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: 2 Date: 3 February 2010

Author's response to reviews: see over
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.

The three reviewers have given us the opportunity to improve the manuscript considerably in particular by improving the description and documentation of our statistical methods.

Below is our answer to the critique (in New Times Roman and blue) and our major text revisions (in italics).

We are looking forward to your reply.

Sincerely yours,

Niels Olivarius

Re: MS: 9209087633210401
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 BMC Medicine

Dear Prof Olivarius

Peer review of your manuscript is now complete and, in light of the reports I'm very sorry to say it seems to us that, on this occasion, it would not be appropriate for BMC Medicine. Your manuscript does not represent a profound step forward in understanding to be of broad interest to people outside the field.

The reviewers’ comments are accessible in PDF format via the links at the bottom of this email. Please contact editorial@biomedcentral.com if you have any problems opening the files.

However, should you be able to we feel that your manuscript would be suited to the scope and readership of another of our journals, BMC Endocrine Disorders (http://www.biomedcentral.com/bmcendocrdisord/)

We have copied over the details of your manuscript to BMC Endocrine Disorders, and if you wish to proceed with the review process in BMC Endocrine Disorders, you can follow this link: http://www.biomedcentral.com/author/manuscript/details/view.do?manuscriptId=3327425223420145

Should you wish to submit to BMC Endocrine Disorders, we would be grateful if you could address the referees comments in a revised manuscript and provide a cover letter giving a point-by-point response to the concerns.

You will need to arrange payment with BMC Endocrine Disorders at the same time. Please note that the article processing charge for manuscripts published in BMC Endocrine Disorders is £1025.

Thank you for your interest in BMC Medicine.

With best wishes,

Mick

Mick Aulakh, M.Sc.
Assistant Editor, BMC Medicine
BMC-series
Reviewer's report
Title: Predictors of mortality of patients newly diagnosed with clinical type 2
    diabetes: a 5-year follow up study
Version: 2 Date: 21 December 2009
Reviewer: Gunthram Schernthaner

Olivarius et al have analyzed the predictors of mortality from a population-based
sample of 1,323 persons newly diagnosed with clinical diabetes and age above
40 years. The authors had already published two times about mortality in the
same cohort (Olivarius et al. J Diab Comp 1997, 11:83-89; Hansen LJ, Olivarius
Nde F, Siersma V. 16-year excess all-cause mortality of newly diagnosed type 2
main topic of the present manuscript was the evaluation of a simple
questionnaire about the self-rated general health (SRH). SRH was evaluated with
a single question: in general, how would you rate your health at present? The
response categories were excellent, good, fair, poor and very poor. The authors
concluded that patients who rated their health as less than excellent had
increased 5-year mortality, similar to that of patients with prevalent CVD, even
when biochemical, clinical and life-style variables were controlled for.

Criticisms:
1) the majority of all patients responded for the questionnaire with either good
   (n=439) or fair (n=574), whereas only a small proportion answered with excellent
   (n=157) or poor (n=123). In my opinion this rather unequal distribution is critical
   for the whole analysis. How did the patients differentiate between good and fair?
   It is true that the distribution is unbalanced, but it is to be expected that relative few patients rate their health as extreme
   as excellent and poor. This is also observed in other studies of self-rated health. The statistical analysis takes the
   unbalanced distribution into account. As far as we know, no study has examined how patients differentiate between the
   single categories. Responders’ more general grounds for rating their health are discussed on the basis of the available
   literature in the 2nd paragraph in the discussion section.

2) In Table 1 the classical CVD risk factors did not predict mortality, which is
difficult to accept and understand. How good and representative were the
measures? Any valid standardization of lab values?
   If you take into account that our patients are newly diagnosed and that patients are examined by their doctor as soon as
12 days after diagnosis on average, it is perhaps not surprising that the traditional risk factors like blood glucose level,
total cholesterol and blood pressure did not predict mortality. Newly diagnosed diabetic patients are in a physiological
interrupted (non-steady) state, and the measurement of the risk factor in question cannot be taken as indicative of its set
point for the individual patient. In this way a true association between a risk factor and death will be difficult to detect
because of the increased variability of risk factors. This is discussed in the Discussion section in the paragraph just
before “Conclusions” in the context of regression dilution bias.

