July 30, 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 further careful revisions in response to the remaining Editor and Reviewer comments, which were 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 now suitable for publication.

We look forward to your thoughts.

Best regards,

Dariush Mozaffarian, MD DrPH

**Reviewer: 1**
Michael Alderman
Emeritus Professor of Medicine and Public Health
Albert Einstein College of Medicine

*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.*

We appreciate the reviewer's perspective on the evidence base for health effects of sodium. As in all fields from clinical medicine to genetics to physics to global warming to sustainability, we recognize the absence of 100% perfect agreement among all scientists on every topic. In this case, sodium clearly raises BP, and virtually all studies have shown harms for high intakes – the only questions are whether a J-shape exist, and if it does, at what level.

In this case, as for all scientific fields, while 100% agreement between all scientists is not feasible, there is evident broad scientific consensus. Based on all available evidence, the current scientific consensus is clearly that higher sodium intake increases CVD events, and that the optimal intake level is around 2000 mg/d or less. This consensus has been reached by different independent groups including the US Dietary Guidelines Advisory Group, the Institute of Medicine, the American Heart Association, the World Health Organization, the UK Food Standards Agency, and the UK National Institute for Health and Clinical Excellence, to name a few. We have also reviewed the evidence and arrived at the same conclusions.

While we appreciate this reviewer's difference of opinion, we trust he will agree that his perspective represents a minority view, and that multiple established, independent scientific agencies have reviewed all of the evidence and arrived at conclusions similar to ours. We respect his perspectives and his views, and his statements deserve some moderation by these points.

To clarify in detail the prior evidence and broad scientific consensus, we have added detailed additional Supplementary Materials: "Evidence for Optimal Intake Levels and Causal Effects of Sodium."

*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.*

We agree with these general reflections.

*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 0bservational 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.*

Please see our response above, as well as the detailed additional Supplementary Materials we have added, "Evidence for Optimal Intake Levels and Causal Effects of Sodium." In extended surveillance in a large, randomized, controlled sodium reduction trial, which overcomes many important limitations and biases of some prior observational studies, subjects with intakes <2.3 g/d experienced 32% lower CVD risk than those consuming 3.6-4.8 g/d, with evidence for linearly decreasing risk.

*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.*

We respectfully disagree with this perspective. A study that assessed sodium consumption in countries around the world demonstrated extremely wide variation in mean sodium intake across countries.[1] For example, regional means in 2010 ranged from 2.18 to 5.51g per day. Moreover, as discussed in the paper, the examples of the UK and Turkey show that significant (>10%) reductions can be achieved in reasonable timeframes.

*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.*

We appreciate that acute adverse effects of extreme, rapid sodium reduction cannot be excluded. A recent meta-analysis of 74 trials confirms that effects on renin are time-dependent and decrease over time.[2] This makes clinical and intuitive sense: for instance, there is little evidence that countries around the world with substantially lower sodium intakes have systematically higher levels of any of these biomarkers or related disease risks.

We also note that, while these potential acute effects are frequently invoked as a possible counter to benefits of BP-reduction, there is also evidence for additional, long-term harms of sodium beyond effects on BP. This included ecologic and animal-experimental evidence that chronically high sodium induces BP-independent toxicity including myocardial, vascular, and renal fibrosis.[3] Such potential harms are not incorporated into any of our risk estimates.

*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.*

We are perplexed by this comment. First, industry reformulates its products continuously without broad experimental evidence. Second, there is substantial experimental evidence that sodium reduction reduces BP, a causal risk factor for CVD. There is also interventional evidence from the UK and other nations that the policy we have modelled, to alter processed foods, is effective at reducing Na and BP.

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

The report cited concludes that "mean estimated salt intake decreased by 1.4g per day, from 9.5g per day in 2000/01 to 8.1g per day in 2011." Moreover, "the decline across survey years was significant ($p<0.05$)", and "the same finding held when looking at men and women separately." A substantial decline (5.1%) has also been identified just for the years 2005 to 2011 in a separate independent analysis by the Institute for Fiscal Studies (link below), using consumption data from a representative sample of British households. These economists found that "the decline in average salt content of grocery purchases was *entirely* due to product reformulation by firms." We have cited this paper in the Discussion section of the manuscript. http://www.ifs.org.uk/publications/7330

*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.*

Fig 2 in that report shows a spline plot across the full range of comparison: no evidence was seen for a non-linear or J-shape effect.

