

The authors thank the Editors, and the Reviewers for their comprehensive and constructive comments. We appreciate the effort involved in reviewing our work critically and for the opportunity to respond. Please find below our point-by-point responses to editor and reviewer comments.

Reviewer #1:

1. Overall, I believe there is some potential for insights from the data, but I do not think it is presented in a clarified way that provides significant insight or fills gaps of knowledge. I do not find the description of the cohort to be particularly important or a gap in the literature (ie the prevalence of conditions in this cohort) and a significant amount of time in the paper is dedicated to this. The proving of a relationship between insulin resistance and beta cell dysfunction with glycemic outcomes does not appear to be novel or exciting. So the only measure that is not intrinsically linked with these variables is hypertension. It may be more compelling if those without dysglycemia within the population are studied separately and are studied for their association of beta cell dysfunction/HOMAIR with hypertension or other measures like dyslipidemia or waist circumference. For example in the following paper: “Esteghamati, Alireza, Omid Khalilzadeh, Mehrshad Abbasi, Manouchehr Nakhjavani, Leila Novin, and Abdul Reza Esteghamati. "HOMA-estimated insulin resistance is associated with hypertension in Iranian diabetic and non-diabetic subjects." *Clinical and experimental hypertension* 30, no. 5 (2008): 297-307.” Or perhaps they could explore which of these measures, HOMAIR or oDI, is associated the most with glycemic outcomes?

Response: We thank the reviewer for the insightful comment. In this study, we have described the relationship between measures of beta cell dysfunction/insulin resistance (IR) and cardiometabolic traits in a cohort of young Indian men. As suggested by the reviewer, we have modified the paper to reduce the description of the cohort in the methodology section, and shifted material to supplementary appendix.

The reviewer has suggested evaluating the relationship between measures of beta cell function/IR and other cardiometabolic risk factor such as hypertension, dyslipidemia, waist

circumference and metabolic syndrome. We have performed this analysis which is reflected in tables 2-4 and supplementary tables 1-3 of this paper.

We thank the reviewer for suggesting this reference that explores the relationship between HTN and IR in Iranian subjects; this study has now been cited in our paper. Furthermore, we have explored the association for HOMA-IR and oDI with cardiometabolic risk factors using logistic regression analysis.

2. The clumping of the subjects of dysglycemia and those without into these quartiles for analysis does not make sense to me. I think the abstract spends too long describing the cohort in question without describing the relationship between the measures on beta cell dysfunction and insulin resistance which I think is the main point. I think it can be substantially shortened. While the authors do describe the need to specifically study this population (young Indian men) I think the background confuses their aims. Are they trying to describe prevalence of certain conditions in this population? If so this may not be the appropriate cohort to make conclusions for the general Indian population. I think they need to describe how showing beta cell dysfunction/insulin resistance as early markers of metabolic disease/independent, independent of dysglycemia is relevant to clinic care. I do not believe they do so adequately.

Response: Thanks for your comment. We will like to clarify that we included subjects with both normoglycemia and dysglycemia (prediabetes and diabetes) in this cohort; however, glycemia was not our exposure variable. The exposure variables were measures of beta cell function/IR and outcome variables were cardiometabolic risk factors such as presence or absence of HTN, metabolic syndrome, dysglycemia and dyslipidemia. The exposure and outcome variables have been clearly explained in the methods section.

In this study, our main objectives are to describe: a) burden/prevalence of glycemic and cardiometabolic traits in young Indian men and b) relation of these to parameters of insulin action and beta cell function.

As suggested by the reviewer, the clinical relevance of this work has been added.

“We evaluated a large cohort of young Asian India men for the burden of cardiometabolic risk factors in relation to parameters of insulin resistance and beta-cell function. Apart from the traditional risk factors such as age and BMI, across which abnormal cardiometabolic traits increased, we found that individuals in the most severely affected quartiles of insulin resistance (HOMA-IR), beta cell function (oDI), and a combination of both, had a significantly higher burden of dysglycaemia, hypertension, metabolic syndrome, and adverse lipid parameters. These findings highlight the importance of using parameters of insulin resistance and beta-cell function in phenotyping individuals for cardiometabolic risk”.

3. In terms of the Methods, I find the division into the different quartiles and phenotypes to be extremely confusing and unjustified. Why can these not be studied as continuous variables with other statistical measures for association? Does having the categories in addition the phenotypes helpful? The way these are parsed out into so many different categories I do not find helpful. In terms of the discussion, I did not agree with the following statement: “Our study findings add to the limited and evolving understanding of diabetes pathophysiology in South Asians.” Because there is not really a quantification of the pathophysiology of this. I did not get a sense from the paper that they were describing the diabetes phenotype of the population.

Response: Thanks for the insightful comment. We would like to clarify that the division into different HOMA-IR/oDI categories and phenotypes is in line with the work reported in reputed journals such as Journal of Clinical Endocrinology and Metabolism (JCEM) and Diabetes care. For examples, in this study published in JCEM, the authors used quartiles based classification for IR and beta cell dysfunction

“Wang T, Zhao Z, Xu Y, Qi L, Xu M, Lu J, et al. Insulin Resistance and β -Cell Dysfunction in Relation to Cardiometabolic Risk Patterns. J Clin Endocrinol Metab 2018;103:2207-2215”.

