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Response to Reviewers

Dear Editor,

Thank you for giving us the opportunity to submit a revised draft of the manuscript "The Association Between Restrictive Pulmonary Disease and Type 2 Diabetes in Koreans: A Cross-sectional Study" for publication in the *World Journal of Diabetes*. I appreciate the time and effort that you and the reviewers dedicated to providing feedback on my manuscript and are grateful for the insightful comments on and valuable improvements to this paper. I have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, in blue, for a point-by-point response to the reviewers' comments and concerns.

We hope the revised version is now suitable for publication and look forward to hearing from you in due course.

Sincerely,

Do-Youn Lee, Seung-Min Nam

Response to Reviewer 1

Thank you for your review of our paper. We have answered each of your points below.

1. Authors mentioned that the data was obtained from Korea National Health and Nutrition Examination Survey. Is it from hospital patient records?

   Author response: Korea National Health and Nutrition Examination Survey (KNHANES) is a survey research program conducted by the Korean Centers for Diseases Control and Prevention (KCDC) to assess the health and nutritional status of adults and children in the Korea, and to track changes over time. The survey combines interviews, physical examinations, and laboratory tests. KNHANES interview includes demographic, socioeconomic, dietary, and health-related questions. The examination component consists of medical, dental, and physiological measurements, as well as laboratory tests administered by medical personnel, and all data are made anonymous and can be officially downloaded from the website.

2. It is important to mention the p value to show the significance.

   Author response: p-value <.05 is presented in the data analysis section. However, for table 3 and 4, the very high p-value was indicated separately.

3. Please justify for using multivariate logistic regression analysis, How the HOMA-IR, HOMA-beta, HbA1c, and fasting insulin. Is it a routine practice of perfroming these these tests on all the patients.

   Author response: It is difficult to understand whether there is a problem with the method of statistical analysis or with the subject's data. If my paper does not fit your opinion direction that needs to be corrected, I will try to fix it as much as I can.

4. All the antropometric variables were done freshly or collected from the survey data?

   So explain in detail in the methodology about these parameters.

   Author response: The KNHANES data is the official national disclosure data conducted annually. Therefore, additional new data collection by researcher is impossible

5. Why other statistical methods were not done to see the association of diabetes, restrictive and obstructive pulmonary disease? Express in mean plus or minus SE or p value to show the significance in association.

   Author response: The data in this study are complex sampling design, using logistic regression analysis that is most appropriate to view the association between the variables recommended by the KCDC. For this reason, other statistical analysis is not performed.

6. use some recent literture review to explain the about the work and its connection with other simlar work Table 1 and 2: the units for lipid profile missing Table 2: typographical error: driking water should become drinking water.

   Author response: Variables such as lipid, insulin, FEV1 etc. in Table 1 and 2 are marked in units and modified to red.

   The typographic error in Table 1 and 2 that you pointed out has also been corrected(Driking status → Drinking alcohol status).

Response to Reviewer 2

Thank you for your review of our paper. We have answered each of your points below.

1. The data is from the Korea National Health and Nutrition Examination Survey, please depict more detail about the include and exclud criteria. for example, except for diabetes and pulmonary diseases, what about other diseases? and even people with RPD or OPD, what about the disease duration and treatment state? what about the diabetes treatment state? did they ever accept any drugs?

Author response: The data in this study are public data provided by the Korean Centers for Diseases Control and Prevention (KCDC), and there are limitations to this because there has been no detailed mention of the duration of the disease and the state of treatment. In the case of diabetes, even if data such as fasting glucose and fasting insulin are normal, those who answered "yes" in the survey on whether to take diabetes drugs were classified as diabetic patients. However, the type of medicine was not mentioned, so the analysis was limited. Also, these contents were added to the methods section in 'Type 2 diabetes mellitus and insulin resistance'.

2. The SD for blood pressure, FBG et al. are so small, are the author sure about they are SD?

Author response: Statistics from this study have been re-checked and the same results have been obtained as listed on the table.

3. The analyse is relatively simple and could not be get a good conclusion. I suggest the author check some correlations between FEV1, FVC with diabetes related index such as HOMA-IR, FBG, FIn, BMI, WC et al in the total population. And then do some regression test to see if FEV1 is a risk factor for T2DM.

Author response: The data of the KNHANES used in this research is sampled by the two-stage sampling; complex sampling, and it reflects some elements such as stratification, clustering, and weights. If we analyze such data as pearson correlation coefficient and simple random sampling, we can obtain the biased result in the variance estimates. The statistical analysis of this study used the most appropriate complex sampling analysis method recommended by the KCDC.

4. 5. 6.

its hard to get the conclusion from what the author did.

