June 1, 2016

Dear Dr. Minhas,

We are delighted to submit our revised original research investigation "Population Strategies to Decrease Sodium Intake: A Global Cost-Effectiveness Analysis."

We have made substantial revisions in response to the Editor and Reviewer comments, which were very thoughtful and helpful. Specific changes are detailed in the pages below.

As highlighted by the reviewers, these findings are novel, relevant, and important for the medical, science, policy, and public communities. We believe the manuscript is greatly improved, and we hope it is now suitable for publication.

We look forward to your thoughts.

Best regards,

Dariush Mozaffarian, MD DrPH

Editors Comments:

*Please respond in detail, with a point by point response to the reviews comments about the J shaped curve.

We have responded to this point in detail, as described in our responses below (see each of our responses to Reviewer #4).

*Please respond in detail to the issues regarding the one size fits all approach in the model.

A key strength of our investigation is the explicit accounting for geographic, age, and sex differences in current sodium intake, hypertension prevalence, and CVD rates, not only across countries and regions, but within countries including by age and sex. Importantly, we also further account for differences in the effects of sodium reduction on BP by age, hypertensive status, and race, and in the effect of BP-lowering on CVD by age. Thus, the model includes and accounts for each of these sources of heterogeneity, as well as for the uncertainty in each of these measures.

We note that use of the WHO costing framework already accounts for some sources of variation by country, in terms of specific resources required and costs given country characteristics. Yet, we agree that details of planning, development, and implementation may further vary from country to country beyond what is captured by the costing tool. We also agree that achieved effectiveness will vary from country to country. Our base model assumes an average cost of this framework (adjusted for in-country differences in resource use and costs, based on the WHO costing tool), and an average effectiveness. To understand the robustness of our findings to these assumptions, we tested widely varying costs (including variations in resource use and cost of between 0.25 and 5-fold the base), and intervention effectiveness (including 10% and 30% proportional reductions and 0.5 g/d and 1.5 g/d absolute reductions). Together, these findings provide a broad range of possible scenarios against which to evaluate the cost-effectiveness of the intervention. For a multi-national CEA, we propose that this range of sensitivity analyses (including an up to 20-fold variation in already PPP-adjusted total costs) reasonably accounts for uncertainty and variation across nations.

We agree that a similar intervention may produce a different sodium reduction in different countries. In a country with very high intake, the intervention may produce a much larger absolute decline than in a country with very low intake. In this case, use of similar proportional reductions (e.g. 10% each) is appropriate. On the other hand, one could argue that the intervention could have a similar absolute effect regardless of the starting level. In this case, use of similar absolute reductions (e.g. 1.5 g/d each) is appropriate. To understand the robustness of our findings to varying effectiveness in different nations, we accordingly tested varying intervention effectiveness including 10% and 30% proportional reductions and 0.5 g/d and 1.5 g/d absolute reductions. For readers interested in the effect of different reductions on given countries/regions, we now provide these results for every country in the supplementary materials.

We have clarified each of these important issues in the revised manuscript.

Reviewer: 1

I am fairly familiar with published cost-effectiveness analyses on sodium reduction – and based on this I can confidently say that is a very high quality study. It has very strong methods (especially around various aspects of uncertainty and the use of a Bayesian hierarchical model etc.) and of course has extremely impressive breadth (181 countries). It is a very substantial contribution to the literature.

We appreciate these positive comments, and our aims were indeed to bring both methodological rigor and breadth to this important topic.

1.   Methods – 2nd paragraph on reasons for not considering healthcare savings from avoided CVD events. Including such cost savings would be optimal as per current best health economic practice (see publications on this topic by van Baal). Hence this should be considered a study limitation and noted in the Discussion – but it is also a limitation which is entirely reasonable given the logistics involved in obtaining cost savings data for 181 countries. (Indeed this latter reason is given in the Discussion – but needs to be reiterated in the Methods).

We agree. We have now further emphasized this point in the manuscript Methods and Discussion, as suggested.

2.   In the e-Discussion the intervention is described as involving "drafting a regulatory code, designing enforcement plans" – so this actually looks to this reviewer like mandatory regulations backed up by law are the interventions. This seems to be in contrast to the main text where the intervention is similar to the UK with "government-supported industry targets". Perhaps then the intervention needs to be clarified more in the Methods Section – is this voluntary or mandatory (or a mix of soft and hard law depending on the country – but with the same effect achieved as per the UK intervention). Of course a new law can also be supported by a media campaigns as well.

