

MEMORANDUM

To: The Editor, World Journal of Diabetes.

From: Joseph Yeboah MD, MS on behalf of all the co-authors

Date: 7/25/17

**RE: Heart Rate is an independent predictor of all-cause mortality in Individuals with Type 2 Diabetes:
The Diabetes Heart Study**

First, we want to thank the editors and reviewers for their many helpful and thoughtful comments. In our revision, we have tried to address all of the suggestions that were made. Changes and additions are in **BOLD**. We hope the Editor finds our response satisfactory, and we look forward to hearing about the final decision on our paper.

Reviewer Code: 00058696

Comment: . This is a confirmatory study, but the manuscript is not organized as such. GS Hillis has published: i. a multicenter study; ii. there was a large number of patients; iii. the patients' medication list was better evaluated; iv. the patients rested for a minimum of 5 minutes in the seated position prior to obtaining resting heart rate; v. increased heart rate was associated with increased cardiovascular deaths; but vi. the median follow up was only 4.4 years.

1. In the authors' present manuscript: 1) No hypothesis is presented. . 2) There must be a problem to solve.

Response: We disagree with this reviewer on this comment. The aim of this study is clearly stated at the end of the background section. It is unclear to us what problem this reviewer wants us to solve. This is a retrospective analysis and this paper has been well done accordingly. One does not have to create a problem in order to solve in an analysis. Thanks

2. The authors do not provide a clear contrast between the results of the Hillis study and the similar results of Stettler (reference 23), in comparison to the results of Anselmino (reference 19) who identified no increased cardiovascular risk in diabetic patients. The authors then need to explain how the organization of their present study helps to understand the differences in these previously reported results

Response: Thanks for this comment. We ask this reviewer to take a second look at the study by Hillis et al which showed an association between HR and all cause mortality. Anselmino et al also showed an association in diabetes but not in non- diabetes. Our results are consistent with their findings and we have clearly stated that in our discussion. However, the authors of this study would prefer not to speculate an explanation for the presence or absence of an association. That is beyond the scope of an observational study and will misinform the reader. Thanks

3. In this present study, there is no clear evidence for increased cardiovascular risk (see Table 2) in individuals with increased heart rate; is this because the number of participants is much lower than the number included in the Hillis study or perhaps the Hillis study is too short to judge the risk of death from non-cardiovascular causes?

Response: Thanks for this comment. Yes the P values for CVD mortality were not all significant due to small number of deaths due to CVD. We have added that to the limitations of this study.

4. 4) Abstract, Results: final sentence is not supported by the Authors' results. 5) Abstract, Conclusion: "additional prognostic information can be gleaned from this". This statement has to be removed; the authors do not provide a specific heart rate that can be applied uniformly to judge any risk using a heart rate obtained in a diabetic patient. The heart rates in this study were taken from ECG reports. There was no uniform rest period described prior to these ECGs.

Response: Thanks for this comment. Resting ECGs are done after a resting period contrary to what this reviewer is alluding to. That is why it is called resting ECGs. The heart rate obtained from resting ECG are therefore the resting heart rate of individuals. In DHS RESTING ECGs were done after a uniform resting period- 5 minutes. There is even evidence that resting heart rate obtained from resting ECG are better than those obtained manually due to significant errors in the manual method. We have changed it to "additional information MAY be gleaned....". Thanks.

4.6) In blood chemistries, was a thyroid blood test obtained?

Response: No thyroid function test was not done in the DHS at baseline.

5.7) In the Methods, the authors need to state that the patients' medication lists were not complete.

Response: Done. Thanks

6.8) Results: "Those with resting heart rate greater than the median had higher BMI". In the discussion, this is not well considered. In a systematic approach, was this finding in part related to deconditioning (e.g. less physical activity), heart failure with edema, or metabolic disorders in diabetic patients (i.e. thyroid dysfunction or B vitamin deficiencies). 9) Discussion: "preventive efforts such as aggressive control of hyperglycemia to minimize the prevalence of"; if the authors have some data to demonstrate that improved control of the blood sugar prevents the complication of neuropathy, please put in the data or the reference.

Response: Thanks for this comment. We have modified the discussion accordingly

7.10) In the discussion, one would prefer the authors to provide some idea how they would organize future studies of potential mechanisms for an increased heart rate in diabetic patients. If this mechanism were better understood, then the causes of death might be better understood. At that point, preventive medical care could be considered.

Response: Thanks for this comment. We want to respectfully state that this comment is beyond the scope of an observation study. Thanks

Reviewer's code: 03429673

This is a retrospective data analysis of 1,315 patients with type 2 diabetes to determine the association between resting heart rate (RHR) and all-cause and cardiovascular disease mortality. The authors used Cox proportional hazards regression to calculate HR with adjustment for certain confounders. They concluded that heart rate is an independent predictor of all-cause and cardiovascular disease mortality in this diabetic study population. Overall the manuscript is well written. The main results are clearly expressed in the tables and figures. There are a few concerns about the limitations of this study:

1.This is a retrospective cohort study conducted in a single center. The results suggest association, not causality.

Response: Thanks. We have not inferred causality anywhere in this paper.

