Author's response to reviews

Title: Screening South Asians for type 2 diabetes and prediabetes: (1) comparing oral glucose tolerance and haemoglobin A1c test results and (2) comparing the two sets of metabolic profiles of individuals diagnosed with these two tests

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Author's response to reviews: see over
Date: 2013-01-04
Concerning: Revised manuscript submission

Dear mister Shipley,

Attached you will find the revised version of our manuscript (MS 1500976247817482). We would like to thank the reviewers for their thoughtful and detailed comments on our manuscript. We feel that the comments have helped to improve our paper. Below we have specified how we addressed each comment in the manuscript.

Kind regards, on behalf of all authors,

Linda Vlaar

Reviewer 1: Samiul Mostafa

**Major Compulsory Revisions**

1) Table 2. What about the group who have positive HbA1c and OGTT. Do they have the worst cardio-metabolic profile? Or is power a problem here? On a second point, I note the actual numbers of people with diabetes by either method are mentioned for first time in the manuscript. In the abstract and manuscript the % format is written only. This is a weakness of the study. Please add the actual numbers to the manuscript and abstract.

**Reply:**

Overall, the metabolic profile of those diagnosed by both HbA1c and the OGTT was worse than the profile of those diagnosed by a single criterion. We have added these results as an additional file (Additional file 1). Moreover, we have added the absolute numbers to the abstract (p.3) and the results section (p.10).

2) As this paper focuses on diagnosis of Diabetes there should more detail about the assays used, specifically your HPLC – was it appropriate for diagnostic use (see reference 5), what was the inter- and intra- Coefficients of Variation of the HbA1c analyser? Which haemoglobinopathies could it detect - bearing in mind people of South Asians may possess these? Where glucose samples handled
according to international guidelines – e.g. placed on ice immediately, processed within 30 minutes etc – if not these should be mentioned as limitations.

Reply: The collection of blood samples and the measurements were carried out by the SHL Center for Diagnostic Support in Primary Care, Etten-Leur, The Netherlands. This laboratory is CCKL and ISO-9001 certified and has experience working according to international protocols (http://www.shl-groep.nl/contractresearch/publicaties/). As requested, we have added more information on the analyses under the heading data collection in the Methods (p.8).

3) Abstract conclusion:
‘A combined rather than a single test strategy should perhaps be considered among South Asians’
This is not particularly justified by this paper – it can be seen at most as future research only. Please omit this sentence or rephrase to ‘Future research should investigate if…….’ This is already correctly written in the main text, but should be changed in the abstract as well.

Reply: We have removed this sentence from the abstract (p.4; please also see our reply to reviewer 2 below).

Minor Essential Revisions
Main manuscript
Background
1) ‘A recent study has shown that a substantial benefit can potentially be realised by specifically targeting South Asians for active screening and prevention’. You need to specifically explain to the reader what is this ‘substantial benefit’ than can be realised? It is that you identify people with diabetes earlier?

Reply: With substantial benefit we referred to a reduction in cardiovascular risk, as discussed in the paper by Webb et al. We have clarified this in the text (p.5).

2) ‘The effectiveness of such a screening’ There’s a grammar mistake or word missing here.

Reply: We have removed the ‘such a’ from the sentence (p.5).

3) There is no list of abbreviations – these are usually after the abstract. There are some abbreviations after the tables and figures but these should be there for the main text as well.

Reply: As requested, we have added a list of abbreviations (from the text and tables) after the abstract (p.4).

4) ‘Because HbA1c can be determined in a single fasting blood sample.’ a) HbA1c can be performed in either a fasting or non-fasting blood sample. b) Secondly, be careful about writing ‘in a single sample’ in this paper, as for diagnosis of Type 2 diabetes using HbA1c you need a second positive test on a separate day to confirm diagnosis in all asymptomatic individuals. If the authors are quoting local guidelines or disagree with my understanding, they should provide a reference to their statement.

Reply: We have removed the word ‘fasting’ and have added ‘for screening purposes’ to distinguish the use of a ‘single sample’ in our study from a clinical diagnostic situation for which a second positive test on a separate day is required to confirm diagnosis (p.5).

5) ‘However, studies in several populations showed that screening based on the HbA1c may lead to the identification of fewer new cases of DM’. Most studies show this but not all – e.g. Reference 6 in the manuscript shows either can happen, and Mostafa SA Diabetic Medicine 2010, 72, 762-9 show the
opposite. Please add the phrase ‘most studies’

Reply: Done as requested (p.5).

6) It would be useful to mention to the reader in the introduction that HbA1c is an accepted criterion for Type 2 diabetes at the level of greater than or equal 6.5% in non-pregnant adults, to distinguish its non-use for type 1 diabetes, pregnancy and in children.

