Author's response to reviews

Title: Type 2 diabetes attributed to lower educational levels in Sweden: A burden of disease study

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Author's response to reviews: see over
Responding to reviewers’ comments: We thank all reviewers for their valuable comments that have helped us to improve our manuscript. We have answered the questions one by one.

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<th>Review from Rasmus Hoffman</th>
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<td><strong>Referee: Rasmus Hoffman</strong></td>
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<td>1: The topic of the article, the use of Comparative Risk Assessment methods to estimate the burden of diabetes due to low educational level in Sweden, is clear and interesting. Generally this approach is worth being used, shown and published more often. However, I think that the data used here are not sufficient to provide interesting and valid results, nor are the methods absolutely new or presented on such a high quality level that the article would be worth publishing even without valid results, for example as an illustration of a new method. I see major compulsory revisions needed in order to let this article be an advancement in the field of CRA. See details below: <strong>Major Compulsory Revisions</strong> 1. A causality concept and evidence for causality should be discussed in the introduction (e.g. common causes, contributing causes, necessary causes etc.) All PAF calculation need to assume causality between risk factor and outcome measure. If this is wrong a PAF calculation becomes a misleading calculation exercise.</td>
<td>We do not intend to introduce or illustrate a new method, but to illustrate an example of including SEP into the burden of disease estimates using the CRA methodology. We have therefore changed the title and clarified this in the aims (page 6, l. 1-6). In addition, we have included the issue of causality in the introduction (page 5, l. 4-12).</td>
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<td>2: The lowest age group should be deleted: As it is now, this study can not give valid results for the lowest age group because of misclassification of persons who did not finish their education. Moreover, I recommend that the age dimension will be collapsed altogether because age-differentiation can only be made for the prevalences but not for the RRs. The RR is not only assumed to be the same for all ages (which is probably wrong), it also comes from studies that look at different ages. I see that you partly compensate for this by estimating heterogeneity with random-effect models and sensitivity analysis, but the data basis for the RRs stays weak (see below).</td>
<td>We have excluded the youngest age groups (and consequently excluded text in methods, results, discussion and tables). We already have one overall estimate for all ages (Table 4), and we have also decided to keep separate ages as well. We do not know how the RR is affected by age, but we have clarified this in the discussion and inserted a reference (Huisman, 2004) (Page 17, l. 14-19).</td>
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<td>3: A related recommendation is that you provide confidence intervals for your results, which, I guess, will be very wide and highlight the problems with the data basis. This can be done with bootstrapping based on the standard errors of the RRs and prevalences. Both might be available to you.</td>
<td>We would like to follow this recommendation. However, we would be thankful for your advice of a reference providing/describing the correct formula to use. We have searched the literature of how to calculate CIs for PAFs and the suggestion we have so far is: Laaksonen MA et al. Statistics in Medicine, 2010, 29:860-874, although we are not sure if this is the best one?</td>
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| 4: p.11, l.6: no, there have been studies before (e.g. several papers by Tony Blakely and Nick Wilson around 2005/2006 who used population attributable... | }
risk percent (PAR) to study the impact of smoking on health inequalities, or Mackenbach & Kunst (1997 in SocSciMed) who used PAR as a measure of social inequality in health. Although these studies do not have exactly the same outcome as yours (they look at health inequality and not at burden of disease due to low education) they comprise your calculations and partly even go further: in order to estimate the impact on health inequality of a risk factor, you need to use education as a risk factor for the PAF calculation and apply this to each social group.

Answer from authors

Thank you for providing these articles. We assume that you refer to the sentence that this is the first time to our knowledge that the contribution of SEP as a risk factor using the CRA methodology. We are aware that there are different approaches to estimate the magnitude of socioeconomic inequalities in health (also using PAR), and we have inserted a sentence and references about this (page. 13, l.6-7). However, we have not found a published attempt to include SEP into CRA, and applied it to burden of disease estimates.

Referee: Rasmus Hoffman

5: p.15: low and middle income countries seem to be irrelevant for this study and should be left out of the conclusions. The same is true for the conclusions on the international level in the last sentence. This study has a national perspective on Sweden and the conclusions should rather come from the results: total order of magnitude for the burden, gender- and age differences. To summarize the comments above: Table 1 shows how disparate the data basis for this study is: The studies chosen to calculate a pooled RR are incomparable in region, period, age range, gender, educational categories and control variables. Nobody can expect that all these dimensions are perfectly comparable in such a review but here the data basis suggests a too low validity of the results. To come up with reliable estimates for the impact of a risk factor, a better review is warranted. I wonder if you can use more studies from your review from 2001.

