Author's response to reviews

Title: Incidence of type 2 diabetes in Aboriginal Australians: an 11-year prospective cohort study

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Version: 2 Date: 29 July 2010

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

Thank you for providing reviewers’ comments and the opportunity to revise our manuscript. We have addressed the issues raised by the reviewers, as outlined below:

Reviewer: Christine Meisinger

Major Compulsory Revisions:

1. The methods section is not very clearly written and needs revision. The fact, that not all of the participants got a standardized OGTT to determine glucose status is the main shortcoming of the study. Thus, it is probable, that some of the participants are misclassified.

   It would be desirable to describe the research methods and procedures in more detail. It is not clear for me, how many of the persons got an OGTT (with the determination of both fasting plasma glucose and 2-hr plasma glucose), how many of the persons got a random glucose test only and how many persons got a fasting glucose test only at baseline to determine their status of glucose metabolism.

   We appreciate the reviewer’s thoughtful suggestion. We have provided more detailed information on glucose tests among participants and the approach to identify those with diabetes at the baseline screening (see the methods section of the paper).

This was a population-based study. Of the 897 adults screened at baseline, 802 had plasma glucose tests, and the remaining 95 were unable to undergo the tests. In the revision of this paper, we have excluded the 95 adults in the analysis to ensure sufficient verification of participants’ diabetes status at baseline. The rationale is that diabetes status for the 802 participants could be reasonably confirmed by both enquiries of personal history and results of plasma glucose tests. Without a plasma glucose test (as the case for the 95 participants),
some people with diabetes would remain unidentifiable if purely based on enquiring personal history. Of those 802 adults, 71 had clinically diagnosed diabetes before the baseline examination, and 45 had a new diagnosis of diabetes made at the baseline examination. With the exclusion of these 116 diabetic adults, a cohort of 686 participants who were free from identifiable diabetes at baseline was followed up to 13 years.

With the exclusion of the 95 participants in the analysis, the results presented in tables 1-5 were slightly changed. However, the interpretation of the key findings and conclusions of this study remain unchanged.

As detailed in the last paragraph on page 3, of 802 participants with plasma glucose tests, 414 had 75 g oral glucose tolerance tests (OGTT); 126 had fasting plasma glucose tests without OGTT; and 262 had random plasma glucose tests only. As pointed out by the reviewer, not all participants had a standard OGTT. This is a reality in conducting a population-based study like ours. Undergoing either a fasting glucose or a random glucose test by participants depended on their fasting status when they presented for the screening examination. Even having a fasting glucose test done, some participants could not wait for another two hours for OGTT.

Additional analyses were performed based on a sub-sample of the participants who had OGTTs at baseline and whose diabetes statuses could be accurately defined. Of those 414 participants who had OGTTs at baseline, 44 were confirmed with diabetes. The remaining 370 non-diabetic participants were followed up. Key findings based on those 370 adults are presented below, with comparison of findings based on 686 adults as for this revised paper:

<table>
<thead>
<tr>
<th>Key finding</th>
<th>N=370 Diabetes free participants at baseline confirmed by OGTTs plus person history</th>
<th>N=686 Diabetes free participants at baseline confirmed by any plasma glucose tests plus person history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative incidence of diabetes by age of 60 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>71%</td>
<td>70%</td>
</tr>
<tr>
<td>Males</td>
<td>33%</td>
<td>49%</td>
</tr>
<tr>
<td>Rate ratios of developing diabetes in presence of IFG/IGT at baseline</td>
<td>1.8 (1.1, 3.0)</td>
<td>2.2 (1.5, 3.3)</td>
</tr>
<tr>
<td>Rate ratios of developing diabetes in presence of overweight at baseline</td>
<td>1.9 (1.0, 3.5)</td>
<td>2.2 (1.4, 3.5)</td>
</tr>
<tr>
<td>Rate ratios of developing diabetes in presence of obesity at baseline</td>
<td>4.3 (2.3, 8.0)</td>
<td>4.7 (3.0, 7.4)</td>
</tr>
</tbody>
</table>
The key findings of these two analyses are generally consistent except for a major discrepancy in estimation of cumulative incidence of diabetes for males. It is plausible that the issue of misclassification of diabetes at baseline was minor and acceptable for a population-based study like ours, and key findings based on 686 participants as presented in the manuscript are reasonable and valid.

2. Measurements: new diabetes cases were identified through hospital records and outpatient clinical records. How were these cases diagnosed: through determination of fasting plasma glucose or through OGTT, treatment with hypoglycaemic medication? It is unlikely, that all diabetes cases were captured in this was and thus it is most probable, that the number of incident cases is underestimated. In what direction could these facts have biased the results?

We relied on reviewing of routinely documented diagnosis information in hospital and outpatient records for identification of new diabetes cases. We did not check the documented glucose test results or diabetes medications for further verification of the diagnoses.

