Author's response to reviews

Title: Adiposity markers and risk of coronary heart disease in patients with type 2 diabetes mellitus

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Version: 3 Date: 2 November 2014

Author's response to reviews: see over
Dear Dr. Gabriel,

We would like to thank the reviewers for their comments, which have given us the opportunity to improve our manuscript. Below, we provide point-by-point responses and clarifications in response to the inadequacies identified. All changes made are underlined in the new version of the manuscript.

Please do not hesitate to contact us if you need any additional information.

Sincerely,

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# reviewer 1

Major compulsory revisions:

1. “... First we recommend using the terminology proposed by Sardinha & Teixeira (1) that is a sound and consensual terminological benchmark. Accordingly BMI is used to quantify body mass related to height, not just body mass. Body mass is assessed by weight measurement. Also, not all body indexes used assess BF distribution. Waist circumference (WC), for example, is a predictor of central BF accumulation, therefore it is a predictor of regional BF and not BF distribution. Waist-to-height ratio (WHtR), as WC alone, is a marker of central BF accumulations, but in this case corrected for height. Body adiposity index (BAI) is a predictor of whole body adiposity and therefore it is also incorrect to mention it as a marker of BF distribution. The only studied body indexes that can be unarguably considered BF distribution markers are the Waist-to-hip ratio (WHR) and the Conicity Index (C-index) because they assess the ratio between two quantifying measures (WC and hip or WC and body mass corrected for height, respectively),
therefore these do not give a sense of BF quantity, as the previous indexes, but give a
sense of BF distribution.”
We agree with the reviewer. The background sentences have been modified (page 3, lines 45
to 48).

2a. “Another major comment regards the usage of the model for risk assessment from
the United Kingdom Prospective Diabetes Study (UKPDS). To my knowledge this was a
tool developed and validated in Europe with European subjects, particularly United
Kingdom citizens. The authors should present a rational for the usage of this model in a
South American sample either in the “Methods” if there are scientific rational to support
this option or at least a mention should be made in the “Limitations” paragraph.”
We agree with the reviewer’s comments. However, no specific model for prediction of
cardiovascular risk in Latin American populations exists. We have included our reason for using
the UKPDS in the Methods section (page 6, lines 110 to 111). Also, the absence of a
cardiovascular score validated for Brazilians or Latin Americans with diabetes was reinforced as
a study limitation in the Discussion section (page 10, lines 213 to 214).

2b. “…This raises another question which regards the subjects ethnicity. The authors
mentioned that ethnicity was self-reported and the sample was constituted mostly by
whites. Considering this study was carried out in Brazil one question arises: were they
referring to Latin whites or Caucasian whites. Because many epidemiological studies
usually distinguish between Whites, Latins, Asians and Blacks and find non-neglectable
metabolic-related risk differences.”
We agree with the reviewer, and have modified the Methods section (page 5, line 95) and Table
1 to use the term “white (Latino)”.

3. “The cut off values used in the conversion of some body indexes into dichotomous
categorical variables also seem to lack rational. The cut off values for BMI, WC, WHR and
WHtR are well established in the literature and properly referenced in the paper. However
the cutoff values chosen for the BAI and for de C-Index lack proper explanation and/or
supportive references. The selection of the cut off values, particularly for the C-index
may be influencing the results.”
Regarding the BAI and C-index, the mean values were adopted due to absence of established
cutoff values: for the C-index, > 1.35, and for the BAI, >35 for females or >25 for males. The
Receiver Operating Characteristic (ROC) curve performance of these markers to identify the 10-
year CHD risk in type 2 diabetes has been demonstrated elsewhere [Obes Facts 2012;5(suppl
1):96], and the cutoff values were identified by sensitivity and specificity equilibrium. This
sentence has been included in the statistical analyses section to elucidate the criteria used for
selection of cutoff values (page 7, lines 147 to 152).
4. “Considering the aim of this paper and the previous comment, I wonder why the author’s didn’t use receiver operating characteristics (ROC) analysis. This would have allowed finding the best predictor of increased CHD risk and also the proper cutoff values for the studied sample.”

The performance of body adiposity markers was evaluated by ROC curve analyses elsewhere in the literature [Obes Facts 2012;5(suppl 1):96]. Namely, performance was evaluated using ROC curves through the AUC (mean ± SE and 95%CI). The AUCs of the WHR [0.63 ± 0.03 (0.56-0.69)], C-index [0.59 ± 0.03 (0.53-0.66)], and LAP [0.62 ± 0.03 (0.56-0.69)] were statistically significant (P<0.050) considering a 10-year high risk of fatal CHD new event, although there was no difference across the three markers (P >0.340 for all comparisons). The traditional adiposity markers BMI and WC, like the recent markers WHR and BAI, did not reach statistical significance to estimate 10-year risk of fatal CHD new event (P >0.143). We have cited this reference in the statistical analyses section of the new version of the manuscript (page 8, line 152).

5a. “Only the equipment for Blood pressure is mentioned. The authors need to refer the instruments/equipments (model, brand and manufacturer) used in data collection and analysis. Including those used for anthropometric measurements, for blood collection and analysis.”

We have included the requested information in the Clinical and anthropometric evaluation (page 5, lines 79-80, 97-98) and Laboratory measurements (page 6-7, lines 123-134) subsections in the new version of the manuscript.

5b. “Bibliographic references supporting the techniques and procedures are lacking. For example, the authors mention that WC was measured half distance between last rib and iliac crest, which seems like the WC measurement protocol endorsed by the World Health Organization (WHO), however the authors also mention the umbilicus which is not accounted by the mentioned WHO protocol. A bibliographic reference would have cleared this ambiguity.”

