Author's response to reviews

Title: Relationships between obesity, glycemic control, and cardiovascular risk factors: a pooled analysis of cross-sectional data from Spanish patients with type 2 diabetes in the preinsulin stage

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Author's response to reviews: see over
Re: Resubmission of manuscript for acceptance (Ref.: MS: 7294173181278779)

Title: Relationships between obesity, glycemic control, and cardiovascular risk factors: a pooled analysis of cross-sectional data from Spanish patients with type 2 diabetes in the preinsulin stage

Authors: Luis A Vázquez, Ángel Rodríguez, Javier Salvador, Juan F Ascaso, Helmut Petto and Jesús Reviriego.

Dear Timothy Shipley

Re: Ref.: MS: 7294173181278779

Thank you for considering our manuscript for publication in your journal. The feedback provided by your reviewers was very useful and we have now addressed their comments, as detailed in the accompanying pages. We hope that you will now consider our paper for publication in BMC Cardiovascular Disorders.

Should you have any other questions regarding this resubmission, please feel free to contact me. My details are included below.

Thank you very much for your kind attention, and we look forward to hearing from you.
Yours sincerely

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**Reviewer’s report**

**Title:** Relationships between obesity, glycemic control, and cardiovascular risk factors: a pooled analysis of cross-sectional data from Spanish patients with type 2 diabetes in the preinsulin stage

**Version:** 3  **Date:** 27 May 2014

**Reviewer:** Irene Vinagre

**Reviewer’s report:**

**Major Compulsory Revisions:**

- In the discussion it should be worthy to include some evidence about the relationship between BMI and dyslipidemia and hypertension in type 2 diabetic patients, mentioning a recent Spanish study (Gomis at al. Prevalence of type 2 diabetes mellitus in overweight or obese patients outpatients in Spain. OBEDIA Study. Med Clin (Barc). 2014 Jun 6;142(11):485-92. Epub 2013 May 15). Results of this study have been added to the first paragraph of the Discussion: “This finding is in agreement with that of Gomis et al. (2014), who reported an increased frequency of dyslipidemia and hypertension with increasing BMI among 7371 Spanish patients with T2D (p< .0001)”.

- In the second paragraph of the discussion, I recommend to extend the discussion about the inverse relationship between BMI and age or duration of T2D adding some information of the recent publication of Mata et al. about the catalan population. This publication does not clearly show a relationship between BMI and duration of diabetes, as no statistical analyses were performed on these data. Indeed, the paper itself describes the relationship as “a slight decrease in mean BMI in all groups of patients with longer diabetes duration”. We therefore prefer not to include this information in our discussion of BMI and duration of diabetes. The paper does describe a relationship between obesity and age <55 years (again no statistical data are provided), so we have included this reference in the second paragraph of the Discussion. Moreover, this publication also reported a relationship between glycemic control and diabetes duration that should be included in the discussion These results have been added to the fourth paragraph of the Discussion: “A more recent analysis of the Catalan data similarly revealed deterioration in glycemic control with increasing duration of T2D (Mata-Cases et al. 2014).” (Mata-Cases et al., J Diabetes Metab 2014, 5:2. http://dx.doi.org/10.4172/2155-6156.1000338. Treatment of Hyperglycaemia in Type 2 Diabetic Patients in a Primary Care Population Database in a Mediterranean Area (Catalonia, Spain): “The mean HbA1c value increased slightly with longer diabetes duration, especially in patients treated with insulin alone or in combination with oral agents. There was a slight decrease in mean BMI in all groups of patients with longer diabetes duration, although changes were smaller in patients treated with insulin alone. However, the frequency of
obesity remained high, around 40% to 55%, in all patients. Interestingly, clinical characteristics clearly differed between younger and older patients: patients under 55 years of age were more often smokers and considerably more obese. They also had higher mean HbA1c, but lesser complications.

Minor Essential Revisions:

- Figure 1: The recommended goals are not well seen in the figure. I suggest to write them at the bottom of each chart, next to the legend. The values for recommended goals have been moved from next to the vertical dotted lines to underneath the descriptor for each chart (e.g. HbA1c (%) Target: <7%) as suggested.

Discretionary Revisions:

- Include “type 2 diabetic patients” in line 107 and 112 of Methods to better understand the kind of patients that are included in the study. This information has been added for each of the studies included in our analyses.

- Consider to add that a possible explanation for the higher BMI and worse control of the cardiovascular risk factors in this study compared with the catalan population is that the patients included in this study are younger than in the previous one (lines 244-247). This possible explanation has been included in the fourth paragraph of the manuscript Discussion: “Of note, control of cardiovascular risk factors seemed to be slightly better in the systematic evaluation of patients with T2D recently performed in Catalonia, even though about a quarter of those evaluated were receiving insulin therapy and the Catalan population was slightly older than patients in this analysis [36].”

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable: Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.

