Author's response to reviews

Title: Combining Glycosylated Hemoglobin A1c and Fasting Plasma Glucose for Diagnosis of Type 2 Diabetes in Chinese Adults

Authors:

Miao Mo (10211020008@fudan.edu.cn)
Weijian Zhong (wjzhong@scdc.sh.cn)
Genming Zhao (gmzhao@shmu.edu.cn)
Ye Ruan (yruan@scdc.sh.cn)
Hua Zhang (11211020013@fudan.edu.cn)
Liang Shi (lshi@scdc.sh.cn)
Daijiang Lu (ludaijiang2000@yahoo.com.cn)
Qundi Yang (qdyang@scdc.sh.cn)
Yanyun Li (yyli@scdc.sh.cn)
Qingwu Jiang (jiangqw@fudan.edu.cn)
Rui Li (rli@scdc.sh.cn)
Wanghong Xu (wanghong.xu@fudan.edu.cn)

Version: 2 Date: 5 July 2013

Author's response to reviews: see over
Dear Professor Eloisa Nolasco:

Thank you for your letter of June 4, 2013 informing us to resubmit the above-mentioned paper to your journal for publication. We have revised the manuscript along the lines suggested by the reviewers, as elaborated point by point below (revisions are bolded and marked in red in the hard copies of the manuscript):

**Answers to questions from Reviewer 1 (Hillary Keenan)**

**Compulsory Revision:**

1. **Due to the relatively low end participation rate at 56%; please provide a brief description of data collected on those (those not examined) individuals, or at an ecologic level (equivalent to census tract) who did not participate. Comment on disparities in traits between groups that may affect the conclusion.**

   **Response:** We agree with the reviewer that the difference in characteristics of participants and non-participants may affect the conclusion. Unfortunately, due to the original purpose of this survey was just to identify individuals at high risk of diabetes, we did not collect the information for the non-participants of this study. We added the limitation in the discussion section (Line 298-301).

2. **The ROC is the most common method of graphical demonstration of proxy for a gold standard. An overlay plot of the different diagnostic criterion examined would be informative.**

   **Response:** The Youden Index is often used as a summary measure of the receiver operating characteristic curve (shown as below). In this study, we used Youden Index to identify the optimal diagnosing cut-point, and found that the sensitivity was 0.756, and the specificity reached 0.893 when taking HbA1c ≥ 43 mmol/mol (6.1%) as diagnosing cut-point.
Area Under the Curve

Test Result Variable(s): HBA1C

<table>
<thead>
<tr>
<th>Area</th>
<th>Std. Error&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Asymptotic Sig.&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Asymptotic 95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>.888</td>
<td>.010</td>
<td>.000</td>
<td>.870 - .907</td>
</tr>
</tbody>
</table>

The test result variable(s): HBA1C has at least one tie between the positive actual state group and the negative actual state group.

Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

3. Please explain how the investigators performed the OGTT after determining the FPG of the subject - was this done at the same visit or at follow-up, was there drop-out? Please indicate the level of participation.

   **Response:** The OGTT was performed at the same visit of FPG test. All participants with fasting FPG (at 0-hour) < 7.0 mmol/l had an OGTT. There was no drop-out in the assay.

Minor Revision:

1. Spelling and other minor grammar errors

   **Response:** We have a native English speaker to help to edit the manuscript. The possible spelling and grammar errors have been corrected.

2. Please re-write the sensitivity calculation method as it is not clear.

   **Response:** We now re-write the sensitivity calculation method (Line 182-185)
3. Please label what the p-value in brackets represents in the tables.

**Response:** The value in brackets with the p-value represents Spearman correlation coefficients, which has been labeled in Table 2.

**Discretionary Revision:**

1. The authors could make brief, summary, mention of the ability to detect “pre-diabetes” in the text, but these sections of the tables with are not necessary. The authors need to decide the value of predicting this outcome with the measures or excluding completely.

   **Response:** Brief explanation about pre-diabetes was added at Line 240-241.

**Answers to questions from Reviewer Zhiheng He**

#1. The authors concluded that “The combing use of FPG and HbA1c is a potential alternative to the 1999 WHO diagnostic criteria of T2DM.” This was provocative. While using HbA1c as a diagnostic criterion, positive results on 2 separate days are accepted for making the diagnosis. There is no clear evidence to support that abnormal results within one day can substitute the established diagnostic criteria.

   **Response:** We agree with the reviewer that the conclusion is not proper. We now modify it as “The combing use of FPG and HbA1c is a potential screening and diagnosis approach for T2DM in Chinese adults, especially among those at high risk of the disease.” (Line 48-49). We also make a related change in discussion section (Line 317-319).