3) In table 4 the highest 5 years CVD mortality was noted in patients with good
SRH versus excellent SRH, but the HR was much lower for the category “poor”.
Date by chance to due to much smaller sample size? By contrast the the
predictors of all-cause mortality in patients who died within 3 years of diabetes
diagnosis are more plausible.
   It is one of our main findings that excellent health increases survival. In the univariate analyses in Table 1 (new 1), 3
   (new 3), 5 (new 4), and 6 (new 6) we find a clear trend of increasing mortality from good to poor health. In all the
   multivariate analyses in Table 1 (new 1), 4 (new 3), 5 (new 4), and 7 (new 5) this trend disappears. This could be
because much of the variation in the relation between self-rated health and mortality is explained by other baseline variables than SRH - inclusive of risk factors and complications. In the subgroup analysis in Table 5 (new 4) of “healthy” patients without any known chronic conditions or complications (from a specified list, see Table 5 (new 4)) at diabetes diagnosis, the trend still exists in the univariate analysis and disappears in the multivariate model, which could indicate that the causal pattern behind this trend is only partly explained by the presence of these chronic conditions and complications. This is, however, speculative. In the tables we are testing whether the hazard ratios (HRs) for the different categories of SRH are different. The size of the HRs is not affected by the sample size, but the p-values are. We have added the following foot notes to Table 1:

* Wald test for the equality of the three SRH effects: p-value = 0.22 (model I); p-value = 0.80 (model II) 

...and in Table 3:

* Wald test for the equality of the three SRH effects: p-value = 0.80 (model I); p-value = 0.29 (model II)

(4) In Table 6 the predictors of all-cause mortality in patients who died later than 6 months after diabetes diagnosis are again difficult to understand. In comparison with the rather small group of SRH “excellent” (n=157) all the other groups had increased HRs, but these were not increasing from good to poor Please read our answer to point 3.

(5) Since the authors have already published the 16-year all-cause mortality data in the cohort of these newly diagnosed type 2 diabetic patients, the should also analyze whether the self-rated general health is related to the long term excess mortality.

Such an analysis is definitely relevant in this connection, but unfortunately this is not possible because the Danish Death Registry for some years has been behind in their coding of the death registries. Therefore, we have not yet access to the cause of death for the whole period of time.

Reviewer’s report
Title: Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study
Version: 2 Date: 29 December 2009
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: 2 Date: 29 December 2009
Reviewer: Jan Cederholm

This is an observational study of 1323 patients with newly developed diabetes (almost all type 2), followed for 5 years for total mortality and fatal CVD. It is reported that Cox regression showed that the risks of total mortality and fatal CVD were increased by less than excellent self rated health (SRH), a sedentary life-style, younger age at diagnosis and a history of CVD, and also by male sex, a presence of cancer, and by increased u-albumin excretion for fatal CVD. It is concluded that doctors should be attentive to and discuss sub-optimal health rating, and that life-style changes are relevant in these patients.

Description of selection of the study sample, and assessment of self rated health, smoking, angina, claudicatio, and assays of blood and urine for predictor variables, and assessment of endpoint events, are sufficiently described.

Major revisions:
Statistical analysis:
1. Cox regression was used to analyse total mortality and fatal CVD. Use of Cox needs a test showing that the proportional hazards assumptions were fulfilled for included covariates. It is mentioned in Statistical methods that the analyses of effect heterogeneity in Table 6 and 7 provided a test for proportional hazards,
and after Bonferroni’s adjustment for multiple testing, this assumption was not violated for any of the predictors. I can see that heterogeneity is reported in a column in Table 6, with p values given. The proportional hazards assumptions at Cox regression can be tested with the TEST procedure when using SAS. A product of each covariate and \( \log(\text{time}) \) is added to all existing covariates in the Cox analysis. Then, a proportionality test with the Test procedure gives a Wald Chi-square for all these added products, and this test should have a p value \( >0.05 \) if the proportional hazards assumptions are fulfilled. This is described in SAS Help “Getting started”, and well described from UCLA on the Internet: 
http://www.ats.ucla.edu/stat/sas/faq/test_proportionality.htm

Thus, it should be better described in Statistical methods if some kind of proportionality test was performed, e.g. with the product of each covariate and \( \log(\text{time}) \) added to all existing covariates in the Cox analysis.

