

Author's response to reviews

Title: Estimating health-adjusted life expectancy conditional on risk factors: results for smoking and obesity

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Version: 2 Date: 8 September 2006

Author's response to reviews: see over

Dear editors,

Herewith I submit a revised version of 'Estimating health-adjusted life expectancy conditional on risk factors: results for smoking and obesity' including a detailed response to the comments of the two reviewers indicating the changes made to the paper (see next pages).

We would like to thank the reviewers for their useful comments and remarks. We feel that by addressing the issues raised by Dr Manton and Dr Barendregt, the quality of our paper has improved considerably. Both reviewers demanded more discussion about the sensitivity of our results to the assumptions used in the simulation model and to the input data. Therefore, the discussion section has been expanded to address these comments. Furthermore, we have clarified some issues in the methods section. However, as explained more elaborately in our detailed response, we disagree with the second comment made by Dr. Barendregt about the transparency of the simulation model presented. In our opinion, whether a simulation model presented in a spreadsheet or by the formulas used, is most transparent, is primarily a matter of taste.

We hope you are willing to consider this revised manuscript for publication in Population Health Metrics and we look forward to hearing from you on this in due course.

Yours sincerely,
On behalf of all co-authors,

Pieter van Baal

Reply to remarks from Reviewers

The original text from the reviewers is printed in normal face, while our reaction is printed in bold and italic

Reviewer's report

Title: Estimating health-adjusted life expectancy conditional on risk factors: results for smoking and obesity

Version: 1 **Date:** 10 July 2006

Reviewer: Kenneth G. Manton

Reviewer's report:

1) Assessment of work is question new?

The question is not new in the U.S. Indeed there has been a major controversy at the U.S. CDC (Center for Disease Control) and in the national scientific and popular press about estimates of the health effects of obesity versus smoking as a risk factor for excess mortality. The controversy was generated because a number of analyses produced by CDC in 1999, 2000, and 2001 had suggested the obesity was overtaking smoking as the number one risk factor with regard to excess mortality. In a series of peer-reviewed articles by Flegal and other analysts at CDC using NHANES and other more recent data showed that due to the use of inappropriate statistical methods and old data in the prior CDC studies that the excess mortality due to obesity had been greatly over estimated with smoking remaining the number one risk factor for excess mortality but with obesity being only the seventh ranked risk factor (e.g., Flegal et al., 2004, 2005; Fox et al., 2004). A large part of the reduction of the estimated effect of obesity was due to recent data showing that, in part improved treatment of diabetes and hypertension had reduced stroke and other more immediate causes of death using recent data from NHANES. Furthermore the data indicated that the effects of obesity attenuated with age not being strongly related to mortality or health service use above age 70 to 75. These results seem at variance with the estimates for obesity made in the reviewed paper at age 65. Also of importance in the analyses was the observation that smoking and obesity were correlated, i.e., weight gains of 10 to 15 pounds in smokers were frequently observed; as were weight gains in persons using current medications to control blood glucose levels. New medications may eliminate those gains. I did not see any place in the current model where such interactions were represented or discussed.

We are aware of the discussion around overweight and obesity and follow it with close interest since relative risks are a crucial input for our model and a main driver for our results. First of all, the discussion focuses on overweight, not obesity and in our analyses we have restricted ourselves to obesity. Secondly, in our analyses we estimated life expectancy of a cohort of obese never-smokers. It has been shown that excess mortality due to obesity is strongest for never smokers (see for instance the recent study by Adams, Schatzkin et al in the NEJM 2006: Overweight, Obesity and Mortality in a large Prospective Cohort of Persons 50 to 71 years old). Most importantly, NHANES is just one from the many studies addressing the relation between obesity, age and mortality and also a study with a relatively small sample size. The relative risks employed in the our simulation model are based on a comprehensive review of several of those studies. Although in our model relative risks

decrease with age, the decrease at older ages is not as sharp as observed in NHANES. The results of the already mentioned recent study of Adams, Schatzkin et al in the NEJM 2006 also found higher relative risks of overweight and obesity than Flegal et al. However, to address the discussion around excess mortality associated with overweight we have dedicated a paragraph in our discussion section to this issue.