*3. 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.*

The potential biases in sodium assessment in observational studies, whether utilizing urine collection or diet questionnaires, are well-established. The most important sources of bias include incomplete 24-hour urine collections (sicker individuals providing less urine, artificially lowering their estimated sodium intake); reverse causation (at-risk subjects, such as those with hypertension, actively lowering sodium); confounding by physical activity (given the very strong correlation between sodium and total energy intake, with $r>0.8$); and confounding by frailty and other reasons for low total energy intake (given the very strong correlation between sodium and total energy intake). Accordingly, in many studies and especially those in Western populations, participants with very low estimated sodium intakes (e.g., <2300 mg/d) represent a very small and relatively unique subset of the population. These limitations together could entirely explain the apparent "J-shape" seen in certain observational studies. For example, in one recent large observational study, participants with lowest sodium had numerous more cardiovascular risks at baseline. Appropriately, the authors acknowledged, "reverse causation cannot be completely ruled out and may account in part for the increased risk observed with low estimated sodium excretion." Further, physical activity was self-reported, greatly increasing potential residual confounding, i.e., from those with lowest sodium being most sedentary. Other reasons for very low total calorie intake, which would be very common among those with lowest sodium intakes, were not evaluated in that study. In contrast, during extended surveillance in a large, randomized, controlled sodium reduction trial, which overcame many of these limitations, subjects with intakes<2.3 g/d experienced 32% lower CVD risk than those at 3.6-4.8 g/d, with evidence for linearly decreasing risk.

We have added a discussion of these issues to the Supplementary Materials.

Thank you for your thoughtful review and helpful comments.

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

*This is a very good paper, involving an immense amount of work.*
*I have no major concerns.*

We appreciate these positive comments. Thank you.

*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).*

We agree, and have amended the abstract as suggested.

*Line 35*
*Please say "avert APPROXIMATELY 5,781,000 cardiovascular …."*

Thank you for this point. We have amended the abstract as suggested.

*Line 40*
*Likewise perhaps say*
*"ratio was approximately I$204/DALY."*

Again, agreed.

*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.*

We have added the Cobiac citation to the Introduction, and noted that many found such interventions to be even cost-*saving*. We have added a more detailed summary of these prior studies to the Discussion.

*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".*

Thank you for this important point. We have expanded details on the UK approach, as suggested.

*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.*

Thank you for this point. We agree that not including possible downstream savings from averted cardiovascular disease events means that the overall cost-effectiveness of this intervention is likely even greater than is indicated by our estimates. We have now further specified this in the Abstract.

*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.*

Our paper focused on sodium, and the 0.5 g/d and 1.5 g/d reductions in our modeling refer to sodium. The experienced reductions in the UK and Turkey described in the Methods section were originally reported in g/d of salt; we have now corrected this to the equivalent sodium measure.

*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*

Thank you for this point. We have revised the results section as suggested.

*DISCUSSION*
*Line 15,Likewise perhaps better to say: "estimated to be POTENTIALLY averted annually, at low cost. "*

Agreed, thank you.

*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.*

Thank you for this helpful suggestion. We have further emphasised this point in the discussion, including in the final conclusions.

*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."*

Likewise, agreed. Thank you for this suggestion, which we have incorporated.

*Otherwise very good.*

Thank you for your thoughtful review and helpful comments.

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

*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.*

Thank you for this excellent suggestion. We have added a new Table (eTable 1) detailing the key assumptions.

*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.*

We appreciate this suggestion. These scenarios are included in part as a response to prior reviewer comments, namely, that heterogeneity may exist in absolute and relative effects, and that the best way to understand the sensitivity of the results to alternative assumptions is to vary each dimension (costs and effects) separately. For different countries, there may be different best or worst cases among these. We present all the findings so that reviewers can draw their own conclusions. We have also added a new Table (eTable 1), as suggested above, describing the selection of assumptions.

*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.*

Thank you for these helpful suggestions. We have clarified the interpretation of PPP, the types of interventions, and the description of the program including leading with "industry-agreement."

*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.*

Thank you for raising this important issue. Observations within populations have generally shown that when people are healthier due to population-wide reductions in risk factors, longevity is increased and morbidity and associated healthcare costs are compressed into a later and shorter period of life, with correspondingly significantly smaller total lifetime healthcare costs. This can be contrasted to, for example, prolonging life by secondary and tertiary treatments in diseased patients. Nonetheless, we have added in the Methods section that "such savings could, in theory, be partly offset by new downstream health events resulting from 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.*

Thank you for bringing this to our attention. We have corrected this oversight.

Thank you for your thoughtful review and helpful comments.

**Reviewer: 4**
Guijing Wang
Health Economist
Centers for Disease Control and Prevention (CDC)

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.*

We appreciate these positive comments, and agree with the importance and policy relevance of this topic. We are also very grateful to have the chance to improve the clarity of the presentation based on your suggestions.

