

BCC:

Subject: BMJ - Decision on Manuscript ID BMJ.2015.027854.R2

Body: Dear Mr. Webb

Manuscript ID BMJ.2015.027854.R2 entitled "Population Strategies to Decrease Sodium Intake: A Global Cost-Effectiveness Analysis"

Thank you for sending us your paper, 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.

We hope very much that you will be willing and able to revise your paper in response to the reviewers comments. Thank you for your changes thus far. We recognise this is a contentious area for some and reviewers viewpoints are sometimes more subjective than objective. Nevertheless there appear to be several areas where improvement can be made.

Although we can never promise publication, 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

https://mc.manuscriptcentral.com/bmj?URL_MASK=727b04a747d2426bb565efe329cf7eed

****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: xxx (chair), yyy (statistician), [and list other eds who took part]

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:

*
*
*
*

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

**** Comments from the external peer reviewers****

Reviewer: 1

Recommendation:

Comments:
To The Editor

This further application of a modeling approach derived from an ancient hypothesis that is increasingly disconnected from underlying scientific reality. It assumes a linear relation of sodium to blood pressure and to health outcomes, and that blood pressure is the only physiological consequence associated with different sodium intakes. These 3 assumptions have been disproved. In my opinion, its publication, as is, would be editorial malpractice. However, I appreciate the appeal of this very high profile paper. Hopefully, if BMJ were to accept the piece, it will be accompanied by a rigorous scientific critique

To the Author

This productive group has expanded their modeling approach to estimate the effect on cardiovascular health outcomes as the basis for a cost-effectiveness analysis of sodium reduction under different circumstances throughout the world. They conclude that public education coupled with industry collaboration will both reduce sodium and prevent cardiovascular morbidity and mortality.

Unfortunately, this ambitious undertaking lacks scientific credibility, and its conclusions bear no relevance to what is known about the relation of sodium to health outcomes.

Precise causation for cardiovascular disease, like other complex non-communicable disease, is not available. Instead, a series of risk factors have been identified. Sodium, like blood pressure, and all other essential nutrients, although easily measured, varies over time in individuals. Therefore, epidemiological studies are the method by which risk is established. As a practical matter, for blood pressure and other essential nutrients, the average of the group is assigned to individuals similar to those in the group.

Observational studies have well known potential biases, such as reverse causation, which are generally addressed by investigators. In any event, acceptance of a "risk" relationship requires multiple high quality individual studies in different populations, under different cultures and dietary practices, and producing consistent and reproducible results. Some 6 individual studies and misanalyses of now 30 Observational studies confirm the characteristic pattern of other nutrients in sodium – namely a "J" or "U" shaped relation to health outcomes. The optimal range is from 2.5-3.0 to 5-5.5 gm. of sodium/day. Fortunately, that is the range consumed by about 90% of the world's population. Deficient and excess intakes violating that range are associated with increased cardiovascular risk.

After more than 30 epidemiological studies with about 400,000 participants, not a single one has shown a benefit to those whose sodium intake is <2.0g/d compared to those above 3.0g/d

Thus, any single, simple population wide approach to dietary sodium would, if safe and successful, might benefit some while increasing risk for others. In short, the hypothesized rationale for this model is without scientific support.

The authors suggest industry intervention regarding sodium would be cost beneficial. First of all, given the incredible consistency of sodium intake across decades, countries, and ethnicities suggest that intakes are very resistant to change. Also, while excess sodium (>5.0g/d) will significantly increase blood pressure, intakes <2.3g/d increase plasma renin activity, sympathetic nerve activity, aldosterone, triglycerides, and glucose. Since there is no experimental evidence that altering processed food is either safe or effective, what is proposed is an uncontrolled experiment imposed on billions of people without their consent.

There are a couple of minor points.

1. The English experiment produced no significant change in sodium intake between 2008 and 2011 – its just slightly differing points around a well established mean.

a. www.gov.uk/government/uploads/system/uploads/attachment_data/file/213420/Sodium-Survey-England-2011_Text_to-DH_FINAL1.pdf.

2.

