Author's response to reviews

Title: Estimating the BMI-Mortality Relationship: A New Approach

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Version: 2 Date: 7 September 2011

Author's response to reviews: see over
September 6, 2011

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Dear Dr. Henderson,

We are pleased to submit a revised version of manuscript MS: 6297156475572477, which has been retitled “A New Approach to Estimating the BMI-Mortality Relationship.” We are grateful to both reviewers for their clear and constructive suggestions. As requested, we have resubmitted our manuscript as a Microsoft Word document with all changes tracked. Attached to this letter are specific responses to the comments provided by the two reviewers. All page number references in our responses assume the document is set in “Final” model.

Sincerely,

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Response to Reviewers’ Comments

Reviewer 1

Major Revisions:

1. It is absolutely critical in a study of the present type that the functional form of the continuous variable of interest (here, BMI) be (a) as close to “correct” as is reasonably possible, given the inevitable limitations of the data, and (b) scientifically plausible. Condition (b) is satisfied in the sense that the authors results appear to agree qualitatively with most other studies in the literature. I believe that more could be done with condition (a). Although FP2 functions are certainly more flexible than quadratic polynomials, they still have their limitations. One helpful approach could be to divide BMI into many (say, 25-40) narrow categories and estimate mortality in each category. This can still be done, with adjustment for the important confounders, in a logistic regression model setting. The results can then be plotted against BMI (i.e. against mean BMI in each category) and compared with the results from the FP analysis. If desired, lowess or other suitable smoothing can be applied to the (inevitably noisy) categorical estimates, but this is not essential. The large sample size in the present study makes such a sensitivity analysis feasible. An alternative to the “small-categories” approach would be modelling BMI by using regression splines (or other flavours of splines), but this is not necessarily a straightforward task unless researchers already have considerable experience of the methodology.

As suggested, we have performed sensitivity analysis in regards to the functional form for BMI. We divided BMI into 30 bins (1 bin for each BMI unit between 18-40, for every two BMI units between 40 and 54 and a single bin for BMI above 54) and estimated the logistic regression model, adjusting for age (untransformed) and smoking status. We applied Lowess smoothing to the resulting curves presented in the new Figure 1. A description of this analysis was also included in the Methods section at the top of page 8.

2. The authors nicely demonstrate the existence of a nadir in mortality according to BMI. The nadirs vary according to sex (and in females, also by age). However, they give no model-based estimates of the uncertainty in those nadirs. Confidence intervals for the nadir can quite easily be estimated by the bootstrap method or by the so-called delta method (based on Taylor series expansion). The bootstrap is probably the easier of the two, although it should be possible to use Stata’s remarkable predictnl command to get delta-method based estimates of the SE of the nadir without (much) mathematical or programming pain.

As suggested, we have computed 95% confidence intervals for all nadirs. Standard errors were computed using the Delta method (via Stata’s nlcom command). Confidence intervals were included to accompany all reported nadirs in the Results section of the manuscript and Table 3. We also compared confidence intervals for different models in the Discussion section and added a paragraph describing the computation of the BMI associated with minimum mortality in the Methods Section (page 8-9).
3. The MFP method as described by Sauerbrei & Royston (1999) [reference 31] incorporates a so-called closed test procedure for selecting an FP model. The “hierarchical” selection method described by the authors (middle of page 7) differs from the closed test procedure, and is known to suffer from an increased type 1 error rate (i.e. can give too many “significant” results). The authors state (page 8) that they used Stata’s mfp command to select an FP model. The default and preferred algorithm for FP model selection in mfp is the closed test procedure. Please clarify which procedure was used, and if not the closed test, please justify.

The fractional polynomial model for BMI was computed in Stata using `mfp’ applying the default closed test procedure. We have corrected the Methods section (page 7) to reflect this.

Minor Revisions:

4. The authors state that they excluded individuals below age 18 years and below BMI 18.5. Please say why.

We chose the 18-year threshold because NHIS defines an adult as individual at age 18 or above. The 18.5 BMI threshold was chosen because we wanted to avoid the unobserved confounding caused by sickness among those in the underweight category.

5. Can the authors please be more explicit as to how they applied “sample adult weights from the NHIS” (page 6) to correct their results for sampling bias, e.g. how was this done using logistic regression with Stata?

We have clarified how sampling weights were used at the bottom of page 6 and top of page 7.

