PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Association of body mass index and age with incident diabetes in Chinese adults: a population-based cohort study
AUTHORS	Chen, Ying; Zhang, Xiaoping; Yuan, Jie; Cai, Bo; Wang, Xiaoli; Wu, Xiaoli; Zhang, Yuehua; Zhang, Xiaoyi; Yin, Tong; Zhu, Xiaohui; Gu, Yunjuan; Li, Xiaoying; Wang, Zhiwei; Cui, Shiwei

VERSION 1 – REVIEW

REVIEWER	Gang Hu Pennington Biomedical Research Center, USA
REVIEW RETURNED	05-Feb-2018

GENERAL COMMENTS	This study assessed the association of body mass index with the risk of diabetes in one large study including participants with a wide range of age groups. The material is suitable, the data collection seems to be adequate, statistical analyses are appropriate and the paper is well written. I have several comments that need to be addressed. 1. The analyzed study samples only included 211,833 participants of the original 685,277 subjects. You should compare the characteristics between the subjects included and those excluded in your study. 2. It is mentioned that you used 1999 WHO criteria to diagnose diabetes. However, you did not have data on 2 hour glucose during an OGTT. You should change the text and add more details on this limitation. 3. Please give more details if some participants died during the follow-up. How did you calculate the follow-up period if the participants died during the follow-up? 4. The prevalence of current drinkers and current smokers seems to be low. How do you explain this?

REVIEWER	Deirdre Tobias Brigham and Women's Hospital, Boston, MA USA
REVIEW RETURNED	20-Feb-2018

GENERAL COMMENTS	This manuscript describes an analysis of BMI and age in

	relation to incident diabetes. These relationships are already well established. Participants were Chinese adults enrolled in a healthcare system with at least 2 visits. Median follow-up from baseline visit was 3 years. Incident diabetes is self-reported and does not distinguish between type 1 or 2 diabetes. Results indicate that there is a linear trend between BMI and incident diabetes risk, and that the slope of this association is steeper/stronger at younger age groups. The major limitation of this analysis and its conclusions is that it does not account for the competing risks at older age groups. Table 1 demonstrates the prevalence of several diabetes risk factors is higher at older ages, without accounting for these. A similar table according to BMI strata may also be useful in scoping potential sources of confounding or competing risks. The apparent lower risk of diabetes with smoking status is likely due to reverse causation, and further emphasizes the potential for bias among the higher risk/older age groups. The authors may wish to further elaborate on these potential limitations in the discussion. Additional attention to potential mechanisms, if the results are to believed, may also be helpful for the readers.

REVIEWER	Jennifer L Kuk York University, Canada
REVIEW RETURNED	09-Mar-2018

GENERAL COMMENTS	The authors examine whether the association between BMI and diabetes is modified by age in Chinese adults. Given that the authors examined age*BMI interactions and show it to be significant, it is not appropriate to show collapsed HRs. The authors need to revise the results to show age by BMI stratified HRs (Supp Table 1 with a single reference group). Without this approach, you cannot make your conclusion. It would also be interesting to see if there are BMI*family history interactions and age*smoking effects as well. It would be good to present sex-stratified models if possible . Is there physical activity or dietary information?

VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Gang Hu

Institution and Country: Pennington Biomedical Research Center, USA

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

This study assessed the association of body mass index with the risk of diabetes in one large study including participants with a wide range of age groups. The material is suitable, the data collection seems to be adequate, statistical analyses are appropriate and the paper is well written. I have several comments that need to be addressed.

1. *The analyzed study samples only included 211,833 participants of the original 685,277 subjects. You should compare the characteristics between the subjects included and those excluded in your study.*

Response: We really appreciate the reviewer’s comment. The present study initially included individuals that were at least 20-year-old with at least two visits between 2010 and 2016 (n=685,277). Individuals with visit intervals less than 2 years, diagnosed with diabetes at baseline, or with undefined diabetes status at follow up (n=473,444) were further excluded. Compared with individuals excluded from the present analyses, those included in the analyses were with similar age (42.1 vs 41.9 years old) and similar BMI (23.2 vs 23.3 kg/m^2), and with a relatively higher proportion of males (54.8 vs 52.1%). Excluding these patients might have a possible selection bias. The results and potential limitation have been additionally added in Part Method.

2. *It is mentioned that you used 1999 WHO criteria to diagnose diabetes. However, you did not have data on 2 hour glucose during an OGTT. You should change the text and add more details on this limitation.*

Response: We greatly appreciate the reviewer’s comments. Diagnosis of incident diabetes was defined as fasting plasma glucose of ≥ 7.00 mmol/L and/or self-reported diabetes during the follow-up period. Patients were censored at the date of diagnosis of diabetes or the final visit, whichever came first. Corresponding text has been changed. Diagnosis of diabetes was self-reported combined with fasting glucose level which is more precise. As such, we could have missed some cases of type 2 diabetes. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) and Asia (DECODA) studies show that fasting glucose alone only detected about 68% of new diabetic patients in Europe and 55% of new diabetic patients in Asia. And national surveys have reported 46.6% of Chinese with undiagnosed diabetes had isolated increased 2-h plasma glucose after an oral glucose tolerance test. Therefore, the true estimated incidence of diabetes should be higher than the data from this study. However, oral glucose tolerance tests are not applicable for large sample survey due to its complexity to operate.