Reply: We have changed the sentence in the introduction to: ‘In 2010, the American Diabetes Association updated its recommendations to include glycated haemoglobin A1c (HbA1c) at the level of 6.5% or more (≥48 mmol/mol) as a diagnostic option for non-pregnant adults [5]’ (p.5).

Methods

7) ‘The two large migration waves, around 1975 and 1980, of Hindustani-Surinamese to the Netherlands’. Were your participants first or second generation migrants? Also can your results be generalised to all Hindustani-Surinamese migrants to Netherlands? i.e. how representative is your population of these individuals?

Reply: We invited a sample of around 10000 first and second generation individuals [Vlaar et al, BMC Public Health]. An estimated 150,610 first and second generation Hindustani Surinamese live in the Netherlands, of whom approximately 45000 live in the Hague [louhof et al., Choenni, http://denhaag.buurtmonitor.nl]. Unfortunately national data on type 2 diabetes and associated parameters are not available. However, our results correspond with the patterns of selfreported type 2 diabetes found in the Municipal Health Monitor of the Hague [unpublished]. Moreover, the findings are in line with data on populations of Hindustani Surinamese origin in the HELIUS and SUNSET study in Amsterdam [unpublished, Bindraban et al.] . To inform the reader, we have added information on the country of birth of our participants to the characteristics and results section (P.10, P.24).

8) ‘The OGTT diagnosis of DM was therefore defined as FPG≥26 mg/dl’. If I’m correct, this should be 126 mg/dl!

Reply: Thank you for pointing this out. We have corrected the value to 126 mg/dl (p.9).

9) HbA1c units are expressed in mmol/mol and %. Some countries have adopted using mmol/mol but most others haven’t. Personally I would recommend just using % for now, as some readers will not understand this (or put the % first, followed by mmol/mol). However I acknowledge the authors attempts to use current information here. The editorial team may want a specific format here.

Reply: As suggested, we have put the % first followed by mmol/mol in brackets (entire document).

10) ‘We identified the optimal HbA1c threshold for DM by interpolation from the AUC; it was the point closest to the upper left-hand corner, which maximized sensitivity and specificity’. Was this performed manually or was a specific test used to do this (e.g. Youden Index) which is more accurate?

Reply: We identified the optimal point manually, i.e. we inspected the crosstabulations to select the maximum sensitivity and specificity. This method corresponds loosely with the Youden index (+1). We have specified the manual selection in the methods: ‘…; we selected the point that maximized sensitivity and specificity by inspecting the crosstabulations of the sensitivity and specificity.’ (p.10)

Results
11) The AUC for diabetes and in particular for prediabetes are extremely good compared to other studies which report the overlap between people detected from using the two tests is very weak. It’s worth mentioning this in the discussion.

Reply: We have added a statement on the estimated AUC for diabetes and prediabetes to the discussion. (‘Although the AUROC in our study was high, the low sensitivity of HbA1c for OGTT-defined DM and prediabetes was in line with previous studies…’). (p.12)

Discussion

12) There is the title ‘Discussion’, then subheadings of ‘main findings’ and later ‘Discussion of the main findings’. I don’t think you need the subheadings here. However the editors may advise better here.

Reply: We have left the subheading ‘Limitations’ in the text, but have -as suggested- removed the subheadings ‘Main findings’ and ‘Discussion of the main findings’. (p.12-14)

13) Figure 1 is too detailed e.g. response per age group and gender. Perhaps simplification is required.

Reply: As suggested, we have simplified the figure by removing the response rates by age and sex group. (Figure 1)

Reviewer 2: yaomin hu

In the present study, the Authors assessed 944 South Asians who were screened by means of HbA1c and OGTT in The Hague, The Netherlands. And calculated the area under the curve of HbA1c using the American Diabetes Association classifications. And also studied differences in metabolic characteristics between those identified by HbA1c and by the OGTT alone. And found that HbA1c identified a partially different group than the OGTT. However, both those identified by HbA1c and those identified by OGTT alone were at increased metabolic risk. A combined rather than a single test strategy should perhaps be considered among South Asians.

Given the extremely hot issue and the high number of subjects, the paper is quite interesting, but some minor points need to be issued. In detail: 1) It is well known that measurement of HbA1c displays an extremely high variability worldwide: therefore in the method section, HbA1c test method should be better described. In particular, normal range should be reported.

Reply: We have added more information on the test methods under the heading data collection in the Methods.(p.8) The measurements were carried out by the the SHL Center for Diagnostic Support in Primary Care, Etten-Leur, The Netherlands. This laboratory is CCKL and ISO-9001 certified and has experience working according to international protocols (http://www.shl-groep.nl/contractresearch/publicaties/).

