Author's response to reviews

Title: Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study

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Version: 4 Date: 29 July 2010

Author's response to reviews: see over
To the editors of BMC Endocrine Disorders

29 July 2010

Submission of a revised version of the manuscript “Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study”

Thank you for inviting us to resubmit our manuscript to BMC Endocrine Disorders.

We are happy that the last (statistical) reviewer is satisfied with our survival analyses.

We find that we are able to answer exhaustively to the remaining few minor comments from both reviewers. Below please find our reply in New Times Roman and blue. New text is in italics.

The changes can be identified in the attached marked copy of the manuscript. Furthermore, Table 1 and 3-6 have been changed slightly. A column has been moved from Table 6 to Table 1 as suggested by reviewer 1 below.

We are looking forward to your reply.

Sincerely yours,

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Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study Niels DF Olivarius, Volkert Siersma, Anni BS Nielsen, Lars J Hansen, Lotte Rosenvinge and Carl Erik Mogensen

Dear Prof Olivarius,

Your manuscript has now been peer reviewed and the comments are accessible in PDF format from the link below. Do let us know if you have any problems opening the file. We have recruited Referee 3 (below) to provide us with a specialist statistical report on your manuscript.

Referee 1:
http://www.biomedcentral.com/imedia/1610303426380224_comment.pdf

Referee 3:
http://www.biomedcentral.com/imedia/1742362737418028_comment.pdf
We would be grateful if you could address the comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

Please note that it is our policy to allow a maximum of two revisions on manuscripts under consideration and thus the next revision is the last on which we are willing to seek advice. We therefore urge you to make every effort to fully address the criticisms during this revision.

Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made when revising the manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.

Please also ensure that your revised manuscript conforms to the journal style (http://www.biomedcentral.com/info/ifora/medicine_journals). It is important that your files are correctly formatted.

We look forward to receiving your revised manuscript by 3 August 2010. If you imagine that it will take longer to prepare please give us some estimate of when we can expect it.

You should upload your cover letter and revised manuscript through http://www.biomedcentral.com/manuscript/login/man.asp?txt_nav=man&txt_man_id=3327425223420145. You will find more detailed instructions at the base of this email.

Please don't hesitate to contact me if you have any problems or questions regarding your manuscript.

With best wishes,

Mick

Mick Aulakh, M.Sc.
Assistant Editor, BMC Medicine
BMC-series
BioMed Central

Reviewer’s report
Title: Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study
Version: 3 Date: 14 April 2010
Reviewer: Jan Cederholm

Reviewer’s report
Title: Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study
Version: 3.7m2 Date: 14 April 2010
Reviewer: Jan Cederholm

Reviewer’s report
In my last review I was still puzzled by the presence of age mentioned as one of the predictors (covariates) in Table 1. This was the reason why I asked if mean survival time, as mentioned in the Statistical section, was based on the observed follow-up period for data in Table 2. However, the authors repeat in their reply that age was used as the time scale in the analyses, as also mentioned in the Statistical section. The authors have now also corrected to use life expectancy, instead of mean survival time, both in the Statistical section and in Table 2. However, this raises a question: how can age be used as the time scale for the Cox in Table 1, if age also is presented as one of the predictors (covariates) in this Table 1?

As far as I can see, there are two main choices for the time scale in the Cox, time-on-study (=duration in this sample of newly diagnosed patients) or age at survival (the age at which a patient experiences a total mortality event or terminates participation in the study). If total mortality is the event, birth is the point of origin for this age, and it can be correct to use this age as the time scale for analysis of total mortality. Furthermore, Korn et al (ref 17 in the latest revised version) have argued that a model with age as time scale is generally more appropriate. This has e.g. compelled the European SCORE project to model age in estimation of 10-year risk of fatal CVD.

However, Pencina and D'Agostino at Boston University have underlined that the Framingham study has consistently modelled time-on-study as time scale in research concerning CHD and CVD. Furthermore in a paper 2007 (Statist Med 2007;26:1343-1359) they show with examples from Framingham, that use of time-on-study or age as time scale make no real difference, which they were able to demonstrate by estimation of regression coefficients for some included covariates as risk factors for CHD, e.g. diabetes and smoker. However, they underline strongly that when using age as time scale, it is necessary to adjust for age at study entry. If using an unadjusted age scale, this will give incorrect estimates of the regression coefficients, e.g. the coefficient for diabetes was then found to be weak and non-significant in their modelled example, although diabetes is a strong risk factor for CHD. The unadjusted age model also had a poor calibration compared to age or time-to-study models adjusting for age at diagnosis.

Thus, as I can see the situation in this article: age at survival = age at diagnosis + diabetes duration. This means that the predictor age found in Table 1 is the same as age at diagnosis. This also means that the authors have correctly used age at diagnosis as an adjusting covariate, when using age as time scale for the Cox regression in Table 1.

This also explains that HR for age at diagnosis is less than 1 in Table 1, although mean age at diagnosis was higher in the deceased patients than among survivors in Table 1. I can see that the authors now have included more explaining text regarding this in the Statistical section, which is clarifying. I suggest that the name age at diagnosis is used for this covariate also in Table 1, as the authors now have named this variable as age at diagnosis in the explaining text of the Statistical section. This would make it more easy for the readers to understand this variable in Table 1.

