Author's response to reviews

Title: Risk of type 2 diabetes according to traditional and emerging anthropometric indices in Spain, a Mediterranean country with high prevalence of obesity. Results from a large-scale prospective cohort study

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Author's response to reviews: see over
COVER LETTER

Dear Editor,

Please find below a point-by-point response to all comments and suggestions made by the referees to our manuscript 1322786607799187 (“Risk of type 2 diabetes...”, by Huerta et al.). Furthermore, we have included the required sections that were lacking in the previous manuscript (‘Competing interests’, and ‘Authors’ contributions’), and we have formatted the document in conformity with the journal guidelines.

We have addressed all concerns raised by the referees in detail. We hope this revised version is found satisfactory.

Best regards,
José M. Huerta, Ph.D.

Answers to referee #1.

1. The authors attempted to use the index of \( \frac{PE(RR-1)}{1+PE(RR-1)} \) in method section to show the population risk of diabetes attributable to excess body weight. However, we can’t find the related results in any tables or figures. Though the authors showed the related statement in result section as “The estimated population attributable risk of diabetes in the overweight was 29.8% (95% CI: 18.7 - 41.0%) for men and 37.1% (95% CI: 27.1 - 47.1%) for women.” The authors still should provide a clear calculation process or explanation about the statement.

Our study provides the finest estimations of diabetes risk for overweight and obese people available in Spain. Because of this, we thought it would be interesting to estimate the population risk of diabetes attributable to excess body weight by using population-based calculations of obesity, and to present this result to the international scientific community as a point for discussion of the importance of excess body weight on the burden of diabetes. Now, since the referee asks for further information on this estimation, we think it would be better to present a table (see supplementary Table S6) with detailed data and estimation procedures. However, we do not feel that we can provide estimates of population attributable risk of diabetes in Spain as if it were a result of the present investigation. We have then decided to present the calculation of the cohort’s risk of diabetes attributable to excess body weight as a result, and to further comment (in the Discussion) on how many cases of diabetes would be avoided in Spain, using the most updated information now available, if excess body weight were eradicated.

We have rephrased the statistical analyses and results sections, expanded the discussion accordingly (page 14), and included a new supplementary table (Table S6). All changes are marked in red colour in the revised manuscript.
2. The authors state: "The diabetic men were more prone to smoke, as opposed to diabetic women in table2" in results. Does the smoking factor play a confounder or interaction role in the study? Smoking was included in the models as a potential confounder since, by definition, it is both associated to the exposure (body weight) and the outcome (diabetes), but it is not in the causal pathway.

3. The prevalence rate of obesity is very high in this study showed in table 2, the results of this study should be compared with other countries in Asian with lower obesity rate. We have included a sentence in the discussion highlighting this very high prevalence of elevated BMI and recommending caution in the extrapolation of these results, because both prevalence and strength of associations may vary in other cultural or ethnic settings.

4. The P value should be calculated in table2. As suggested by the referee, we have now included a footnote indicating that near all P-values were significant (most of them were significant at 0.001 level).

5. According to table3, the authors showed the statement in results as “adjustment of BMI models for indices of central obesity did not affect the estimation of diabetes risk in men, but led to an attenuation of risk estimates in women”. How to compare the different risk estimates between male and female based on different referent group? Actually, models were run separately for men and women, and comparisons are made within each sex, but not between sexes. We only intended to describe what happened in each case when waist or waist-derived indices were included in BMI models: models in women were attenuated, and this can be seen by looking at BMI models 1 (without adjustment for waist indices) and 2 (mutually adjusted) in table 3. However, this was not seen when applying the same adjustment in men.

6. The authors showed both table 4 and table 5, the authors should make more discourses or comparisons for these two tables. We have dedicated a whole paragraph in the results section to describe the most important findings of tables 4 and 5. Besides, results from these tables have been included and discussed in the second and third paragraphs of the Discussion. We think that these results have already received sufficient attention in the text. Nevertheless, we are willing to consider any specific point that the referee wants us to discuss further if properly indicated.

