November 1, 2016

Dear Dr. Minhas,

We are pleased to submit our revised original research investigation "Cost-Effectiveness of a Government-Supported Strategy to Decrease Sodium Intake: A Global Analysis across 183 Nations."

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

We believe the manuscript is now suitable for publication, and look forward to your thoughts.

Best regards,

Dariush Mozaffarian, MD DrPH

Reviewer: 1
Guijing Wang
Health Economist
Centers for Disease Control and Prevention (CDC)

Comments:
I still concern about the cost information. Using the government cost only will make the cost-effectiveness ratio much more appealing. For some countries, the government cost might be so low that it is not reasonable to use it for cost-effectiveness analysis.

Thank you for allowing us to address this important point. We model costs to the government only for several reasons. First, this is the cost that is most relevant to budget-constrained governments, since it is the cost of the program they must bear directly and immediately. Second, net industry sector costs for product reformulation in each country would be very difficult to determine because once the relevant reformulation has been undertaken in any single country, the knowledge of that reformulation can be extended with much less additional cost to other countries. For example, multinational companies transfer improved recipes and reformulation strategies across borders costlessly, as do food scientists moving between firms, and so on. Third, we do not model cost savings due to averted cardiovascular disease events from lower health care costs, lower out-of-pocket medical costs, and higher productivity, given both the lack of such cost and productivity data in every nation and, relevantly, our conservative assumption about the full translation of such savings in practice. Applying these other costs in selected nations would almost certainly further improve the estimated cost-effectiveness and could even make the intervention cost-saving. For example, the single-nation studies of sodium reduction policies of which we are aware that model economy-wide costs, cited in our paper and below, find societal cost savings. As such, using the government cost only, as we do, is conservative: it makes the cost-effectiveness ratio less, not more, appealing. We have further emphasised these points in the revised manuscript.

How many countries have specific programs only aiming to reduce sodium reduction?

Many countries have specific programs and legislation with the sole aim of reducing population sodium intake. As of 2012, for example, a total of 29 European countries, consisting of all EU Member States as well as Norway and Switzerland, had salt reduction initiatives in place. Their programs and progress are described in http://ec.europa.eu/health/nutrition_physical_activity/docs/salt_report1_en.pdf We have added this important detail to the Introduction.

Whether sodium reduction is a public health priority in some countries might be questionable.

Thank you for this comment. By providing country-specific estimates of costs, benefits, and affordability for all countries, we are providing data and evidence to enable policymakers to compare sodium reduction to other potential policy priorities in an informed fashion and in their own local contexts.

I would like to see an extended limitation section on the gaps between the assumed interventions and the real world situation.

Thank you for this helpful suggestion. We agree that there are likely to be gaps between the assumed intervention and the real world situation, and have clarified these in the Discussion, as you suggest.

My judgment is that the cost-effectiveness results of this study are unbelievably appealing. There should be a good explanation to this.

The evidence in our study, as well as that in all prior studies of sodium reduction cost-effectiveness, indicates that such policies are indeed highly cost-effective. The explanation is that this policy is relatively cheap to implement, requiring only "soft regulation" rather than the provision of expensive drugs or hospital care, for example; it also results in decreases in cardiovascular disease risk factors at a population-wide scale, rather than, for example, being delivered only to a small number of individuals. Thus, in contrast to other prevention strategies, there are large 'returns to scale' on both the cost side and the effect side. This explanation accounts for the policy's widely-recognized 'best-buy' status, as well as the results of our study, and we therefore believe the policy deserves careful consideration for adoption by governments worldwide. We have added these important details to the Discussion.

Thank you for your thoughtful review and helpful comments.

1. Selmer RM, Kristiansen IS, Haglerod A, et al. Cost and health consequences of reducing the population intake of salt. Journal of epidemiology and community health 2000;**54**(9):697-702

2. Palar K, Sturm R. Potential societal savings from reduced sodium consumption in the U.S. adult population. American journal of health promotion : AJHP 2009;**24**(1):49-57

3. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. N Engl J Med 2010;**362**(7):590-9

4. 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. Ann Intern Med 2010;**152**(8):481-7

Reviewer: 2
Simon Capewell
Chair of Clinical Epidemiology
University of Liverpool

This is a solid and detailed paper. Salt reduction has been demonstrated previously to be cost saving (or at least very cost effective) So it is good to see this confirmed in an impressive global analysis, country by country. I have no major concerns.