We have already done the tests of the proportional hazard assumption with the method outlined by the reviewer, i.e. we test the joint significance of the products of each of the covariates with \( \log(\text{time}) \). We now present these results for Model II (the model on which we primarily base our conclusions) in Table 1 (general mortality) and Table 3 (cardiovascular mortality) in footnotes:

\[ \text{Test for proportional hazards: a Wald test for the joint significance of the interaction between } \log(\text{time}) \text{ and each of the model variables: } p \text{-value } = 0.62 \] (Table 1)

...and

\[ \text{Test for proportional hazards: a Wald test for the joint significance of the interaction between } \log(\text{time}) \text{ and each of the model variables: } p \text{-value } = 0.61 \] (Table 3)

As the \( p \)-values are non-significant, the proportional hazard assumption is fulfilled.

Furthermore, “Statistical analysis” has been changed:

The proportional hazard assumption was tested for Model II by adding the products of each covariate and \( \log(\text{time}) \) to all covariates in the model. The Wald chi-squared test for all these products gives a test for proportional hazard. See footnotes of Table 1 and 3. The analyses of effect heterogeneity in Table 6 also provided a test for proportional hazards.

2. As far as I know, test for heterogeneity should mean that the product of two covariates was added to the Cox analysis, and that the \( p \) value for this product describes the heterogeneity. Please read our answer to point 1.

It is said in the Statistical section that, in a further analysis all interactions between a characteristic and SRH, and the interaction between age and sex, were added to model II. Are such interactions given with \( p \) values in the column for heterogeneity in Table 6?? It should be better explained how and where the interactions between SRH and other covariate characteristic were reported, and the result of such tests.

The \( p \)-values reported in the heterogeneity column in Table 6 (new 6) are the \( p \)-values for the Wald chi-squares test for the null-hypothesis that the HRs <3 years and \( >3 \) years (reported in the columns to the left in the same table) are the same. The interactions between each of the covariates and SRH are now mentioned in the result section:

None of the interactions of the covariates with SRH added to model II in Table 1 were significant after Bonferroni correction (Table 6).

Moreover, the \( p \)-values for the interactions between each of the covariates and SRH are now reported as a column in Table 6 (new 6) with the following footnote:

\[ p \text{-values from the Wald test for the interactions between each of the covariates and self-rated health when these were added to model II (Table 1). The test for the interaction between age and sex had } p = 0.44. \]

3. It is stated in Statistical methods that death intensity was represented in used models as a function of patient age, with characteristics as covariates. It is also said in Statistical methods that the effects of selected characteristics were illustrated in Table 2 by the median survival time as projected by model II. It is also said in Results text, that the results from model II were translated into estimated deviations from the estimated life expectancy in Table 2. However, estimation of life expectancy is a fairly complicated statistical concept, and the
For the given configuration of the covariates in model II the survival function was estimated by N. Breslow’s method of exponentialing the negative empirical cumulative hazard function. See Brelow’s “Discussion of Professor Cox’s paper” [1]. The values (ages) at which these survival functions attained 0.5 were taken as estimates of the median expected survival. These were then compared in Table 2 to illustrate the magnitude of the effects. We have changed the text in “Statistical methods” accordingly: 

4. I suggest that Table 3 and 4 describing fatal CVD are brought together into one single Table 3, with the same layout as Table 1 describing total mortality. This has been done.

5. Tables 5-7 describe various sub-grouping of the total material. Such a sub-grouping should be somewhat problematic, as the total sample is not very large. I suggest that these tables could be included as on-line Supplementary tables, furthermore as these tables are described as Additional analyses in the Results text.

We will be happy to move these tables to an on-line supplement, but as we have understood the instructions for authors, this is not relevant in BMC Endocrine Disorders. If the editors want us to make a supplement, please let us know.

It is somewhat difficult to understand the subgroup analysis in Table 6, firstly analysing HR in those who died within 3 years, and secondly analysing HR in those who died during years 4 and 5? How can results in such subgroups with relatively little difference in death years be interpreted?

I can understand the meaning of the additional Table 7, excluding early deaths within 6 months, as this situation might more strongly affect the SRH.

The analysis in Table 6 (new 6) was made to demonstrate whether the effect of SRH on mortality changes over time as those patients who die a few years after diagnosis may die from undiagnosed conditions that are related to both SRH and death. The 3-year limit is arbitrary but guided by our wish to have approximately the same number of patients in the two groups. Table 6 also provides a test of the proportional hazards assumption, as mentioned above.