As appropriately pointed out by the reviewer, some diabetes cases might not be identified through reviews of hospital based records. This would lead to underestimation of diabetes incidence rates. We have acknowledged this in the discussion of limitations of the study (in the 1st paragraph on page 8).

3. Were the treating physicians of the participants contacted to gather information on incident diabetes?

In this study, we did not contact doctors to collect information on newly diagnosed diabetes cases. All follow-ups were done through reviewing of the hospital based record system, a well established electronic system which captured information related to hospitalisations and outpatient encounters for the participants.

4. How many follow-ups were conducted? Were follow-up information collected exclusively through hospital records or were postal questionnaires or follow-up examinations conducted too? How many of the participants were lost to follow-up?
Follow-ups were purely based on reviews of hospital records. No mail-out surveys or home visits were performed in this study. Residents in the study community received hospital services exclusively from a hospital 80 kilometres away (by sea). It is likely that every hospital care encounter of the participants have been documented in the hospital record system. Out-migration to other communities by the participants may cause loss to follow-up of their hospital care information. In reality, the hospital in our study setting is the only hospital serving the entire region, so that most people who had out-migrated to communities within several hundred kilometres, the usual pattern, would still have their hospital care recorded in the centralised hospital data system. Permanent out-migration is very uncommon. This point has been incorporated into the 1st paragraph on page 8.

5. What further data was collected at baseline examination (e.g. what blood parameters and physical examinations were performed, e.g. waist circumference, blood pressure?). How were the examinations conducted (standardized measurement? Self-report?).

We have provided brief information on baseline measurements in the last paragraph on page 4. More detailed information on baseline examinations and methods used has been referred to a previously published paper (reference 3).

6. Was information on physical activity, diet, smoking, alcohol consumption assessed at baseline? If not, in the limitations section, the authors should add, that important confounders were not assessed in the baseline examination and discuss how this shortcoming could have influenced the results.

As described in the last paragraph on page 4, information on smoking and drinking status was measured at baseline. For the aim of describing incidence of diabetes, there would be no need to adjust for these lifestyle factors. For the aim of examining associations between IFG/IGT and incident diabetes, we have already adjusted for the most important factor BMI. Further adjustment of the lifestyle factors did not alter the estimated rate ratios.

**Minor Essential Revisions:**

7. Page 3, second paragraph, line 7: …criterion for IFG, IFG and IGT may….:

please correct

This sentence has been revised.
8. The term “first diabetic incidence” or “first event” is somewhat misleading for the manifestation of the disease diabetes. Please revise.

We have revised the paper to use a consistent term “diagnosis of diabetes first documented in hospital records”.

Reviewer Karen Yeates

1. Is the question posed by the authors well defined?
The authors report incidence rates of diabetes in an Aboriginal prospective cohort with 11 year follow up. Their research question/hypothesis is not explicitly stated in their methods.

We have clarified our aims in the 3rd paragraph on page 3.

2. Are the methods appropriate and well described?
The methods appear appropriate and are reasonable well described.

The reviewer did not request comments for this question.

3. Are the data sound?
The data appear sound although the authors relied on hospital records for follow up and admittedly there is a risk that they failed to capture a diabetes diagnosis/diabetic incident for individuals included in the analysis. The authors do not comment on the quality of the data made available to them in the medical records at the center studied. This is a remote community, what is the likelihood that individuals have moved to live in other communities and were not captured? The authors should comment on this further.

The centralised hospital record data system was well established in this study setting. At routine practice, diabetes diagnoses were made by health practitioners following clinical guidelines. We have acknowledged that misdiagnosis of diabetes might occur at routine practice in the first paragraph on page 8.

We have also discussed the issue of moving out to other communities by participants and the potential to cause loss to follow-up of hospital care information (in the 1st paragraph on page 8).

4. Does the manuscript adhere to the relevant standards for reporting and data deposition?
Yes.

5. Are the discussion and conclusions well balanced and adequately supported
by the data?
Yes.

6. Are limitations of the work clearly stated?
To some extent, however, the authors should comment further on the generalizability of this study to Aboriginal people as a whole in Australia. This cohort was established in 1992 in a remote community. What do the authors believe the generalizability is to all Aboriginal Australians?

We have commented on the generalisability of the findings to other Aboriginal populations in Australia in the 1\textsuperscript{st} paragraph on page 8.

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished?
Not really.

We have acknowledged previous published work based on the baseline screening data (References 3 and 26).

8. Do the title and abstract accurately convey what has been found?
The title is appropriate. The abstract conveys their overall message.

9. Is the writing acceptable?
Yes.

\textbf{Discretionary revisions:}
It is acceptable for publication. There are a few grammatical errors that require further proofreading.

We have proof read the paper and made corrections as necessary.

We hope this revision meet with your satisfaction.

Best wishes,

Dr Damin Si