Thank you for this important point. Based on the modest magnitude of effect, we modelled a program of government-supported industry targets, similar to the UK model. As you know, a program of mandatory regulations would likely have larger effects, at lower cost; but may be less politically feasible in many countries. We have clarified both of these issues in the Methods.

3.   Following on from the above, the Discussion could potentially be a little stronger around discussing the issue that in some countries, sodium reduction might be achieved most efficiently and cost-effectively through straight out new mandatory regulation. Nevertheless, the UK approach of voluntary agreements (possibly with the implicit threat of regulation if not successful) might still be the most feasible approach in some countries (depending on the political setting).

We agree; these relevant issues have been added to both the Methods and the Discussion.

4.   Fairly optional – but it would be good to provide more context around other possible strategies the authors could mention that taxing salt may also be an option for countries (as per various modelling studies [1] [2] and currently utilized in 3 countries [see the recent systematic review by Trieu et al 2015

in PLoS One]). Indeed, this could be more cost-effective than voluntary regulations since it can raise revenue for fiscally constrained governments – and allow improved spending on health. Other salt reduction measures could also be mentioned, e.g., improvements in food labelling

We have added a very brief mention of other policy options in the Discussion as suggested.

5.   Many of the published cost-effectiveness studies around sodium reduction indicate that such interventions are actually cost-saving (when considering averted healthcare costs – and even when extra health costs associated with longer lives are also allowed for [2]). So it could be stated more clearly in the Discussion that if such costs were considered in this type of modelling, then it could be likely that such sodium reduction interventions would be cost-saving (from a health sector perspective). Furthermore, if a wider societal perspective was taken (to include reductions of productivity loss) then sodium reduction interventions may be even more attractive.

We agree, and have added these points to the Discussion as suggested.

6.   Fairly optional – but could say in the Discussion that the WHO benchmarks for CE thresholds do have limitations [3] – but that the WHO benchmarks are still probably the most practical approach for studies such as this.

Thank you; we have added this point to the Methods.

Fairly minor:

7.   At first use of "UI" use "uncertainty interval"
Thank you, corrected.

8.   In the Discussion – where "vascular stiffness" is mentioned, could clarify that this is "independent of raised blood pressure"?
Thank you. This has been clarified.

9.   Table 1 – the "Population" – presumably this should also say "adult"
Thank you, corrected.

10.   Figure 3 – at least on my PDF version, the alignment of the words with the dots could be improved.
Thank you, corrected.

11.   References need to be in BMJ style.
Thank you, corrected.

Thank you for your thoughtful review and helpful comments.

References

1.   Smith-Spangler CM, Juusola JL, Enns EA, Owens DK, Garber AM: Population strategies to decrease sodium intake and the burden of cardiovascular disease: a cost-effectiveness analysis. Annals of internal medicine 2010, 152(8):481-487, W170-483.
2.   Nghiem N, Blakely T, Cobiac LJ, Pearson AL, Wilson N: Health and economic impacts of eight different dietary salt reduction interventions. PLoS One 2015, 10(4):e0123915.
3.   Marseille E, Larson B, Kazi D, Kahn J, Rosen S: Thresholds for the cost-effectiveness of interventions: alternative approaches. Bull World Health Organ 2015, 93:118-124.

Additional Questions:
Please enter your name: Nick WILSON
Job Title: Associate Professor
Institution: University of Otago, Wellington

Reviewer: 2

This is an interesting topic and policy relevant for population health promotion.

We appreciate these positive comments, and agree with the importance and relevance of this topic.

1. Intervention costs and effectiveness of interventions are questionable. Obviously, one framework of planning-development-partial implementation-full implementation should not work for all the countries.

Thank you for raising this important issue. We note that use of the WHO costing framework already accounts for some sources of variation by country, in terms of specific resources required and costs given country characteristics. Yet, we agree that details of planning, development, and implementation may further vary from country to country beyond what is captured by the costing tool. We also agree that achieved effectiveness will vary from country to country. Our base model assumes an average cost of this framework (adjusted for in-country differences in resource use and costs, based on the WHO costing tool), and an average effectiveness. To understand the robustness of our findings to these assumptions, we tested widely varying costs (including variations in resource use and cost of between 0.25 and 5-fold the base), and intervention effectiveness (including 10% and 30% proportional reductions and 0.5 g/d and 1.5 g/d absolute reductions). Together, these findings provide a broad range of possible scenarios against which to evaluate the cost-effectiveness of the intervention. For a multi-national CEA, we propose that this range of sensitivity analyses (including an up to 20-fold variation in already PPP-adjusted total costs) reasonably accounts for uncertainty and variation across nations. We have added further discussion of these important issues to the manuscript.