6. It is surprising that the hazard ratio for age and total mortality in Table 1, and for age and fatal CVD in Table 3, was less than 1, as mean age was considerably higher in deceased patients.

We modelled death intensity as a function of patient age (see “Statistical analysis”). The fact that the HR for age is less than 1 implies that young patients have a relatively higher mortality than old patients. This is in accordance with previous research.

Minor revisions:

The definition of fatal CVD seems to be broadest possible according to ICD-10 codes I00-I99. Why was it not selected to include mainly ischemic heart diseases, cerebrovascular diseases and peripheral artery diseases?

Only 164 patients died from CVD during follow up. This means that we do not have sufficient statistical power to make an analysis of e.g. deaths from MI or stroke.

It is mentioned in methods that HbA1c was analysed. Was HbA1c not available as predictor in all included patients?

In this manuscript it has been important for us to use predictor variables measured very close to the day of diabetes diagnosis. By using the diagnostic plasma glucose we have reached this goal. If we had used HbA1c the number of missing values would have been between 10 and 20% dependent on the number of days we had allowed to pass from day of diagnosis until day of sampling of blood for HbA1c. This would have weakened our multivariate statistical modelling.

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an
article of importance in its field

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

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.

Reviewer’s report
Title: Predictors of mortality of patients newly diagnosed with clinical type 2 diabetes: a 5-year follow up study
Version: 2 Date: 31 December 2009
Reviewer: Teruo Nagaya

Reviewer’s report:
General:
The authors present predictors of mortality during a 5-year follow-up in 1323 patients with diabetes mellitus (DM) newly diagnosed at baseline. Especially, self-rated health (SRH) was used and discussed as a predictor of mortality. However, sample selection and statistical methods have some deficits.

Subjects:
Although DM was newly diagnosed in 1323 patients at the baseline of the study, 298 (22.5%) patients of them died during a 5-year follow-up. Even in relatively healthy subjects without any other diseases (n=696, Table 5), the mortality was 14.5% (101/696). The high mortalities indicate too late detection of DM or advanced stage of other complications (cardiovascular disease etc.). Therefore, appropriate medical treatment is probably a major factor influencing mortality of the patients. How were the patients medically treated for DM and other diseases? Could the patients easily use medical supply? The authors presented no data or discussions on medical treatment for DM and other illnesses of the patients during the follow-up. These data (with analysis) and intensive discussions should be added.

The purpose of this manuscript is to analyse the predictive value for mortality of variables measured as close to the day of diabetes diagnosis as possible. This possibility is unique for our study as it is seldom to find large, population-based, well-described samples of newly diagnosed diabetic patients in the literature. It is beyond the scope of our manuscript to study the influence of the course of diabetes treatment on mortality. Information about pharmacological treatments, risk factor levels and incidence of (new) complications during follow up are intermediate or mediating variables in our analyses, and it is therefore not relevant from a methodological point of view to include them in the analyses.

For the too late detection of DM, screening (early detection) and educational system for patients with preclinical DM/hyperglycemia in general populations should be discussed to improve the prognosis of DM patients.

We have been very careful to describe our patient sample as having “clinical, symptomatic diabetes” as our patients’ diagnosis was based on a relatively high diagnostic glucose limit and most patients had symptoms [2]. In order to discuss this methodological precondition in the manuscript we have added the following sentence to the Discussion section:

Since our patient sample was established in the early 90’s, screening for diabetes has been intensified. These initiatives to identify patients earlier in the natural history of diabetes have probably decreased the variability of many of the baseline variables measured in our study. There is, however, no reason to suppose that the causal patterns underlying the associations that we have identified are different nowadays.

A part of patients had cardiovascular disease (378 patients) or cancer (63 patients) at baseline of the study. Naturally, the two diseases influence baseline serum tests, BMI, heart rate, blood pressure, lifestyles and SRH. Subsequently
the two diseases increase mortality of the patients, and 141 (51%) patients out of 278 patients deceased had cardiovascular disease at baseline (Table 1). In such a DM population with other severe diseases, predictors of mortality of DM patients can not correctly be drawn. Therefore, the patients with the two diseases at baseline should be excluded from the study.

