Author’s response to reviews

Title: The product of fasting plasma glucose and triglycerides improves risk prediction of type 2 diabetes in middle-aged Koreans

Authors:
Joung-Won Lee (joungwon@korea.kr)
Nam-Kyoo Lim (namkyoo.lim@gmail.com)
Hyun-Young Park (mdhypark@gmail.com)

Version: 1 Date: 14 Feb 2018

Author’s response to reviews:

Detailed Response to Reviewers

February 15, 2018

Reviewer

BMC Endocrine Disorders

Manuscript ID: BEND-D-17-00165

Title: The product of fasting plasma glucose and triglycerides improves risk prediction of type 2 diabetes in middle-aged Koreans

Dear Reviewers:

We would like to thank you and the reviewers of the BMC Endocrine Disorders for taking the time to review our article. We have made some corrections and clarifications in the manuscript after going over the reviewers’ comments.
We revised the manuscript and blue highlighted lines were marked in revised text. Here we have addressed the concerns of the reviewers on separate pages, as well as our response to the specific comments.

We hope that the revised manuscript will better meet the requirements of your journal for publication. We thank the editor and the reviewers for the BMC Endocrine Disorders once again for the constructive review of our paper.

Sincerely,

Editor-in-Chief:

1. Although “fasting glucose” was excluded as covariate in the final model, we omitted to delete it in the manuscript and tables. In revised text and table, “fasting glucose” was deleted.

Reviewer #1

1. TyG index, LAP, and TG are compared to WC for predicting diabetes. However, the correlation between WC and BMI is usually high (r ~0.8), and BMI is already in the basic prediction model (age, body mass index, family history of diabetes, hypertension, current smoking, current drinking, and fasting plasma glucose). Therefore, WC may not add too much predictive discrimination to BMI.

Authors’ response

In the systematic review, more than 30% of the diabetes risk models stating its components included both BMI and WC [1]. As the reviewer pointed out, the correlation between WC and BMI was high (r=0.84 in men, r=0.74 in women) in the present study. Though there is no universal agreement of variable inflation factors (VIF) for detecting multicollinearity, the VIF
value in excess of 5 or 10 has been frequently used [2-4]. In the present study, the calculated VIF for all covariates such as WC and BMI, in the multivariate model, were below 5.0, indicating no severe multicollinearity among covariates. Moreover, as LAP consists of WC and TG, the prediction improvement needs to be compared when WC or TG-related indices are added to the basic model.

2. The authors demonstrate that TG increases the predictive discrimination of the basic model. However, the authors do not demonstrate that TyG index is better than TG for predicting future diabetes. For example, AROCs for basic model + TyG index are marginally better than those of basic model + TG in both men (0.705 vs 0.700) and women (0.674 vs 0.672).

Authors’ response

We added a table of the AROCs of TG-related indices and WC for predicting T2DM. In both sexes, the AROCs of TyG index were better than the AROCs of TG for predicting future diabetes (0.623 vs. 0.592 in men, 0.644 vs. 0.627 in women). Although the predictive discrimination between TyG index and TG increased when each index was added to the basic model, AROCs of basic model + TyG index were slightly better than those of basic model + TG. The reclassification ability of basic model + TyG index was also better than that of basic model + TG.

3. The authors put emphasis in the reclassification ability of TyG index. However, there are some considerations to make: a) there are not clinically relevant strata in the prediction of diabetes (in contrast to clinically relevant strata for predicting future coronary heart disease); and b) the IDI for the basic model + TyG index is not much different than that for the basic model + TG in either men (0.012 vs 0.007) or women (0.022 vs 0.020).
Authors’ response

To the best of our knowledge, there is no TyG index criterion yet. On the other hand, several studies conducted in Europe and Asian have shown that the risk of incident T2DM was increased with increasing TyG index [5-7]. Some researchers have proposed a cut-off value of TyG index of 8.8 for T2DM and insulin resistance [6, 8]. The subjects in the present study were classified by the cut-off value of TyG index of 8.8. The adjusted odds ratio (95% CI) of incident T2DM in the subjects with TyG index ≥ 8.8 was 1.95 (1.73-2.20) compared to the counterparts. We also have proposed sex-specific cut-off points of TyG index as predictors of T2DM based on the maximized Youden index. In the present study, the cut-off points of TyG index are 8.86 in men, 8.52 in women, respectively. Compared to the counterparts, the adjusted odds ratio (95% CI) of incident T2DM in the men with TyG index ≥ 8.86 and in the women with TyG index ≥ 8.52 were 2.01 (1.69-2.39) and 2.16 (1.82-2.56), respectively. Therefore, TyG index is recommended as a screening tool for the prediction of T2DM.

We have accepted another reviewer's advice about adding regular exercise data into the model. The IDIs for the basic model + TyG index were higher than the basic model + TG in men (0.023 vs. 0.007) and women (0.029 vs. 0.019).

4. It would be useful that the authors state, in the Results section, the significance of the findings regarding the AROC, cNRI, and IDI for the readers that are not familiar with those terms.