Answer from authors

We have changed the introduction and conclusions regarding middle-and low-income countries. However, we do find this issue rather important since it is likely that the RRs are reverse for some economies, which is mentioned in the discussion (p. 14, l. 1-7).

We have also changed our conclusions according to your comments (p. 18). We agree that it may be problematic to combine data from various regions, periods, age ranges and control variables (although educational categories were very similar and we only included studies that separated men and women), which we also have discussed further (page. 15, l. 13-21).

However, we doubt that a new review would advance the knowledge (we believe that we have captured a large amount of the published evidence in this field) although more studies is warranted.

Unfortunately, we cannot use more data from the systematic review from 2011, since many studies only used 2 levels of education (in that study we compared lowest versus highest SEP). However, the associations we find from this rather small meta-analysis are very similar to the original one.

Referee: Rasmus Hoffman

6: Given that the use of social variables in CRA measures are not really new (although it has been rarely applied and is certainly interesting), the paper in its current form is neither a method paper nor a research article with valid results. At least one of these aspects should be improved, by either considerably improving the methodological insights (biases, assumptions of the PAF approach etc.) or by making the results more valid and interesting, e.g. by offering confidence intervals that would contribute to a saver
interpretation of the few differences you can offer (gender, age and between measures).

**Answer from authors**

We can see this point and have therefore changed the title, aims (p. 6, l. 1-6), and conclusions (p. 18), in order to clarify the aims with this paper. The issue of CIs are answered under question 3.

**Referee: Rasmus Hoffman**

**Minor Essential Revisions**

7: p.5, top: the justification given in the GBD literature for not including education is correctly referred, but I think an additional and a clearer argument is that causality between education and health has not been proven yet. Related to this: if we increase education in a population we cannot simply assume that the effect of education will be the same; there might be diminishing returns of education because it not only has a health-effect on its own, but also a hierarchy effect within a social structure.

**Answer from authors**

We have clarified the issue of causality in the introduction (p. 5, l. 5-15).

8: The last sentence of the CRA section is too vague: “incorporate (in)to” is too vague as a method description. Also the calculation of YLL, YLD and DALY could be explained in a few sentences: How did you get from the PAF to the life-table measures?

**Answer from authors**

We have moved this paragraph to the PAF description, and clarified it (p. 10). We have explained calculation of YLL, YLD and DALY briefly (p. 9-10). After estimating the PAFs from RR and prevalence data, we applied these estimates to the YLLs, YLDs and DALYs by multiplying them with the PAFs (percentages). This is now explained (p. 11, l. 7).

9: Next to the problem of having a very different choice of control variables across studies (Table 1), there is evidence that using adjusted RR in PAF calculations can also lead to substantial biases compared to the correct method of stratifying the analysis by category of the confounding variable (Darrow & Steenland 2011 in Epidemiology).

**Answer from authors**

Thank you for pointing this out, however, the nature of meta-analysis prevents us from handling this issue, since we use data from other articles, and therefore we must follow the choice of adjustment made by authors of the original articles. We acknowledged this problem in detail in our original meta-analysis that we refer to. We used two ways to overcome this problems 1) sub-analysis, what we run by stratifying the selected study by adjustment strategy 2) sensitivity analysis. Since either of these tests altered the final results, we used multi-adjusted variables.

10: In the method section it remains unclear whether the same RRs that you obtained for the incidence of diabetes between educational groups are also used for mortality differences. This would not be a trivial assumption. Furthermore, which causes of death are studied? Only diabetes or also other causes that are influences by diabetes? (Or all cause mortality?) Are these causes competing risks?

**Answer from authors**

We have only used incidence of type 2 diabetes in our PAF estimates of diabetes burden attributed by lower educational levels. We have clarified that we have not used mortality estimates (which perhaps would be appropriate when estimating the attributable role of low education on YLL) and also inserted 2 references about this (page 16, l. 14-22).

We are only looking at diabetes mortality and not the causes that are influenced by diabetes, clarified (page 9, l. 17). According to the BoD estimates for Sweden, mortality from diabetes includes all deaths with diabetes as
underlying cause of death, even if stroke or MI are immediate causes or death, this is the basis of the cause of death register.

