Author's response to reviews

Title: The impact of education on risk factors and the occurrence of multimorbidity in the EPIC-Heidelberg cohort

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Version: 2 Date: 28 August 2008

Author's response to reviews: see over
Submission of the revised manuscript MS: 2079963154204693
The impact of education on risk factors and the occurrence of multimorbidity in the EPIC-Heidelberg cohort

Dear Dr Norton,

We thank you very much for the opportunity to provide a revised version of our manuscript. We thank the reviewers for their helpful comments and suggestions. All comments of the reviewers were considered and replied in detail. All modifications are marked in the revised manuscript.

The authors have read and approved this revised manuscript, which is currently not submitted for press at any other journal. We apologize for the delay due to holidays.

We look forward to a more favourable consideration the revised manuscript and remain
Yours sincerely,

Gabriele Nagel
The impact of education on risk factors and the occurrence of multimorbidity in the EPIC-Heidelberg cohort
Gabriele Nagel, Richard Peter, Stefanie Braig, Silke Hermann, Sabine Rohrmann, Jakob Linseisen

Reply to the comments of the reviewers / 1st revision

General comments:
We thank the reviewers for their detailed comments, all of which we considered for the modification of the manuscript and commented in detail. Concerning the presentation of the results on the trajectory of education on multimorbidity, we have minimized the presentation of results of stratified analyses.

Specific comments:
Reviewer: C Schooling

1. Did the authors use logistic regression to examine the association of education with multi-morbidity about 9 years later? Please could the authors explain why they did this in preference to a prospective analysis using a Cox proportional hazard model. I recognize that time on study might be meaningless as a timescale in their situation, but they could use attained age as the timescale with adjustment for baseline age.
We agree with the reviewer, that we did not exhaust the prospective study design. However, the follow-up is relatively short and was performed in waves of equal time intervals. We aimed to display the overall burden of disease including prevalent and incident morbidity. Since we used data up to the end of the third follow-up we considered a cross-sectional study design more appropriate. In addition, the use of groups of disease constricted the definition of onset of disease. We reported on cumulative prevalence of diseases.

2. Why did the authors exclude anyone below the age of 50? Do they think that the associations between education and multimorbidity change with age, and if so why? Do they get the same results if they include the younger people?
Participants younger than 50 years were excluded, because for the investigation of multimorbidity our study sample is still quite young when confined to the age 50+. It is well documented that multimorbidity is relatively frequent in older age. Our work adds evidence that multimorbidity is already present in middle aged participants. We would like to avoid dilution of effects by including subjects below age 50. For a separate analysis in these ‘younger’ adults, the number of study participants is too small.

3. The Results provide analysis stratified by smoking status and by obesity status. However the reason for this analysis is not given, nor is this analysis described in the methods. Do the authors think a priori that the association of education with multimorbidity would vary with smoking status or obesity and if so why? In addition, the interaction p-values provide no evidence that the effect of education on morbidity varies with smoking status or obesity, so Table 5 should be removed, and all reference to it.
According to the suggestion of the reviewer we have deleted the results on Smoking status and BMI stratified analyses in Table 5 (Please see also General reply).

4. There does seem to be evidence of different effects of by age-group, so instead of Table 5, there should be a Table showing age-stratified results.
Table 5 shows analyses stratified by age (≤ 60 and >60 years) for multimorbidity and metabolic diseases.
Minor Essential Revisions

1. (lines 86-9) The last paragraph at the end of the introduction should also state the authors intend to examine the mediating role of health behaviour in the association between socio-economic position and multi-morbidity.
We have changed the paragraph accordingly (line 87).

2. (lines 121-3) Please could they clarify the definition of metabolic disease.
We have used the wording ‘metabolic disease’ in order to separate from the metabolic syndrome, for which more rigid definitions exist. The definition has been rephrased (line 128) and the wording ‘metabolic diseases’ is used throughout the manuscript and indicates the presence of at least one metabolic disease.

3. (lines 126-30) Please could they clarify the categorization of education. The problem is that the distribution of education in their sample is different in men and women, most likely because of historic attitudes to men and women. More men (33%) have ‘high’ education than women (20%), so it is not clear whether education represents the same thing in men and women. Can they re-group education, so that there are approximately equal proportions of men and women with low, medium and high education?
In our study, the definition for educational attainment was identical for men and women. In Germany, we have a public schooling system with three distinct degrees. All children should have equal access to education. The chosen groups reflect the German schooling system. We have added a comment in the method section (line 135).

4. (line 142) Was BMI treated as a continuous or categorical covariate? Given that BMI may have a U shaped relation with morbidity, categorical might be better.
In the multivariate models, BMI was included as continuous variable. In the method section we have defined the continuous variables (lines 155-157). Due to the low number of subjects below BMI 20 (2%), the U-shaped form of the association between BMI and morbidity is not relevant in this study.

5. (line 151) Please could they explain how they obtained the p-values for interactions in the Statistical analysis section.
A detailed description is now added in the statistics section (lines 157-159).