We can fully go along with these considerations, and we have changed “Age” to “Age at diabetes diagnosis” in Table 1 and 3-6.
2. I find it acceptable that the authors now have included my suggested more recent reference for analysis of life expectancy (Nelson et al, 2007, ref 19 in this revised version). Although their previous reference included the most well-known statisticians Cox and Breslow, this reference was old, from 1972, and not easily found nowadays when searching references by the Internet. The term life expectancy is now used everywhere in the paper concerning the results in Table 2. The authors have preferred to calculate median life expectancy from the 0.5-point of the survival curves, instead of calculating life expectancy from the area under the curve.

Articles analysing life expectancy are not frequent in the literature, although e.g. a recent paper by Leal, Gray and Clarke from Oxford and Sydney have performed such analyses and presented tables of life expectancy related to various risk factors using the UKPDS Outcomes Model (Eur Heart J 2009;30:834-839). However, it should be noted that the UKPDS Outcomes Model is based on parametric proportional hazard risk equations. The reference by Nelson et al (19) has used Cox regression. It has also been suggested that the Gompertz distribution might be better for analysing total mortality, which is exponential (sigmoidal), and said to be suitable for analysing total mortality including patients of high age. However, SAS version 9 still has very little to offer regarding Gompertz, and I find it sufficient that Cox regression was used here for calculation of life expectancy.

Thank you for this comment.

3. Results of the test for the proportional hazard assumption of the Cox Model II is given in the text below in Table 1, that is adequate.

Thank you.

4. Control for interaction between self-rated health (SRH) and other covariates is important for reliable statistical results. This has been well performed. However, I suggest that the data for interaction in all patients should be included in Table 1, not in Table 6 as now.

As pointed out by the reviewer, it is much more relevant to show the interaction results in Table 1, but this table was very large already. We have however followed the suggestion and moved the results from Table 6 to Table 1, which is still quite readable.

5. I agree with the authors that confounding, and residual confounding, is a most important issue in epidemiology, especially in research about SRH, and this has been sufficiently adressed in this article, according to available baseline data, and with the now added complementary analysis in all patients of confounding by urinary glucose and several symptoms at diagnosis, and with a reasonable underlining by the authors that the possibility of residual confounding still cannot be ruled out.

Thank you.

6. The authors have now fully responded to my comment regarding the clinical usefulness of this model for SRH-rating, as only excellent health differed considerably from all other alternative ratings. I agree that the fully adjusted Model II should be used for conclusion on these findings, and the authors have
now also added trend analysis on the SRH-rates. However, I still say that the results imply that this model for SRH seems not too suitable for general clinical use. An alternative is the EQ VAS Score, using a thermometer-like scale from zero (worst) to 100 (best). Hayes, Clarke et al have demonstrated that a multivariate adjusted 10-point higher EQ VAS score was associated with a 6% (95% CI 1–11) lower risk of vascular events, and a 22% (95% CI 15–28; p<0.001) lower risk of diabetes complications in a larger study of 7,000 patients with type 2 diabetes (ref 6 in this paper). They used time-on-study as time scale at Cox regression, and adjusted also for diabetes duration. EQ VAS Score and this reference is only mentioned by the authors in the Introduction as “evidence of SRH is scarce for people with diabetes”, and in the Discussion as " evidence of associations … SRH with morbidity and mortality … is only slowly emerging for people with type 2 diabetes”.

I suggest as a minor revision that the authors should somewhat more discuss on the clinical usefulness of the SRH-rating in this paper, compared with the results using the EQ VAS Score in the study by Hayes, Clarke et al.

The EQ VAS Score of the EuroQol-5D has been validated in many populations, and it is tempting to employ this VAS scale because it is easy to use across populations. It is, however, unsettled whether a VAS scale with 101 points has the ability to detect as small differences in self-reported health as the scale intends to do, and the content validity depends on patients actually being able to report their health in many categories/qualities. Actually, people tend not to use the full range of a VAS scale. I.e. the distance between the data points in the middle of the a VAS scale as deduced from the raw, ordinal data is in reality much smaller once data are transformed into interval level data [1]. Some of the evidence that exist to support the psychometric properties of VAS scales suggests that they are ordinal, but VAS results tend to be analyzed as results from an interval scale [1]. Nevertheless we could easily have ended up choosing a VAS scale when we planned this study, but we preferred the well-known SRH ordinal scale with five categories (reference 12-14) because we wished to use an instrument that was meaningful to the patient and easy to understand (Please find the wording of the question in Additional Material). The content validity of such an instrument has been examined by Manderbacka (reference 23) with qualitative methods, and her very interesting paper is a great help for researchers to decide how their results perhaps can be used in the doctor’s communication with the patient. In our paper we propose that doctors are more attentive to patients who do not rate their health as “excellent”, a word from the SRH-question. On a VAS scale the conclusion, perhaps, could have been that patients who rate their health as less than 80 need our attention, but this piece of information is difficult to implement into daily clinical practice. So we find the SRH-question with 5 categories more suitable for clinical use than the VAS scale. We have added the following sentences (in italics) about the interpretation of our results in the Discussion section:

