Author’s response to reviews

Title: Diabetes mellitus type 2 in urban Ghana: characteristics and associated factors

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Author’s response to reviews:

Dear Editor

Thank you for inviting a revision of our manuscript entitled “Diabetes mellitus type 2 in urban Ghana: characteristics and associated factors”. We submit a revision taking account of the reviewers’ helpful comments (see below).

Sincerely,
Frank Mockenhaupt

Response to reviewers' comments

Reviewer's report
Reviewer: Isabela Bensenor

Major Compulsory Revisions:

1. The study is interesting because show some results of diabetes and hypertension in Ghana permitting comparisons with other studies and evaluating the consequences of urbanisation in African countries. However, it is a study using a convenience sample and the main consequences are an imbalance among the groups with diabetes and hypertension patients being older than controls, and a higher frequency of women in the sample. This is an important point that should be better discussed in the limitations of the manuscript.

Response: We emphasize the above mentioned issue in the revised discussion (P.13, Ll.8): “Importantly, the present study was not matched for e.g., age and sex, and used a convenience sample. Women predominated. [...]“
2. In the methods section, it is necessary to explain with more details the statistical analysis including more information about the variables included in the multivariate model. Is it the same model used for diabetes, hypertension, diabetes with and without hypertension?

Response: The respective section has been re-written for clarity (P.7; Ll.24): “We applied an explorative analysis, i.e., not hypothesis-driven, of factors associated with DM2 and/or hypertension. For that, all factors found to be univariately associated with e.g., DM2 were entered into a logistic regression model, a priori including age and gender, and odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated. Stepwise backward removal of parameters loosing significant association in multivariate analysis (P > 0.05) identified factors associated with e.g., DM2 independently of each other. These models were applied separately for DM2, DM2 only, DM2 with hypertension, and hypertension only."

3. It is a cross-sectional study evaluating diabetes and hypertension and its associated factors and not really a case-control analysis. All the information was collected at the same moment. This needs to be changed in the methods section.

Response: We respectfully disagree. The study is a case-control study in that cases and controls were purposefully recruited. The fact that information was collected at the same moment does not affect this study design.

4. Table 1 is too long and have to be shortened. Some variables could be dichotomized as occupation that can be divided in employed/unemployed, and formal education and literacy that could be combined together. Data about weight is not necessary, nutritional behavior can be described only in the text. These are some examples to guide the authors. In the place of family history of diabetes and hypertension it should be better to add the final variable diabetes and hypertension (including history and levels of fasting glucose and blood pressure). I think the authors could include data about body fat using BIA and only comment in the text about body fat using skinfolds that is less reproducible, but it is not necessary to include both data on table 1.

Response: Tab. 1 has been shortened. Nutritional data have been added to the text.

5. Other important point is to compare the results according to gender in table 1. You should include only diabetics, only hypertensives and both for all tables.

Response: The data have been stratified by gender and are presented in a new Supplementary Table 1.

6. I do not think it is necessary to include an analysis for diabetics with or without hypertension. I would like to see the values only adjusted by age and after the multivariate to evaluate the participation of the other associated factors beyond age.

Response: We respectfully disagree with omitting the important and interesting stratification by hypertension, not lastly because diabetes risk factors have
different weight in the resulting subgroups (Tab.2). Associated factors adjusted only by age are presented in Supplementary Table 1, legend.

7. Table 2 have to be shortened with the collapse of the groups with small number of participants.

Response: In line with the recommendation of the second reviewer, we removed Tab. 2 from the main body of the manuscript and made it Supplementary Table 2. We prefer to keep the separate listing of those medications taken only by few individuals for reasons of preciseness and because this information is relevant for clinicians.

8. Table 3 shows the same data of table 1 presented in a different way but essentially they are the same. The authors could think about to use ANCOVA in table 1 (rather than Mann-Whitney-U-test) and adjust all continuous variables according to age.

Response: Tab. 1 shows the actual results and univariate comparisons, Tab 2 (formerly Tab. 3) gives adjusted odds ratios from multivariate analysis. The new Supplementary Table 1 displays age-adjusted comparisons of data (stratified by gender). Results of age-adjusted comparisons irrespective of gender are given in the legend. All tests have been performed as non-parametric analyses adjusted for age (quantile regression for numeric and logistic regression for binary variables); ANCOVA assumes normally-distributed residuals

Minor Essential Revisions:
1. The first sentence in page 12 is confuse.
Response: Changed to (P.12, L.13): “In comparison to African and African American DM2 patients, Caucasian DM2 patients show [...]“

2. The last paragraph in page 13 is not based on data of the study being excessively generic.
Response: We respectfully disagree. This paragraph provides possible explanations for the association of indicators of low socio-economic status with increased odds of diabetes. Though, we did not assess e.g. sympathetic activity in our study. However, such might explain the increased odds of diabetes in individuals affected by psycho-social stressors. Illustrating such links is thus justified and related to our findings.

3. Part of the conclusion is also generic and not related to the objectives of the paper.
Response: We note the reviewers criticism but think that a conclusion may also include more generic statements considering the overall context.