*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 is more work to do to figure out the cost information.*

Thank you for raising this important issue. We agree that it would be helpful to have more consistent wording to describe the intervention throughout, and have revised the manuscript accordingly. We have also highlighted that the exact description of the intervention components and their costs are detailed in eTable 1. Regarding costs, these are costs to the government only. We have also clarified this in the text.

*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.*

These are good points. In most countries with less advanced food processing industries, sodium intakes are much lower than in Western or Eastern countries. In these countries, the results for percentage reductions may be more relevant than absolute reductions. In the US, many voluntary efforts by companies are ongoing to reduce sodium, and the FDA has recently released voluntary sodium targets. Thus, such a program, if implemented as in the UK, could have a reasonably similar chance of success. In comparison, for certain Asian nations such as China, substantial sodium is added at home, making education and media efforts more relevant. Nevertheless, even with an up to 5-fold increase in total costs, our multi-national investigation suggests that a government-supported sodium reduction program would be highly cost-effective for nearly every country in the world. We have amended the Discussion to address these issues (see “Sources of heterogeneity”).

*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.*

From past experiences with additives (e.g., trans fat), some companies begin reformulations early, as soon as they see any major government action looming. Other companies start later. Also, for some products, small reductions immediately are feasible; with more significant reduction taking more time. Thus, assuming an approximately even effect over time is reasonable and consistent with empirical experiences.

The 10-year period was selected based on the approximate period of the UK intervention, and its results, to-date. A shorter period could bias choices against programs which take a number of years of activity to start accumulating meaningful benefits. Much longer periods could be unrealistic for many government decisions, as the time horizon of policy decision-makers is often rather short. We have clarified these justifications for our selected time period in a new Table, eTable 1.

*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?*

Yes, this was a typo. We evaluated 9 world regions, defined as in Table 1.

*Fifth, if 1$I=1$US, why don't simply use $US.*

The international dollar ($I) provides accurate cross-country comparisons that take into account not only currency differences but also purchasing power. One I$ in any given country can be interpreted as the funds needed to purchase the same amounts of goods/services in that country as one US$ would purchase. Thus, *I$1=US$1* conceptually and practically, but not as a direct conversion of currency. For countries with lower income than in the US, conversion of our findings from I$ to US$ would substantially increase the apparent cost-effectiveness (i.e., the cost in US$ per DALY saved would be much lower). For the US itself, an I$ is equal to a US$ by definition, so our results for the US can also be directly compared with other studies focused on the US that simply use US$. We have clarified these points in the Methods text and Table footnote.

*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.*

Thank you for raising this point. We agree that there is likely to be heterogeneity in effectiveness across countries. We therefore consider and present varying alternative scenarios in the sensitivity analyses, which we show in detail.

*Seventh, result section on page 29 & 30 presented e-supplement material. If in e-supplement, should not be important enough in manuscript text.*

Due to usual restrictions on the total number of tables/figures that may appear in the main manuscript, several relevant findings are presented in the supplementary materials, with succinct descriptions in the text. All sections in the e-supplement material are referred to in the appropriate section of the main text.

*Finally, findings of this study should be compared with similar sodium reduction studies conducted in US, UK, Canada, Australia, etc. Comparing with clinical trial studies is ok, but changing the whole population characteristics.*

Thank you; we agree. We have amended the discussion to compare our results with similar studies conducted in relation to particular countries. Thank you again for this very helpful suggestion.

Thank you for your thoughtful review and helpful comments.

1. Powles J, Fahimi S, Micha R, Khatibzadeh S, Shi P, Ezzati M, Engell RE, Lim SS, Danaei G, Mozaffarian D, Global Burden of Diseases N, Chronic Diseases Expert G. Global, regional and national sodium intakes in 1990 and 2010: a systematic analysis of 24 h urinary sodium excretion and dietary surveys worldwide. *BMJ open*. 2013;3:e003733
2. Rhee OJ, Rhee MY, Oh SW, Shin SJ, Gu N, Nah DY, Kim SW, Lee JH. Effect of sodium intake on renin level: Analysis of general population and meta-analysis of randomized controlled trials. *Int J Cardiol*. 2016;215:120-126
3. Mozaffarian D, Fahimi S, Singh GM, Micha R, Khatibzadeh S, Engell RE, Lim S, Danaei G, Ezzati M, Powles J. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371:624-634
4. Sadler K, Nicholson S, Steer T, Gill V, Bates B, Tipping S, Cox L, Lennox A, Prentice A. National Diet and Nutrition Survey - Assessment of dietary sodium in adults (aged 19 to 64 years) in England, 2011. *UK Department of Health*. 2012