We apologize for this oversight. In our study, WC was measured at the midpoint between the lowest rib and the iliac crest, according to WHO protocol. We have modified the description in the Methods section of the new version of the manuscript (page 5, lines 99 to 101).

5b1. References are also lacking in other instruments/techniques/procedures described in the “Methods”: the Friedewald’s needs a reference; as do all laboratory measurements and anthropometric measurements. Many time there are modified versions of the same instruments and, without proper referencing, one cannot be sure which version of the instrument was used.

The requested references have been included in the Laboratory measurements subsection of the Methods section (pages 6 and 7, lines 123 to 134).
5c. The authors mentioned a nutritional assessment but I could not find which instrument was used and therefore I could not replicate this assessment nor have a critical overview of it. We apologize for this error. We have changed the term “nutritional evaluation” to “anthropometric evaluation” in the Methods section (page 5, line 77).

5d. The Physical activity assessment was made using Kuopio Ischaemic Heart Disease Risk Factor Study 12-month Leisure-Time Physical Activity (LTPA) questionnaire, which has been used in subjects with type 2 diabetes (2). This questionnaire was adapted from the Minnesota Leisure Time Physical Activity Questionnaire (3) and was properly tested in the population of Eastern Finland (4, 5). The author mentioned that they adapted the questionnaire to «local habits». I wonder if this was validated and if the questionnaire is actually measuring what the authors claim it is. Physical activity is an important control variable and therefore this is not a minor issue.

In the original questionnaire, skiing is one of the activities described. However, as it does not usually snow in Brazil, we removed this activity from our questionnaire in the interest of better comprehension by patients. No other changes were made, and this minor adaptation was not validated. We have included a brief explanation in the new version of the manuscript (page 5, line 89).

6- Diabetes is a disease with a long time course and is mostly progressive in the damage it imposes to patients’ overall organs and health. I wonder why the authors didn’t accounted this variable as a control variable in the statistical analysis.

We have included diabetes duration (years) in the adjusted model of multiple logistic regression (Table 3), as suggested by the reviewer (page 21). This inclusion did not change our original results, especially regarding the association between C-index and high CHD risk (OR = 1.69; 95%CI 1.03-2.78; P = 0.039).

7- The discussion should be more deep and sound. There is an important, quite recent, study by Ashwell and colleagues (6) endorsing WHtR as the best body composition marker to assess cardiovascular risk, which is mentioned in the introduction section of this paper. Yet this study is not mentioned nor discussed in the discussion section of this paper. The discussion is much directed to C-index and overlooks the results obtained for the other variables. Authors were too concerned in leading the reader to the conclusion and did not show similar interest in understanding the results.

In the systematic review and meta-analysis performed by Ashwell and colleagues [Obes Rev 2012;13(3):275-86], the WHtR is described as a better screening tool than WC to discriminate diabetes, hypertension, dyslipidemia, the metabolic syndrome, and cardiovascular outcomes in adults. However, in our sample, no association was observed between waist-to-height ratio and
10-year risk of fatal CHD events. We have included this aspect in the discussion section of the new version of the manuscript (page 10, 207-211).

Minor essential revisions:

1- In the 2nd sentence of the “Background” section: it is not clear what you mean by «Although diabetes was once considered equivalent to coronary heart disease...»;

Thank you for your comment. Cardiovascular disease is the leading cause of morbidity and mortality in patients with type 2 diabetes [WHO 2003; Diabetes Care. 2013; 36(Suppl 1):11-66]. In these patients, the risk of death from vascular causes is 2.32 times higher than in persons without diabetes [N Engl J Med 2011;364:829-41], and diabetes was once considered a coronary heart disease (CHD) risk equivalent [Diabetes Care. 2013; 36(Suppl 1):11-661]. This concept was reinforced by a landmark Finnish population-based cohort study published in the late 1990s [N Engl J Med 1998;339:229-34], which study suggested that the risk of coronary events was similar in diabetic patients without previous myocardial infarction and in nondiabetics with previous myocardial infarction. However, this observation was not confirmed in other population samples [Circulation 2004;109:855-60]. Indeed, it is now recognized that CVD risk varies among patients with diabetes, and accurate estimation of risk depends on individual characteristics [Circulation 2007;115:114-26]. This explanation has been added to the Background section in the new version of the manuscript (page 3, lines 25 to 34).

2- In the last sentence of the “Background” section the acronym UKPDS should be within the parenthesis and the fully written form should appear first in the text.

We apologize for this error, and have corrected the sentence in page 4, lines 57 to 58.

3- In the last sentence of the “Results” section is not clear what “its” refer to.

“its” refers to the association between C-index and presence of high CHD risk. The sentence has been changed for clarification in the Results section (page 9, line 185).

Discretionary revisions:

1- The first sentence of the “Results” section should be included in the “Methods” section, in the paragraph regarding the description of the sample;

We agree with the reviewer and have changed the Methods section accordingly (page 4, lines 63 to 64).

2- Table 2 needs revision to enhance its’ readability:

a. The normal level column can be removed and in the legend the authors can mentioned that normal level served as a reference;

b. Tables’ first row need revision: normal levels, instead of levels normal... and so on.

c. Table could have a symbol to facilitate identification a visualization of
significant results.
We have adjusted the information in response to the reviewer’s comments. “Table 2” was changed “Table 3” because we changed Figure 1 to tabular form (Table 2) in the new version of the manuscript (page 21).

3- Data presented in figure 1 is better presented on a table.
We converted the data shown in Figure 1 into tabular form and now present it as Table 2, as suggested by the reviewer (page 20).