We agree that CVD, cancer and other chronic conditions at diabetes diagnosis are very important confounders of the relationship between SRH and mortality and as such these variables are included in Model II (e.g. in Table 1 (new 1)). Moving from Model I (without chronic conditions and complications) to model II (with these variables), the effect of SRH is lessened, but it is still statistically significant. These models are made on the basis of specific hypotheses (see below) and they are methodologically sound. Undiagnosed conditions, however, may have contributed to precipitate the diabetes diagnosis, and these conditions may be associated with both poor SRH and high risk of death. We approached this unobserved heterogeneity among our patients in their susceptibility to dying in three additional analyses, one of which was an analysis of “healthy” patients (without CVD, cancer, diabetic retinopathy, peripheral neuropathy and albuminuria) in Table 5 (new 4). In this analysis the HRs were not changed substantially (compare Table 1 (new 1) with Table 5 (new 4)).

The authors considered that 97.6% of 1323 patients had type-2 DM. If so, the residual 2.4% (type-1 or secondary DM? or others?) should be excluded from the study.

We are not able to identify all the patients with probable type 2 diabetes, as we have no information about antidiabetic treatment during the 5 years of follow up in the comparison group [3]. Accordingly, we are unable to make the exclusions suggested by the reviewer.

Why do not the authors use drinking habit as a lifestyle factor of subjects (an independent variable)? Drinking habit is a popular habit of humans, and light-moderate drinking could be preventive against DM and decrease all-cause mortality in general populations.

We have no data on drinking habits in this study.

The authors try to compare predictors of mortality between patients with DM and those with cardiovascular disease. However, correctly to compare the predictors between the two groups, both of the two groups should be newly diagnosed at baseline.

All patients included in this study are members of the same cohort of newly diagnosed diabetic patients. The patients with CVD are defined as newly diagnosed diabetic patients with CVD.

Statistical methods:
total person-years (person-days) should be presented. (men/women, survived/deceased)
This information has now been added to the manuscript in the beginning of “Results”:
The total number of person-years in the study was 6447 (survived: 5568, deceased: 880; men: 3084, women: 3363)

Authors/scientists should estimate statistical models based on their hypothesis and previous evidence before the beginning of analysis. Post-analytic selection of the models using AIC/BIC may be just statistically logical, but may neither be always biologically logical nor be related with authors’ hypothesis. For an example, comparison of results from Model 1 and Model 2 in Table 1 suggests that SRH are associated with yes/no of cardiovascular disease and subsequently that OR by SRH and OR by yes/no cardiovascular disease are confounded with each other. Therefore, Model 2 may not be suitable for the study objectives.

We agree with the reviewer that statistical modelling must be based on specific hypotheses, and this is definitely what we did in these analyses. Our aim was to identify baseline predictors of mortality, but with special reference to the predictive value of SRH. If we had not chosen to focus on SRH we might have been content with the univariate Cox models and the multivariate Cox model II with all baseline variables inclusive of chronic conditions like CVD. Instead we planned and made two other Cox models in order to assess the effect of SRH while adjusting for possible confounding effects of other characteristics. Model I adjusted for SRH and all other baseline characteristics except chronic conditions. This was because we assumed that the chronic conditions could influence SRH more than socio-demographic variables and risk factors. In model III, SRH was omitted from the full model (model II) to examine
whether SRH mediated the effect of the remaining characteristics on mortality by comparing hazard rates with those in model II. I.e. every single model tests a specific hypothesis, and we are observing how the effect estimates differ between the three models. The over-all comparison of the three models was done by AIC/BIC, and the overall effect of SRH was analysed with a Wald test. Backwards elimination could be an alternative to the proposed specific modelling, but the backwards elimination is truly based on post-analytical selection, and we wanted to analyse our data based on specific hypotheses.

Generally, statistical power for detecting interactions (p.8) between two variables is low. The sample size (n=1323) is too small correctly to test interactive effects. We agree with the reviewer that interactions are harder to detect than main effects. We did the analysis of interactions, however, in order to make model control. We did not find any interactions, but we may have overlooked some existing interactions because of the relatively small sample size. The alternative is not to do an analysis of interactions which could mean that we overlooked some important interactions. Allow us to add, that when it comes to population-based samples of persons with clinical, newly diagnosed diabetes, our sample is among the largest in the world.

n available in each model should be cited.
This information has now been added to all tables either in headers or foot notes.

Which journal?: Not appropriate for BMC Medicine: an article of only archival interest, but might be suited to BMC Endocrine Disorders
What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions
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.

Reference List