6. The authors state that they used 5-year mortality as the main outcome variable. However, it isn’t clear if any times to death were censored in the follow-up interval 0 to 5 years. If so, the mortality results could be biased downwards, since some deaths might have been missed.

All respondents were tracked for at least five years and times to death should not be censored. We have clarified how data were linked to the National Death Index at the top of page 6.

7. The authors state (page 7) that “the MFP method also scaled and centered variables in model selection process to improve model fit”. This is not correct. The scaling is to improve numerical stability and the centering is to provide the model intercept with a sensible interpretation.

Thank you for the correction, we have made this modification at the top of page 8.

8. Are the results in these graphs shown in Figure 4 adjusted for confounders? If so, I wonder how the results in the graphs were calculated. For example, the categorical model and the FP2 model for males (bottom left panel) seem to disagree somewhat as to the general level of mortality. The categorical model suggests slightly higher mortality. One has to be careful to ensure comparability of estimates with this sort of analysis.
This discrepancy was due to misspecification in the categorical comparison model. We have corrected the comparison model and revised Figure 4 (now Figure 5) accordingly.

9. Page 4: “obesity … society faces”: presumably US or Western society, not society globally?

We have changed this statement to “… Western society faces”.

10. Page 4: “Some studies have concluded no relation” – please provide citation(s).

We have added reference 1 on page 4, which finds no relation between BMI and mortality.

11. Page 5: “endogenously select the best fitting model”: please explain this phrase.

We intended to convey the fact that the MFP approach uses the data itself to determine the best fitting functional form. We have modified this phrase on page 5 and the Objectives section of the Abstract accordingly.

12. Page 5: the NHIS is conducted annually. Why did the authors select data (only) from 1997-2000 for their analysis?

Our goal was to estimate the BMI-mortality relationship using the latest available data. In order to guarantee 5-year follow-up given NDI death data, we chose 2000 as the endpoint. The starting point was chosen because the NHIS sampling process changed between 1996 and 1997. Additionally, because our analysis assumes 5-year mortality is constant over the sample period, and given that we had sufficient statistical power with our sample, we did not add data prior to 1997.

13. Page 5: “BMI missing or … a BMI of over 99.99”: does this throw doubt on the quality of the BMI data?

As pointed out by Reviewer #2 (comment #6), we employed the complete case approach to handling missing data, which assumes data are missing completely at random. We have pointed this out as a limitation in the Discussion section.

14. There are several typos in the manuscript that need to be corrected.

We have reviewed the manuscript and to our knowledge have fixed the typos we identified.

15. Figure 1: the relationship between mortality and age looks linear, but the authors selected an FP1 model in the main analysis. Can they explain this apparent discrepancy?

This discrepancy resulted from oversmoothing of the Lowess plots. We have revised Figure 2 (previously Figure 1) after reducing the bandwidth (0.2 for female sample and 0.15 for the male sample). Also, Lowess plots for age over the full male and female sample, respectively, presented below are slightly convex.
Reviewer 2:

Major Revisions:

1. The title of the paper is misleading. The authors applied the usual MFP procedure which is not a new approach. Thus, the title has to be changed.

   *We have rephrased the title to “A New Approach to Estimating the BMI-Mortality Relationship”*

2. Page 5, line 11: "The purpose of this study is to estimate the relationship between adult mortality and obesity using …". If it is really the main aim of the paper to estimate a relationship the paper is better placed elsewhere. However, in the Abstract it is stated that "This study tests a flexible modeling approach …" which means that the paper also has a methodological focus. The latter has to be strengthened and the main methodological aim (e.g. the comparison of the MFP procedure with common regression approaches using categorized variables) should be described consistently in the Abstract and the Background.

   *We have modified the aim in the last paragraph of the Background section to be consistent with the methodological aim of this paper as described in the Abstract.*

3. Following comment (2) the main results are not given by the estimated regression curves or the estimated nadirs. The main results are the disadvantages (bias, power, etc.) of regression approaches using categorized variables compared to the MFP procedure. The paper (Abstract, Results, Discussion) has to be revised accordingly.

