Author's response to reviews

Title: A systematic review of economic evaluations of interventions to tackle cardiovascular disease in low- and middle-income countries

Authors:

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Author's response to reviews: see over
Dear Editors, *BMC Public Health*

**Re:** A systematic review of economic evaluations of interventions to tackle cardiovascular disease in low- and middle-income countries

**Authors:** Marc Suhrcke, Till A. Boluarte, Louis Niessen

Please accept this letter and attached manuscript as our re-submission to *BMC Public Health*. Thank you for the constructive feedback. The comments from the reviewers have been very helpful in aiming to improve the quality of this paper. I hope that you will find our handling of the comments of the reviewers complete and that the revisions made since the previous version will meet the standards of *BMC Public Health*. We have put significant work into addressing the comments of the reviewers and the required editorial changes.

Concerning editorial requests, we now included a PRISMA checklist for systematic reviews. However, some items do not apply to our review since we did not perform a metaanalysis of results.

Concerning the reviewer's comments, we will discuss each comment below in the order as they appeared in the documents.

Thank you for considering our article again.

Till A. Boluarte

**Reviewer 1:**

**Major Essential Revisions**

Poland is classified as a high income country by the World Bank so I was surprised to see it in the search strategy. Perhaps this is a recent change in its classification? But in any case the paper from Poland really should be removed from the analysis, and all the tables and text modified accordingly.

*We removed all studies from Poland from the analysis and corrected the text and tables accordingly*

In the discussion section – the comments re the Choosing the Right Model citing in detail the work of Unal seem a little bit out of place – and could be written in any review of economic evaluations. The authors need to ensure that they make a connection with the studies in this analysis – what can be said about the 18 studies with models in the paper?
We revised this section and tried to make a stronger connection to the first part of our article.

**Minor Essential Revisions**

In Annex III it would be helpful to split the table of studies into two – one for modelling studies and one for empirical studies.

*We adjusted the tables accordingly*

In the tables it is important if possible to provide a little bit more information on the type of modelling approach used and certainly the duration of time period used in models.

*We included the information on the time period, and adjusted the tables accordingly. While it might have been desirable to add a comparison of the modelling approaches between papers, this objective could not be achieved within the scope of the present paper, as there typically was not enough information in the papers about the precise modelling strategy. It would have required contacting the authors of several of the papers to be able to give meaningful, systematic comparisons, and we felt this would be beyond the primary objective of the paper.*

It would also be helpful to clarify the primary source of effectiveness data for models for each individual study – domestic, other low/middle income country or high income country.

*We included the information, and adjusted the tables accordingly*

For empirical studies it is also important to state the duration of the empirical study and length of follow up. This also helps the reader judge whether discounting was indeed appropriate or not.

*We included the information where available, and adjusted the tables accordingly*

For the table it is important to state the size of population samples in intervention and control groups for empirical studies.

*We included the information where available, and adjusted the tables accordingly*

Can you clarify in the text whether any price years have been standardised. I dont think so but it is helpful to clarify.

*Price years have not been standardized – we included a sentence clarifying this in the header of the respective tables*

**Discretionary Revisions**

In terms of limitations, the authors might want to consider the capacity for undertaking economic evaluations in low and middle income countries. Just what scope is there for health economists?

Re this capacity issue – it might be interesting to note the proportion of authors on these papers who are based in the countries of study.
We included a brief discussion with the respective analysis in the introduction to the "transferability of results" section.

Is it a significant limitation not to be able to look at Chinese bibliographic databases? Is there an emergence of Chinese economic evaluations and Chinese research? Might the analysis be somewhat different if Chinese language journals, many of which are not abstracted in English, could have been searched.

We included a brief discussion on this issue citing recent work in the limitations section.