Referee: Rasmus Hoffman

11: Discretionary Revisions
p.5, l. 6: “shown”
l. 11: no comma
p.6: what is the theoretical minimum exposure for education?

Answer from authors
We have made these changes. The theoretical minimum risk exposure is high educational level, which is explained (p. 11, l. 1-3).

Referee: Rasmus Hoffman
12: p.7, l. 16: after mentioning that you use the most-adjusted, please refer to table 1.
p.8, l. 16: explain Dismod II
l. 20 “is” at the wrong place

Answer from authors
We have made these changes and explained Dismod II (p. 9, l. 13).

Referee: Rasmus Hoffman
13: p. 9 please provide the formula in better print quality.
p. 10, last but 3 line: throughout the paper the age range 15-19 vs. 16-19 is not consistent.

Answer from authors
We have deleted these age groups

Referee: Rasmus Hoffman
14: p. 12 bottom: the comparison between the original study and “this study” can be made clearer.

Answer from authors
Done

Referee: Rasmus Hoffman
15: p. 13, l. 7: this is an unclear formulation; how can one third be unequally distributed?
l. 11: excess mortality can be 70% but a RR should then be 1.7.
p.14, l.5: shouldn’t it be “under”estimated contribution?
l. 18 “… their educational ambitions and their socioeconomic position”
Maybe Table 3 is better placed after Table 1

Answer from authors
Clarified this.
We have inserted the RR and CI:s as well for clarification.
Correct, this is changed
Deleted
Agree, have switched place

Referee: Rasmus Hoffman
16: In reference 2 no authors mentioned
In reference 13 The Lancet
For Table 1 the title or the column headers should say what kind of RRs are shown.

Answer from authors
Has been changed.

Referee: Rasmus Hoffman
Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.

Review from Anton Kunst
Minor essential revisions
1: In the Discussion section, the authors may evaluate whether the impact of education on DM mortality is of similar size as its impact on DM prevalence. This is an implicit assumption made when the same PAF estimates are applied to both YLL and YLD. The authors may refer to studies that distinguish
between mortality, incidence and/or prevalence, such as Espelt A et al in Diabetologia. 2008 Nov;51(11):1971-9.

**Answer from authors**

We have clarified this in the discussion, and also referred to that article (p. 16, l. 14-22) (and the latest one from Espelt, 2011).

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**Referee: Anton Kunst**

2: In the Discussion section, the authors may evaluate whether a more refined educational classification should have been applied in this study, or in future studies. It should be noted that in the younger age groups, almost 50% of women are in the highest educational level. Further distinction might be made at higher educational levels. Note that the use of a higher reference group (tertiary or university education) is likely to result in higher PAF values.

**Answer from authors**

We have clarified this in the discussion (p. 16, l. 14-22) (and the latest one from Espelt, 2011).

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**Answer from authors**

We have inserted a sentence about this in the discussion (p. 16, l. 14-22). Since most articles investigating educational levels and type 2 diabetes incidence used maximum three levels, we could not use a more refined educational classification in the analysis.

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**Referee: Anton Kunst**

3: The PAF approach is suggested to be a novel methodological approach. However, this approach has been applied several times before in the study of health inequalities. Recent examples include Mackenbach et al in J Epidemiol Community Health. 2010 Dec 19, and Moussa KM et al in Tob Control. 2009 Apr;18(2):92-7. I recommend that the authors acknowledge such previous work outside the CAR framework.

**Answer from authors**

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**Referee: Anton Kunst**

4: The authors suggest that the association between educational level and DM is about constant among high income countries or ‘economies’. However, the evidence of the above-mentioned study of Espelt et al (2008) clearly indicates that there are large differences within Europe, especially between north and south, in the magnitude of inequalities in DM prevalence and mortality. This should be acknowledged and take into account at several places, including the Conclusion paragraph.

**Answer from authors**

We have cited this article, and inserted this in the discussion (p. 16, l. 14-22).

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**Answer from authors**

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**Referee: Anton Kunst**

5: In mainstream health inequalities literature, nearly all “risk factors” for DM are considered as “intermediaries” in the causal pathway between educational level and DM. Only a few factors are usually regarded as true “confounders” to this relationship, such as age, sex and country of birth. I therefore suggest the authors to revise the paragraph on “potential confounders” at page 13-14, and give much greater emphasis to “intermediaries”. The key question may be: how should intermediaries be addressed within the CRA framework?