In the discussion part, please add some potential mechanisms how polmonary patient as risk to T2DM. all the mechanism the authors currently gave were all about those risk factors established in the development of T2DM, such as HOMA-IR, accumulation of fat in the abdominal cavity, WC and BMI. All these are certain risk factors for T2DM, one can't say because RPD patients had higher of these index, and the RPD patient at high risk of T2DM.

The whole result part and part of the discussion need complete revise.

Author response: I revised the manuscript after collecting your opinions up to 4-6. There was a significant association between RPD and T2DM. However, association between RPD and IFG was weak or not. I think this suggests that T2DM is the cause, not the result of the RPD. Therefore, these parts are added to the discussion section. If my response does not fit your opinion direction that needs to be corrected, I will try to fix it as much as I can.

Response to Reviewer 3

Thank you for your comments. Our answers to your points are as follows.

1. There was a significant association between RPD and T2DM. However, association between RPD and IFG was weak or null. This suggests that RPD is not a cause of T2DM but rather consequence of T2DM. This point should be discussed more precisely.

   Author response: I found out from your review that there was something I missed. Therefore, these parts are added to the discussion section. Please check again if there is anything wrong with this part.

2. In this study, the proportion of IFG seemed too high. The reason should be explained and discussed.

Author response: A previous study found that the prevalence of Korean adult IFG increased from 21 percent to 25 percent from 2006 to 2013. The data from this study is based on 2015 and seems to have increased the proportion as it is limited to those aged 40 or older who conducted the pulmonary function test out of a total of 7,380 people. However, it is believed that the potential confounding will not have a significant impact on the results as this data is a vast amount of data from the Korean population. These contents were added to the research limitations. If my response does not fit your opinion direction that needs to be corrected, I will try to fix it as much as I can.

Reference

Noh, Junghyun, et al. "Trends in the pervasiveness of type 2 diabetes, impaired fasting glucose and co-morbidities during an 8-year-follow-up of nationwide Korean population." Scientific reports 7 (2017): 46656.

3. Were there any patients with FEV1/FVC <0.7 and FVC <80%? How were they classified?

   Author response: In this study, if FEV1/FVC < 0.7 subjects are classified as obstructive pulmonary disease group regardless of FVC.

   - Normal group: FEV1/FVC ≥ 0.70, FVC ≥ 80 % predicted
   - OPD group: FEV1/FVC < 0.70

- RPD group: FVC < 80 % predicted, FEV 1 / FVC ≥ 0.70

4. Page 4. Meaning of the sentence "In the relationship between T2DM and pulmonary disease, there is a theory that an increase in the inflammatory response derived from obesity causes insulin resistance and increases the risk of cardiovascular disease associated with obesity[12]." was not clear. This sentence should be revised.

Author response: I revised the above contents to "In addition, an increase in the inflammatory response derived from obesity causes insulin resistance and increases the risk of cardiovascular disease associated with obesity[12]".

5. Abstract. RPD and OPD should be spelled out in their first appearances.

Author response: Thank you for your feedback. I accepted your opinion and revised it.

6. Terms "RPD", "OPD", "restrictive pattern" and "obstructive pattern" should be unified into "RPD" and "OPD" throughout the manuscript.

Author response: Thank you for pointing this out. I unified into "RPD" and "OPD" in all part of manuscript.

7. The manuscript should be edited by a native English speaker.

Author response: I revised the manuscript to reflect the opinions of the reviewers, and then edited to native English speakers. However, the response is being delayed and the deadline for the manuscript is approaching, so we decided to submit the original first. I sincerely ask you to understand this.

The requested revision has been completed. Thank you for your comments. Our answers to your points are as follows. 1.I think the first paragraph of the introduction part should focus on the changes of lung function in T2DM instead of the disadvantages of T2DM, which is almost well known to everyone. - Author response: Thank you for pointing this out. The first paragraph of the Introduction part was revised with a focus on changes in pulmonary function. In addition, it has been revised and added to ensure smooth connection with the second paragraph. 2. The conclusion of this study was that restrictive pulmonary function, not obstructive, is highly relevant to T2DM regardless of the risk factors of various T2DMs that can be mediated or confused. however, the author said in their response to reviewer, that T2DM is the cause, not the result of the RPD. It is confused and please clarify the relationship. - Author response: Thank you for your feedback. To avoid confusion in conclusions, we added this part. 3. I really suggest that the author should colored those part they revised. - Author response: There was an error in the process of uploading the file, so the modified part does not appear to be red. I uploaded the modified part with the original file marked in red, so please check. 4. It is better to have some subtitle for the result part. - Author response: I found out from your review that there was something I missed. Subtitles were attached to the result section, and each paragraph was divided. 5. I didn't find the tables in the download file. - Author response: Added table file.