Author's response to reviews

Title: The prevalence of diabetic complications and multimorbidity in the population with Type 2 Diabetes Mellitus in the Basque Country

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Version: 2 Date: 17 September 2014

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

Thank you for giving us the opportunity to revise the paper entitled “The prevalence of diabetic complications and multimorbidity in the population with Type 2 Diabetes Mellitus in the Basque Country” (MS: 7891789881360847). The review article is submitted through the electronic system of the Journal.

The authors have answered point by point all questions suggested by reviewer. You can find information on the second page of this letter.

Correspondence regarding this submission should be directed to me at the following address:

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Thank you very much for all your comments about our submission.

Yours sincerely,

Edurne Alonso Morán.
Editor's comments:

1] The Introduction should be shortened.

We have shortened the introduction

2] In the Conclusion of the Abstract: comparison with other Spanish populations should be avoided since this was not the aim of this study.

We have removed from abstract conclusions the comparisons with other studies. We have just mentioned that “In the type 2 diabetes mellitus population living in the Basque Country, incidence rates of diabetes complications are not as high as in other places. However, they present a high prevalence of diabetes related and unrelated diseases. Multimorbidity is very common in this group, and is a factor to be taken into account to ensure correct clinical management.”

3] In the Discussion authors also should also comment on the changing incidence of DM complications over the years.

We have added to discussion section the following paragraph in relation to incidence changing: “In this study, we could see a reduction in the rate of incidence of diabetes-related complications from 2007 to 2011. Adequate control of type 2 diabetes risk factors is high in the Basque population [29]. In addition, other studies have reported decreasing incidence of several complications such as amputations [26, 30, 31] and preventable hospitalisations [32]. Vamos et al. [26] found that the incidence for amputations decreased by 9.1% in the four-year study period and a series of studies.”
Reviewer's report

**Title:** The prevalence of diabetic complications and multimorbidity in the population with Type 2 Diabetes Mellitus in the Basque Country

**Version:** 1  **Date:** 7 August 2014

**Reviewer:** John Doupis

Reviewer's report:

The authors of this manuscript investigated the prevalence of diabetic complications in the population with Type 2 Diabetes Mellitus in the Basque Country. The study was nicely designed and the data were nicely analyzed and presented. Although the results are not a “breakthrough” in diabetes research it is always good to get new epidemiological data about type 2 diabetes and its complication from different countries worldwide.

It would be nice if authors provided data regarding the effect of classic risk factors like glucose control, duration of diabetes, hyperlipidemia, age etc. ... in the development of the diabetic complications.

The classic risk factors of type 2 diabetes are the scope of other article that we have under review.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests
Reviewer’s report

Title: The prevalence of diabetic complications and multimorbidity in the population with Type 2 Diabetes Mellitus in the Basque Country

Version: 1 Date: 18 August 2014

Reviewer: Conor Teljeur

Reviewer’s report:

This is a good quality study on a large population that gives useful information of the prevalence of multimorbidity in a population with Type 2 Diabetes Mellitus.

Major compulsory revisions:

1. Overall, the main issue with the article is the quality of the English. There are numerous instances of unusual phrasing which may render the meaning of the text ambiguous. Rather than list all of them, I will refer to ones that are particularly problematic. However, they should all still be dealt with. I would advise the authors to have the manuscript checked by someone with English as a first language to improve the text.

   We have sent the manuscript to an English reviewer.

2. The article would benefit from an additional paragraph in the Discussion section highlighting the potential policy implications of the findings. What preventive care or service delivery changes could be implemented with the results of this study? What needs to be done next, now that we have good information on multimorbidity?

   We have added to discussion section: “This study provides relevant epidemiological information about the prevalence and incidence of diabetes-related complications, in addition to, multimorbidity in this patient group. Moreover, it has been utilised to confirm differences between sex and age that could be employed to define interventions focused on certain patient profiles. Moreover, it could even be used as a support for a future diabetes registry to improve the disease monitoring and research in our community.”

While I have marked these as major compulsory revisions, I do not believe they are particularly onerous. The quality of English must be of a certain standard. Inclusion of text on policy implications should not be difficult to prepare and it will increase the value of the study and make it more citable.
Minor Essential Revisions:

Abstract

3. First sentence - "divers'"? Perhaps "...associated with a diverse range of pathologies."

   We have changed divers’ by “associated with a diverse range of pathologies”

4. Second sentence - "The aim of the study was..." - past tense should be used.

   We have changed “this study aims to determine...” by "The aim of the study was to
determine..."