6. (line 146) Please provide a referenced justification for analyzing men and women separately, or analyze them together. There appears to be no evidence of different effects by sex, so sex-specific analysis is difficult to interpret.
As suggest by the reviewer, we have added a reference on gender-specific morbidity in the method section (line 150). It is well-established that sex-specific patterns of lifestyle habits and morbidity exist, e.g. smoking, cardiovascular disease, and COPD. In addition, other authors have also reported gender-prevalence rates of multimorbidity (Fortin et al. 2005, van den Akker et al. 1998). Please see also reply to the following comment.
In addition, for German women the chance to achieve a higher educational degree increased during the past decades. Thus, for older women the educational status is not necessarily equal to the social status.

7. (line 176-181 and lines 184-5) Please consider removing this text. Slight differences between groups are to be expected on any stratification.
We agree with the reviewer that slight differences between groups could be due to stratification. However, mortality and also the spectrum of diseases differ by gender (Klenk et al. 2007). Thus, there is a rationale for reporting these results.
8. (line 197-199) Please clarify what they are saying about alcohol and diet. Do they mean that alcohol and diet were unrelated to multimorbidity or do alcohol and diet not modify the associations of education with multimorbidity?
We have rephrased the sentence now referring to the results of the fully adjusted models (lines 207-210). The introduction of further potential confounders such as alcohol consumption and diet did not substantially change the estimate.

9. (lines 201-216) Please consider removal.
In agreement with the reviewer we have removed the text.

10. (lines 251-254) Is it correct that they found effect modification in the relation of education to multimorbidity by smoking status? Because the p-values reported for these interactions (lines 208-9) are quite large. When this is straightened out please review lines 253-6.
We have removed this text, because in our data no statistically significant effect modification was present.

11. Please keep the discussion focused on the topic of education and multimorbidity, e.g. remove lines 282-3.
As suggested by the reviewer we have removed the sentence.

12. (lines 301-304) Is it correct that they found that the relation between education and multimorbidity differed by sex, given the p-values on line 183? If not, these lines should be removed.
The strength of association between education and multimorbidity differed by gender. However, none of the interaction terms for education and gender reached statistical significance. As suggested by the reviewer we have changed the wording to express that there could be differential associations by gender (line 296).

13. (line 332) Higher rather than increasing BMI
We have changed the wording accordingly.

14. (line 334) Please can they show evidence in the results for ‘gender specific pathways differentially influencing the association between education and multimorbidity’ or remove this statement.
As suggested by the reviewer we have removed the sentence.

Discretionary Revisions
15) Table 3 does not really seem necessary
So far, there is little information on the prevalence of multimorbidity. Thus, we consider the relationship according the number of diseases as interesting information for the readers.

Reviewer: jean-bernard Ruidavets

Minor comments
1) In table 1: chronic condition of hypertension is given for women but not for men.
In this table, 179 women with cancers represent 2.8% whereas 50 subjects with hyperuricemia represent 3.8%. All the data reported in this table should be carefully checked.
Thank you for this comment. The numbers in table 1 have been checked carefully.
2) In table 1, the marginal numbers concerning the various educational levels must be reported for men and women. We now provide the marginal numbers by education and gender in table 1.

3) In table 3, the number of subjects must be reported too. In «Results» multimorbidity rates should be reported for each sex. We now have reported the number of subjects per stratum in table 3. The prevalence of multimorbidity is now presented by sex in the result section (line 167).

4) We noticed discrepancies between OR in the text and OR in tables (line 179 in particular) in the «discussion» indications of tables should be checked (line 257). We clarified that the age-adjusted results we cited (line 185), because later in the text we describe the changes by introducing smoking habits and BMI. The cross-reference to table 2 has been changed accordingly (line 252).

Major comments
5) After a thorough reading of the paper, it was impossible to know if incident pathologies only have been taken into account in the analyses. Were subjects with pathologies at inclusion excluded from the analyses or were those analyses carried out for all the subjects, including subjects with pathologies at inclusion and those for whom the disease occurred during the follow up? If incident pathologies only were taken into account, it should be accurate to justify the use of a logistic regression in multivariate analyses. We were interested in the cumulative prevalence of burden of disease. Therefore, we didn’t want to exclude prevalent disease, as it would have been necessary to utilize the prospective study design. Instead we applied the logistic regression modelling (please see also general reply and reply to comment 1 of reviewer #1).

6) No information concerning participants’ follow-up is reported and more particularly concerning subjects lost for follow-up: their number, distribution according to sex, their educational level etc…
According to the reviewer’s comment, we now provide data on the completeness of the follow-up of the cohort (lines 123-124). In general, the participation rate was fairly high with rates above 90 % in all follow-up rounds. We also provide now information on the overall loss for follow-up at the end of the 3rd follow-up round in the methods section.

7) Only some pathologies (those more easily identifiable by patients) reported by subjects were checked by a comparison with their medical records. What about the results obtained after the confrontation between reported and checked data? The authors mention validation studies carried out for some pathologies, details should be provided concerning these validation studies.
In the methods section as well as in the last paragraph of the discussion it is indicated that all cancer cases have been verified (no selective verification). The situation is different for other diseases; only for few selected diseases small validation/pilot studies have been conducted. This information is now included the methods section (lines 118-120). It is a limitation that not all self-reported diseases could have been verified. However, the observed prevalence rates are in good agreement with prevalence rates reported from medical claim data. The main original objective of EPIC was to investigate the association between nutrition and cancer and, therefore, these self-reports are being verified. However, we are currently also on the way of systematic verification of other chronic diseases, e.g. MI and stroke. In a former study also the diagnosis of asthma has been verified (Nagel & Linseisen 2005).