2) the overall content of the paper is too general. Some studies have already published similar results by using similar methods. To specify this paper, the author should explain more details about the background of the study. Authors should further discuss the feasibility of the presented screening model (combined strategy) in their society.

Reply: Thank you for pointing this out, We are aware of previous studies on the diagnostic value in other populations, including India and one in the UK (which we have now discussed in more detail in the introduction; p.5-6). Data on the characteristics of those diagnosed is lacking for South Asians
migrants living in industrialised countries. We have now explicitly mentioned this in the discussion (p.12).

Second, the reviewer correctly states that the feasibility of model should be discussed. We rewrote the statement in the discussion to reflect potential issues with the feasibility (p.13). In addition, we have removed the statement on the combined strategy from the abstract (p.3).

3) Is there any difference between yours and other data? If yes, did the difference of population characteristics influence on your results? Is there any similar study from Asian targeted general or high risk population?

Reply: There is a previous study on the diagnostic value in India. Although this study is not on a migrant population, we have discussed it in more detail (please see previous point). There is no other study describing differences in the characteristics of those diagnosed by either method from a population of similar origin. We have tried to reflect on the similarities between our findings and those of others in the results but could unfortunately draw no firm conclusions about the influence of the ‘South Asian population’ characteristics, as our study did not include a comparison group.

Reviewer 3: Bernd Kowall
For South Asians living in the Netherlands, the authors address the question to what extent HbA1c and OGTT based diagnoses of diabetes identify the same subjects of having the disease. They state that the overlap is only partial, and that subjects identified as having diabetes or prediabetes by HbA1c or by OGTT only do not show a different profile of metabolic risk factors.

**Major comments**

1. The authors should explain in some more detail why their study in South Asians is important (for example, ethnic differences in HbA1c).

Reply: We have changed the introduction. As the reviewer indicates, there are indeed ethnic differences in glycemia. We have added the following to the introduction (p.5): This is relevant because the overlap between the HbA1c method and other methods may vary across ethnic groups and across different contexts [6]. Moreover, one recent study shows that the HbA1c levels and OGTT fasting and 2-h glucose levels were higher among South Asians in the UK than among Europeans [13].

2. In table 2, the HbA1c group includes OGTT based diagnoses of T2DM (and of OGTT based prediabetes, respectively). I suggest comparing three groups: diagnosis by HbA1c only, diagnosis by OGTT only, and diagnosis by both criteria. Of course, the power to find differences in metabolic factors is poor when comparing three small groups with a diagnosis of T2DM – but this is clearly a disadvantage of the study. Please adjust the comparisons for age and sex – the p-values given in table 2 refer to the comparison of crude data.

Reply: We have added a table to the results with the requested comparison between the groups identified by a single versus both criteria (Additional file 1). Overall, the metabolic profile of those diagnosed by both criteria was poorer than the profile of those diagnosed by a single criterion. Given the small number of individuals, particularly with diabetes, we are hesitant to add further adjustments for age and sex. The lack of differences between groups in age and sex (Table 2) suggest that this omission may not have had a strong effect on the results. However, we do agree that this is a flaw in our analysis. We have now explicitly mentioned this in the discussion: ‘In addition, the small number of individuals diagnosed implied that no adjustment could be made for relevant parameters, such as sex and age, in the comparisons of characteristics’. (p.14)

3. In identifying persons with prediabetes, the degree of overlap by the two criteria strongly depends on the exact criteria. For HbA1c, 6.0 – 6.4% and 5.7 – 6.4% have been suggested; for impaired fasting
glucose, there is 110 – 125 mg/dl (WHO) and 100- 125 mg/dl (ADA). For both criteria, the authors chose the wider intervals which led to the inclusion of subjects with glucose levels which are only slightly above normoglycaemia. It would be interesting to see the results for the narrower intervals.

**Reply:** We chose the wider intervals based on the high risk of type 2 diabetes in the South Asian population. Furthermore, the study in India by Mohan et al in 2010 showed that a value of 5.6% optimally identified IGT or IFG. A change in the criteria indeed has an impact on the prevalence and overlap (not the AUC). However, this change would not have affected our overall message.

4. For OGTT based prediabetes, the authors should also differentiate between IFG and IGT, and look whether the overlap of HbA1c with IFG and IGT, respectively, is different.

