MJ - Decision on
Manuscript ID
BMJ.2015.027854.R1

Body:

Dear Mr. Webb

Manuscript ID BMJ.2015.027854.R1 entitled "Population Strategies to Decrease Sodium Intake: A Global Cost-Effectiveness Analysis"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying. The paper received some uncritical and effusive reviews, however, more enlightening were the insights from reviewers who provided counter-viewpoints and elaborated on important detail. The paper was at the threshold for rejection based on the reviewers comments about the model validity across countries and clinically (J shaped curve). Therefore, if this paper is to be progressed it is imperative that the reviewers comments are addressed in detail, point by point. You may wish to consider seeking the input or support of a cardiovascular epidemiologist or someones else with sufficient expertise in CV modelling and/or hypertension.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Yours sincerely,

Rubin Minhas
Dr Rubin Minhas
BMJ Associate Editor
rm1000@live.com

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Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: Raphael, Jose Merino, Alison Tonks, Wim Weber, Elisabeth, Jessame Bagganel, Helen MacDonald

"concerns are largely addressable, topic is interesting", "interesting and may be worth pursuing with caveats", "may not be able to take this further until serious reviews addressed", "interesting topic, but has flaws. "

Outcome: Put points

Decision: Put points

Detailed comments from the meeting:

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below.

Please also respond to these additional comments by the committee:

*Please respond in detail, with a point by point response to the reviews comments about the J shaped cuve
*Please respond in detail to the issues regarding the one size fits all approach in the model
*Please respond to all other comments, point by point

** Comments from the external peer reviewers**

Reviewer: 1

Recommendation:

Comments:
Review of: "Population Strategies to Decrease Sodium Intake: A Global Cost-Effectiveness Analysis"

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.

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).

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.

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).

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 utilised 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, eg, improvements in food labelling

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.

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.

Fairly minor:

7. At first use of "UI" use "uncertainty interval"
8. In the Discussion – where "vascular stiffness" is mentioned, could clarify that this is "independent of raised blood pressure"?
9. Table 1 – the "Population" – presumably this should also say "adult"
10. Figure 3 – at least on my PDF version, the alignment of the words with the dots could be improved.
11. References need to be in BMJ style.

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

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

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Reviewer: 2

Recommendation:

Comments:
This is an interesting topic and policy relevant for population health promotion. However, many major concerns should be addressed. First, 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. If the full-implementation stage begins in year 6, the intervention effects should likely start thereafter. This nature on sodium reduction and hypertension/CVD should be considered in the model. How can the intervention costs and effects on sodium intake in each country aggregated into country groups by income level and/or geographic regions? This is highly problematic. Secondly, it was not clear why the 10-year period is chosen for the analysis. What will be the cost-effectiveness results if using 5-year or 15-year as the time horizon? Because Sodium intake affects hypertension immediately and CVD in longer run, are these facts considered in the model? Third, again 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? Finally, two minor issues: Why don't use U.S. $ directly. Few people understand the international $. And what is standardized population?

Additional Questions:
Please enter your name: Guijing Wang

Job Title: Senior Health Economist

Institution: Centers for Disease Control and Prevention (CDC)

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Reviewer: 3

Recommendation:

Comments:

Originality - does the work add enough to what is already in the published literature? If so, what does it add? If not, please cite relevant references.

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.

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.

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.

Research Question - clearly defined and appropriately answered?

Yes. The research question is clearly specified and appropriately addressed.

Overall design of study - adequate ?

Yes.

Participants studied - adequately described and their conditions defined?

Not applicable.

Methods - adequately described? Complies with relevant reporting standard - Eg CONSORT for randomised trials ? Ethical ?

The methods are succinctly but adequately described

Results - answer the research question? Credible? Well presented?

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.

Interpretation and conclusions - warranted by and sufficiently derived from/focused on the data? Message clear?

The overall message/ conclusion is admirably clear, succinct and well written.

References - up to date and relevant? Any glaring omissions?

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. O'Donnell M et al. Urinary Sodium and Potassium Excretion, Mortality, and Cardiovascular Events 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 emphasise that this worse case (and highly implausible scenario) for sodium reduction has been addressed in the sensitivity analyses.

Abstract/summary/key messages/What this paper adds - reflect accurately what the paper says?

Yes. Excellent abstract

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

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Reviewer: 4

Recommendation:

Comments:
See comments to the authors.

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.

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.

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. Moreover, individual variation, including a rise in pressure includes a rise in pressure. would presumably effect th

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. This is, of course, consistent with the pattern for all other essential nutrients. The usual range, 2.5 – 5g/day is associated with optimal health outcomes, with increased risk (both physiological and CVD events) increasing above and below that range. Interestingly, above 6g.day, increased CVD and all cause mortality is found only in those with hypertension. Below 2.5, increased CVD mortality is most common in the healthiest 60 – 70% of the population. 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.

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".

This modeling exercise should confront the body of evidence and IOM (2013) report conclusions. The methodology was appropriate in 1991, but the accumulation of scientific evidence since then has rendered invalid its application in 2015.

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.

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

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

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Date Sent: 27-Oct-2015