2. If the full-implementation stage begins in year 6, the intervention effects should likely start thereafter.

Empirical experience with other national efforts to reduce additives, such as trans fat in the US, Denmark, and other nations and sodium in the UK, suggest that reductions begin as soon as national government efforts start in earnest. For example, when national nutrition facts labeling of trans fat was proposed in the US, many companies began to eliminate trans fat from their products even before the labeling went into effect. For those food products that can be easily reformulated or removed from the market, action happens very quickly (often even preceding finalization of the government process); other products need a bit more time; and other products, substantially more time. Thus, we modeled 1/10th progress in each year, over 10 years.

3. How can the intervention costs and effects on sodium intake in each country be aggregated into country groups by income level and/or geographic regions?

All analyses were performed by estimating costs at the national level and effects on sodium intake, BP, and CVD by age-sex-country strata. Effects across within-country strata were summed to derive national effects. To aggregate findings across countries by income level or geographic region, we calculated the population-weighted average of costs and CVD events across the relevant nations, as done by other similar CEA.

4. *It was not clear why the 10-year period is chosen for the analysis. Because Sodium intake affects hypertension immediately and CVD in longer run, are these facts considered in the model?*

Thank you for these important questions.

This timeframe was selected based on the experience of the UK, which achieved a 14.7% (1.4 g/d) reduction in population sodium consumption over 10 years. Similar programs in other nations, such as Turkey, achieved similar sodium reductions over shorter periods (4 years). We chose to be conservative and use a longer time period of 10 years, which is also the framework for costs from the WHO costing tool.

Randomized trials of BP-lowering therapies demonstrate rapid reductions in CVD events, within less than one year. Our intervention is scaled over 10 years (e.g., a 10% reduction in sodium over 10 years), and thus assuming concurrent gradual benefits in CVD is biologically reasonable. We have added this point to the Methods.

5. *Coming back to area variations, because the current sodium intake levels as well as hypertension/CVD prevalence levels differ across countries and regions, the effectiveness of intervention on sodium intake as well as on hypertension/CVD prevalence should differ. I don't believe the model can handle these issues well. For example, in high sodium intake countries with high prevalence of hypertension/CVD, a 10% reduction in sodium intake may be highly clinically effective. In such regions, 15% sodium reduction may be a reasonable or feasible target. Could the model use different sodium reduction targets for the analysis?*

Agreed: these are crucial points. A key strength of our investigation is the detailed accounting for these differences in current sodium intake, hypertension prevalence, and CVD rates, not only across countries and regions, but within countries including by age and sex. Crucially, we also further account for differences in the effects of sodium reduction on BP by age, hypertensive status, and race. Thus, the model includes and accounts for each of these sources of heterogeneity, as well as for the uncertainty in each of these measures.

We also agree that a similar intervention may produce a different sodium reduction in different countries. In a country with very high intake, the intervention may produce a much larger absolute decline than in a country with very low intake. In this case, use of similar proportional reductions (e.g. 10% each) is appropriate. On the other hand, one could argue that the intervention could have a similar absolute effect regardless of the starting level. In this case, use of similar absolute reductions (e.g. 1.5 g/d each) is appropriate. To understand the robustness of our findings to varying effectiveness in different nations, we accordingly tested varying intervention effectiveness including 10% and 30% proportional reductions and 0.5 g/d and 1.5 g/d absolute reductions. For readers interested in the effect of different reductions on given countries/regions, as you suggest, we now provide these results for every country in the supplementary materials. We have clarified these issues in the manuscript.

6. *Finally, two minor issues: Why don't use U.S. $ directly. Few people understand the international $. And what is standardized population?*

As you know, international dollars provide accurate cross-country comparisons that take into account not only currency differences but also purchasing power. One $I in any given country can be interpreted as the funds needed to purchase the same amounts of goods/services in that country as $1 US would purchase. Thus, in a sense, $I is directly interpretable to US dollars. We have clarified this in the paper.

eTable 1 provides an example of the estimated resource needs for an example country of 50 million people, split into provinces of 5 million each. We have revised the terminology to "example", rather than "standardized", country. We have also clarified in the table footnotes the characteristics of this example country.

Thank you for your thoughtful review and helpful comments.