2) The methods seem in general satisfactory, but, as indicated in 1, some assumptions appears unrealistic. One assumption that is problematic is that the risk cohorts are defined to be homogenous discrete groups (see definition above equation 1). The risk categories are not, in fact, homogenous meaning that, over age, the heaviest smokers and the most obese trend to die early reducing the mean level of smoking, and possibly obesity, with age. This would lower the risk at later ages as the risk factor average value is reduced by selection on a heterogeneous population. Obesity has a more complex age trajectory than smoking in that body composition (lean vs. fat body mass) changes with age related endocrine and metabolic changes implying that BMI is not a measure whose health implications are stable over age due to changes in metabolism.

This is a very good point. Ideally, BMI should be modeled as a continuous risk factor. However, the classes used in our model are common practice and also used by the WHO to define overweight and obesity. Using more classes would mean more data that would be difficult to get or even non-existent. The calculations are made using risk factor class averages calculated using data on risk factor distributions in the Netherlands. To what extent the risk factor class averages calculated using the current risk factor distributions in the Netherlands can be used as an approximation to simulate average relative risks of a cohort depends on the stability of these distributions over time. In the methods section we have provided more details about the methodology with which the relative risks for the classes were estimated. Furthermore, this issue is addressed in the discussion section.

A second assumption is that no transitions occur between risk factor classes over time (where risk factor classes are homogenous). I would question the validity of this assumption. A concern with the three categories selected for BMI is that the U.S. studies found that the relation of risk to BMI was non-linear (e.g., quadratic) with a large flat interior region centering on a BMI of 25-29 which had the lowest risk level “consistent with estimates of health optimal BMI levels made by Fogel and Costa of about 27.2. Significant risk elevations were restricted to the morbidly obese” a relatively small proportion of the population.

In our model the non-linear relationship between BMI and RR has been taken into account. However, due to the use of three classes, the non-linearities can not be observed. For each class mean relative risk for those classes were estimated using the current BMI distribution in the Dutch population. This has been clarified in the methods section.

3) I am not familiar with the datasets employed but apparently the disability weights are derived from “a large panel of experts”, i.e., based on subjective probability assessments. Disability is likely multi-dimensional and not easily scalable

on a single 0.0 to 1.0 scale. Disability weights could be constructed from objective measures of function.

The disability weights employed in our study are firmly established in the scientific literature as a way to scale the multi-dimensional construct of disability between 0 and 1. To emphasize the fact that the disability are not an objective measure of function we have added the following sentence in the methods section: 'since the construct of disability encompasses multiple dimensions that are not necessarily of cardinal nature, all valuation methods to scale disability to a 0 to 1 scale imply value choices'

4) The data appears to correspond to standards for reporting and data disposition.

5) The discussion and conclusion appear to correspond to the numerical results reported. Not much discussion is provided at the end of the paper about the implications of the results about compression.

We have expanded the discussion section and integrated this comment with the first comment by Dr. Barendregt. Furthermore, possible implications of our findings with respect to health care utilization are addressed in the discussion section.

6) The title and abstract appear to reflect the topic of the analyses.

7) In general the writing is acceptable. There are a few sentences that need revision. In terms of the overall impression, I think the results of Flegal et al on obesity versus smoking in the U.S. needs to be discussed given that the U.S. evidence on obesity effects appear contradictory. Also the implication of the assumptions about obesity and smoking categories on results need to be better discussed. These are compulsory changes. In terms of recommendation, I feel that a decision would be difficult to reach without a response to the above question. In terms of the interest level of the article, I found the article to be of importance in its field " but with questions about its conclusions.

These comments as elaborated on above are all addressed in the discussion section. Furthermore, we have clarified the issues regarding the use of disability weights and the estimation of relative risks in the methods section.

