Author's response to reviews

Title: Association of HbA1c and cardiovascular and renal disease in an adult Mediterranean population

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Author's response to reviews: see over
Dear Editor:

Thank you for the review and comments about our manuscript #7027031399171241. Please note that the title of this manuscript has been slightly changed, in accordance with a suggestion by the reviewers. The new title is “Association of HbA1c and cardiovascular and renal disease in an adult Mediterranean population”.

Please find below our answers to the major and minor criticisms from the Reviewers, as requested in your mail. All the major and minor criticisms have been taken into account and modifications have been included in the manuscript.

Please find enclosed the new version of the manuscript, which we hope is now acceptable for publication.

Yours sincerely,

M. Rosa Bernal-López
BRIEF LIST OF CHANGES MADE IN THE MANUSCRIPT

1. Full names of all ethics committees have been included in Methods section.

1. A “Competing interests” section has been included between the conclusions and authors’ contributions

2. We have moved the Funding statement to the Acknowledgements section

3. A more expanded comment highlighting the limitations of a cross-sectional design study has been added in the limitations of this study. In particular, a brief comment indicating that causality between HbA1c levels and our clinical end-points (CKD or CVD) cannot be inferred from a cross-sectional study has been added.

4. We have deleted statements about an increased risk or relative risk throughout the manuscript. In addition, we have used the term “association” or “relationship” to define the link between HbA1c levels and clinical end-points.

5. A brief comment indicating the low prevalence rates of CVD and CVD has been included in the limitations paragraph.

6. A more specific statement has been added at the end of the Discussion section to make the final conclusions more robust.

7. A brief comment stating that various clinical conditions of our population, including CKD or CVD, were obtained by chart review over the previous three months before their inclusion in this study has been included in the Methods section.

8. A more extended comment about the findings of our study may not be generalizable to other Caucasian populations with differing diets and lifestyles has been added in the Discussion.

9. We have corrected the word “undertaken” to “undertook” in the abstract (Method section).

10. The number and proportion of males has been included in table 1.

11. Estimation of glomerular filtration rate by CKD-EPI formula has been included in the manuscript. A reference has also been added.

12. Serum creatinine is expressed in µmol/l. In addition, the urinary albumin/creatinine ratio is given in mg/mmol in accordance with the editorial guidelines (table 1).
13. The HbA1c measurements are reported in IFCC (International Federation of Clinical Chemistry) units (mmol/mol) followed by NGSP units. A brief comment explaining the conversion from IFCC to NGSP units has been included in the footnotes of table 1.

14. Displacements of data in table 2 have been corrected.

15. The association between HbA1c and clinical end-points (CKD or CVD) by multivariable logistic regression analysis in the two subsets of diabetic and non-diabetic patients has been added in the result section. A brief comment has also been included in the Discussion.

16. We now mention in the abstract that serum creatinine was measured in our study.

17. The comment stating the interaction of unique environmental and demographic factors in the province of Malaga (Spain) has been deleted in the Introduction.

18. A reference indicating the definition of diabetes by HbA1c 6.5% has been included in the manuscript.

19. A brief statement indicating whether new markers of glycemia, such as glycated albumin, may reflect a stronger association with clinical end-points (CKD or CVD) has been added in the Discussion.

20. The expression “37 vmmol/mol” has been corrected to “37 mmol/mol”.

21. Finally, we have made several language corrections.
RESPONSE TO EDITORIAL REQUEST

1. We have included the full names of all the ethics committees in the methods section.

2. We have included in the manuscript a “Competing interests” section, between the conclusions and authors’ contributions.

3. We have moved the Funding statement to the Acknowledgements section.

4. Finally, we have made several language corrections.

COMMENTS TO REVIEWER NAVIN JAIPAUL

We thank the reviewer for the comments, the responses to which are listed below.

Major Compulsory Revisions

1. As indicated, this is a cross-sectional design study which does not allow us to elucidate causality, nor the exposure risk. In other words, whether HbA1c concentrations and cardiovascular and renal disease are causally related cannot be concluded from a cross-sectional study. A more expanded comment has been added to the limitations paragraph of the study.

2. In addition, we have deleted statements concluding increased risk or relative risk in order to avoid misleading estimates about our findings, as suggested. Instead, we have used the term “association” or “relationship” to define the link between HbA1c levels and clinical end-points throughout the manuscript, including the title.

