Author's response to reviews

Title: Prevalence and incidence density of chronic comorbidity in type 2 diabetes patients: an exploratory cohort study

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Author's response to reviews: see over
Dear Dr Lee and Dr Alam,

Thank you for giving us the opportunity to revise our manuscript. Below we give a point by point response to the Reviewers' comments. We have addressed the comments to the best of our abilities and hope and expect that the Editor and the Reviewers will evaluate the revised manuscript as improved compared to the version as submitted on June 13.

Throughout the manuscript we highlighted the changes made, including improvements in the English language or style.

We agree with Professor Mercer that more emphasis could be put on the exploratory nature of the study. We added such a statement in the title and abstract of the manuscript.

The recent work by Barnett et al. obviously deserves citation in the current manuscript. It was published around the date of our first submission to *BMC Medicine*, but we added the reference to the revised manuscript.

**National representativeness**
We examined the national representativeness of the CMR practices in detail in response to Professor Mercer's comment *(is the data likely to be nationally representative or not?)*. Table 1 presents the age and gender distribution of the practice population in comparison with population figures from Statistics Netherlands throughout the years [1]. Data on age and gender distribution of the total Dutch population are available from Statistics Netherlands for round decades. Due to a gradual transition to a new computer system in the four CMR practices, the CMR has been able to provide complete data for all four practices up to and including 2008. This means that we can directly compare age and gender distributions between national data and CMR data from 1980 until 2000, and after 2000 we can compare trends.

**Table 1** Comparison of age and gender distribution between CMR and national data

<table>
<thead>
<tr>
<th>Age (%)</th>
<th>1980</th>
<th>1990</th>
<th>2000</th>
<th>2008</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-40</td>
<td>29.3</td>
<td>31.5</td>
<td>36.6</td>
<td>33.0</td>
<td>30.0</td>
</tr>
<tr>
<td>40-65</td>
<td>27.7</td>
<td>25.6</td>
<td>29.1</td>
<td>28.6</td>
<td>33.4</td>
</tr>
<tr>
<td>65-80</td>
<td>8.9</td>
<td>9.3</td>
<td>9.4</td>
<td>9.9</td>
<td>10.3</td>
</tr>
<tr>
<td>80+</td>
<td>2.2</td>
<td>2.2</td>
<td>2.6</td>
<td>2.9</td>
<td>2.7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gender (%)</th>
<th>1980</th>
<th>1990</th>
<th>2000</th>
<th>2008</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>49.9</td>
<td>49.6</td>
<td>48.5</td>
<td>49.4</td>
<td>49.1</td>
</tr>
</tbody>
</table>

CMR, Continuous Morbidity Registration
SN, Statistics Netherlands

Table 2 shows the distribution of the social economic status (SES) of subjects as registered in the CMR compared to data from Statistics Netherlands [1]. Since 2001 Statistics Netherlands provides data on educational level annually. The CMR registration of SES is based on occupational and not educational level, based on the Dutch Standard Classification of Occupations. Consequently, these data may not be entirely comparable, although a strong association between occupational level and

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educational level exists. Data derived from the CMR database may be less representative for factors such as urbanisation and migration. We cannot quantify these data since the CMR does not collect data on, for example, ethnicity of registered subjects. However, neither the CMR nor Statistics Netherlands includes information on ethnicity or urbanisation in their definition of SES, so we are unable to explore the representativeness of the CMR population for these characteristics.

Table 2 Comparison of SES distribution between CMR and national data

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2006</th>
<th>2008</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CMR</td>
<td>SN</td>
<td>CMR</td>
</tr>
<tr>
<td>Low (%)</td>
<td>37.4</td>
<td>38.9</td>
<td>34.1</td>
</tr>
<tr>
<td>Middle (%)</td>
<td>44.6</td>
<td>40.7</td>
<td>41.9</td>
</tr>
<tr>
<td>High (%)</td>
<td>17.9</td>
<td>20.4</td>
<td>24.0</td>
</tr>
</tbody>
</table>

Data are shown for those patients of whom SES data were available.
SES, social economic status
CMR, Continuous Morbidity Registration
SN, Statistics Netherlands

From this additional examination we conclude that data from the CMR can be considered as representative for the Netherlands.

