

## **Author's response to reviews**

**Title:** Counting drugs to understand the disease: The case of measuring the diabetes epidemic

### **Authors:**

Henrik Stovring ([hstovring@health.sdu.dk](mailto:hstovring@health.sdu.dk))

Morten Andersen ([mandersen@health.sdu.dk](mailto:mandersen@health.sdu.dk))

Henning Beck-Nielsen ([henning.beck-nielsen@ouh.fyns-amt.dk](mailto:henning.beck-nielsen@ouh.fyns-amt.dk))

Anders Green ([agreen@health.sdu.dk](mailto:agreen@health.sdu.dk))

Werner Vach ([wvach@stat.sdu.dk](mailto:wvach@stat.sdu.dk))

**Version:** 3 **Date:** 4 January 2007

**Author's response to reviews:** see over

# Reply to Prof. RJ Glynn

## Major compulsory revisions

1. *The authors acknowledge the limitations of their approach related to undiagnosed and untreated diabetes. The relevant literature should be discussed. For example, F Sartor and D Walckiers (Am J Epidemiol 1995; 15: 782-787) argue that their approach may be reasonable.*

A paragraph has been added to the Introduction (Addition 1, page 2-3) which mentions three earlier works (among them Sartor and Walckiers) on estimation of diabetes prevalence from pharmacoepidemiological data, and we note the difference between these approaches and the present.

2. *Current estimates for the prevalence of undiagnosed diabetes should be included. In the US, the current estimate is 30% (CC Cowie et al. Diabetes Care 2006; 29: 1263-1268). Some discussion of the expected number of diabetics who are controlled by diet is also needed. Will the percentage of diet-controlled diabetics vary by age or gender? The prevalence of diabetes among people age 65 or older in the current study is about half the prevalence in this age group in the US. How much of this difference is due to undiagnosed and untreated diabetes vs differences between countries?*

We have added a discussion of the number of diabetics not captured by the pharmacoepidemiological database (Addition 2 and 3, page 8). Based on two contemporary Danish studies (Drivsholm *et al* and Kristensen JK *et al*), it appears reasonable to assume that approximately three quarters of all diabetics are identified from claims data only. We now cite these two studies (Addition 3, page 8). Although we do not state this in the paper—as we do not have data that allow a direct comparison—it would seem reasonable to conclude that the observed difference between Denmark and the US is real.

3. *Some studies suggest that there are systematic differences between those who are treated and untreated and this limits the usefulness of estimates of diabetes prevalence and incidence based on records of filled prescriptions (e.g. RJ Glynn et al. Am J Epidemiol 1999; 149: 541-549 and RJ Glynn et al. J Clin Epidemiol 1999; 52: 781-790). Is it likely that the systematic discrepancies observed in those papers are lessened in the more homogeneous population in Denmark?*

The results of Glynn *et al* are now mentioned, and we briefly comment that we could not identify similar age-dependent cessation rates in our Danish material (Addition 2, page 8).

4. *It is important to evaluate whether increased prevalence in diabetes is due more to increased incidence or greater survival among previously diagnosed diabetics. However, the finding of increased incidence with time is subject to potential bias if detection of diabetes is improving with time. This possibility requires discussion. For example, in*

*the US it used to be said that half of all diabetes was undiagnosed but now the percentage is 30%. The paper needs to consider the biases that would arise from greater attention to detection and treatment over time.*

As stated above we have added reference to two Danish studies, that indicates that the proportion of pharmacologically treated diabetes has remained roughly constant over the study period. We do however agree that incidence is likely to be more sensitive than prevalence to a change in detection rates. Unfortunately, this cannot be studied with this type of data. A discussion of this was given rather prominent attention in our first submitted version, where it lead us to conclude that this obstacle could only be overcome with a dedicated diabetes database. Hence, we hope to be allowed to maintain the discussion as it stands with the additions mentioned above. Apart from this, we believe “...our results to be of genuine public health interest in themselves, as they pertain to that group of diabetics which must generally be considered most severely afflicted, and thus requiring most care” to quote Addition 3 in the Discussion.

### **Minor compulsory revisions**

None.

### **Discretionary revisions**

None.

# Reply to Prof. Y Cheng

## Major compulsory revisions

- *The major challenges with this kind of data are the potential for select bias and for limitations in generalizability. As authors mentioned, only subjects with treated diabetes were included and persons with undiagnosed diabetes were excluded in this study. Since the probabilities of medical access and willingness to participate may vary with different characteristics such as social economic status, age, sex, health status, and body, such differences among different subgroups could give a biased conclusion when we compare risk of diseases. The other limitation of pharmacy data is also the lack of potential intervening variables such as obesity. These limitations may need to be discussed.*

As described in the reply to the other reviewer, Prof. Glynn, we have added a discussion (Addition 2, page 8) on the access to health care in Denmark—which is generally unrestricted—and on the need for more detailed data to allow analyses that may relate observed trends in incidence, prevalence, and mortality to other covariates.

## Minor compulsory revisions

- *Page 6, line 2: delete an extra ‘.’*  
Done.
- *Figure 1 and 2: keep the style of legend same.*  
Done.

## Discretionary revisions

- *Risk and rate are different conceptually, even in some situations incidence density (person years as denominator) is as same as cumulative incidence (a population at risk as denominator). In this manuscript, the denominator of prevalence is using a population at risk, and incidence and mortality are using person-year. For consistency with prevalence, authors may consider using cumulative incidence without changing any numbers, if one year duration was used.*

While cumulative incidence and mortality are useful proxies, incidence and mortality are by default modeled as rates (as prevalence is described by proportions), and so we prefer to maintain the presentation of rates for incidence and mortality.