ESPS PEER-REVIEW REPORT

The Impact of Diabetes Mellitus on Risk of Cardiovascular Disease and All-cause Mortality: Health Outcomes and Pharmacoepidemiologic Profiles in the U.S. Adults (please note, the title has been updated as below).

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[Y] Grade C: Good		[ ] Duplicate publication	
[ ] Grade D: Fair	[ ] Grade C: A great deal of language polishing	[ ] Plagiarism	[ ] Rejection
[ ] Grade E: Poor		[ ] No	[Y] Minor revision
	[ ] Grade D: Rejected	BPG Search:	[ ] Major revision
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[ ] No	

COMMENTS TO AUTHORS

This is an interesting manuscript about the epidemic of diabetes and its impact on the risk of call-cause and CVD mortality, and the patterns of antidiabetic medications and its impact on health outcomes in the U.S. adults. However, there are several issues that need attention.

1. The title "The Impact of Diabetes on Cardiovascular Disease" does not accurately reflect the major topic and content of the study. In fact, this manuscript focuses on the impacts of diabetes on the risk of call-cause and CVD mortality.

Authors' response: Thank you. We have revised the title as "The Impact of Diabetes Mellitus on Risk of Cardiovascular Disease and All-cause Mortality: Evidence on Health Outcomes and Antidiabetic Treatment in U.S. Adults".

2. The definition of diabetes and its type（type 2 or type 1?）

Authors' response: The National Health Interview Surveys (NHIS) do not have information on whether a patient with DM is type 1 or type 2. We are unable to distinguish these two types of DM from the data we used. However, as the participants in the NHIS were aged 18 and older, and by nature more than 85% of the total number of DM are type 2 DM, we would assume that findings from the result should be a better presentation for patients with type 2 DM. We discussed this limitation in our resubmission. (Pages 13-14).

3. Fig 2---the author should provide the definition of CVD（includes HTN?）In this manuscript---page 4-5：Mortality data are defined using ICD-10: CVD (ICD10: I00-I78)."--In fact, HTN (ICD10: I10)

Authors' response: In the analysis**,** CVD includes heart disease (ICD10: I20-I51), and cerebrovascular disease (ICD10: I60-I69), it did not include hypertension (HTN). We have corrected this in the resubmission (Page 5).

4. Statistical analysis--- Changes in the prevalence of DM from 2000 to 2009 by sex and ages were tested using simple learn (linear?) regression models.

Authors' response: Yes, because the data has shown an approximately linear correlation trend.

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COMMENTS TO AUTHORS

This is a well written and conducted epidemiological study showing that diabetes is a major risk factor for death and CV death independent of other concomitant risk factors, that the use of anti diabetic treatment reduces the burden of risk. There are only a few issues that it would be useful to address:

1. Would it be possible to weigh the risk in patients with known CAD and diabetes yes/no. This would confirm that diabetes could be likened to overt CAD.

Authors' response: Yes, we re-analyzed the data by excluding patients with heart disease and stroke at baseline (the results are shown in Table 3, Model 5). Overall, all HRs are attenuated, except for a slight but non-significant increase in HR for death from cerebrovascular disease (Table 3, Model 3, and page 8 in the resubmission).

2. The data on medical treatment are very interesting: do Authors have data on the additive effect of CV active medications? How Authors put these data into perspective considering that a tight glycemic control with a low Hbc1a is related to a higher incidence of death?

Authors' response: Thank you for the comment. Unfortunately, the NHIS dataset did not have serum biomarker measures, including HbA1c. We are unable to quantitatively test the impact of anti-diabetic drug uses on HbA1c control, and their independent and additive impact on CV mortality. We have added this limitation in the resubmission (Page 14).

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COMMENTS TO AUTHORS

GENERAL COMMENTS In this review paper, authors examined the burden of DM and its impact on CVD and all-cause mortality in the U.S. adults between 2000 and 2009 years. They showed that the prevalence of DM significantly increased in all age groups for males and females in the last decade and DM patients had higher risk of death from all-cause and CVD compared to those without DM. The study was reasonably well conducted and may be helpful for developing strategies and designing medical therapy against DM.