7. Why only BMI and WC data were plotted in Figure1, Why are the WHtR (with largest AUC) and WHR data not included? Why is the waist-to-hip not analyzed in Table5? To compare, the authors should put the same kinds of anthropometric variables in different tables or in figure. Our first interest in presenting these tables was to provide a graphical image of the relationship of overall and central obesity in predicting diabetes risk, and that is why we focused on BMI and waist circumference as the reference indices. However, following the suggestion of the referee, we agree that waist-to-hip and waist-to-height
ratios should consistently appear in all tables and figures, so we have made the appropriate changes to Table 5 and Figure 1 to include the lacking data and graphics.

8. Please define “correctly classified” showed in Table 5?
We have defined the term, as suggested. Please find the changes in the footnote of Table 5. The table is clearer now and we thank the referee for the suggestion.

9. The authors also should discuss the different pattern at same anthropometric variables between male and female for Figure 1 in discussion section.
We have already dedicated a long paragraph in the Discussion to try to explain why anthropometric variables had a greater influence in women than in men, pointing out to the possibility that gluteo-femoral fat depots, characteristic of women, might have a role in this effect. We have now expanded the discussion on this point, also according to the comments of referee 2. Since we have no clear explanation for this, we can only speculate about this different anthropometric pattern between men and women.
Answers to referee #2.

1. The protective effect of peripheral obesity is discussed but never tested. I would like to see an analysis of the importance of waist after adjustment for hip, and not as a simple ratio that probably decreases the impact of waist. Furthermore, an analysis of the protective role of hip circumference after adjustment for waist. This was previously done by Cameron et al, and it would be very interesting to see if this also applies to a Caucasian population. See below.

   In response to the referee’s suggestion, we have now included hip circumference as an exposure variable in table 3, both without and with mutual adjustment by the rest of anthropometric variables considered. Previously, we had discarded this inclusion because of the lack of statistical association, and the fact that the usual index waist-to-hip ratio had already been analysed. However, in the light of the evidence provided, and our own results, we now think it is of no minor importance the inclusion of and discussion on this variable. Therefore, we have expanded the paragraph in the Discussion addressing the different pattern of influence of anthropometric indices in T2DM risk between men and women to discuss in further detail the effect of hip circumference. Surely and in-depth analysis of the independent effect of hip circumference on chronic disease risk in the presence of BMI and waist circumference is much warranted and deserves a separate study within EPIC.

2. I am bit confused by the date set for the diagnosis of DM. It is either exact day or midway day between first report and previous negative report. Wouldn’t be more consistent to use midway day for all time points, irrespective of drugs or self-report. DM has long phase undetected irrespective if the diagnosis was set by drugs or self-report.

   We agree that any date that is defined as a starting point for diabetes is a compromise because the disease is rarely diagnosed at first symptoms, and because the underlying mechanisms that lead to diabetes might start long before any clinical sign is evident. However, from an epidemiological point of view, we need to define an incidence date, and we have tried to define as such the date which was closest to the diagnosis in the medical records. Only when this date was lacking we used an approximation other sources. Further details on case ascertainment and verification can be found in the EPIC-InterAct baseline paper, now available (Langenberg C et al. Diabetologia, 2011; 54:2272). Some changes have been introduced in the Methods section plus a sentence referring to this paper for further information (page 7).

Minor Essential Revisions:

3. SI units should be used consequently for an international audience.

   Done.

4. As the population obviously is not population based, the effect of selection bias should be discussed. Could these data be generalised? Furthermore, the huge dominance of women in the population raises concern about the generalizability.

   We have now addressed these limitations in the Discussion (last paragraph).
5. The supplementary analyses related to Suppl table 1 to 5 is more confusing than clarifying, consider deletion.

We think supplementary information is robust and consistent and may be of interest to many readers. Since the Journal allows including supplementary data without much restrictions, we would prefer to keep these tables as part of the article. However, if the referees and the Editor think that they are better suppressed, we have no major objection in considering deleting this material.
