Author's response to reviews

Title: Association between random glucose and all-cause mortality: Findings from the Mortality Follow-up of the German National Health Interview and Examination Survey 1998

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Author's response to reviews:
James Mockridge, PhD
Berlin, September 19, 2018
Editor, BMC Endocrine Disorders

Dear Dr. Mockridge,

Thank you for giving us the opportunity to revise our manuscript entitled "Association between random glucose and all-cause mortality: Findings from the mortality follow-up of the German National Health Interview and Examination Survey 1998" (BEND-D-18-00176).

We uploaded the revised manuscript as well as a manuscript version with changes marked in green color and now provide the email addresses of all authors on the title page of the revised manuscript.
We thank the reviewers for their comments and have revised the manuscript according to their suggestions as described in the point-to-point response as follows:

Reviewer 1

Random glucose concentration was related to mortality in a German cohort free of known diabetes. Strengths include design. Weaknesses include possible selection bias due to non-response and exclusions, small n of deaths and wide CI in extreme categories, and failure to use software accounting for survey design in regression analyses and seeming overlap with their previous work (ref 12). Given the large body of published work on relationship between HbA1c levels and all-cause mortality with similar findings, the value of this study is unclear. Omit the repeated claims of "first study investigating the association of random glucose and all-cause mortality." The J-shaped association based on only 10 deaths should be omitted/deemphasized and/or a caveat on wide CI added to conclusions.

1. Potential selection bias due to non-response and exclusions

The reviewer is right that selection bias may still be possible although non-response was partly compensated by applying survey weights considering deviations between study participants and the German population aged 18-79 years at large throughout the analyses. We clarified the intention for using survey weights in the method section (see Methods, Statistical analyses, page 11, last paragraph). We also added a paragraph to the discussion of study limitations and strengths order to acknowledge the remaining potential for selection bias due to selective participation or exclusions of participants (Discussion, Limitations and Strengths, points 4 to 6, page 19).

2. Small number of deaths wide CIs

In order to emphasize this point, we refer to the wide confidence intervals resulting from the small number of deaths by adding “leading to wide confidence intervals” to the discussion of study limitations, point 1 (see Discussion, Limitations and Strengths, page 18, first paragraph).
3. Failure to use software accounting for survey design in regression analyses

We revised the paragraph on Statistical Analyses in the method section, in order to clarify that we used SAS procedures accounting for survey design for all statistical analyses except for two analyses where accounting for survey design is not possible in SAS so far (Spearman correlation and spline modelling) (see Methods, Statistical analyses, page 11, last paragraph).

4. Seeming overlap with previous work (ref 12)

Our previous work (original ref 12: Paprott et al.) aimed to answer the question whether diagnosed and undiagnosed Diabetes as well as prediabetes are significantly related to increased risk of death. We revised the introduction for clarification that the present analysis aimed to fill the knowledge gap regarding the association between random glucose and death from all causes for two reasons: (1) High risk groups with hyperglycemia identified by HbA1c and fasting glucose do not necessarily overlap, and (2) it is not always feasible to measure fasting glucose in epidemiological studies, hence the predictive value of random glucose would be valuable to know. Previous studies have reported a strong relationship between random glucose and risk of incident diabetes, but evidence regarding the relationship to mortality has been scarce (see Introduction, page 4, last paragraph).

5. Omit the repeated claims of “first study investigating the association of random glucose and all-cause mortality.

We omitted repeated claims and limited mentioning to the first chapter of the discussion section (see Discussion, Overall findings, page 14, end of first paragraph).

6. J-shaped association based on only 10 deaths should be omitted/deemphasized and/or a caveat on wide CI added to conclusions

We omitted the expression “J shaped association” throughout the manuscript. The discussion of study limitations now refers to the fact that small numbers of deaths are reflected by wide confidence intervals (see Discussion, Limitations and Strengths, page 18, first paragraph; please
also refer to our answer to point 2 raised by this reviewer). We also added a sentence to the
discussion section to emphasize that the increased risk of all-cause mortality among individuals
with low levels compared to reference level should not be overinterpreted for very low and high
glucose limits (see Discussion, page 16, second to last paragraph; please also refer to our answer
to Reviewer 2, point 2.

7. Intro

Please clarify "There is also ample evidence, that applying currently recommended diagnostic
criteria for the diagnosis of previously unknown diabetes or prediabetes using fasting glucose
and HbA1c are not identifying the same people (14)."