**Answer from authors**

We cannot detect the variables that hypothetically may act as mediators, since the nature of the meta-analysis prevents us from doing this (i.e., we do not have access to any raw data since we use numbers from published articles). We have discussed the adjustments made (confounding control) by the authors and instead mentioned what possible adjustment from intermediates would lead to in our results. Moreover, we discuss the causal chain between distal risk factors and end endpoints such as disease. However, we do not have the ambition in this paper to investigate how intermediaries should be addressed within the CRA framework hence we have only made minor clarifications on this issue (p. 17, l. 8-10).
### Referee: Anton Kunst

**6:** With regards to the role of age, the authors recognise that associations may vary by age, but they conclude that “the ways this may have influenced the results is difficult to predict”. This is not true. A highly predictable finding is that, among elderly people, the relative magnitude of health inequalities (expressed in terms of RR’s) diminish with increasing age. See e.g. the paper of Huisman M, in J Epidemiol Community Health 2004;58(6):468-75. Taking into account diminishing RR’s would result in lower PAF values for higher age, and thus revert the age pattern that has been observed in the current study (higher impact at higher ages).

**Answer from authors**

Thank you for this reference. We have included this references as well as a description about this in the discussion. (Page 14, l. 8-13).

**Referee: Anton Kunst**

**7:** I suggest removing the age group 15-29 years from the analysis, or to confine the analysis to 20-29 or 25-29 years olds, because the population distribution according to completed educational level cannot be assessed for generations younger than about 25 years. The authors recognise that the results for the youngest group is biased due to this measurement problem. A common approach in much of the health inequalities literature is to confine the analysis to people older than about 25 years (see e.g. Huisman et al, cited above). An additional advantage of restricting the analysis to those age 20 or 25 and over, is that “contamination” with Type I DM cases is further reduced.

**Answer from authors**

We agree and we have deleted the age group 16-29, which has resulted in some changes in methods, results, discussion, and tables.

### Referee: Marc Fleurbaey

**1:** Report for PHM on "Type 2 diabetes attributed to lower educational levels in Sweden: A burden of disease study" The authors advocate incorporating socioeconomic status (income, education, or similar variables) into the global burden of disease studies, and take as an example the impact of low status in Sweden on the healthy years lost to type 2 diabetes. The general thesis of the paper is convincing, even if it is not totally obvious to see how an example proves the idea to be feasible worldwide. The paper is overall well written. I have rather minor comments.

I couldn't understand the PAF formula on p. 9. Please explain better. In particular, explain the expression RR-1. The formula should actually be derived, not just explained.

**Answer from authors**

RR-1 estimates the excess risk, and is thus used to calculate the proportion of excess risk of burden of diabetes attributable to lower SEP groups. We have changed the text for better explanation (p. 10, l. 4-17).

**2:** The young people should be distributed among various levels of education according to reasonable expectations of their final level of education. It is absurd to count them all as uneducated and let their mere presence inflate the burden of disease artificially.

**Answer from authors**

We agree and we have deleted the age group 16-29, which has resulted in some changes in methods, results, discussion and tables.

**3:** I am skeptical about the CRA methodology that pools countries and age groups in order to estimate the link between risk factor and disease. The
results are then impossible to use for national policy purposes. A policy raising education levels in Sweden will have an impact that is specific to Sweden and cannot be estimated from international data. The authors do acknowledge this problem, in particular because type 2 diabetes is likely to occur more in educated subgroups in low-income countries. They recommend using estimates for similarly developed countries. But it seems that policy relevance is maximal if local estimates (country, relevant subpopulation by age and location) are used. What the authors could do here is compare worldwide metaestimates with local estimates that are specific to Sweden (they quote one crude study) or neighboring countries.

**Answer from authors**

We agree that it questionable to combine estimates on socioeconomic indicators from different countries. We have discussed this more thoroughly (p. 15, l. 13-21), as well as revised the conclusions (p. 18). Unfortunately, we have used all data we could find on SEP and type 2 diabetes incidence (from the international literature). It would of course be possible to perform an incidence study on this issue for Sweden and then compare with these findings, which may be a good next step.

**Referee:** Marc Fleurbaey

4: Typos:
p.9 : 2.74 should be 1.31 on the next to last line.
write "therefore" rather than "therefor" (two occurrences)

**Answer from authors**

We have inserted these changes.

**Referee:** Marc Fleurbaey

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:** I declare that I have no competing interests