Author’s response to reviews

Title: Estimation of Progression of Multi-state Chronic Disease Using the Markov Model and Prevalence Pool Concept

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Version: 6 Date: 30 August 2007

Author’s response to reviews: see over
Dear Editor,

Thank your for your letter and referee comments from August 6, 2007. We thank the reviewers and the editor for the useful comments and suggestions. We have revised the paper as requested. The important issues raised by the reviewers have been clarified, corrected, and elaborated. We hope the correction of the revised manuscript is satisfactory and meets the requirements of highly-reputed journal. Please find the revised manuscript and a detailed reply to the referee. We are happy to make further changes if required.

Yours Sincerely

Tao-Hsin Tung (Corresponding author)
Reply to Referee 1

General

This is much improved. I appreciate the authors efforts in improving the readability of the article, I think it will substantially enhance its impact. There are only two remaining points that need clarification and a few minor edits.

Ans. Thanks for the reviewer’s useful comments.

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

1/ p4 para 3: please clarify this sentence "Fourthly, since certain disease states could not be directly observed the identifiable problem, while parameters estimated, may be presented." Is something like this what you mean?

"Fourthly, since certain disease states could not be directly observed, there may be difficulty estimating the model parameters as the models may not be identifiable."

Also, I think you would refer to the "identifiability problem" rather than the "identifiable problem".

2/ Page 20 para 3: Does this example refer to the diabetes population example or are you introducing a new example at this point? It seems to be referring to an example that involves cancer.

"Thirdly, results from our approach can be readily applied to design of studies. Suppose we wish to design a randomized trial of screening in this population."..."Clinical cancers arising spontaneously would be expected to have a different mortality rate ?4 from those arising from progression of asymptomatic screen-detected cases." It wasn't clear to me that cancers were being screened for in the diabetes population, I thought it was just diabetes. Please clarify.

Minor editing suggestions:

4/ p 3 para 3 "survival analysis. The later usually provide more information on the occurrence of"should be "latter"

5/ p4 para 2: I think "or consider covariates" should be "or considered covariates" (to match tense with the first example in the sentence "previous studies...did not take relevant risk factors ")
Discretionary Revisions (which the author can choose to ignore)

6/ Page 19 1st para:
I would start a new "limitations" paragraph after the following sentence: "In this study, we propose a new approach, based on the E-M algorithm, to estimate the progression of a multi-state chronic disease using the prevalence pool concept and Markov process models." And as the limitations paragraph is largely based on my comments I took the liberty of suggesting a somewhat shortened and streamlined version below: "One limitation of our approach is that the prevalence pool concept is only appropriate in a population where rates of disease are assumed to be at a steady state and this assumption may not necessarily apply to diabetes today, given the recent rapid increase in incidence of diabetes in some countries today. Furthermore, our population data sample was restricted only to subjects with complete OGTT data, and thus some selection bias might have occurred. Finally, Type 2 diabetes occurs in older populations for whom death is a significant competing risk; both subjects without disease and those with asymptomatic disease may also die from other causes. We did not have enough data information to formulate a more complete model which includes competing mortality. Further studies are needed to explore how competing risks could influence the parameters of natural history."

Ans. Thanks for the reviewer’s useful comments. The descriptions have been corrected.