“SRH is known to be associated with mortality and morbidity in the general population [2-5], while evidence of these associations is only slowly emerging for people with type 2 diabetes [6-8]. A large study with 2.4 years of follow-up used the EuroQol visual analogue scale (VAS) for self-rated health and found that a 10-point higher VAS score was associated with a 6% lower risk of vascular events [6]. We found that patients who rated their health as less than excellent had increased 5-year mortality, similar to that of patients with a history of CVD already at diabetes diagnosis (Table 2). The high response rate for our SRH-question (97.6%) indicates that the question was meaningful for the respondents, and it may be that the results from an ordinal scale with 5 categories are easier to use in the doctor-patient encounter than the results from a VAS scale.”

However, I find the results in Table 2 interesting, that this questionnaire was able to show a reduced life expectancy for all other ratings of SHR versus excellent SHR, quite comparable to the reduced life expectancy caused by a history of CVD which is a strong risk factor for mortality. The authors conclude that doctors should be more aware to discuss perceptions of health with patients having
newly onset diabetes, and to be attentive of sub-optimal self-rating. This should add to clinical skills.

**Level of interest:** An article of importance in its field  
**Quality of written English:** Acceptable  
**Statistical review:** Yes, and I have assessed the statistics in my report.  
**Declaration of competing interests:** I declare that I have no competing interests

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**Reviewer’s report**  
**Title:** Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study  
**Version:** 3  
**Date:** 6 July 2010  
**Reviewer:** Lianming Wang

**Reviewer’s report:**  
The statistical analysis is correct and the results make sense. The paper is well written. I have only a few comments.

1. Please switch “at a young age” and “at an older age” in lines 8 and 9 on page 8 since the definition and interpretation do not match. In general it should be cautioned to use age as a predictor in Cox model. The use of “age of diagnostic” and the interpretation of its effect on mortality hazard are correct. 

   We have changed the text according to this suggestion.

2. In the univariate analysis shown in Table 1, there seems a trend on the estimated three self-rated health effects (SRH), with worse health status having shorter (residual or remaining) life. This is as expected. However, this trend is not clear in the multivariate analysis and the Wald test of the equality of the three SRH effects does not reject the null hypothesis in Table 1. This may be due to the introduced confounding predictors in the model. The authors may want to consider fitting a constrained Cox model, in which the linear part is $\gamma_1 x_1 + \gamma_2 x_2 + \gamma_3 x_3$, where $x_1$, $x_2$ and $x_3$ are all binary variables, $x_1$ takes 1 if the SRH is not better than good, $x_2$ takes 1 if SRH is not better than fair, and $x_3$ takes 1 if SRH is (very) poor. All the coefficients ($\gamma$) are restricted to be nonnegative, and this model can be used to compare any people with different SRH categories. For example, $\exp(\gamma_1)$ indicates the hazard ratio of mortality with good SRH versus that with excellent SRH, $\exp(\gamma_2)$ indicates the hazard ratio of mortality with fair SRH versus that with good SRH, and $\exp(\gamma_1 + \gamma_2)$ indicates the hazard ratio of mortality with fair SRH versus that with excellent SRH. In general, incorporate such constraint can improve model-fitting. The author may choose to ignore this since it will require too much additional work.

The reviewer suggests a constrained Cox regression model parameterized in such a way as to be able to compare the hazards between any two SRH categories. While it is a good idea to stress the ordinal nature of the SRH categories by forcing the hazard ratios to be increasing (as the suggested model implies), the implementation of such a constrained Cox model is cumbersome. In the SAS PROC PHREG procedure - the
software we used in our analyses - there is no straightforward way of applying constraints to the parameters. We have consulted with our colleague professor Thomas Scheike at the Biostatistical Department, University of Copenhagen who is experienced in developing new statistical methods for survival analysis. He does not know of any statistical software that has implemented constrained Cox regression. I.e. we would have to move from SAS to another statistical software platform like R or C and program the constrained Cox regression ourselves. However, he added that an implementation of non-negativity constraints on specific coefficients may be handled by writing $\gamma = \exp(\theta)$ for such coefficients $\gamma$. Applying the chain rule will see to that the maximization of the score function is not complicated much - provided that you are familiar on an operational level with the workings and programming of Cox regression procedures. Given the hazard ratios as they are in e.g. Table 1 and the tests (on equality of the three SRH effects) we have performed already, we cannot imagine that a constrained Cox model would add much to the results and conclusions already presented. Hence, we feel that the relatively large amount of additional work involved will not be weighed up by the potential new insights. As it seems from the reviewer’s last sentence above that this is the opinion of the reviewer too, we have not made this constrained Cox model.

3. The word “CVD” is defined in line 10 page 3 but is first used in the last sentence of page 2.
Yes, CVD should be defined in both the abstract and the main text, and the definition has now been added to the abstract.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests:
I declare that I have no competing interests.

Reference List