5. Second paragraph - "...compared with those of an adjusted age and sex [matched?] population."

   Since the comparisons between general population without T2DM and population with T2DM can be confusing and only appear in the last table of results, we have deleted this from the article, making an only description from patients with T2DM about the related and unrelated pathologies.

6. Third paragraph - "unrelated" rather than "non-related"

   We have changed the expression “non-related” by the expression “unrelated” in all the
document

Background

We have made several changes in introduction section because other reviewers have asked too. The order of some paragraph has changed.

7. The first paragraph needs to be rewritten for clarity. The language is clumsy.

   We have rewritten the first paragraph: “The prevalence of type 2 diabetes is increasing worldwide [1], probably due to a longer life expectancy of the general population, a sedentary lifestyle and, above all, to increasing obesity. Prevalence in Spain has been estimated at 13.8% (43% unknown diabetes) [2].”

8. Second paragraph - spell out "vs." instead of using the abbreviation.

   This expression has been removed.

9. Third paragraph - say "subjects without diabetes" rather than "nondiabetic subjects."
We agree, we have changed the expression by “...than those without diabetes”

10. Third paragraph - the second sentence repeats what is already stated in the second paragraph - is this repetition necessary?

We have deleted the paragraph 3 but we have added to the paragraph 2 the first line of the deleted paragraph 3: “...This excess mortality is higher in women than in men [3, 5, 6], and life expectancy is shortened in 7-10 years [7].”

11. Fifth paragraph - perhaps clarify with "... and many have limited themselves to examining a short pre-defined list of the most common chronic diseases."

Reference 17 did not restrict itself to a short list.

We agree and we have changed the phrase by “Previous studies have examined coexisting chronic pathologies in patients with type 2 diabetes mellitus [16, 17].” and we have added another citation of Luijks H. et al. (Prevalence and incidence density rates of chronic comorbidity in type 2 diabetes patients: an exploratory cohort study).

Methods

12. Second paragraph - what are "electronic medical record models"? Is 'model' necessary?

We have rewritten second and third paragraph and it does not appear this term. Anyway, it is not correct; the right term is Electronic Health Record (EHR).

13. Second/third paragraph - are records available for every primary care visit and hospital discharge? Is there any information on how many diagnoses codes are recorded for a visit? Are ICD9 codes used for both primary and secondary care visits? Referring to another publication isn't enough when this describes the data used in your study.

We have rewritten both paragraphs for better understanding.

14. Fourth paragraph - Why only 35+ - was type II diabetes really that rare in the 30-34 age group? Perhaps give some indication of evidence to support the chosen cut-off point. Also, might be clearer to state that patients aged less than 35 years were excluded rather than referring to 34 as the threshold, as the text is slightly confusing.

We have changed by “Although type 2 diabetes can occur at any age [21], it is more common after age 40; patients aged under 35 were excluded.”
15. Fifth paragraph - should the last year end on 31-08-2011 rather than 21-08-2011?

It was a mistake, the last year end on 31-08-2011. We have changed it.

16. Fifth paragraph - what is the "established cut-off point"? Do you mean the last date in the study period (i.e., 2011)? It should be clearly stated what is meant.

We have clarified this issue: “During each time period, a patient was considered as presenting type 2 diabetes mellitus if the illness onset date was prior to the established cut-off point (i.e. prior to 01-09-2007, or prior to 01-09-2008 and so on), and in addition…”

17. Fifth paragraph - the inclusion criterion of living in the Basque Country is already stated in the previous paragraph.

We have deleted from this paragraph the repeated information.

18. Sixth paragraph - it states that the hospital admission due to specified diagnoses were "determined independently". What does that mean? Do you mean separately for each observation period or does it refer to how the records were identified?

Yes, it means “separately for each observation period”. We have reformulated the sentence: “Hospital admission because of acute myocardial infarction, major amputation or avoidable hospitalisation (Ambulatory Care Sensitive Conditions [ACSC]) [23] was determined separately for each observation period”

19. Sixth paragraph - can you reference the "related comorbidities" or clearly indicate how you decided on that list?

We have referenced the related comorbidities of type 2 diabetes : “Related chronic comorbidities, that, according to the bibliography [8], included 7 pathologies: ischaemic heart disease, renal failure, stroke, heart failure, peripheral neuropathy, foot ulcers and diabetic retinopathy.”

