PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (see an example) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below. Some articles will have been accepted based in part or entirely on reviews undertaken for other BMJ Group journals. These will be reproduced where possible.

ARTICLE DETAILS

TITLE (PROVISIONAL)	**Joint analysis of multiple biomarkers for identifying type 2 diabetes in middle-aged and older Chinese**
AUTHORS	Wu, Hongyu; Qi, Qibin; Yu, Zhijie; Li, Huaixing; Sun, Qi; Lin, Xu

VERSION 1 - REVIEW

REVIEWER	***Oscar H. Franco*** Clinical Lecturer University of Cambridge No competing interest
REVIEW RETURNED	20-Jun-2011

RESULTS & CONCLUSIONS	Overall the message is well presented but further clarity could be provided: implications, further research? impact on policy and public health? guidelines
GENERAL COMMENTS	Overall this is a well presented and clearly written manuscript. I just have a couple of comments: 1) Where there differences in the findings when participants were compared by gender? and by age group? 2) Beyond the evaluation of prediction using ROC curves, could the authors compare reclassification of the biomarkers score with the prediction rules used in current practice in China? 3) Please discuss further the implications of the findings. What would be the impact of current findings on current guidelines? public health? 4) Please discuss the practicalities of measuring the listed biomarkers in primary care or large populations. Would it be feasible? cost-effective?

REVIEWER	***Martin Clodi*** Universitätsklinik für Innere Medizin III
REVIEW RETURNED	27-Jun-2011

GENERAL COMMENTS	**Joint analysis of multiple biomarkers for identifying type 2 diabetes in middle-aged and older Chinese** Hongyu and colleagues focus on a very interesting and important topic. Predictive values of different biomarkers for diabetes and hyperglycemia are analysed in a relatively large cohort of 3189 Chinese patients. Among the tested markers adiponectin, PAI-1, IL-

	6 and ferritin were associated with the prevalence of type 2 diabetes. Based on these findings the authors calculated a biomarker risk score predicting the risk of type 2 diabetes and hyperglycemia. It is concluded that a combination of the tested biomarkers with traditional risk factors significantly improves the prediction of diabetes and hyperglycemia. **Major Points:** - In this article the authors conclude that the biomarker risk score improves prediction of diabetes and hyperglycemia. Please further specify the term hyperglycemia. Assuming that impaired fasting glucose is referred as hyperglycemia, please replace hyperglycemia by impaired fasting glucose. - Please indicate the exact prevalence of diabetes and impaired fasting glucose in your collective. - Were follow up examinations performed after inclusion of the patients in your study ? - When analysing the biomarkers separately the AUC of the receiver operated curves is quite low, please address this topic in your discussion. - Discuss the relatively low BMI of your cohort. **Minor Points:** - Please check the spelling

VERSION 1 – AUTHOR RESPONSE

Reviewer1: Oscar H. Franco
Clinical Lecturer
University of Cambridge
No competing interest
Overall this is a well presented and clearly written manuscript. I just have a couple of comments:

1) Where there differences in the findings when participants were compared by gender? and by age group?
We have added the information in Page 11: “After adjustment for age, sex, region, residence, smoking, alcohol drinking, physical activity, family history of diabetes, and BMI, the ORs for type 2 diabetes and IFG with each point increment of BRS were 1.28 (95% CI 1.22-1.34; P <0.001) and 1.16 (95% CI 1.12-1.20; P <0.001), respectively (Table 2), meanwhile, similar ORs were observed among both sexes (P for interaction=0.48 and 0.49 for diabetes and IFG, respectively) and age groups defined by the cutoff of 60 years (P for interaction=0.38 and 0.49 for diabetes and IFG, respectively).”

2) Beyond the evaluation of prediction using ROC curves, could the authors compare reclassification of the biomarkers score with the prediction rules used in current practice in China?
We appreciate the reviewer’s suggestion. In the current study, besides ROC curves, net reclassification improvement (NRI) and integrated discrimination improvement (IDI) statistics were also used to test the discriminative ability. It was found that “adding the biomarkers risk score into the

conventional risk factors significantly improved IDI (IDI=0.0669, P<0.0001). The NRI was estimated at 25.7% (P<0.0001), resulting from net of 16.7% of cases classified up and net 9.0% of non-cases classified down (Table 3)". Considering that no well-established diabetes prediction model is available in China at present, we could not compare the reclassification of the biomarkers score with the prediction rules used for Chinese. However, the conventional risk factors included in the current analysis were those commonly used in both Asian and other ethnics.

