Reviewer’s report

Title: Insulin resistance and systemic metabolic changes in oral glucose tolerance test in 5,340 individuals: An interventional study

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Reviewer: Samantha Thomas

Reviewer's report:

Review for Insulin resistance and systemic metabolic changes in oral glucose tolerance test in 5,340 individuals: An interventional study

Abstract:

Methods:
1) There is no mention of the statistical methods used to analyze the data. The unadjusted and/or adjusted analysis methods should be described.
2) The median age and proportion male should go in the results section.

Results:
1) "P &lt; 0.0006" - this value doesn't make sense as a reported p-value. Conventionally, p-values are reported with 2 decimal places for non-significant results, and up to meaningful significant figures for significant results. Was this p-value reported this way because p=0.0006 is the significance level after adjustment for multiplicity? If so, this needs to be clarified. Otherwise, the p-value should be reported as p&lt;0.001. I do see that these methods are described in the methods section, but some clarification would be helpful in the abstract.

Methods:
1) It is somewhat confusing that OGTT, which stands for oral glucose tolerance test is considered a before and after type of event, as though the point at which the glucose is ingested is the "test". Perhaps this is commonly-used terminology, but it needs a little clarification as to what exactly is baseline - is this the moment when the glucose is ingested, or right before?
2) The subjects included were all born in 1966, that is clear, but what do the authors mean when they say that "Data collection between 2012 and 2014 was used in this study"? Did the authors use the NFBC66 to identify subjects, and then contact them to request enrollment in the study? Or are subjects of the NFBC66 already being followed and having samples collected regularly? The cohort selection is not clear. The same is true for the Oulu1945 cohort.
3) In the statistical methods section, the authors state "The significance of a change was evaluated via t-test by comparing the metabolite concentration at post-load time points against the fasting baseline." Was an unpaired or paired test used for this comparison? It should be a paired test, but it is unclear.
4) Were measures examined for normality? Or were measures normalized prior to analysis? I see that the authors mention this for the linear modeling, but not for the univariate modeling.
5) Were other covariates included in the linear models? Only group is listed as a predictor, but it
seems that other patient factors may also be important to adjust for like age and gender.

6) In the linear model, change from baseline to 2 hours was used as the outcome. Was baseline value included as a covariate? Individuals with lower baseline values will have the opportunity for different amounts of change compared to those with higher baseline values, so including baseline value as a covariate may increase the predictive utility of the model.

7) Were 76 different linear regression models used, one for each measure? Were all subjects included in all models? Did any subjects have measures that were unusable or below minimum threshold?

8) In order to test for a difference in the trajectory of change over time between groups, were models with interaction terms not considered? This would be the most appropriate method statistically to test if there are differences in trajectories over time.

Results:
1) Are the proportions reported the mean change for all subjects? If so, it would be helpful to report standard deviation or interquartile range along with the % change.
2) The authors mention that "The results were consistent when stratified by sex.", but this is not mentioned in the methods - what is the rationale for stratifying by sex as opposed to including sex in the adjusted modeling?
3) The authors do mention adjusting for some factors in the results section - this should go in the methods and the approach should be described in more detail. For instance, were 4 adjusted models conducted for every one of 76 measures?
4) It seems that most of the results reported are descriptive and gathered visually from the trajectory plots. More formal statistical modeling and testing would strengthen the descriptive and visually-gathered results.

Discussion:
1) The first sentence states ""We used four time points of OGTT data from two independent cohorts of 5,340 individuals" this implies that there were 2 cohorts, each with N=5340. This should be reworded to clearly describe the population and 2 cohorts.
2) The authors do point out that "ethnic and socioeconomic context should be taken into account when extending these results to other populations." This is a great point as this population is limited to Finnish individuals and these associations may not be present or may be expressed differently in diverse cohorts.

This study does reveal that IR individuals are prone to reduced response to glucose ingestion compared to IS individuals - which helps strengthen this result seen in several smaller studies, and that many of the affected markers are consistent with those seen in fasting-state studies. Additional results that reveal similarities between IR individuals with normal glucose and pre-diabetes and new diabetes individuals is interesting and may be important for treatment of IR individuals in the future. These results also offer more information on how these measures are affected by insulin resistance vs. glucose metabolism. I do believe that this is meaningful work, but the statistical analysis approach needs some improvements. Namely, utilizing paired tests and adjusted modeling with interaction terms to assess differences in trajectories of change over time.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No
Does the work include the necessary controls?
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Yes

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