE, Moxham T, et al. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane Review). *Am J Hypertens*. 2011;24:843–853.
22. Anand SS, Dagenais GR, Mohan V, et al. Glucose levels are associated with cardiovascular disease and death in an international cohort of normal glycaemic and dysglycaemic men and women: the EpiDREAM cohort study. *Eur J Cardiovasc Prev Rehabil*. 2012;19:755–764.
23. Cogswell ME, Mugavero K, Bowman BA, Frieden TR. Dietary sodium and cardiovascular disease risk—measurement matters. *N Engl J Med*. 2016;375:580–586.