20. Sixth paragraph - no harm in explicitly listing the sources in the last sentence rather than forcing the reader to figure out from the previous pages.

We have deleted the last sentence of this paragraph.

21. Seventh paragraph - again, it is not enough to state that something was done previously and give a reference. You should give the reader at least some information about the 'database' rather than requiring them to read another paper.
We have explained better the criteria for chronic conditions: “To study the chronic diseases, a list of 52 health problems was developed and specific criteria were defined to consider that particular disease as active during the period from 01/09/2010 to 31/08/2011 by adapting a methodology previously reported by other authors [24]. In most cases, criteria were based on considering that a person has a chronic disease because they have been assigned the corresponding diagnosis (for example, hypertension); for some illnesses other criteria were applied: diagnosis or prescription of specific medications (e.g., for hypothyroidism and Parkinson’s); repeated diagnosis over several years (low back pain); any history of the diagnosis together with prescription of specific drugs in the previous year (asthma and epilepsy); diagnosis the previous year or repeated prescriptions over several months (depression and anxiety); or repeated prescriptions to treat the given health problem (treated dyspepsia). Further information of this methodology can be found in previous publications [25].”

22. Seventh paragraph - you mention 52 health problems which reduced to 43 after excluding T2DM and the associated comorbidities, of which you list seven in the previous paragraph. Forty three plus one plus seven = 51. What is missing?

It was missing ADHD, we have changed by 44 conditions in the text and we have added ADHD to table 5.

23. Eighth paragraph - perhaps it would help to clearly state that you set the alpha level at 0.05 in the analyses.

We have added that “Values with p value under 0.05 were considered to be significant.”

24. Eighth paragraph - there is no mention of whether or not you considered adjusting for multiple hypothesis testing. Given that you do not mention any prior expectations about gender and age differences it may have been justified.

As we sais before: Since the comparisons between general population without T2DM and population with T2DM can be confusing and only appear in the last table of results, we have deleted this from the article, making an only description from patients with T2DM about the related and unrelated pathologies.

Results

25. First paragraph - one decimal place is sufficient.
We have changed by one decimal

26. Second paragraph - the text uses the phrase "renal failure" while Table 2 uses "kidney failure" - it would be better to have consistent terminology.

We have changed by renal failure in all the paper.

27. Second paragraph - rather than listing those for which the difference was not statistically significant (which is four out of eleven), maybe list those for which the gender difference was highly significant. One reason is that the p-value for gender difference in major amputations is 0.0519 which, whilst not achieving statistical significance in the strict application of 0.05, still shows evidence of a difference.

We have changed by: “It was observed that the prevalence of renal failure, heart failure, peripheral neuropathy, and foot ulcers was higher in women than in men, while the prevalence of ischaemic heart disease and stroke was higher in men than women.”

28. Third paragraph - again, terminology needs to be consistent - ictus/stroke.

We have changed by stroke in all the paper.

29. Third paragraph - can you include in brackets the p-value for 32% lower probability of suffering avoidable hospitalisation.

We have added the p value: “In addition, women also presented a 32% lower probability of suffering avoidable hospitalisation than men (P<0.001), a 50% lower probability of myocardial infarction (P<0.001) and a 45% lower probability for major amputations (P=0.004) than men”

30. Third paragraph - the results here contradict some of those presented in the previous paragraph/Table 2. It begs the question of what present the Table 2 data when age is clearly important? Also, why not extend Table 3 to include the incident outcomes?

We have only presented rates of prevalences and incidences in table 2 and in table 3 the logistic regression analysis. Moreover, we have included incident outcomes as you have suggested.

31. Fourth paragraph - the word 'significant' has quite specific connotations when describing a statistical analysis. Do you mean the number of heart attacks and amputations was not substantial? If you carried out a test that produced a significance value then you should describe it.
We do not want to say that the number of heart attacks or amputations is not substantial. Anyway, we have added to table 3 the logistic regression on heart attacks and amputations.

32. Sixth paragraph - data on the general population are introduced here for the first time. Perhaps it is alluded to in the Methods with reference to previous publications, but that is not sufficient. The Methods section should clearly state that this will be used in the analysis. Also, why is the comparison restricted to the chronic conditions rather than also including the incident events?

By the fact that the comparisons between general population without T2DM and population with T2DM can be confusing and only appear in the last table of results, we have deleted this from the article, making an only description about the related and unrelated pathologies of patients with T2DM. Then, we have deleted the eighth paragraph.