Additional Questions:
Please enter your name: Guijing Wang
Job Title: Senior Health Economist
Institution: Centers for Disease Control and Prevention (CDC)

Reviewer: 3

1. It is generally accepted that population level sodium reduction is potentially a highly cost effective public health intervention. Thus this paper cannot be regarded as novel or highly original. However it provides an extremely detailed and comprehensive estimates of the cost effectiveness of sodium reduction strategies worldwide. Given the scope and execution of the analyses, it effectively extends and complements earlier papers focused on specific countries and regions. The findings are clear and definitive and I expect that this paper will become one of the standard references on the cost effectiveness of population level sodium reduction strategies.

We appreciate these positive comments, and agree with this specific originality and importance of our investigation.

2. Importance of work to general readers - does this work matter to clinicians, patients, teachers, or policymakers? Is a general journal the right place for it? The work is primarily of relevance to policy makers. However it is also highly relevant to clinicians given their key role in guiding and informing the policy agenda.

We agree with and appreciate these positive comments.

3. Scientific reliability: No issues of concern. The authors draw on high level and relevant expertise in public health nutrition, epidemiology and economics. The sensitivity analyses addressing the effects of altering the lower threshold for benefits of sodium reduction is of particular significance and is clearly described.

We appreciate these comments. Our aim was indeed to bring methodological rigor to this important topic.

4. The results address the research question and are credible. The presentation of findings from cost effectiveness studies of this nature in a general medical journal with a largely non specialist readership poses significant challenges. The authors have addressed this challenge well. The tables and figures provide a clear and comprehensive overview of the main findings. There may be an issue in relation to the number of tables and figures for the print version of the paper. The overall message/ conclusion is admirably clear, succinct and well written.

Thank you for these helpful and positive comments.

5. The authors should cite recent studies that have suggested an increased risk of cardiovascular disease or death among people consuming less than 3.0 g of sodium per day, as compared with average intake, e.g. N Engl J Med 2014; 371:1267. While this paper and others with similar findings have significant methodological flaws, it is important in the discussion of the current paper to emphasize that this worse case (and highly implausible scenario) for sodium reduction has been addressed in the sensitivity analyses.

This is an excellent point. We have added this citation to the Methods as well as more detailed discussion of these issues of the dose-response relationship between sodium intake and CVD, including conclusions of current national and international bodies. More details can be found below in in our responses to Reviewer #4.

Thank you for your thoughtful review and helpful comments.

Ivan J Perry, MD, PhD
Professor of Public Health
Department of Epidemiology & Public Health
Room 4.18
Western Gateway Building

Additional Questions:
Please enter your name: Ivan Perry
Job Title: Professor of Public Health
Institution: University College Cork

Reviewer: 4

1. This modeling exercise should confront the body of evidence accumulated over the past 25 years, as well as the conclusions of the 2013 Institute of Medicine (IOM) report. The methodology applied in this kind of modeling exercise was appropriate in 1991, but scientific evidence accumulated since then has rendered invalid its application in 2015.

We appreciate your perspective, and agree with the importance of addressing these issues.

As you know, the 2013 IOM report was not intended to identify the optimal level of sodium consumption nor to systematically review all available evidence that would be needed to make such a determination. That IOM committee was tasked with a very focused question: to assess, based only on studies of clinical events (i.e., not reviewing any other type of data), whether sufficient evidence existed to support a 1500 mg/d target for all or subsets of the population, as opposed to a 2300 mg/d target for all. This task was assigned for a very specific reason: due to multinational food industry questioning of the 2010 DGAC conclusions that 1500 mg/d should be the target for all Americans, rather than 2300 mg/d. The 2013 IOM report did not systematically assess whether sufficient evidence existed from other types of evidence (e.g., trials of BP and other surrogate endpoints, cross-national analyses, animal experiments) for a 1500 vs. 2300 mg/d target. The 2013 IOM report was also not a comprehensive review nor assessment of the CVD effects of sodium reduction generally.

The 2013 IOM committee concluded, appropriately, that based only on studies of clinical events and not considering other types of evidence, insufficient evidence exists to support a 1500 mg/d target for all or subsets of the population, as opposed to a 2300 mg/d target for all. We agree with that conclusion, for that specific question, based on that selected evidence. So that their report would not be incorrectly characterized as a comprehensive review or assessment of the CVD effects of sodium reduction generally, the 2013 IOM report made sure to emphasize that, based on prior IOM reports and other available data, the body of evidence still supports sodium reduction to reduce CVD. (We detail the two conclusions of the IOM report, for general populations, in our further responses below.)