2.The proposed underlying mechanism that affects RHR is cardiac autonomic dysfunction in diabetic patients. This may be influenced by not only A1c (a surrogate marker for diabetes control) and duration of diabetes, but also the presence of diabetic complications such as diabetic neuropathy, nephropathy and retinopathy. Adjusting for those diabetic complications may be helpful and relevant. It would be better if the authors could retrieve data on diabetic complications and adjust for those confounders.

Response: Thanks for this comment. We agree with this reviewer that these may confound this association. As clearly stated in our limitations, this is an observational study and so our results could definitely be due to residual confounding. DHS did not collect data on diabetic complications such as neuropathy, nephropathy etc.

3.. RHR could be significantly affected by certain medications, e.g. beta-blockers and non-hydro-pyridine calcium channel blockers. It would be much better if the authors could retrieve pharmacy data and adjust for certain medications as confounders. The association between higher RHR and the presence of type 2 diabetes was documented by analysis of data from the 2010-2013 Korea National Health and Nutrition Examination Survey (KNHANES). (PLoS One. 2016 Dec 16;11(12):e0168527. doi: 10.1371/journal.pone.0168527. eCollection 2016.) The predictive value of RHR for CV morbidity and mortality and all-cause mortality has been reported in diabetic patients: (Eur J Prev Cardiol. 2016 Aug;23(12):1298-306.) (Diabetes Care. 2012 Oct;35(10):2069-75.).

Response: medication data was poorly collected in the DHS as stated in the methods section and in our limitations. We are therefore unable to adequately adjust for them in our analysis.

4.The findings from this manuscript would not contribute to the existing literature. In addition, higher RHR has been reported to be associated with both cardiovascular and non-cardiovascular mortality In general population. This association suggests that RHR probably is a marker of overall well-being, rather than a specific disease marker. (Am J Cardiol 2017;119:1003-7).

Response: Thanks. We believe our study adds significantly to current literature.

Reviewer's code: 03699916

This study is a well-design observational study. In this study, authors investigate the association of resting heart rate with all-cause and cardiovascular disease (CVD) mortality in the Diabetic patients from analyses of 4 different models. Authors demonstrate that heart rate is an independent predictor of all-cause and CVD mortality in this population with type 2 diabetes. The only limitation is that in all models the factor of medication is not possible to include, however the authors provide a reasonable explanation. Furthermore, the conclusions of the study come from the whites and blacks, therefore the results may not be extended to other race/ ethnicities as authors suggestion. However the results of this study may be suggested that the same study should be done in other race/ ethnicities. The manuscript is well written and the English is good, and it is relevant for the readership of WJD. It is suggested to be accepted for publication in WJD.

Response: Thanks for this comment

Reviewer's code: 00506294

The article: "Heart Rate is an independent predictor of all-cause mortality in Individuals with Type 2 Diabetes: The Diabetes Heart Study" is an interesting clinical research based on data of the Diabetes Heart Study with many subjects and the authors demonstrate that heart rate is an independent predictor of all-cause mortality in this population with type 2 diabetes mellitus and they show the relationship between heart rate increase and the degree of mortality. The study is well designed and the statistical methology is correct and the conclusion can to be considered.

Response: Thanks for this comment

Reviewer's code: 02446566

This manuscript describes simple and interesting result that high resting heart rate predict mortality even in diabetics who frequently have neuropathy in sympathetic and/or para-sympathetic nervous system. The author has found that older participants had lower heart rate. Then, for an elderly patient, 1SD increase from median may have more risk as compared with the result from the whole age group. If data available, I want a table of median resting heart rate for several age groups. Increased resting heart rate may result from small stroke volume and shift of pressure-volume curve. minor point Page 5 third line from the bottom "HBA1c" may be "HbA1c". Page 6 line 15 "if all-cause" may be "of all-cause"

Response: Thanks for this important comment. Our sample size is small especially the number of mortality and CVD mortality that occurred. so stratification by age group leads to smaller groups with no meaningful results. We however adjusted for age in our models. We do not have data on stroke volume etc. We have made the minor corrections

Comment: Overall, the authors made minor changes addressing some, not all my concerns. This is a retrospective study without adjusting for at least one significant known confounder (i.e. medications, especially those that could affect heart rate significantly) due to incomplete documentation. In the limitation section, the authors imply that with adjustment, the hazard ratio could have been higher by stating "These medications are in general used by sicker patients and would have resulted in reduced heart rate. Thus the inclusion of T2DM on medications that reduce resting HR is likely attenuate the associations found in this study." Caution is highly suggested here since the other possibility is that the "sicker patients" on medications could have worse mortality even though they might have lower resting heart rate. In addition, higher resting heart rate has been reported to be associated with both cardiovascular and non-cardiovascular mortality In general population. This association suggests that resting heart rate probably is a marker of overall well-being, rather than a specific disease marker. (Am J Cardiol 2017;119:1003-7). The authors may consider revise the limitation section with more objective and balanced statements, and recognize that lack of adjustment for such an important confounder is a limitation, not a "strength" .

Response: We have reworded and eliminated the part of our limitation that this reviewer disagree with. We have added one statement in bold to clarify.

Comment: The manuscript would also benefit from a final round of careful proofreading.

Response: We have proofread it. Thanks

Comment: (Reviewer 00058696) In the Introduction, the" center for disease control" should be capitalized and I believe that the authors are referring to the "Centers for Disease Control and Prevention" (e.g. CDC Atlanta).】

Response: We have corrected this in the introduction. Thanks