#2. It was not clear from the manuscript whether the simultaneous use of FPG and HbA1c will be for screening test or for diagnosis confirmation.

   **Response:** The original purpose of the survey is to screen individuals at high risk of diabetes. Taking advantage of the data, we tried to evaluate whether the combing use of the FPG and HbA1c can be used for diagnosis of diabetes. We now make it clearer in the manuscript.

#3. In the methods section, the description of ”physically disabled” were elusive and should be clearly defined. I was not able to know whether the authors have considered other conditions that might affect the results of HbA1c, e.g. hemoglobinopathy such as thalassemia, which is common in China; or renal insufficiency which is frequently associated with anemia that may underestimate HbA1c. What about those subjects who have received blood transfusion shortly prior to the test? These should be clearly defined and probably should be excluded from the study.

   **Response:** Physically disabled represented those who lack of ability to move freely. As it was inconvenient for them to come to community health care center to take the blood tests, we
excluded them from the survey. Regarding the other conditions, we did not collect the information. We discussed the potential influence of these conditions and suggested that combined use of FPG as diagnostic method may make up for the limitation (Line 289-296).

#4. Hemoglobin levels for the different groups should be listed in the Table 1 if available.

Response: HbA1c levels for different subgroups were listed in table 2.

#5. In page 15, table 1, Information should also include the percentage of subjects on anti-hypertensive medication and lipid lowering medications. Statin use should also be listed given its effect on diabetes.

Response: We agree that the use of medicine may affect the results. Unfortunately, we did not collect the information on use of medicine in this survey.

#6. Additional table should be provided to list and compare sensitivity, specificity, PPV, and NPV for by FPG alone, by 2HPG alone; by HbA1c alone; and by FPG+HbA1c.

Response: We now list and compare the sensitivity, specificity, PPV, and NPV in Table 6.

#7. Table 5 was very confusing and should be reformatted for clarity. Sensitivity, specificity, PPV, and NPV can be listed and compared in a separate table.

Response: We now list and compare the sensitivity, specificity, PPV, and NPV in Table 6.

#8. In the background section, it should be noted that lack of standardized HbA1c was probably another major reason why HbA1c has not been adopted as the diagnostic criteria in China, in addition to the lack of knowledge about racial-specific standard. In the United States, it took a long time before HbA1c was standardized and adopted as a diagnostic criteria.

Response: We now change the sentence as “…mainly due to lack of a standardized approach to measure HbA1c, short of knowledge about racial-specific standard and a deficiency of an optimal cut-point for detecting T2DM in the population.” (Line 90-91).

#9. Since HbA1c measurement is the core of the study, detail information regarding its measurement should be provided including the machine and protocol used. The reported CV for HbA1c was reported as <6.13%, which appears to be less stringent than those reported in the literature. Please explain and discuss about it.

Response: One of the limitations of this study is that the biochemical assays were conducted in several community health care centers. Although all centers used HPLC method and followed a similar protocol, they used different kind of machines to assay HbA1c. The inter-lab bias in
measurements cannot be excluded. The reported CVs for the measures were the largest one from the community health care centers involved. We now explain more about it (Line 302-303).

**#10. In page 9, it was not clear why the authors chose WC about 85 cm in male and 80 cm in females. Appropriate literatures should be cited to give the rationals. This also applies to the other parameters such as HW (hypertriglyceridemic waist phenotype), which is not a conventional measure and reported with different cutoff in the literature.**

**Response:** Now we cite reference 17 and 18 in this section (Line 166, 168).

**#11. Many of the references were not properly cited. For example, in Page 9, reference 23 was not a representative study to back up author’s argument. I am under the impression that the authors lack the understanding of up-to-date litterateurs in diabetes and randomly select reference without really reading the contents. All references should be re-examined before used.**

**Response:** We now re-examine all references, delete some inappropriate literatures such as former ref. 8, 11, 13 and 23, update ref 18 and 20, and add ref 17-19 to this paper.

**#12. The language of this manuscript needs to be significantly improved. The authors might need editorial assistance from someone who use English as a native language.**

**Response:** We have a native English speaker to edit this paper.

We thank reviewers for their helpful comments and suggestions and hope the revised manuscript has addressed all their concerns. I look forward to hearing from you regarding the likely date of publication.

Sincerely yours,

Wang-hong Xu, MD, PhD
Associate professor
Department of Epidemiology
School of Public Health, Fudan University
138 Yi Xue Yuan RD
Shanghai, 200032, PRC
Tel: 86-21-54237679
Fax: 86-21-54237334
E-mail: wanghong.xu@fudan.edu.cn