1. Minor Since authors ascribed the increased trend of DM prevalence to an increased rate of obesity, it would be interesting to present a correlation figure for this relationship.

Authors' response: Thank you. We have updated Fig 4, it depicts the positive correlation between increased prevalence of obesity and diabetes by age and gender in the resubmission.

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COMMENTS TO AUTHORS

This is a timely, interesting and informative report. Some changes may improve the presentation:

1. Please, delete the first sentence. It is hard to explain diabetes as a primary cause of death (ketoacidosis? hypoglycemia? infection? aging?).

Authors' response: Thanks. We understand this concern. A death is caused by multiple risk factors, such as a patient with diabetes might be died due to diabetic ketoacidosis, infection, aging and multiple comorbidity, etc. However, when giving a report of the major cause of death, the primary disease that led a patient to be discharged is commonly listed as the primary (or first-list) cause of death at clinical settings. To be better understood, we have revised this sentence by addressing the "clinically listed DM as the main cause of death". Please see page 3 in the resubmission.

2. Introduction is biased towards their expectations and, in fact, figures on cardiovascular disease

death are not prominent.

Authors' response: The leading cause of death is slightly different in individual countries, but in most counties including the United States, the top five causes of death are heart disease, cancer, chronic lower respiratory disease, accidents (unintentional injuries), and stroke. For example, in 2013, a total of 614,348 Americans died from heart disease, and 591,699 from cancer, 147,101 from chronic lower respiratory disease, 136,053 from accidents, and 133,103 from stroke. We have added a new reference to support our statement (Ref 10) in the resubmission.

3. Consequently, in discussion on metformin effect, both the references and explanations are too simplistic.

Authors' response: We have added some more discussion on the protective effect of metformin on health outcomes in the resubmission (page 12).

4. I suggest a shift towards all-cause mortality and this includes cancer. You may wish to report some other ideas; see Oncobiguanides: Paracelsus' law and nonconventional routes for administering diabetobiguanides for cancer treatment. Menendez JA, Quirantes-Piné R, Rodríguez-Gallego E, Cufí S, Corominas-Faja B, Cuyàs E, Bosch-Barrera J, Martin-Castillo B, Segura-Carretero A, Joven J. Oncotarget. 2014 May 15;5(9):2344-8.

Authors' response: As the present study focuses on the impact of diabetes on cardiovascular disease, including all-cause mortality, we did not separate the analysis for cancer from all-causes although it can be an interesting subtopic. As metformin, like other factors (such as physical activity) may have anticancer effect as well, we added a brief discussion on metformin used in anticancer treatment, (i.e., the oncobiguanides effect) in the resubmission (page 13).

5. Limitations also look simplistic and unnecesarily justified. I suggest something like "as discussed we may no always control adequately for confounding factors. We may not even know about them and chance cannot be discarded although it is highly unlikely".

Authors' response: We revised our discussion on in the limitation section, and added the suggested sentences in the resubmission (Pages 13 and 14).

6. I would change the title considerably.

Authors' response: Thank you for the suggestion. Taking the resubmission opportunity, we revised the title as "**The Impact of Diabetes Mellitus on Risk of Heart Disease, Stroke and All-cause Mortality: Evidence on Health Outcomes and Antidiabetic Treatment in U.S. Adults**", because the present study is characterized by (1)

using large-scale data from nationally representative health surveys, (2) focusing the analysis on the burden of DM and its impact on the risk of mortality from heart disease, stroke and all-cause, and (3) may serve as one of the first reports to address glucose-lowering medication and health outcomes using population based surveys.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Diabetes
ESPS manuscript NO: 26062
Title: The Impact of Diabetes Mellitus on Risk of Cardiovascular Disease and All-cause Mortality: Evidence on Health Outcomes and Antidiabetic Treatment in U.S. Adults
Reviewer's code: 02141286
Reviewer's country: Canada
Science editor: Fang-Fang Ji
Date sent for review: 2016-03-28 15:06
Date reviewed: 2016-04-25 07:53

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COMMENTS TO AUTHORS

1. The study does not take into account the contribution of other factors especially hypertension in the development of cardiovascular events. The multivariate analysis adjusts for age but does not include hypertension.