In the Methods section of the paper we added data serving as background information for the CMR practices. We also included our observation that the CMR data can be considered representative for national data concerning age, gender and SES distribution, with reference to the Statistics Netherlands website.

Control group and subgroup analyses
(The lack of control group is a weakness, which could easily be rectified, and I was unsure exactly why this 'fell outwith the scope of the study' as stated in the discussion. I was also very surprised that the exploration did not include age, gender, and SES. This could add greatly to the study.)

In the revised manuscript we now explain in more detail in the Discussion section why we think that adding a control group, or correcting the estimates for age, gender or SES is not appropriate in this exploratory study, in which we investigate a broad range of comorbid conditions in our cohort with diabetes patients. However, we did distinguish comorbidity rates for males and females for specific conditions or clusters such as urogenital diseases, breast cancer and incontinence. General patient characteristics were tested for gender differences (Table 1 in the revision). We believe that the focus of the paper should be the uncorrected rate of comorbidity in type 2 diabetes patients, since (a) we studied this wide range of comorbid diseases and (b) we seem to be the first to report incidence densities of these comorbid diseases both before and after the diabetes diagnosis. The current results can be a starting point for further exploration of specific combinations of comorbid diseases. Our next aim for further research will be to explore the association between comorbidity and the glycaemic regulation of type 2 diabetes. This was the objective when we first started the present work, but then we realised that a thorough epidemiologic description including incidence data should precede it, because this has been unavailable so far.

Number of patients
Dr Grant expressed concerns that we may have missed a substantial number of cases of type 2 diabetes since we included 714 new cases within our study period which comprises 22 years. (I was surprised that there were only 714 new DM cases in 22 years in the four study practices. This raises the concern that substantial number of cases may have been missed...)

The CMR registration network is known for its long-term morbidity recording which occurs systematically and accurately, and diagnoses of diabetes made by the GPs in the CMR practices have shown to agree with international criteria. [2] The Primary Care Research Department from Radboud University Nijmegen Medical Centre performs annual checks on data of registered diabetes patients from the CMR practices and in case of questions or incompleteness, queries are performed. Therefore we feel confident that we did not miss substantial numbers of incident cases.
of type 2 diabetes. We provide a calculation supporting this feeling in the following paragraph. Furthermore we added the number of patients in the abstract. Thank you for reminding us of this point.

In the Methods section of the paper we added information on the total practice population of the four CMR practices, which comprised approximately 12,000. The proportion of adult (age ≥ 18) patients in the CMR is approximately 20%, i.e. 9,600 patients [3]. Incidence data from the National Public Health Compass, which is published by the National Institute of Public Health and the Environment (RIVM) commissioned by the Dutch Ministry of Health, show that an estimated 71,000 patients have been diagnosed with diabetes in the Netherlands in 2007. These data include both type 1 and type 2 diabetes and come down to an incidence of 4.6 per 1,000 men and 4.1 per 1,000 women. [4, 5] Applying these figures to our adult CMR population would result in approximately 42 new cases per year, or 924 cases in the 22 years of our study period (1985-2007). The proportion of incident cases of type 2 diabetes among all (i.e. including type 1) diabetes patients in the CMR database for adults within our study period is 94%. This would result in 869 cases of type 2 diabetes as calculated with national incidence data from 2007.

Taking into consideration the impressive increase in diabetes diagnoses in the past two decades [6], a calculation of the expected number of patients in our study with national incidence data from 2007 results in an overestimation. The CMR database shows that incidence of type 2 diabetes doubled between 1985 and 2006. This in combination with the quality control in the CMR gives us confidence that the number of 714 patients in our study population should be regarded a reliable figure.

We would like to thank Dr Grant for his second comment. (There is clearly an ascertainment bias since greater exposure to care leads to more diagnoses. This is mentioned in the discussion, but the larger point can be made that regardless of the bias, this is what patients are experiencing, and these data may in fact be under-reported since other patients may remain undiagnosed.)

We fully agree with him and added this point in the Discussion section. We also included the paper he suggested as a reference in the Discussion section.

Finally we replaced the word “underexposed” in the Background section with “unexplored”.

We hope that after this revision you will be able to accept our manuscript for publication in *BMC Medicine*.

Looking forward to receiving your further decisions.

On behalf of all authors,

Yours faithfully,

Hilde Luijks, MD

References