Reference 22 is a post hoc analysis of a subset, not protected by randomization, of participants in an earlier study. Average sodium intakes were well within the means seen universally, and no comparison was presented of those whose intakes were <2.3 g/d to the middle range.

a. More to the point is the recent meta-analysis (Graudal. AJH May, 2016), in which 99,225 subjects with sodium intakes between 2,645-4,945 g/d were compared to 27,250 subjects with intakes <2,654 – all participants in prospective completed studies – not post hoc subsets.

Additional Questions:

Please enter your name: Michael Alderman

Job Title: Emeritus Professor of Medicine and Public Health

Institution: Albert einstein College of Medicine

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 a very good paper, involving an immense amount of work.

I have no major concerns.

However, one might, perhaps offer a couple of suggestions to make it even better.

ABSTRACT

Line 25. Please specify that the intervention is modelled on the UK success (1.4g/day reduction in salt consumption).

Line 35

Please say "avert APPROXIMATELY 5,781,000 cardiovascular"

Line 40

Likewise perhaps say

"ratio was approximately I\$204/DALY."

INTRODUCTION

Basically fine, although a little brief at only two paragraphs.

BMJ readers might welcome a slightly more detailed summary of previous studies, Notably that many reported likely cost-SAVINGS, such as Bibbins-Domingo, Smith-Spangler, Barton and Cobiac (Heart 2010;96:1920e1925. doi:10.1136/hrt.2010.199240).

Please also add the Cobiac reference.

METHODS

Basically fine.

Line 11 onwards. This merits slightly more detail on the (effective) UK approach.

The successful UK intervention (1.4g/day reduction consumption) resulted from a powerful healthy alliance involving an NGO (CASH), an government agency (FSA) and two successive government ministers of public health. The latter applied sustained pressure on the industry to pursue progressive reformulation involving food-group-specific targets and independent monitoring. This was reinforced by a sustained media campaign demonising salt. The total effect was thus a lot stronger than simple "voluntary reformulation" (which has signally failed in Australia and elsewhere). Indeed, the UK approach has been described by Mwatsama and others as "soft regulation".

Line 46. not including estimated healthcare savings from prevented cardiovascular disease events is an important limitation; so I am pleased to see that is picked up in the Discussion.

Page 25, line 22 onwards.

Here and elsewhere there is potentially confusing use of the word "sodium".

While referring to 0.5g and 1.5g reductions which actually pertain to salt (sodium chloride, not sodium).

The authors have a choice.

The tough one is to recalculate and re-write all these values as mg of sodium.

The easier option would be to simply ask MS Word to replace every "sodium" with "salt".

Particularly given that the BMJ is a UK based journal.

RESULTS

All the results are estimates, dependent on a variety of assumptions. This is amply demonstrated in the subsequent sensitivity analyses. Therefore, adding the word "approximately" here and there would be both scientifically honest, and also warmly welcomed by many BMJ readers.

For instance, Line 13 says

"over 10 years, the intervention averted an estimated 5.78 million cardiovascular disease-related.."

?Perhaps amend that as

"over 10 years, the intervention could have averted approximately 5.78 million cardiovascular disease-related.."

Page 29, line 22 would likewise be better stated as:

"Globally, the estimated average cost-effectiveness ratio of the 10-year intervention was APPROXIMATELY I\$204 per DALY saved..."

Etc etc

DISCUSSION

Line 15,

Likewise perhaps better to say:

"estimated to be POTENTIALLY averted annually, at low cost. "

Page 32, line 56.

Again, please add a couple of sentences to highlight the previous studies which suggest cost-SAVINGS. That would further strengthen the Discussion.

Page 34, line 46 onwards.

This sentence could be made even better along the lines of:

"We did not evaluate other potential intervention STRATEGIES to reduce sodium, such as mandatory quality standards, TAXATION OR MULTI-COMPONENT APPROACHES SO EFFECTYIVE IN JAPAN OR FINLAND. THESE might be more effective and less costly, although PERHAPS less feasible in certain nations."

Otherwise very good.