In the revised manuscript, we provide more discussion of data on the dose-response relationship between sodium intake and CVD, including citing the 2013 IOM report and other reports of national and international organizations.

2. An exercise in modeling, while not providing actionable information, can make an important contribution to scientific progress. Their value, however, depends upon the validity of the underlying assumptions upon which the model is based. To be make a meaningful contribution, this model must provide compelling evidence that each of its underlying, separate components are valid. For example, does blood pressure to CVD events have a linear relation to outcomes in the general population? To my knowledge, there is no evidence that reducing systolic BP to less than 140 mmHg is beneficial. In fact, in several randomized trials, reductions to less than 140 mmHg have led to increased morbidity and mortality. Thus, there is no support for the hope that the vast majority of adults could benefit from reducing pressure – and some evidence of potential harm.

We respectfully disagree with this perspective. Prospective cohort studies, of course, show log-linear reductions in CVD risk with lower BP levels, including below 140 mm Hg (*Lancet* 2002; 360: 1903–13). Recent meta-analyses of RCTs have also addressed this question. Among 108 RCTs (464,000 subjects) of BP-lowering (vs. placebo or drug-drug comparisons), all classes of drugs generally had very similar effects as that predicted by cohort studies of BP in general populations (Law et al BMJ. 2009;338:b1665). Furthermore, percentage reductions in CHD and stroke were very similar regardless of BP before treatment, down to 110 mm Hg systolic and 70 mm Hg diastolic (see Fig 5 in that report).

In a separate meta-analysis of 19 trials (44,989 subjects) specifically designed to test the question of more intensive vs. less intensive BP-lowering, patients randomized to more intensive BP-lowering had mean BP levels of 133/76 mm Hg, compared with 140/81 mm Hg in the less intensive treatment group (Xie X et al., Lancet 2016;387:435-43). Intensive blood pressure-lowering treatment achieved RR reductions for major cardiovascular events (14% [95% CI 4-22]), MI (13% [0-24]), and stroke (22% [10-32]), with nonsignificant trends in reductions for CVD death (9% [-11 to 26]) and total mortality (9% [-3 to 19]). The reduction in major cardiovascular events was consistent across patient groups, and additional blood pressure lowering had a clear benefit even in patients with systolic blood pressure lower than 140 mm Hg.

The recent SPRINT trial further confirms this prior evidence even among very elderly subjects (age 75+ years, mean age 80) (JAMA. 2016 May 19. doi: 10.1001/jama.2016.7050.). In this RCT, intensive (<120 mm Hg) compared with standard (<140 mm Hg) SBP targets led to significantly reduced CVD (HR, 0.66 [95% CI, 0.51-0.85]) and all-cause mortality (HR, 0.67 [95% CI, 0.49-0.91]). The rate of overall serious adverse events was not different between treatment groups (HR, 0.99 [95% CI, 0.89-1.11]).

Of course, the purpose of our present investigation is not to provide a detailed review of the evidence linking BP reduction to CVD. Such evidence has been reviewed and summarized elsewhere. We have added a brief discussion of these issues, including the relevant citations above, to the Methods.

3. Moreover, the model assumes that reduction of sodium, from any starting level, will have the same effect on blood pressure. Unfortunately, a substantial body of evidence that this is not the case. Indeed, the blood pressure effect is very different with meaningful blood pressure reduction with a 1 gm fall in sodium intake (about 1/3 of average daily intake) producing a 2 –3 mmHg fall in average systolic BP. By contrast, with intakes less than the fall is less than 1 mmHg.

We have published a recent meta-analysis of RCTs demonstrating a linear dose-response relationship between sodium reduction and BP reduction (NEJM 2014). We have added this citation to the manuscript. We agree that individual characteristics alter the magnitude of BP reduction for any given decrease in sodium. A strength of our analysis is that we explicitly account for this variation, including by age, race, and hypertensive status.

4. As for the CVD effect, over the 30 years, findings in more than 30 studies involving a 500,000 subjects throughout the world, is consistent with a "J" shaped relation of sodium intake to health outcomes. There is no evidence that intakes of less than 2.5 grams/d is associated with superior health outcomes compared to those with 2.5 – 5.0 g/day.