3. A brief comment indicating the low prevalence rates of CVD and CVD has been included in the limitations of this study, as suggested.

4. As suggested, a more specific statement has been added at the end of the Discussion section to make the final conclusions more robust.

5. A 130/80 mmHg blood pressure target might be more appropriate for defining hypertension in CKD patients, as commented by the reviewer. However, we
analyzed a non-selected sample of individuals who had no a priori CKD. In accordance with other community-based cohort studies, assessing the relationship between several risk factors and CKD, hypertension was defined as a systolic blood pressure $\geq$140 mmHg and/or a diastolic blood pressure $\geq$90 mmHg, or treatment with antihypertensive drugs as in our study (Elsayed EF, Am J Kidney Dis 52:29-38, 2008; Gomez-Huelgas R, Int J Clin Pract. 2011;65:35-40). In any case, when hypertension, defined by the two targets, was entered in the adjusted analysis, the results did not change (data not shown). A brief comment indicating that we studied an unselected population has now been added in the methods section.

6. We obtained clinical information of prior diagnosis for various clinical conditions of our population, including CKD or CVD, by chart review over the previous three months before including the subject. Thus, we identified acceptable clinical end-points up to the time of starting our study. A brief comment about this has been included in the Methods section.

7. In agreement with the reviewer, the findings of our study may not be generalizable to other Caucasian populations with differing diets and lifestyles. Accordingly, a more extended comment has been included in the study limitations section.

**Minor essential revisions**

1. In abstract methods section, line 2, we have corrected the word “undertaken” instead of “undertook”.

2. In table 1, the number and proportion of male subjects has been included
COMMENTS TO REVIEWER MICHAL MELAMED

The authors thank the reviewer for the comments, the responses to which are set out below.

Major Compulsory Revisions

1. As indicated by the reviewer, for the estimation of kidney function we used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. In agreement with the reviewer the CKD-EPI formula may better estimate the glomerular filtration rate in individuals with normal function. This has been modified in the current version of the manuscript in the Methods section. In addition, the reference indicating the CKD-EPI equation has been included in the text.

2. In table 1, serum creatinine is now expressed in $\mu$mol/l. In addition, the urinary albumin/creatinine ratio is given in mg/mmol in accordance with the editorial guidelines.

3. In table 1, the HbA1c measurements are reported in IFCC (International Federation of Clinical Chemistry) units (mmol/mol-no decimal point) followed by NGSP (National Glycohemoglobin Standardization Program) units (%-one decimal), as recommended by both IFCC network and NGSP network (Hoelzel W, et al. Clin. Chem. 2004; 50: 166-174). A brief comment explaining the conversion from IFCC to NGSP units has been included in the footnotes of table 1.

4. Displacements of data in table 2 have been corrected.

5. As indicated by the reviewer, we also assessed the association between HbA1c and clinical end-points (CKD or CVD) by multivariable logistic regression analysis in the two subsets of diabetic and non-diabetic individuals. Similar significant associations were found between HbA1c levels and the clinical endpoints (CKD or CVD) in the diabetic (odds ratio 1.03, 95% CI 1.03-1.6, $P=0.025$) and non-diabetic populations (odds ratio 1.1, 95% CI 1.1-3.4, $P=0.010$). This has been added in the results section. In addition, a brief comment has been included in the Discussion section and abstract.
**Minor essential revisions**

1. We have mentioned in the abstract that serum creatinine was measured in our study, as indicated by the reviewer.

2. The comment about that the interaction of unique environmental and demographic factors in the province of Malaga (Spain) has been deleted as they do not affect the results, and in any case no further mention is made of these in the text.

3. The definition of diabetes, including HbA1c>6.5%, has been made according to the American Diabetes Association (Diagnosis and classification of Diabetes Mellitus. *Diabetes Care* 34 Suppl 1:S62-69, 2010). A reference indicating this definition has been included in the text.

4. As indicated by the reviewer, causality between HbA1c levels and our clinical end-points (CKD or CVD) cannot be inferred from a cross-sectional study. Accordingly, we have used the term “associated” to establish the relationship between HbA1c levels and the clinical end-points of our study throughout the manuscript, including the title and the abstract conclusions.

5. As suggested, a brief statement indicating whether new markers of glycemia, such as glycated albumin, may reflect a stronger association with clinical end-points (CKD or CVD) has been added in the Discussion.

6. On page 6, the expression “37 vmmol/mol” has been corrected by “37 mmol/mol”.