Authors' response: In the resubmission, we added and adjusted covariates, including hypertension (Page 8, and Table 3, model 4). After this adjustment, the values of HRs decreased as compared to Model 3, specific attenuated in the HR of DM for risk of stroke (cerebrovascular disease) in males (p=0.06), and females (p=0.013). A brief description is added in the resubmission.

2. The univariate analysis showing an increase in prevalence of diabetes does not adjust for age.. As individuals with DM are considerably older and the population is aging over the years being examined.   Age adjustment needs to be undertaken.

Authors' response: Thanks. The prevalence of diabetes increases with age. By taking the age-effect in consideration, we presented prevalence of diabetes by four age groups in detail (Table 2, Figures 1, 3 and 4), instead of using an overall age-adjusted rate as we are most interested in the differences by age. In multivariable analysis, we adjusted for age and other covariates (Tables 3, 5, 6, 7).

3. The data on diabetes medications is interesting but incomplete. All sulfonureas are combined. It would be better to analyze glyburide separately form the others.

Authors' response: Sub-form of sulfonylureas are not recorded separately in the NHIS-MEPS liked-file, we are unable to test the difference in detail. We have discussed this limitation in the resubmission (Page 14).

4. It would also be of interest to look separately at the each of the newer diabetes medications rather than lumping them together.

Authors' response: Unfortunately, the detail data is not available in most national population surveys, including the NHIS-MEPS linked files. We have discussed the limitation in the resubmission (page 14).

5. The authors state "Of the total study sample, within an average 7.39 (SD=3) years follow-up, the results show that after adjustment for age and race/ethnicity, male patients with DM versus non-DM had 1.56 times higher risk of death from all-cause (HR=1.56, 95%CI: 1.49-1.64), 1.72 times higher from heart disease (HR=1.72, 95%CI: 1.53-1.93). However at baseline there was a higher proportion of persons with heart disease. This needs to be excluded i.e the incidence of heart disease needs to be calculated in persons free of heart disease at baseline.

Authors' response: We re-analyzed the data by excluding patients with heart disease and stroke at baseline (the results are shown in Table 3, Model 5). Overall, all HRs are attenuated, except for a slight but non-significant increase in HR for death from cerebrovascular disease (page 8 in the resubmission).

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Name of journal: World Journal of Diabetes
ESPS manuscript NO: 26062
Title: The Impact of Diabetes Mellitus on Risk of Cardiovascular Disease and All-cause Mortality: Evidence on Health Outcomes and Antidiabetic Treatment in the U.S. Adults
Reviewer's code: 02976486
Reviewer's country: China
Science editor: Fang-Fang Ji
Date sent for review: 2016-03-28 15:06
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COMMENTS TO AUTHORS

Comments to the Author comments to the authors: The paper has an introduction to make a proper review of the topic and adequately justify the objective. There is also a proper experimental design and methodology, which allows to validate the findings. These findings may add new evidence the patterns of antidiabetic medications usage, and the impact of DM on all-cause and CVD mortalities. General comments.

1. Please clarify if the DM in the study included type I and type II DM, because the prevalence and the treatment are different. Also please describe the reason why they (DM) should be mixed together to analyze the data instead of by strata.

Authors' response: The National Health Interview Surveys (NHIS) do not have information on whether a DM is type 1 or type 2 DM. We are unable to distinguish these two types of DM from the data we used. However, as the participants in NHIS were aged 18 and older, and by nature more than 85% of the total number of DM are

type 2 DM, we would assume that findings from the result should be a better presentation for patients with type 2 DM. We discussed this limitation in our resubmission. (Pages 13-14).

2. I suggest the statistical methods such as t-test, Chi-square etc. should be subscripted under all the tables 1-7 with P values in the paper.

Authors' response: Yes, statistic methods are listed under Tables 1-7.

3. I suggest that in the discussion section the obesity rate in Figure 4 should be removed for the too much outlying information in line " The results show a significantly increased obesity rate from 2000 to 2009 in both gender (Figure 4)".

Authors' response: Thank you. We have updated Fig 4, which depicts the correlation between prevalence of obesity and diabetes between 2000 and 2009 by age and gender.