Author’s response to reviews

Title: CARDIOVASCULAR RISK REDUCTION OVER TIME IN PATIENTS WITH DIABETES OR PRE-DIABETES UNDERGOING BARIATRIC SURGERY: DATA FROM A SINGLE-CENTER RETROSPECTIVE OBSERVATIONAL STUDY

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Author’s response to reviews:

Reviewer reports:

Ilaria Cavallari (Reviewer 1): The authors have adequately addressed all the comments. Thank you for your advice and suggestions.

Mario Luca Morieri (Reviewer 2): I thank the Authors for their response to my previous comments, I found the new version of the manuscript improved.

However, there are still some comments, in particular in the results section that required further revision to allow sufficient clarity, transparency, and interpretation of the analysis done by the Authors.

Previously point Point 2), Authors have modified the sentence as follow:

"Higher glucose levels at baseline were clearly associated with a higher CVD risk (OR = 4.35 [2.73, 6.99], p < 0.001) and the effect. The difference between baseline and month 12 was also statistically significant (OR = 0.31 [0.26, 0.36], p < 0.001). Nevertheless, after the intervention all patients reached similar levels of CVD risk regardless of their previous status. Therefore, patients with higher fasting glucose levels are the ones that benefit the most from the intervention regarding CVD risk (OR = 0.44 [0.27, 0.71], p < 0.001)"
New comments: While the text is now much clearer than before, the numbers in the brackets are still not clinically interpretable, and requires more details described in the methods. Usually, Odds Ratio are used for their easy interpretation. Please specify in the brackets how to interpret this OR or maybe consider to report the estimates (logOR) that might be easier to understand "e.g. for each mg/dl increase in glucose there was an … increase risk of having one higher unit (%) of CVD risk)" or otherwise these numbers are useless and create confusion. Similarly the effect on changes between baseline and 12-month, elaborate in the methods how the analysis was done and clarify in the text how to interpret those numbers. (as suggested also by the STROBES guidelines).

ANSWER:

We understand the reviewer’s concerns regarding interpretation of the results. Unfortunately, the relationship between fasting glucose levels and CVD risk cannot be modeled using a linear regression. CVD risk values are bounded between 0 and 1 and also display a non-linear trend, so it is not feasible to use a linear regression model for this data. The right model for capturing this relationship is a beta regression. Since the link function for the beta regression is the logit, coefficient estimates of this model are interpreted as log(Odds), that are interpreted as OR when exponentiated [1]. The reviewer asks for a sentence similar to “for each mg/dl increase in glucose there was an … increase risk of having one higher unit (%) of CVD risk)”, but this would only be possible with a linear regression. In our case, the increase in CVD risk related to one mg/dl increase in glucose is not constant. It depends on the baseline CVD risk for that specific case and can only be calculated from the OR using the following formula:

$$\Delta \text{CVD} = \frac{(\text{OR} \times \text{CVD}_{\text{baseline}})}{(\text{OR} \times \text{CVD}_{\text{baseline}} - \text{CVD}_{\text{baseline}} + 1)} - \text{CVD}_{\text{baseline}}$$

Since this formula is also difficult to interpret, we have provided marginal effect plots of the fitted models (Figures 1 and 2) showing the relationship between CVD risk and the studied variables (fasting glucose levels and month (0 to 12) in the case of figure 1; diabetes status and month (0 to 12) in the case of figure 2. We believe this marginal effect plots can ease the clinical interpretation of our findings.

Nevertheless, since it might not have been clear in the previous version of our manuscript the key role of the marginal effect plots in easing the interpretation of our models, we have added the following sentence to our methods section in the statistical analysis paragraph:

“In order to ease the interpretation of the beta regression results, we provided marginal effect plots of the different fitted models depicting the estimated relationships between the different studied variables and CVD risk”.


Point 3)
The authors modified the sentence as follow:

"At baseline, patients with type 2 diabetes showed a statistically significant higher CVD risk compared to patients with pre-diabetes (OR 3.23 [2.32, 4.50], p<0.001). Patients with pre-diabetes showed a significant reduction in risk (OR: 0.49 [0.40, 0.60], p<0.001) 12 months after surgery, compared to their baseline risk. Nevertheless, at that time point (month 12), patients with type 2 diabetes showed a larger reduction in CVD risk than those with pre-diabetes (OR 0.40 [0.30, 0.63], p<0.001)."

New comment:

Similarly to what specified above, while the text is clear, these results and numbers can't be understood by the readers.

Eg. In the first sentence, if authors say: "at baseline patients with type 2 diabetes showed a statistically significant higher CVD risk compared to patients with pre-diabetes" then they report an Odds ratio, but readers can't understand if this is to % CV point or to presence of high CV risk (cut-off of 20%).