Declaration of competing interests:

- I have received lecture fees from Eli Lilly in the last five years.
Reviewer's report

Title: Relationships between obesity, glycemic control, and cardiovascular risk factors: a pooled analysis of cross-sectional data from Spanish patients with type 2 diabetes in the preinsulin stage

Version: 3 Date: 6 July 2014 Reviewer: Christian Delles

Reviewer’s report:

The authors provide an interesting manuscript on the relationship between CV risk factors and BMI and HbA1c strata in insulin-naive patients with T2D. Their data are pooled from five independent studies that were conducted in Spain. Even if the individual studies had different inclusion criteria and objectives the common denominators (patients not on insulin, studies conducted within one country) compensate for some of the weaknesses.

The main limitation of this paper is its cross-sectional nature. However, this limitation has been adequately discussed by the authors. I have only a few comments.

Major Compulsory Revisions

I would like the authors to provide summaries of the clinical and demographic characteristics of each of the five studies in a supplementary table. Currently only the pooled analysis is presented in Table 1 but it will help the reader (without the need to go back to the original literature) to see individual study data. Basically, the data mentioned in table 1 should be given for each individual study. An additional table has been created, containing the same variables as Table 1, showing findings for each of the studies contributing to the analysis. This has been included as a Supplementary table.

I was also wondering about data on antihypertensive and lipid lowering therapy and if such treatment has been taken into account when the data were analysed. Where blood pressure and lipids are analysed as quantitative traits the values should be adjusted for treatment effects. Data were not analysed according to antihypertensive and lipid lowering therapies, and these therapies were not considered in the analyses as the paper is focused on the degree of control of CV risk factors in T2D patients and not on the efficacy/effectiveness of treatments, adherence or any other treatment characteristics. Where available, we have included the proportions of patients receiving antihypertensive or lipid lowering therapy in Supplementary Table 1. We have also added the following text to the Discussion section: “Patients included in our analyses were taking a variety of medications for control of blood pressure and lipid levels, and the blood pressure and lipid levels presented in this manuscript are unadjusted for such medication usage. Although this is consistent with the context of summarizing CV risk factors in real life, it limits our ability to assess "underlying" blood pressure or dyslipidemia in isolation".
Minor Essential Revisions

I find the focus on macrovascular complications a bit artificial. I fully appreciate that most of the traditional risk factors are associated with macrovascular events but all the study can provide is a description of risk factors across BMI and HbA1c strata. Whether or not this really translates into different event rates remains unclear and cannot be answered by this study. I suggest toning down some of the introduction and also introduce the macrovascular event concept again in the discussion and discuss it briefly but critically. The reason I am so keen on a critical discussion is that microvascular complications of diabetes such as diabetic nephropathy are at least as important as macrovascular complications, and they may very well be driven by factors other than traditional risk factors. We have amended the Background and Discussion sections of our manuscript based on these helpful comments. In the Background, we have added the following: “In addition, macrovascular complications have considerable medical relevance because cardiovascular disease is the leading cause of death in people with T2D [8,14]. Microvascular complications, such as persistent albuminuria, are also important contributors to cardiovascular risk and may be driven by non-traditional risk factors”. We have also removed the following text: “This may allow clinicians to better tailor preventive and therapeutic interventions, as well as to evaluate the effectiveness of management strategies.” In the Discussion the following text has been amended: “The limitations include the nature of this post-hoc analysis, performed with heterogeneous observational studies, which were designed with different objectives; the lack of an internal control with a parallel group of individuals without diabetes. As this was not a longitudinal analysis, CV event rates could not be provided; we instead report a description of CV risk factors across BMI and HbA1c strata. Moreover, clinical data with known therapeutic or prognostic implications, such as the presence and extent of retinopathy, persistent albuminuria, or non-traditional cardiovascular risk factors/markers were not captured. Regarding body composition, waist circumference data were not available for about 40% of the sample, and data were incomplete to evaluate the ‘healthy’ or ‘unhealthy’ metabolic condition of the obesity seen in patients [46].

I also suggest adding the very recently published paper by Jais et al. (Cell, Volume 158, Issue 1, p25–40) to the discussion - it provides nice mechanistic data why higher BMI is not always bad. This paper has now been incorporated into the Discussion of the manuscript: “Our analyses did not show that BMI and waist circumference were associated with HbA1c. This finding is not unexpected, as some individuals with BMI in the obesity range are otherwise metabolically healthy [41]. Indeed, obesity does not seem to always be harmful, and there are some phenotypes in which chronic metabolic inflammation, probably a pivotal condition in obesity and diabetes, is not present. Investigations are therefore underway to identify predictors or biomarkers of healthy versus unhealthy obesity, such as heme oxygenase-1 (Jais et al. 2014), to allow clinicians to better
personalize treatment.”

Level of interest: An article of importance in its field. Quality of written English: Acceptable. Statistical review: Yes, and I have assessed the statistics in my report. Declaration of competing interests: No conflict to be reported.