3. *Please give more details if some participants died during the follow-up. How did you calculate the follow-up period if the participants died during the follow-up?*

Response: We greatly appreciate the reviewer's comments. Actually, regarding its retrospective nature of this large population study, no data were available on death information during the follow-up. Missing information of these individuals might have a possible selection bias. The potential limitation have been additionally added in Part Discussion.

4. *The prevalence of current drinkers and current smokers seems to be low. How do you explain this?*

Response: We totally agree with the reviewer's comment. The total number of smokers and drinkers were relatively small, with the total smoking rate was only 20.0% and the drinking rate was only 2.2% in this population. There are some explanations for the relative low rates. First of all, this low rate of prevalence is expected due to the relatively young age of the participants, which may lead to the relative low prevalence. Secondly, for missing values of drinking status and smoking status, we coded them as a missing indicator category for categorical variable, thus the denominator of the rate might be slightly overestimated.

Reviewer: 2

Reviewer Name: Deirdre Tobias

Institution and Country: Brigham and Women's Hospital, Boston, MA USA

Please state any competing interests or state 'None declared': None declared.

Please leave your comments for the authors below

This manuscript describes an analysis of BMI and age in relation to incident diabetes. These relationships are already well established. Participants were Chinese adults enrolled in a healthcare system with at least 2 visits. Median follow-up from baseline visit was 3 years. Incident diabetes is self-reported and does not distinguish between type 1 or 2 diabetes. Results indicate that there is a linear trend between BMI and incident diabetes risk, and that the slope of this association is steeper/stronger at younger age groups. The major limitation of this analysis and its conclusions is that it does not account for the competing risks at older age groups. Table 1 demonstrates the prevalence of several diabetes risk factors is higher at older ages, without accounting for these. A similar table according to BMI strata may also be useful in scoping potential sources of confounding or competing risks. The apparent lower risk

of diabetes with smoking status is likely due to reverse causation, and further emphasizes the potential for bias among the higher risk/older age groups. The authors may wish to further elaborate on these potential limitations in the discussion. Additional attention to potential mechanisms, if the results are to believed, may also be helpful for the readers.

Response: We greatly appreciate and totally agree with the reviewer's comments. First of all, actually, table 1 demonstrated systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, LDL-C were higher at older ages, and HDL-C was lower at older ages, which are confounding factors may distort the association between BMI and risk of diabetes. Therefore, further adjustment for systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, LDL-C, and HDL-C were performed based on the current multivariable model, and it attenuated the association between BMI and diabetes risk, but BMI as a continuous variable remained a statistically significantly predictor of diabetes in the multivariable model. Secondly, according to your suggestion, table showing the confounding or competing risks according to BMI strata has been added as supplementary table 1. Thirdly, reverse causality or confounding by smoking status, metabolic risk factors has been considered a possible explanation of different effect of BMI on risk of diabetes. However, after conducting extensive sensitivity analyses excluding current smoker, current drinkers, individuals with hypertension, high-TG, low-HDL-C, the primary findings did not substantially change. The risk of incident diabetes remained increased by BMI values, and age still had modified effect on the association between BMI and the risk of incident diabetes (age × BMI interaction, *P* < 0.0001). Although we did the subgroup sensitivity analyses for our finding, we could not completely excluded reverse causality or the effects of unmeasured confounding factors. The potential limitation has been added in Part Discussion. Finally, additional potential mechanisms has been added in Part Discussion.

Reviewer: 3

Reviewer Name: Jennifer L Kuk

Institution and Country: York University, Canada

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

The authors examine whether the association between BMI and diabetes is modified by age in Chinese adults.

*Given that the authors examined age*BMI interactions and show it to be significant, it is not appropriate to show collapsed HRs. The authors need to revise the results to show age by*

BMI stratified HRs (Supp Table 1 with a single reference group). Without this approach, you cannot make your conclusion.

Response：We greatly appreciate with the reviewer's comments. In the study, the normal BMI group (18.5-<24.0 kg/m^2) was chosen as the referent category in each age group, which method was once performed in an article published on LANCET [1]. Of course, Supplementary Table 2 has been revised according to the suggested method and the largest number group was chosen as a single reference group, and the trend is similar.

*It would also be interesting to see if there are BMI*family history interactions and age*smoking effects as well.*

It would be good to present sex-stratified models if possible.

Response：Thanks for the reviewer's suggestion and we greatly appreciate it. Accordingly, we performed unadjusted and multivariable adjusted model in male and female separately. Similar trend were detected separately in male and female, and the results have been added in table 3.

Is there physical activity or dietary information?

Response：Thanks for the reviewer's suggestion and we greatly appreciate it. Actually, physical activity, energy intake and dietary patterns are important lifestyles related to obesity and diabetes, however, the related information were not collected during the health examination survey. In the follow up survey, we will collect the information of physical activity and dietary patterns.

Reference:

1. Global, B.M.I.M.C., et al., Body-mass index and all-cause mortality: individual-participant-data meta-analysis of 239 prospective studies in four continents. Lancet, 2016. 388(10046): p. 776-86.