References

Flegal, K. M., B. I. Graubard, and D. F. Williamson. 2004. "Methods of calculating deaths attributable to obesity," *American Journal of Epidemiology* 160(4): 331-338.

Flegal, K. M., Graubard, B. I., Williamson, D. F., & Gail, M. H. (2005) Excess deaths associated with underweight, overweight, and obesity. *Journal of the American Medical Association*, 293, 1861-1867.

Fox, C. S., Coady, S., Sorlie, P. D., Levy, D., Meigs, J. B., D'Agostino, R. B., Wilson, P. W. F., & Savage, P.J. (2004). Trends in cardiovascular complications of diabetes. *Journal of the American Medical Association*, 292, 2495-2499.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No, the manuscript does not need to be seen by a statistician.

Reviewer: Jan J Barendregt

Reviewer's report:

General

Re: estimating health-adjusted life expectancy conditional on risk factors: results for smoking and obesity This article reports the estimation of life expectancy (LE) and health adjusted life expectancy (HALE) of cohorts of people who either smoke, are obese, or neither. The estimation is done using a dynamic population model. The results show reasonable losses in life years and health life years for smokers and obese. It concludes that relative compression of morbidity will occur when smoking and obesity is prevented.

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

I have two main problems with this article.

1) The calculation of a HALE requires an estimate of age-specific total morbidity. The authors use the Dutch Burden of Disease study for this purpose (ref 7). However, in that study 48 diseases were distinguished, leading to an under-estimation of total morbidity. This is particularly important at high ages, when a considerable part of morbidity is difficult to attribute to specific causes. The conclusion on compression of morbidity is very sensitive to this issue, because the extra life years lived by the non-smokers and non-obese are of course at high ages. ***Indeed, this is a very crucial point. A sharper decrease in the health status of the cohorts at older age might change our conclusion. We calculated that the Dutch BOD accounted for approximately 70% of the morbidity of the Global Burden of Disease 2000 (European region A). Therefore, in the discussion section we have integrated this comment by elaborating on the Dutch Burden of Disease study and its consequences for our findings with respect to compression of morbidity.***

2) I think it is methodologically wrong to use a dynamic population model to estimate a cohort. You can do it, of course, but it is overkill: it could just as well be done in a multi-state life table (the authors are aware of this, see ref 25). Such a life table can be implemented in a spreadsheet, that could easily be made available on the web. Now we are referred for the RIVM Chronic Disease Model to an internal, and therefore presumably not peer-reviewed, RIVM report. When a population projection is made, it is necessary to use a dynamic population model, but when cohorts are modelled, transparency requires that a life table is used. ***First of all, we agree that it would be methodological overkill to build a dynamic population model only to estimate healthy life expectancy cohort. However, building a cohort model in Excel while in possession of a dynamic population model (implemented in Mathematica) that is perfectly suited to address the same question would be a waste of time. Implementation in a new software environment would imply new debugging and could possibly***

introduce errors. More importantly, whether a cohort model presented in Excel is transparent primarily is a matter of taste. In our opinion, presenting all mathematical equations and data to build a simulation model is more transparent than providing thousand of numbers in several worksheets. A nice analogy would be presenting a recipe instead of just serving dinner. In our opinion, scientific community is better off with recipes. Moreover, most important calculation steps are in the so-called pre-processing phase of the simulation model, that is, the translation of empirical data into model parameters. Often, these steps are often undocumented and left out in presentations of models in Excel, while these calculation steps are crucial for the results. Therefore, presenting a model in Excel is not perse more transparent, since we do not know how the model parameters where obtained.

Furthermore, we agree entirely with the comment with respect to the necessity of peer review of simulation models. Therefore, we have presented all methodological assumptions, the associated mathematical equations, in our submitted paper. The reference to the internal RIVM report is merely for completeness, for details of the simulation model not relevant for this paper. Furthermore, we added a file with all the input data.

Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct)

Discretionary Revisions (which the author can choose to ignore)

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

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

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.