Reviewer's report

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

Version: 5 Date: 19 July 2007

Reviewer: Timothy Hofer

Reviewer's report:

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.

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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 refering 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 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."

What next?: Accept after minor essential 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.

Declaration of competing interests:
I declare that I have no competing interests