Author's response to reviews

**Title:** Methods of Competing Risks Analysis of End-Stage Renal Disease and Mortality among People with Diabetes

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**Version:** 2 **Date:** 22 September 2010

**Author's response to reviews:** see over
I. Reviewer's report

Title: Methods of Competing Risks Analysis of End-Stage Renal Disease and Mortality among People with Diabetes

Version: 1 Date: 11 April 2010

Reviewer: Michael Schemper

Reviewer's report:

Major compulsory revisions:

1. p. 4 top: It is not true that "the disease-free survival time analysis by standard methods, ..., does not distinguish different causes in the presence of competing risks." The whole paragraph should be deleted and you should start describing the appropriate methods for cause specific hazards (1) and subdistribution hazards (2). Also you should systematically cite or present the appropriate tools under both approaches, for univariate description, for k-sample testing, and for the modelling of prognostic factors. Note that for (1) the KM method (1-S(t)) is used, censoring survival time by competing events.

Response: Thank you and we have provided revisions on Pages 4 & 5.

2. There are various pros and cons for both approaches, nicely summarized by your cited Pintilie (Stat.Med. 2007) reference!

Response: Thank you. We have provided revisions on Page 17.

3. From p.8 on, alternatively either Z(t) (time dependent covariate) or just Z is given in formulae. This should be unified!

Response: Thank you. The formulae are now consistent.

4. p.13, line -3: Per definition dependent and independent variables in regression can't interact: the relationship is one-sided. Interactions can be produced by main effects.

Response: In the text, we wrote that a dependent variable (age) had a significant "impact" on the independent variable (ESRD),. We did not use the term "interact". For clarification, we have changed "Impact" to "effect".

5. p.16, line 9: Overfitting a Cox model has nothing to do with violation of the proportional hazards assumption!

Response: Thank you. We have corrected that.
Minor essential revisions:

6. p.4, line -2: a risk (in this context) is never censored, only times can be.

**Response:** Thank you. We have corrected that.

7. p.5, line -4: what are your relative effects? hazard ratios?

**Response:** Thank you. We have clarified that.

8. p.7, line 3: age 20

**Response:** Thank you. We have changed that.

9. p.9, line 9: (twice) type of event rather than cause of event

**Response:** Thank you. We have changed that.

10. p.9, line -2: either z is included in both parentheses or in none!

**Response:** Thank you. We have revised the text.

11. p.11, line -7: improve expression "highest level of attention"

**Response:** Thank you. We have revised the text.

12. p.12, line -4: correct sentence

**Response:** Thank you. We have revised the sentence.

13. p.14, line 5: improve precision in your writing! Male sex cannot be associated with anything. Perhaps you mean 'Male sex increases the probability of .... '

**Response:** Thank you. We have revised the text.

14. p.19, line 5: stata

**Response:** Thank you. We have corrected that.
15. Title for Table 3: constant and different ratios?

Response: Thank you. We have corrected that.

16. Figures 2 and 3: line types are unexplained

Response: Thank you. We have explained the lines.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published
Statistical review: Yes, and I have assessed the statistics in my report.
Declaration of competing interests: I declare that I have no competing interests
II. Reviewer's report

Title: Methods of Competing Risks Analysis of End-Stage Renal Disease and Mortality among People with Diabetes

Version: 1 Date: 16 April 2010

Reviewer: M Schumacher

Reviewer's report:

Review by Prof. Schumacher:
The manuscript presents an interesting case study on the development of end stage renal disease (ESRD) in patients with diabetes. Since death without previous occurrence of ESRD is a competing event, statistical methodology for time-to-event data has to be applied that takes competing risks into account. This is explained and exemplified with data from a cohort study of patients with diabetes.

Major points:
1. Since the manuscript is intended for a methodologically orientated journal, background given in the introduction could be shortened. The regression models considered should be more precisely defined.

Response: Thank you. We have done so.

2. There is absolutely no need to include the Lunn-McNeil model since this is a special case of the cause-specific hazards model making an extra, but unnecessary assumption (that, by the way, seems to be violated in the data example). So I suggest to skip that model completely.

Response: Thank you. We understand your point that the LM model requires an extra assumption (the hazards for different risk types are proportional), which is often unrealistic. However, we think that the approach proposed by Lunn-McNeil is attractive because of the ease of implementation and its close link to the Cox model. It also allows a joint estimation of the parameters associated with each different types of event and direct testing of the difference between regression parameters with different types of events. Since the main purpose of this manuscript is to illustrate the application of techniques for competing risks data analysis, we prefer to include this model in the text.

3. The cause-specific hazards and the subdistribution hazards models are more or less presented side-by-side without discussing relationships and potential differences. This should have a more prominent role in the manuscript, see e.g. references [2] and [40] and the recently published paper Grambauer N et. al.: Proportional subdistribution hazards modeling offers a summary analysis, even if misspecified. Statistics in Medicine 2010, 29:875-884.
Response: Thank you. We have added this on Pages 5 & 18.

Minor points:

4. In references to Fine and Gray [15] the latter is often misspelled.

Response: Thank you. We have corrected that.

5. p.18. 2nd line f.a.: “Comparing the CIF curves is analogous to the log-rank test and is identical to the log-rank test in the absence of competing risks [36]” (not “censoring”!).

Response: Thank you. We have corrected that.

6. p19, 4th line f.a.: The statement on software availability is not correct, please give the actual status.

Response: Thank you. We have corrected that.

7. Tables 1 and 2 should be merged into one table.

Response: Thank you. The Tables have been merged.

8. Table 3 should be skipped.

Response: Thank you. Please see the response for # 2.

9. Figure 2 and 3: part (c) should be skipped.

Response: Thank you. Please see the response for # 2.

In conclusion, I recommend a major revision of the manuscript.