Authors’ response

As the reviewer pointed out, we have added the detailed description of cNRI and IDI in statistical analysis. “Pencina et al. have suggested category-based NRI and IDI for calculating the usefulness of a new marker in prediction models. The category-based NRI measures the accuracy of reclassification based on how well the subjects are reclassified as upwards for events and downwards for non-events. However, the category-based NRI can be affected by the number and choice of categories. The continuous (category-free) NRI is an expanded method to solve limitation of the categories. They also proposed the integrated discrimination improvement (IDI)
that calculates the extent of average sensitivity and ‘1-specificity’ when a new marker is added to the basic model.” it was added to the statistical analysis.

5. In the Abstract Conclusions: "Therefore, TyG index should be considered as a screening tool for identification of patients at high risk for T2DM in practice." Similar statement is also in the last paragraph of the manuscript. The authors have study the predictive discrimination of TyG beyond that of a basic model. However, the authors have not examined the TyG index as a screening tool for the identification of individuals at increased risk of diabetes. How can the TyG index be used as a screening tool?

Authors’ response

As the reviewer pointed out, we have changed the previous sentence to “Considering the prediction ability of TyG index and national health care of Korea, TyG index can be a useful screening tool for incident T2DM in middle-aged Koreans.”

To the best of our knowledge, there is no TyG index criterion yet. Some researchers have proposed a cut-off value of TyG index of 8.8 for T2DM and insulin resistance [6, 8]. As the reviewer pointed out, we have proposed sex-specific cut-off points (men: 8.86, women: 8.52) of TyG index as predictors of T2DM based on the maximized Youden index.

Reviewer #2

A. Abstract: in the "methods section" it is mentioned that "7,708 Koreans aged 40-69 years without diabetes at baseline were selected from the Korean Genome and Epidemiology Study". It is important to clarify if subjects were randomly selected from the larger study sample or if the subjects participating in the present study are actually those who were eligible. In the latter case, it is proposed that the Authors revise the wording in this sentence from "were selected" to "were eligible".
Authors’ response

As the reviewer suggested, since using the term “were eligible” is clearer than “were selected”, it was corrected accordingly.

B. Introduction: Line 43: revise to "...waist circumference (WC) has also been used."

Authors’ response

As the reviewer pointed out, we have changed the previous sentence to “Lee et al. selected waist circumference (WC) instead of BMI in their diabetes risk model considering its association with diabetes. In the systematic review, more than 30% risk models include both BMI and WC among stating its components [1].

We deleted repetitive sentence “Lee et al. also proposed a simple diabetes risk model for Koreans that was derived from the KNHANES, which included WC instead of BMI” in discussion.

C. Methods:

C1. Line 48: although the Authors included a reference to the paper describing the methodology followed in more detail, it is recommended that some more information is included in this manuscript too regarding the areas/regions where this study was conducted.

Authors’ response

As the reviewer pointed out, we have changed the previous sentence to “The Korean Genome and Epidemiology Study (KoGES) consists of a gene-environment model and population-based studies [9]. KoGES: Ansan and Ansung study is an ongoing prospective cohort study conducted
in urban (Ansan) and rural (Ansung) areas in Korea with biennial follow-ups, which started in 2001.”

C2. Statistical analysis: did the Authors check for collinearity between WC and BMI in the multivariate model? If yes, please indicate the results.

Authors’ response

As the reviewer suggested, we tested multicollinearity for all covariates based on the variable inflation factor. The calculated VIF for all covariates in the multivariate model, were below 5.0, indicating no severe multicollinearity among covariates.

D. Results

D1. Table 1: how do the Authors justify the large difference between the number of smokers between men (n=1,753) and women (n=142)?

Authors’ response

In the 2008 Korean National Health and Nutrition Examination Survey, the self-reported smoking prevalence were 44.7% and 5.9% in men and women, respectively [10]. Jung-Choi et al. tested cotinine-verified smoking prevalence rates for the possible under-reporting of smoking [10]. The cotinine-verified smoking prevalence were 50.0% and 13.9% in men and women. Considering both results, there are gender differences in smoking in Korea.

D2. Table 3: the model should be also adjusted for behavioural data (e.g. dietary intake, physical activity level). The Authors mentioned in the Discussion as a limitation of the present study that
no such adjustments were made. Still, if these data are available, it would be important to add them as covariates in the model.

Authors’ response

We agree with the reviewer and actually Baik et al. had reported that dietary information improved cardiovascular disease risk prediction models [11]. However, dietary information has been excluded from the questionnaire in medical check since 2009. On the other hand, physical activity information from the questionnaire is obtainable from KoGES and medical checks. Therefore, we have added regular exercise data into the model as a covariate.

E. Discussion

E1. Lines 30-31: the Authors suggest that "WC is not easily used in practice because of measurement inaccuracy", which is true. However, the collection of blood samples causes more burden and costs more. Therefore, it needs to be clearly highlighted what is the added value of using the TyG index as a screening tool. Would it be more meaningful to use this index in the clinical practice (i.e. in a hospital), instead of using it in the general population (e.g. by health care professionals who do not necessarily ask for blood examination or cannot prescribe it)?

Authors’ response

We agree with the reviewer, and have highlighted the usefulness of TyG index for T2DM in the medical check-ups. We have proposed the cut-off points of TyG index for T2DM which are 8.86 in men, 8.52 in women, respectively. Considering NIH’s universe coverage, the health promotion that offered the general health check-ups for 17.6 million Koreans in 2016, and its following examination rate (77.7%), there should be less burden caused by blood tests than other countries [12].
References