We appreciate these positive comments. Thank you.

Minor stylistic concerns.
BMJ is a UK based journal,
so might it be better to consistently say "salt" rather than "sodium"?

Thank you for this suggestion. Your previous suggestion that we use either “salt” or “sodium” consistently throughout the paper was very helpful. We chose “sodium” both because this is used predominantly in the literature and because our all calculations and results are in terms of sodium rather than salt.

The units also vary unnecessarily
sometimes g/day (conventional for WHO & UK), but occasionally mg/day (potentially confusing).

Thank you for spotting this. We have standardised all units to g/day.

The Discussion is good.
But it might also make the point that mandated reformulation has a further benefit, it tends to REDUCE socio-economic inequalities:

D Gillespie, K Allen, M Guzman Castillo et al. The health equity and effectiveness of policy options to reduce dietary salt intake in England: policy forecast. PLoS ONE 2015; 10 (7) e0134064 doi: 10.1371/journal.pone.0127927

Thank you for this helpful suggestion, which we have incorporated.

Otherwise happy.

Thank you for your thoughtful review and helpful comments.

Reviewer: 3
Lawrence J Appel, MD, MPH
Professor of Medicine
Johns Hopkins University

I read the response statement by the authors, the original reviews by 4 referees, and the revised paper. Except for a few sections, listed in my critique for the authors, I found the paper reasonably clear and now suitable for publication.

We appreciate these positive comments, and are glad that you agree that the paper is now suitable for publication. We are very grateful for all your suggestions to improve the clarity of exposition, in both this and your previous set of comments, which we feel have improved the paper a great deal.

I emphasis 'reasonably clear', because this is a policy-oriented paper which requires an understanding of metrics and analyses that are not familiar to most clinicians. Naturally, some individuals, including referee #1, disagree with core assumptions, but as the authors point out, the vast majority of scientists believe that the BP effects of sodium reduction are sufficient to guide policy making.

We appreciate your reiterating the fact that there is broad scientific consensus on this point. We hope this paper has a large policy impact in reducing sodium intake and cardiovascular disease worldwide.

Comments for authors
This revised paper is now much clearer. Still, I found certain sections difficult to read and have a few suggestions to improve clarity.
Page 9 – eTable 2, not eFigure 1, displays the relative contributions of different components.

Thank you for raising this. In fact, eFigure 1 shows the 'realised' relative contributions of different components across world regions (a function both of quantity requirements, which vary with country sizes and administrative structures, and of local *prices*), whereas eTable 2 displays resource *quantity* requirements only (not prices) for an example country. We have clarified this in the text.

Page 11 and 12 – the section on potential heterogeneity was difficult to read, in large part because key information about references, specifically, the reference threshold of 0.05xGDP/capita, is not displayed in Table 2 or any figure or table. It would be useful to see the threshold clearly displayed as a column by region and country.

Thank you for this excellent suggestion. We have added a column to Table 2 with the reference threshold of 0.05xGDP/capita.

Figure 2 – It would be helpful to the reader to see marks on the colorimetric legend at 1 (indicating cost-effective) and 3 (indicating highly cost effective).

Thank you for this helpful suggestion, which we have incorporated.

Figure 3 – there needs to be additional explanation of the 3 hashed lines, i.e. the meaning of 0.01, 0.05 and 0.1. Are these figures relevant for policy making?

Thank you for raising this. A measure of intervention costs as a multiple of GDP per capita helps policymakers assess affordability in the context of their own country's level of economic development. We selected 0.01x, 0.05x and 0.1x GDP as reasonable 'round' fractions against which to compare our estimates of the affordability of the intervention for the world's 20 most populous countries. All these

levels are far below the usual reference of cost-effectiveness (3.0xGDP) or high cost-effectiveness (1.0xGDP). We have clarified this in the Figure 3 legend.

Thank you once more for your thoughtful and helpful comments.