3) Please discuss further the implications of the findings. What would be the impact of current findings on current guidelines? public health?
We have further discussed the implication in Page 14 : "Taken together, these findings highlight that combining multiple circulating biomarkers might provide an additional objective tool in estimating the diabetes risk beyond the conventional risk assessments in clinical practice. These results might provoke using these biomarkers in practice to assess diabetes risk, and benefit those high risk individuals from early preventive intervention. Nevertheless, more studies especially prospective studies are needed to verify these findings."

4) Please discuss the practicalities of measuring the listed biomarkers in primary care or large populations. Would it be feasible? cost-effective?
We have discussed about this in Page 15: "In addition, with the advance of the biomarker measurement technology, we are able to simultaneously assess multiple biomarkers with one blood sample (For example, adiponectin, resistin and PAI-1 were simultaneously measured in our study). Thus, the cost for testing these biomarkers has been reduced, which made it feasible to measure multiple biomarkers in practice of primary care or large populations in the future. On the other hand, if we could prevent a high risk person becoming a clinically overt diabetes patient by early detection and intervention, the overall healthcare cost will be significantly cut down."

Reviewer: 2
Martin Clodi
Universitätsklinik für Innere Medizin III

Hongyu and colleagues focus on a very interesting and important topic. Predictive values of different biomarkers for diabetes and hyperglycemia are analysed in a relatively large cohort of 3189 Chinese patients. Among the tested markers adiponectin, PAI-1, IL-6 and ferritin were associated with the prevalence of type 2 diabetes. Based on these findings the authors calculated a biomarker risk score predicting the risk of type 2 diabetes and hyperglycemia. It is concluded that a combination of the tested biomarkers with traditional risk factors significantly improves the prediction of diabetes and hyperglycemia.

Major Points:
1) In this article the authors conclude that the biomarker risk score improves prediction of diabetes and hyperglycemia. Please further specify the term hyperglycemia. Assuming that impaired fasting glucose is referred as hyperglycemia, please replace hyperglycemia by impaired fasting glucose.
We appreciate the reviewer's suggestion. We have reanalyzed the data and replaced "hyperglycemia" with "impaired fasting glucose (IFG) in Page 11, Table 2 and figure 2.

2) Please indicate the exact prevalence of diabetes and impaired fasting glucose in your collective.
We have added the prevalence in page 10 :"the prevalence of type 2 diabetes and IFG were 13.6% (n=434) and 26.9% (n=858), respectively."

3) Were follow up examinations performed after inclusion of the patients in your study ?
The current study was a cross-sectional study and we have not performed any follow-up examination after recruiting the participants. We are going to conduct a 6-year follow-up study this year.

4) When analysing the biomarkers separately the AUC of the receiver operated curves is quite low, please address this topic in your discussion.
We appreciate the reviewer's comment. We have discussed this in Page 15 as follows: "As each of these biomarkers might involve in one or more specific pathways link with type 2 diabetes, it was not surprising to find the low value of the AUC for each separate biomarker in discriminating diabetes individuals. However, adding any one of these biomarkers to the conventional factors could significantly improve the power of discriminating the participants with and without type 2 diabetes."

5) Discuss the relatively low BMI of your cohort.
The relative low BMI in our study was consistent with the findings from other Chinese or Asian populations. We have discussed this in Page 13: "Meanwhile, most of these systems were derived from white populations. Till now it is lack of diabetes risk evaluation systems in Asian populations, especially in Chinese who were having lower average BMI levels but similar or even higher prevalence of diabetes than Western populations."

Minor Points:
- Please check the spelling
We appreciate the reviewer's suggestion and have check carefully throughout the manuscript

VERSION 2 - REVIEW

REVIEWER	***Oscar H. Franco***
REVIEW RETURNED	10-Jul-2011

GENERAL COMMENTS	Reviewer completed checklist only. No further comments were made

REVIEWER	***Martin Clodi***
REVIEW RETURNED	10-July-2011

GENERAL COMMENTS	Dear Authors I am very happy with your answers and the quality of the paper has improved.