Additional Questions:

Please enter your name: Simon Capewell

Job Title: Chair of Clinical Epidemiology

Institution: University of Liverpool

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 3

Recommendation:

Comments:

General points

This paper, a cost-effectiveness analysis (CEA), provides estimates of the cost-effectiveness of sodium reduction by region and country across the world for national programs that rely on non-regulatory approaches, namely, mass media messaging to populations and voluntary reductions by industry. As a CEA, it is heavily dependent on assumptions, even more so in this paper, given its scope. While the objective is important, I have concerns about presentation, as well as suggestions. Clearly there are multiple levels and types of uncertainty. It would be ideal if the authors could have a table that displays key assumptions (for cost and effectiveness) for their base scenario. Some of the key assumptions are not displayed quantitatively, even in the appendix; for example, CVD risk reductions per mmHg, even if sample estimates. Without such an exposition of input data, it is difficult to comment on the credibility of their findings.

I also suggest that they drop the 30%, 0.5 g/d, and 1.5 g/d in the main text; there is virtually no discussion of these alternative reductions/scenarios. Rather, they should consider using an alternative framework - plausible worse case, base case, plausible better case. This is similar to the presentation by Coxson with 3 different models (Hypertension, 2013). The reason for this suggestion is that currently the authors vary each assumption separately. It is quite possible that several assumptions could be leaning in the same direction (e.g. higher costs, reduced effect size). Such a display might mitigate perceptions of bias, given that selection of assumptions requires judgment, and that the authors are well-known advocates of sodium reduction.

Specific points

1) Abstract - PPP is unclear. The conclusion mentions the types of interventions for the first time; these should be mentioned in the introduction. Also, I would re-order, starting with 'industry-agreement' as this is likely to be the primary contributor to sodium reductions in the UK, as mentioned in the discussion.

2) Methods - it is debatable whether leaving out 'healthcare savings' leads to a conservative estimate of cost-effectiveness, because of downstream health events that might occur because of enhanced survival.

3) Methods – the estimated absolute changes in sodium intake levels in UK and Turkey are wrong – these are changes in gm of salt, not gm of sodium. I assume that these estimates do not affect the modeling, but the authors must comment.

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

Additional Questions:

Please enter your name: Lawrence J Appel

Job Title: Professor

Institution: Johns Hopkins University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

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Reviewer: 4

Recommendation:

Comments:

I appreciate the opportunity of reviewing this manuscript. This is an important and policy relevant topic, but I found the analysis and writing are confusing. First, the objective of this study is not well defined. In the beginning of the abstract, the objective is just stated as 'a policy intervention'. In the middle of the abstract, the intervention is 'A policy that combines government-supported education and target industry agreement ...'. In conclusion of the abstract 'National education and industry-agreement strategies ...'. In the methods of page 24, the intervention consists of three component, (a), (b), and (c). And in the conclusion of the manuscript on page 35, the intervention is 'a government-supported, voluntary, coordinated national policy ...'. All these definitions of intervention mean different things. It is so hard to figure out what are exactly the intervention activities and their costs. And cost to whom (government, industry, or others). There are more work to do to figure out the cost information. Second, for most low income countries, food processing industry might not be advanced developed as in industrialized countries. Thus, government and food industry partnership might not be as important as in developed countries. Also, in developed countries such as USA, there are few success partnerships between government and food industry in sodium reduction. All these issues have not been incorporated into the analysis in this study. Third, the program has 4 stage, planning stage year 1, development year 2, partial implementation year 3-5, fully implementation year 6-10. If so, health effects of the program should start from year 3. Thus, "We assume the intervention scale up linearly over 10 years , " is not right (page 24). Also, 10-year is an arbitrary number, should be better justified. Fourth, the regions are confusing, what are " across 21 world regions"? as mentioned in abstract. Later on and tables use 9 regions? How these regions defined? Fifth, if 1\$I=1\$US, why don't simply use \$US. Sixth, a big assumption is that assuming the intervention will successfully reduce salt intake by 10% in 10 year across all the countries. This is not a reasonable assumption. Seventh, result section on page 29 & 30 presented e-supplement material. If in e-supplement, should not be important enough in manuscript text. Finally, findings of this study should be compared with similar sodium reduction studies conducted in US, UK, Canada, Australia, etc. Comparing with clinical trail studies is ok, but changing the whole population characteristics.

Additional Questions:

Please enter your name: Guijing Wang

Job Title: 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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g. Footnotes and statements

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