**Reply:** We have done the analyses for IFG and IGT:

<table>
<thead>
<tr>
<th></th>
<th>IFG</th>
<th>IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC (those with DM excluded)*</td>
<td>0.75 (0.70-0.79)</td>
<td>0.72 (0.66-0.78)</td>
</tr>
<tr>
<td>Sensitivity (those with DM excluded)*</td>
<td>0.70</td>
<td>0.72</td>
</tr>
<tr>
<td>Specificity (those with DM excluded)</td>
<td>0.66</td>
<td>0.64</td>
</tr>
<tr>
<td>Overlap (those with DM excluded)*</td>
<td>43.0%</td>
<td>25.6%</td>
</tr>
</tbody>
</table>

As requested, we have added a statement on the difference in overlap to the results section. (p.10)

5. The authors give sensitivities, specificities, and positive predictive values for the identification of OGTT based diagnoses by HbA1c. In a way, this suggests that the OGTT is a gold standard for the diagnoses of (pre)diabetes. The authors should discuss that the best criterion for the diagnoses of diabetes might be the one that goes together with the best prognosis of complications.

**Reply:** We agree with the reviewer on this point. We have added the following sentence to the discussion: ‘However, this should also depend on the association of either criterion with the occurrence of complications.’ (p.13) Moreover, we have specified in the methods that we chose the OGTT as a reference based on current practice at the time the study was initiated (versus “new recommendations”). (p.9)

**Minor comments**

1. In table 1, HbA1c based prediabetes is defined by 6.0 # HbA1c < 6.5 %. I guess this is a mistake (5.7 as lower limit instead).

**Reply:** We apologise for this error. This has been corrected. (p.24)

2. Table 2: Please state to which comparisons p-values refer.

**Reply:** We specified this in the table (‘p-value for HbA1c vs. OGTT only’). (p.25)

3. The AROCs in figure 2 can be omitted. AROCs always look nice, but here they do not give any information in addition to the diagnostic criteria mentioned in the results part.

**Reply:** As requested, we have omitted Figure 2, and inserted all the information in the figure on sensitivity, specificity and PPV in the results section. (p.11)

**Reviewer 4:** Tomoko Nakagami
This study has evaluated the efficacy of the use of \( \text{HbA1c} \) as a screening test for diabetes or pre-diabetes on a 75 gram oral glucose tolerance test (OGTT) in 944 South Asians living in the Haugue of the Netherlands. The study showed that \( \text{HbA1c} \) showed high predictabilities for diabetes and pre-diabetes on an OGTT. However, the overlap between \( \text{HbA1c} \) and OGTT classification was partial both for diabetes and pre-diabetes, respectively. People with diabetes identified by \( \text{HbA1c} \) had similar (no statistically different) means for CVD risks to those identified by sole OGTT. The same trend was found for people with pre-diabetes. Thus the study has concluded that a combined rather than a single test strategy should be considered in the screening for diabetes or pre-diabetes among South Asian populations.

**Major comments**

1. The study was nicely planned and performed, although the participation rate was low. Since data analyzed Asian Indians including immigrants are still scanty, the overall flow of the main text sounds common \( \text{HbA1c} \) screening story. The overall discussion should be expanded based on data from Indian ethnic group to specialize this paper, as majority of cited references were data from Caucasoid populations.

   **Reply:** We appreciate that the reviewer recognizes that the data on Asian Indian populations are still scanty. We have added more information of the importance of this study to the background (see our reply to reviewer 2, point 2 and reviewer 3, point 1). (p.5-6) Moreover, we have placed more emphasis on the little available evidence for Indian origin populations by adding specific information on the available data from India to the discussion. (p.12-13)

2. The author has stated that a combined rather than single test strategy should be considered. etc.. This statement is not clear. Please clarify what is a combined strategy? Does it mean the combination use of \( \text{HbA1c} \) and OGTT? If yes, this combination is too costly and not realistic (not only for Indians but also other ethnic groups). If no, please explain.

   **Reply:** We agree with the reviewer that a combined use of \( \text{HbA1c} \) and the OGTT may not be feasible. We have added a sentence to the discussion (‘In addition, a combined testing strategy may not be feasible or acceptable in the local context, e.g. due to budget restrictions.’) and added a remark about the feasibility to the conclusion. (p.13, p.15) Moreover, we have removed the statement on the combined strategy from the abstract. (p.3)

**Editorial comments:**

We recommend that you copyedit the paper to improve the style of written English. If this is not possible, you may need to use a professional language editing service. For authors who wish to have the language in their manuscript edited by a native-English speaker with scientific expertise, BioMed Central recommends Edanz (www.edanzediting.com/bmc). BioMed Central has negotiated a 10% discount to the fee charged to BioMed Central authors by Edanz. Use of an editing service is neither a requirement nor a guarantee of acceptance for publication. For more information, see our FAQ on language editing services at http://www.biomedcentral.com/info/authors/authorfaqs#12.

**Reply:** The manuscript has been edited by Ms. Van Roosmalen-Lyman, who is a certified English language editor.