Author's response to reviews

Title: National and Subnational mortality effects of metabolic risk factors and smoking in Iran: comparative risk assessment

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Author’s response to reviews: see over
Reviewer #1

Major Compulsory Revisions
1. Please revise the whole of Discussion. The present content of this section is not adequate for publication.

We have done our best to revise and expand the Discussion section to address this comment.

2. The order of paragraphs in Discussion is not appropriate. Particularly, it is obvious that the last paragraph is not in the right place. Please have a paragraph for concluding the paper nicely, mentioning what to be done in future research in terms of not only measurement methods but the literature on risk factor and disease control in Iran and other countries.

We have also done our best to reorganize the Discussion section to address this comment.

3. Please expand discussions on implications of your findings for public health policy. Currently you just briefly mention each risk factor by one or two sentences in the 4th paragraph of Discussion, which is not sufficient.

See item 1 above. This is done in the revised manuscript.

Minor Essential Revisions
4. Please correct minor errors in English language.

We have revised the paper with particular attention to language issues. We welcome further changes from the journal's production team.

Reviewer #2

Major compulsory revisions
None.

Minor essential revisions
The data in the first paragraph on population should be referenced. Also, the proportion of people of older than 64 should be given to have some anchor on the demographic change described.

We have referred to the General Population and Housing Census as the source for this information, and have added the proportion of people over 64 years of age (p. 4).

I would be interesting to see, how many deaths occurred in the age group 64+ where no exposure data was available, and thus had to be estimated from age trends and other countries.

We have provided this information in Discussion (p. 15).
The modelling of simultaneous impact of more than one risk factor should be elaborated on.

The joint effects of multiple risks were not a focus of the current manuscript but will be subject of ongoing research. For this reason, we have not elaborated in the current manuscript.

It would be interesting to see, who many uncertainty would be due to the various factors. The uncertainty seems overall low, especially since a) the risk relations were all imported from other countries, b) all ages 64+ had to be estimated, which surely accounted for sizable numbers. Thus, the specific assumptions of uncertainty analyses should be made available to the reader. This is especially important, as most CRAs struggle with level of uncertainty and various solutions are possible within the framework described.

The paper formally incorporates the statistical uncertainty associated with RRs and with the regressions used to estimate exposure in oldest ages. The Reviewer is however correct that this statistical uncertainty excludes the more fundamental uncertainty associated with extrapolation, i.e. the uncertainty due to selecting a specific extrapolation models among the range of possible models. As the Reviewer and Editors are aware, current methods for analyzing disease and risk factor burden are not able to account for the variations in modelling approaches. As the research community works on developing such methods, we have stated this unquantified component of uncertainty in revised Methods (p. 10).

The references should be checked again. By chance I discovered the following ref with full first names spelled out which is surely correct:

We appreciate the careful reading by the Reviewer, which led to catching the mis-formatting by our reference manager program. We have checked and corrected the references.

Reviewer #3
Overall
This is an excellent paper.
The topic is of wide interest – not least in the context of the forthcoming UN high level meeting on NCD control.

There is a dearth of studies of this quality on attributable burdens of NCDs from middle income countries.

An array of appropriate methods to deal with data limitations have been used and clearly described.
The discussion and conclusions are balanced and appropriate.

Minor essential revisions
1. Clarification of role of smoking prevalence data
There is scope for confusion when these are discussed as the methods state that smoking effects were estimated using the Peto Lopez method. Eg at p 13, 3rd para might be reworded along the following lines:

‘...the highest reported prevalence of recent smoking, the age-standardised mortality attributable to this risk factor (calculated using lung cancer mortality to estimate exposure) was largest ...’

We have used the suggested clarifications in the paper (p. 13).

2. Clarification of the correlation coefficients for the mortality completeness estimates.

Does rSEG refer to the correlation between the 2 completeness estimates when each are estimated using the SEG method ... or when using SEG for adults and the sources noted in the next sentence for the under 5 mortality? In either case is a coefficient as low as 0.16 satisfactory?

\[ r_{SEG} \] indicates the correlation between completeness of adult mortality estimated using SEG method and completeness of child mortality using Gaussian process regression (Rajaratnam 2010). Correlations with child mortality completeness, always estimated using the same method, were used to choose a method for adult mortality, since the former tends to be estimated more accurately. We agree with the Reviewer that the correlation coefficient is rather small. It is nonetheless larger than those for the other two methods. For comparison, the correlation coefficients between rates of change for adults and child mortality in recent global analyses were 0.24 and 0.35, for males and females respectively. Clearly, this demonstrates the need for further research on adult mortality estimation, currently underway by some of the co-authors of our manuscript.

Typographical
Abstract
Methods second last word: ‘to risk’ has no space (could be a pdf artefact).

We have corrected this in the paper (p. 2).

P 8, 2nd para, 2nd sentence: second and third words suggest a typo here.

We were unsure which words this sentences referred to. We welcome clarifications so that we could correct the above typo.

P 9, 2nd para, 4th line: ‘epidemiological’

We have corrected this in the paper (p. 9).

Some of the citations are defective:
Eg 34, 38 (lacks year etc), 40, ‘Bank’.

We have corrected these references and appreciate the careful reading by the Reviewer.

Discretionary revisions
1. A little detail on the methodology of the sbp measurements
Although the interested reader could theoretically pursue the cited primary sources it would be helpful to have just a little information on the protocol for sbp measurement in the risk factor surveys as the sbp data play such an important role in the analyses and may be subject to substantial measurement artefacts in a middle income country with a continental climate. This should include whether the surveys were conducted on a comparable round the year basis in all regions, and if not whether seasonal variation (and/or variation in ambient temperatures) may be adding 'noise' to the blood pressure estimates.

The survey was carried out in a single season in the whole country. This has been stated in the revised manuscript (p. 6). We have provided overview of measurement methods in the revised manuscript. More detail is provided below and can be included in the paper if deemed necessary by the Editors.

“Blood pressure was measured with a standard mercury sphygmomanometer and a cuff of suitable size to the individual’s arm circumference after an adequate rest period of at least 15 minutes. Korotkoff phases I and V were used for SBP and DBP, respectively. Three measurements were taken in the sitting position for each participant with a 30-second interval between measurements.

2. Would the confidence intervals be more appropriately described as ‘uncertainty intervals’ given their method of estimation?

We agree with the reviewer and have changed all "confidence intervals" to "uncertainty interval".

3. Table and figure captions should be more informative.

We have expanded the captions to the best of our ability and welcome specific suggestions for further changes from the Editors.