33. Eighth paragraph - the choice of conditions to highlight lower prevalence in the T2DM population is curious. Migraine, for example, has a low prevalence in either population. No test for significant difference is presented. Incidentally, the higher prevalence of substance abuse in T2DM patients is curious.

The same that we have explained in point 32. However, we have added differences between sexes who have diabetes type 2 in each chronic disease.

Discussion

34. Second paragraph - the greatest value is in how the T2DM population compares to the general population and to other similar studies, so this should come up front. Paragraphs 2 and 3 should probably be swapped around.

We have added some bibliography for comparing incidence outcomes. The second paragraph is: “Compared with other studies [26–28], we have obtained lower rates of incidence for avoidable hospitalisations, acute myocardial infarction and major amputations. Moreover, as Vamos et al. [26], we have found that sex was statistically significant for major amputation and women presented a 45% lower probability than men of being affected; the same applied to myocardial infarction (50% lower) and for avoidable hospitalisations (32% lower).”

35. Fourth paragraph - should be amalgamated with the fifth paragraph.

We have joined both paragraphs.
36. Fifth paragraph - the first sentence should state "In our analysis of gender differences in multimorbidity, men presented..."

We have changed the sentence by “In our analysis of sex-related differences for multimorbidity, men presented a greater...”

37. Fifth paragraph - are there plausible reasons for the observed gender differences or is this something that requires further study? Think of how these differences might feed into policy for health promotion or service delivery.

We have added that “This study provides relevant epidemiological information about the prevalence and incidence of diabetes-related complications, in addition to, multimorbidity in this patient group. Moreover, it has been utilised to confirm differences between sex and age that could be employed to define interventions focused on certain patient profiles. Moreover, it could even be used as a support for a future diabetes registry to improve the disease monitoring and research in our community.”

38. Sixth paragraph - "population with diabetes" rather than "diabetic population".

We agree, so we have put “… almost all the population with diabetes type 2 in the geographical...”

39. Sixth paragraph - reference 17 was not limited to complications and found 189 conditions. Perhaps rephrase the last sentence.

We have deleted this line from the strengths since there are other studies that describe a full list of chronic conditions not associated with diabetics’ complications (i.e. Teljeur C et al. and Luijks H et al.)

Conclusions

40. First paragraph - include acronym (CPG) after Clinical Practice Guidelines as it appears later in the paragraph.

We have not included the acronym (CPG) because, now, it does not appear anymore.

41. First paragraph - perhaps clarify that "90.36% of T2DM patients aged 35 years and over". It’s a pity that the equivalent figure for the non-T2DM population isn’t available.

We think that in conclusions should not appear this because it appears in abstract, results and discussion.
42. Table 1 The title could change to "Incidence of complications of diabetes over the study period". The label "Incidence (%)" needs to go above columns "Year 1" to "Year 4". The label above the first column should be "Complication" or similar. The final column should read "Percentage increase from year 1 to 4".

We have changed the title by “Incidence of complications of type 2 diabetes over the study period”. We have change the label above column one by “Type 2 diabetes complications” and the final column should by "Percentage increase from year 1 to 4”.

43. Table 2 The label above the first column should be "Complication" or similar. The "Prevalence (%)" and "Incidence (%)" labels need to go above columns "Total" to "Females". For Retinopathy, the p-value is 0.836 but the values for males and females are virtually identical, so I would expect a p-value close to 1. Do the subsequent decimal places make such a difference?

We have change the label above column one by “Type 2 diabetes complications”. We have put "Prevalence (%)" and "Incidence (%)" above columns. In relation to the p-value, the prevalence looks like the same but if we extend the decimals it is not the same.

44. Table 3 It probably makes sense to put the two parts side by side and present the table in landscape.

As you have suggested, we have presented table 3 in only one side putting the file horizontally.

45. Table 4 Were these figures not also available for the population without T2DM?

As we said: Since the comparisons between general population without T2DM and population with T2DM can be confusing and only appear in the last table of results, we have deleted this from the article, making an only description from patients with T2DM about the related and unrelated pathologies.

Then, we are not going to include this issue.

46. Table 5 Was it not possible to do statistical tests for difference between T2DM and No T2DM?

Since we have deleted this part, we have made comparisons between genders using Pearson’s test (we have added this to methods section).
**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

I declare that I have no competing interests