In our study, we have reported the data in relation to parameters of insulin resistance and beta cell function, both relevant to the pathophysiology of diabetes. Previous studies on this subject

were performed in a relatively older population (mean age in 40s or 50s), in those at high risk for diabetes, screened and selected for clinical trials or in individuals of this ethnicity residing outside South Asia. Thus, this study addressed the unmet need to evaluate the burden of cardiometabolic risk factors in young South Asian adults.

4. Their discussion of the limitations of the paper was also quite brief Could also comment on a variety of other potential confounders that do not appear to be adjusted for in the odds ratio including smoking history, alcohol history, and BMI to name a few that could have also been adjusted for. The supplementary tables require listing of adjusting variables in them. The supplementary tables also need much clearer establishment of what the categories are being compared to. I think the first 5 tables are very redundant. I think this may be helped by reducing the amount of categories/phenotypes described or doing so only by continuous measurements. I think there needs to be a considerable decrease in the amount of relationships described.

Response: Thanks for the insightful comment. We did not obtain history of smoking or alcohol in this cohort; BMI was not adjusted since it is a mediating variable for several outcomes including dysglycemia, dyslipidemia and hypertension. Thus, we have only adjusted for age and family history of diabetes. As also suggested by other reviewer, we have expanded upon the limitation section to include:

“Our study provides a cross-sectional association between cardiometabolic risk factors and parameters of insulin action/beta cell function, however, causality cannot be ascertained. We did not evaluate the study participants for cardiovascular complications such as coronary artery disease and peripheral vascular disease. However, it may be too early for these complications to manifest in this young cohort. In this regard, it would be of interest to follow this cohort longitudinally and evaluate incident glycemic and cardiometabolic deterioration, and development of cardiovascular complications, based on baseline quartiles of oDI and HOMA-IR”.

The adjusting variables have now been listed in the supplementary tables. Also, the reference categories have now been added in these tables. As described above, we have used quartiles/phenotypes-based approach based on a standardized format previously published in reputed journals and would wish to persist with the same.

Reviewer #2: It is an interesting research article evaluating 635 young North Indian men for burden of cardiometabolic risk factors, in relation to parameters of insulin resistance (HOMA-IR) and beta cell function (oral disposition index or oDI). The authors found that diabetes/prediabetes overweight/obesity, metabolic syndrome and hypertension were present in 5.4/46.8%, 61.1%, 40.6% and 19.4% of participants, respectively. The prevalences of dysglycemia, metabolic syndrome, and hypertension were significantly higher in participants in the worst HOMA-IR and oDI quartiles. The adjusted odds for dysglycemia, hypertension and metabolic syndrome were significantly higher in individuals in worst quartile of HOMA-IR. Finally, it was concluded that the burden of cardiometabolic risk factors is high among young Indian males, highlighting the importance of using parameters of insulin resistance and beta-cell function in phenotyping the cardiometabolic risk in such a population. The manuscript is well-written in English, and the content is directly relevant to the clinical application in Indian men. There is one suggestion as follows. 1. In the reference no. 3 (Diabetes mellitus and its complications in India Nat Rev Endocrinol 2016;12:357), the cardiovascular complications include coronary artery disease (CAD) and peripheral vascular disease. Nevertheless, in this study examining cardiometabolic risk factors, only hypertension was included. The authors should further evaluate, or at least discuss in detail, other cardiovascular risk factors such as CAD.

Response: Thank you so much for your comment. We agree that this study only discusses cardiometabolic risk factors, and not the hard outcomes, i.e., cardiovascular complications. The ascertainment of these complications would require a longitudinal follow-up of this cohort. We have included this as a limitation.

“Our study provides a cross-sectional association between cardiometabolic risk factors and parameters of insulin action/beta cell function, however, causality cannot be ascertained. We did not evaluate the study participants for cardiovascular complications such as coronary artery disease and peripheral vascular disease. However, it may be too early for these complications to

manifest in this young cohort. In this regard, it would be of interest to follow this cohort longitudinally and evaluate incident glycemc and cardiometabolic deterioration, and development of cardiovascular complications, based on baseline quartiles of oDI and HOMA-IR”.

Reviewer #3: This paper has some important findings among among young Asian Indian males. My suggestions to improve the manuscript are as follows. 1. In the supplementary table 1, the association of HOMAIR with metabolic variables should be analyzed using , but not Category 2. 2. They are the same in supplementary table 2,3. The The variable should be disposition index and insulin resistance/disposition index respectively. 3. In the introduction, the relationship of HOMAIR and disposition index with cardiometabolic risk factors should be illustrated.

Response: Thank you for your insightful comments. As also pointed by reviewer #1, we have added the reference category (category 1) in supplementary tables. The introduction and discussion section have been revised in keeping with reviewer #1, 2 and your comments, and the revised version addresses your comment.

2 Editorial Office's comments

1) Science Editor: The aim of the study is not clear, and should be better explained. The novelty of results presented in this paper is scarce. The rationale for dividing subjects into quartiles and phenotypes has not been fully explained. The analysis of confounders in the assessment of the odds ratio is incomplete. The number of references cited in the manuscript is inappropriate, since authors only considered a total of 19 references. As a consequence, the discussion section does not provide a comprehensive analysis of available evidence and the scientific value of results obtained by authors does not emerge clearly.

Response: We thank the editor and reviewers for their constructive comments. We have revised the manuscript, keeping all reviewer comments in consideration, and have submitted a point-by-point response to each reviewer’s comments. We hope that the manuscript in its current form is suitable for review by the journal.