   *To strengthen the methodological aims of this paper we have modified the Abstract, Results and Discussion as follows. The Results section has been restructured to highlight the results of the MFP estimation and then compares the BMI-mortality curve from the MFP model with the linear-quadratic and categorical models. We compared the models with regard to model fit, shape, the nadir and the magnitude of mortality estimates. Subsections have been added accordingly. The Discussion section focuses on the implications of model differences. The majority of the epidemiological discussion has been deleted. We retained one paragraph that compares our results with those from previous studies for the purpose of addressing comment #1 from Reviewer 1 regarding the scientific plausibility of the BMI-mortality curve obtained using the MFP approach. Finally the Methods and Results subsections of the Abstract have been modified to better highlight the finding that important differences across models exist.*

4. Page 8, lines 8-10: Which graphical checks were used?

   *Lowess smoothed curves (Figure 2) were the graphical checks used. We added this clarification at the bottom of page 8.*

5. Reasons should be presented for the chosen approach to adjust for selection bias. Sensitivity analyses should be performed to show the robustness of this approach.
Sampling weights were used to address sampling bias, and not selection bias as was mistakenly stated in the paper. We have modified the bottom of page 6 and the top of page 7 to reflect this.

6. The complete case approach was applied to deal with missing data, which is prone to bias. The application of this approach may be adequate in a methodological paper with the main goal to compare several approaches in the case of complete data. However, the limitation that the estimates may be biased due to missing data should be mentioned.

We have included the potential for biased estimates with the complete case approach as the third limitation on page 16.

7. Only 3 explanatory variables were considered: BMI, age, and smoking. Again, this may be adequate in a methodological paper with the main goal to compare several approaches in the case of only 3 important covariables. However, the limitation that the estimates may be biased due to ignorance of further covariates (e.g., physical activity) data should be mentioned.

The possibility of omitted variable bias in parameter estimates has also been included as a limitation on page 16.


Consistent with comment #2 by Reviewer 1, we have added confidence intervals to all computed nadirs and added a comparison of the confidence intervals produced by different regression approaches in the Discussion section.

9. The Discussion section starts with the description of the epidemiological findings regarding the BMI-mortality relationship and includes a lengthy discussion of the own findings compared to that of other epidemiological studies. Most of this discussion should be removed and the Discussion section should concentrate on methodological issues.

We have modified the Discussion as suggested. Refer to comment #3 by Reviewer 2 for more details.

10. The paragraph on limitations contains only the model choice (logistic vs. Cox model) and the performed pooling of data. The existing further limitations (missing data, possible confounding) should be added.

We have added these limitations as suggested. Refer to comments #6 and #7 by Reviewer #2 for more details.

Minor Essential Revisions
11. In the Background of the Abstract it is stated that "This study tests a flexible modeling approach … to examine the relationship between mortality and obesity measured as BMI>30." However, the main approach is given by the MFP procedure in which BMI is used as continuous variable. Thus, not the relationship between mortality and obesity measured as BMI>30 is investigated but the relationship between mortality and BMI as continuous variable is investigated and compared to a common regression approach using BMI as categorized variable. Thus, the statement has to be changed.

*We have omitted the statement “BMI > 30” in the Background subsection of the Abstract and added a sentence in the Methods subsection indicating that we evaluated the model produced by the MFP procedure against other commonly used models.*

12. Page 11, line 1: "Figure 5" should be "Figure 4".

*Done.*

13. The labeling of Table 2 is incomplete; probably, the numbers in brackets represent SEs; this should be stated clearly.

*We have modified the caption in Table 2 to indicate standard errors are in parentheses.*

14. The title of Table 2 is hard to read. Please move the formulas into a footnote for Table 2.

*Done.*

15. Please use different line types in Figure 3 for smokers and nonsmokers.

*We’ve changed Figure 3 (now Figure 4) to a black and white figure with a dotted pattern for smokers.*

Discretionary Revisions

16. Sensitivity analyses were performed by using 3-year mortality as outcome. The following sensitivity analyses would improve the paper (in addition to the sensitivity analyses concerning the authors’ approach to adjust for selection bias, see above):
   - Regression analyses without extreme BMI values
   - Exclusion of persons that died early

*We repeated the multivariable fractional polynomial method (including checks for interactions) after omitting extreme BMI values and also after omitting early deaths. Although the best fitting FPs were different, we found that the shape of the BMI-mortality curves produced by the two models corresponded with the main model. Also, interactions identified in the main model remained significant in the two comparison models. We provided graphical comparisons in Figure 1 and noted the model similarities in the Results section (page 10).*
17. If the authors consider to write an additional paper presenting the epidemiological results for another journal the following papers may be interesting:

- Neovius, M., Sundstrom, J. & Rasmussen, F. (2009): Combined effects of overweight and smoking in late adolescence

We appreciate the references. Should we pursue an epidemiological paper, we will consider including them.