We agree that there is controversy over the precise ideal level of sodium consumption. As we and others have detailed previously, the unique biases of sodium assessment in observational studies, whether utilizing urine collection or diet questionnaire, are recognized.[1] Some of the most important and best documented are incomplete 24-hour urine collections among sicker individuals, which causes a spurious association between low estimated intake and disease risk; reverse causation causing at-risk subjects, especially those with high blood pressure who are at higher risk, to actively lowering their sodium; confounding by physical activity, given the strong positive correlation between sodium intake and total energy intake; and confounding by general health and appetite, due to the same strong correlation between sodium intake and total energy intake.

The overall impact of these biases is conceptually similar to the "J-shape" initially seen between BMI and mortality, which disappears when appropriately adjusting for their presence. During extended surveillance in a large sodium reduction trial, which overcomes many of these limitations, subjects with intakes<2300mg/d experienced 32% lower CVD risk than those consuming 3600-4800mg/d, with evidence for linearly decreasing risk.[3]

Every major national and international organization that has reviewed all of the evidence agrees that high sodium increases CVD risk, and that lowering sodium reduces such risk. While the precise optimal level remains uncertain, the optimal intake identified by these organizations ranges from < 1200 mg/d (UK National Institute for Health and Clinical Excellence 2025 target) to < 1500 mg/d (American Heart Association) to < 2000 mg/d (World Health Organization) to < 2300 mg/d (2015 Dietary Guidelines for Americans) to < 2400 mg/d (UK Food Standards Agency). We utilized <2000 mg/d (WHO) for our main analysis, and in sensitivity analyses, also evaluated a higher cutpoint of 3000 mg/d for optimal intake.

We have added more details on these issues to the Methods.

5. This data and the multiple adverse effects associated with too little sodium intake, and the well demonstrated dissociation of blood pressure and morbidity and mortality, in multiple observational studies, led the Institute of Medicine to specifically conclude that "blood pressure is not a surrogate for the health effects of sodium reduction".

We are unaware of any formal IOM conclusion in this regard.

The 2010 IOM report on biomarkers pointed to the wide acceptance of BP as a surrogate marker of CVD. This committee identified blood pressure as "an exemplar surrogate endpoint for cardiovascular mortality and morbidity due to the levels and types of evidence that support its use" (IOM, 2010, p. 39).

In the 2013 IOM report, the conclusions for sodium intake in the general population were:

"Conclusion 1: Although the reviewed evidence on associations between sodium intake and direct health outcomes has methodological flaws and limitations, the committee concluded that, when considered collectively, it indicates a positive relationship between higher levels of sodium intake and risk of CVD. This evidence is consistent with existing evidence on blood pressure as a surrogate indicator of CVD risk.

Conclusion 2: …The committee determined that evidence from studies on direct health outcomes is inconsistent and insufficient to conclude that lowering sodium intakes below 2,300 mg per day either increases or decreases risk of CVD outcomes."

We agree with these conclusions, and our analysis is consistent with these conclusions (using a cutpoint of 2000 mg/d; as well as 3000 mg/d in sensitivity analyses).

6. A small point is that the claim of falling sodium intake in Great Britain needs to be understood in the context of time. Comparing 2 points in time might leave some unaware that, over a wider period, average Sodium intake has varied widely within the worldwide range of 2.5 – 5.0 g/day and over a wider time frame there has not been a reduction in sodium intake.

Data from other countries, such as the US, over similar periods do not show any decline or major variation in sodium intake. Our recent report on national sodium intakes (BMJ Open, 2013) also did not identify major declines in most countries in the last two decades; indeed, slight increases were identified in many countries.

Thank you for your thoughtful review and helpful comments.

Additional Questions:
Please enter your name: Michael H Alderman
Job Title: Professor of Medicine and Public Health Emeritus
Institution: Albert Einstein College of Medicine
Reimbursement for attending a symposium?: Yes

1. 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**(10):1173-86 doi: 10.1161/CIR.0000000000000015[published Online First: Epub Date]|.
2. O'Donnell M, Mente A, Rangarajan S, et al. Urinary sodium and potassium excretion, mortality, and cardiovascular events. N Engl J Med 2014;**371**(7):612-23 doi: 10.1056/NEJMoa1311889[published Online First: Epub Date]|.
3. Cook NR, Appel LJ, Whelton PK. Lower levels of sodium intake and reduced cardiovascular risk. Circulation 2014;**129**(9):981-9 doi: 10.1161/CIRCULATIONAHA.113.006032[published Online First: Epub Date]|.
4. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. N. Engl. J. Med. 2014;**371**(7):624-34 doi: 10.1056/NEJMoa1304127[published Online First: Epub Date]|.