This is highly confusing. Please either report the mean CV risk % the two groups and the P value for the difference between them. Or if they want to report OR then clarify the text. For example "Diabetes status, as compared to prediabetes, was associated with a higher risk of having a CVD risk above 20% (OR …)".

Similarly, in the sentences on changes from baseline to 12 month, it is much easier to report the mean difference % with C.I. from baseline to 12 months instead of an O.R. that is really hard to understand clinically. How was it estimated?

ANSWER:

We have provided a detailed answer to the issue of interpretation of our results in the previous point. Nevertheless, we will address the specific concern raised in this point 3:

It is not adequate to compare mean differences in CVD risk between the two groups because, as stated in the previous answer, CVD risk does not follow a normal distribution. Also, when performing a hypothesis test, it is not possible to include other covariables as we did when fitting our model (we included in the same model diabetes status and month and their interaction). As stated before, in order to ease the clinical interpretation of the results we provided a marginal effects plot of the fitted model.

Additional point:

Regarding this previous comment and answer regarding OSA:
Please define cut-off used to define OSA. Did all patients underwent polysomnography before and after surgery? please clarify.

Answer:

All the patients underwent polysomnography before surgery. After surgery, resolution of OSA was considered if CPAP (Continuous Positive Airway Pressure) was removed by the physician pneumologist.

New comment: If I understand your answer, you consider only OSA patients if on CPAP treatment. Regardless of index (e.g. Apnea/hypopnea index). Anyway, please specify the definition you used in the methods.

ANSWER:

We agree with the reviewer that to diagnose OSA is necessary the Apnea/hypopnea index. This study is performed by pneumologist. We have not reported this index, because we have not collected this specific data. We assumed that pneumologist has used this index to diagnosed patients after doing polysomnography. Now, we clarify in the text (Methods section, study measures, paragraph 6): “OSA was diagnosed through polysomnography before surgery. Improvement/resolution of OSA was considered after performing a new polysomnography and indicating the discontinuation of CPAP by the physician pneumologist after surgery”.

Regarding this previous comment and answer:

Results: in the following sentence pg 6-7: "Higher glucose levels at baseline were clearly associated with a higher CVD risk (OR= 4.35 [2.73, 6.99], p < 0.001)." It is unclear the unit for the reference, to which unit is the OR referred to? Please specify.

Answer:

Since we are using fasting glucose levels as a continuous variable in the logarithmic scale, the OR refers to an increase of one unit (in the log scale) in these levels. (odds(x+1)/odds(x)).

New comments: As stated above, these Odds Ratio have almost no meaning clinical interpretation (moreover if you performed the analysis in the log scale of glucose levels). Please consider expressing these analyses in different ways. Or alternatively, for clarity and transparency, elaborate this in the text so that readers can understand the meaning of your results i.e. the O.R.

ANSWER:

As stated before, we already have provided an alternative way of expressing our results, that is the different marginal effects plots of the fitted models. We are aware of the difficulty in
interpreting our results in OR, but we want to stress that providing other more interpretable estimates would come at a high cost, they would be not valid.

Additional point:

As specified by reviewer 1.

Among the limitations helpful for discussion and interpretation of this paper, it should be specified that your primary outcomes (CV risk estimated with FRS) is strongly influenced by the presence of diabetes. Thus much of the higher benefit of bariatric surgery found from the studies among subjects with diabetes Vs those without is derived from the remission of diabetes status. While changing in other metabolic trait were similar in the two groups.

ANSWER:

We agree with the reviewer that CV risk estimated with FRS is strongly influenced by the presence of diabetes. We reinforce this comment in Discussion (Paragraph 3):

“CVD risk estimated with FRS is strongly influenced by the presence of diabetes. Thus much of the higher benefit of bariatric surgery found from the studies among subjects with diabetes versus those without is derived from the remission of diabetes status. While changing in other metabolic trait were similar in the two groups”.

Clearly specify in the text of figure legend to what the P values in the Figures are referred to.

ANSWER:

P values in the figures refer to the interaction between the two variables included in each model (glucose levels with month and diabetes status with month). We have added this information to both figures.

Figure 1: Marginal effects plot of the model explaining the relationship between fasting glucose levels and CVD risk at baseline and at 12 months. On the X-axis, the logarithm of the fasting plasma glucose levels is represented for baseline (red) and for month 12 (blue). The Y-axis represents the CVD risk in scale 0-1. P-value refers to the interaction between fasting plasma glucose levels and month.

Figure 2: Marginal effects plot of the model explaining the relationship between diabetes/prediabetes status and CVD risk at baseline and at 12 months. On the X-axis, the two groups of patients are represented for baseline (red) and for month 12 (blue).

The Y-axis represents the CVD risk in scale 0-1. P-value refers to the interaction between diabetes status and month.