Reviewer 2:

Major compulsory revisions:

1. Better connect results of systematic review with discussion. See above. (While the discussion of methodological weaknesses of the studies reviewed is important and raises interesting questions, it seems to pertain more broadly to economic evaluation of interventions in LMICs rather than specifically to CVD intervention studies. The article would be more cohesive if it better connected the systematic review results in part 1 with the discussion in part 2. One way to connect the two parts of the article is to more specifically address particularities of CVD in the methodological section and conclusions; for instance, what are the specific transferability issues related to CVD? Other issues in the article are specified below)

We reviewed our paper throughout and in particular the discussion around methodologies to make it more relevant to our analysis on CVD.

2. Clarify when discussing efficacy versus effectiveness. Most studies reviewed are assessing efficacy, rather than effectiveness. In several places the article raises issues about effectiveness and real world conditions. It would be very interesting to see a discussion of how efficacy and effectiveness vary for CVD. There is literature from HIV specifically addressing adherence, access, and some of the other issues raised here. This literature might inform a discussion.

We included a section in the methodological aspects discussion where we further analyze the importance and root-causes for differences between effectiveness and efficacy of CVD interventions.

3. Provide a summary of systematic review results. Although a ranking cannot be provided because of differences across studies, the article loses power by not summarizing what is learned about the cost-effectiveness of various interventions. More explanation of differences across studies would be useful to explain why interventions can’t be ranked.

We included a summary of results based on method called "hierarchical decision matrix" as suggested by Nixon et al. 2001. We further emphasized the differences between studies (e.g. intransparency of included costs).
Discretionary revisions:

1. Issues of “mass medicalization.” It’s not clear what is meant here. Is it a real issue, and if so, how would it be assessed by an economic evaluation? (3rd para in discussion section, and later)

We specified the issue of "mass medicalization" as concerning the healthcare budgets of countries, i.e. devoting large proportions of the budget towards a single therapeutic area

2. Blood pressure thresholds. Most recent proposals suggest lowering thresholds such that a large number of people would be at-risk. The discussion section of the paper suggests the opposite. The point is made that extensive pharmacological treatment is expensive, which is appropriate but then the suggestion is made that population-based approaches may be more cost-effective. However, the article does not provide evidence for this supposition. In fact, in several places in the article the authors suggest a bias for prevention (also conclusion) that does not appear to be supported by the results. In fact, the article points out that such interventions (population-based, non-clinical) have not been adequately studied.

We clarified the discussion around thresholds as clinically justified – however with consequences on national health budgets. We further detailed the hypotheses that with acknowledgement of a larger population "at risk", that broad population interventions may render more cost-effective. We explicitly added that the evidence for such a hypothesis is still missing

3. Transferring results from developed to developing countries. This is a major topic in the discussion, but is not well fleshed-out. Would be useful to describe what it means, how authors deal with this in different ways, and what the particular aspects are that pertain to CVDs. Discussion of ISPOR recommendation and RWD belongs earlier in the article.

We further detailed the discussion on transferring results and included the discussion around RWD into the "efficacy vs. effectiveness" discussion.

4. Modeling approaches. Also an important topic in the discussion which would benefit from more fleshing out to indicate what different approaches to modeling are relevant to CVD and how much they can be relied upon.

We reviewed this section to make it more relevant to CVD and therefore connecting it to the main analysis of our article

5. Ambiguity between primary and secondary prevention. I was surprised that the review produced more studies about primary than secondary prevention as that is not what the literature normally suggests. I looked carefully at the list of studies reviewed and would re-categorize some of the studies listed as secondary rather than primary prevention (Ker, Robberstad, Araujo…) Suggest that there be a more complete definition of primary and secondary. One reason for the ambiguity is that different medical fields use these terms differently.

We added a reference for our definition of secondary prevention in the results section. We also included a paragraph where we discuss the ambiguity of interpretation and consequent limitations. We also emphasized the different definitions among medical fields.
6. Writing is not clear and succinct. Repetitions appear throughout the article; for instance, the issue of societal perspective appears more than once, lack of data in developing countries is mentioned several times, a few words are missing (the beginning of the conclusion should mention economic evaluation rather than just burden of cardiovascular disease as a neglected topic.)

*We reviewed the writing to strengthen the context and make the text more accessible to the reader.*