We revised the introduction for clarification (see Introduction, page 4, last paragraph; please also
refer to our answer to point 4 raised by this reviewer).

8. Methods

Authors state: "Cox regression was performed by PHREG which permitted consideration of
weights but not accounting for cluster sampling." Please repeat Cox regression using a package
such as Stata, SUDAAN, etc. than does account for survey design to obtain accurate variances.

This is a misunderstanding since we did use SAS procedures accounting for survey design for all
analyses except for two analyses were accounting for survey design is not possible in SAS so far,
i. e. Spearman correlation in CORR and spline modelling in SURVEYPHREG (see Methods,
Statistical analyses, page 11, last paragraph, please also refer to our answer to point 3 raised by
this reviewer).

9. Results

Major subcategories of mortality (at least CVD, nonCVD, injury) should also be shown.

The reviewer points to a very interesting and important issue. However, unfortunately, only all-
cause mortality is available in our mortality follow-up data so far. In addition, case numbers
would be even smaller than for all-cause mortality leading to uncertainty in estimates.
Reviewer 2

This is a nicely written and conducted study. ADDITIONAL REQUESTS/SUGGESTIONS:

This is a good manuscript. The only comments I would make relate to a more indepth discussion of how random glucose compares to HbA1c given that there is not a requirement to fast on both tests.

1. More in depth discussion of how random glucose compares to HbA1c given that there is not a requirement to fast on both tests

We revised the introduction section by pointing out that measuring random glucose has its own value besides measuring fasting glucose or HbA1c. Both, fasting glucose or HbA1c are established measures for the diagnosis of diabetes in the clinical setting as well as in epidemiological studies. However, there is evidence have the advantage of being more precise in assessing diabetes risk and diagnosis, random glucose is easier to assess (independent from fasting state) and causes lower costs than fasting glucose or HbA1c and thus often assessed in epidemiological studies. These points were added to the introduction part (see Introduction, page 4, last paragraph).

2. Further, I would not make so much about the J shape as the number of deaths in the < 4.3 mmol/l group is pretty small.

We omitted the expression “J-shaped” throughout the manuscript and added a sentence to the discussion section to emphasize that the increased risk of all-cause mortality among individuals with low levels compared to reference level should not be overinterpreted (see Discussion, page 16, second to last paragraph; please also refer to out answer to Reviewer 1, point 2 and point 6).

3. I would explore who these people are. Are they sick? Do they have cancer?

Further did you exclude those with cancer? It makes no sense that these people have high waist circumference. This needs checking. I would remove those who drink alcohol and see if this J shape changes. Also remove smokers and see what happens.
We thank the reviewer for these suggestions and conducted several additional analyses. People with random glucose < 4.3 mmol/l are not sicker than people with higher random glucose levels as can be seen in Table 1: The proportions of all five chronic diseases were lower as compared to all other random glucose level groups, e.g. for cancer 2.5% compared to 2.8-5.7%. Furthermore, the proportions of other disease-related risk factors (older age groups, male sex, obesity, high waist circumference, current smoking, high alcohol consumption and low physical activity) were lowest for people with random glucose < 4.3 mmol/l and increased then monotonically with increasing random glucose level.

As suggested by the reviewer, we conducted several sensitivity analyses. Repeating the Cox regression model 4 for participants without cancer (n=10 events in < 4.3 mmol/l group) or without any of the five chronic diseases (n=6 events in < 4.3 mmol/l group) revealed estimates (HRs 2.09 (95% CI 0.88-4.98) and 2.38 (95% 0.75-7.58)) which were similar to the estimates in whole study population as shown in Table 2 (HR 1.94, 95% CI 0.85-4.45). Excluding participants with alcohol consumption would lead to one event in each the lowest and the two highest groups.

Furthermore, excluding current smokers from the analyses led to a HR of 1.02 (95% 0.41-2.51) diminishing the effect. However, number of events was only 4 in the lowest random glucose group which seems to be too low for reaching valid estimates.

We thought carefully about including these findings into the revised manuscript, however, the number of cases are too low in these subgroups; therefore they are not presented.

We look forward to hear from you and hope that the revised manuscript is acceptable for publication.

With best regards,

Dr. Christa Scheidt-Nave