Reviewer's report
Reviewer: Sargoor Veena
- Major Compulsory Revisions

Abstract, Results section:
1. Mention the cut off limits to define overweight, central obesity, hypertriglyceridaemia and hypercholesterolaemia.

Response: Done as requested.

2. Author mentions that Diabetes was independently associated with various factors but they have not mentioned independent of what?

Response: Re-phrased to “Factors independently associated with DM2 included […]”

Method
1. Recruitment procedures and examinations: 1st paragraph-Simplify the method of selection of controls to make it more reader friendly.

Response: Re-phrased to (P.5, L1.16): “Patients encouraged members of their community to participate in the study as preliminary controls. After exclusion of DM2 and hypertension (see below), the latter where included into the study as controls (n = 222).”

2nd paragraph-What is the rationale for measuring axillary temperature and tuning fork test?

Response: Body temperature was measured as a standard clinical parameter to detect e.g. a current infectious disease. Tuning fork tests were performed to detect peripheral neuropathy which was observed in 13 patients as mentioned in the results section.

2. Anthropometrical examinations and nutritional interviews
1st paragraph- Give the detailed methods-for first 2 sentences

Response: Done as requested.

2nd paragraph-mention what micro- and macro- nutrients were calculated.

Response: Done as requested.

3. Definitions

What protocol is used to define diabetes?

Response: As stated in the M&M section, diabetes was defined as a fasting plasma glucose of \( \#7 \) mmol/L and/or documented anti-diabetic medication according to WHO definition (World Health Organization: Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. 1999.)

Statistical Methods
1. Mention about the distribution of variables

Response: We clarified in the respective section that (P.7, L1.22): “Between-group-comparisons of continuous parameters were done by Mann-Whitney-U-test and of proportions by chi2-test.“ For continuous variables, the Mann-Whitney-U-test is appropriate for variables with either non-parametric
or parametric distribution, although slightly more conservative estimates are provided for the latter. It is not feasible to name those variables which have a parametric or non-parametric distribution but this can be seen with the help of the standard deviation, e.g. in Table 1.

Results

1. Table 1 is too big. Shorten it. No need to repeat the value of results given in the table again in the text. Interpret the results of table 1 and give the values wherever necessary if not presented in the table. For gender give values for both male and female. Likewise for binary variables give values for both in the table so that it is easier to understand. Mention the units of variables in parentheses in the table. Include height in Table 1 (anthropometry).

Response: We have shortened Tab. 1 which was also requested by reviewer 1. Because of redundancy with BMI and for shortness, height has not been included. Likewise, for shortness, self-explanatory variables, e.g. unemployment (%), are shown as such. Gender-related data are shown in the new Supplementary Table 1.

2. What is the rationale for giving Table 2? I do not think this table is necessary. It can be given as a supplementary table if necessary.

Response: Medication forms an essential portion of the clinical description. However, in line also with the respective comment of reviewer 1, we now present these data as Supplementary Table 2.

3. Table 3 Mention the units of variables and the cut off either in parentheses or in the foot note. Consistency needs to be considered.

Response: All factors in the former Tab. 3 (now Tab. 2) are self-explanatory. Where needed, e.g. for triglycerides, the cut-off value is given or explained in the table legend.

4. Over all the results section needs reduction in the content to make the section more reader friendly and all the tables needs proper formatting with proper heading, and footnotes to understand without reference to the text.

Response: We re-phrased portions of the results section, and added “%” to Tab. 1 where needed. Tables can largely be understood without referring to the text. In the text, we avoid redundancy with results shown in the Table but summarize the findings presented there.

Discussion

1. Overall discussion has covered all the points. It would be useful if they mention about the characteristics related to diabetes and hypertension in this population comparing to other developing countries and developed countries.

Response: We agree that it would have been interesting to compare our study population with other non-African developing countries. However, we are afraid that this would be beyond scope and too far-reaching. We therefore prefer to limit these comparisons to other African populations, African Americans and
Caucasians.

- Minor Essential Revisions
Check for typos and English language throughout the manuscript
Response: Done as requested.

Reviewer's report
Reviewer: REKIA BELAHSEN
Comments
• In the Methods section:
Could the authors give the justification of tobacco abstinence for the number of hours before the examination day as mentioned in their experimental protocol (page 3, paragraph3)?
Response: Tobacco abstinence has been requested as nicotine affects the sympathetic and parasympathetic nervous system potentially inducing a hepatic glucose output prior to laboratory procedures. No changes.

• In the Results section:
Major Comments
1- A major critic is about the variables age and sex and the results from the data analyses according to age and sex that should be considered.
In page8, 2nd paragraph & Table1: I wonder if the authors could make more analyses concerning the interaction of the 2 variables that are age and sex in relationship with the associated factors: Indeed it is already know that all the cardiovascular (CVD) risk factors increase with age, and this is also reported in this manuscript by the authors as shown in the Table 1. Also, a difference of the prevalence of all these CVD risks in males and females was reported before; However, the authors gave only the mean age of participants that was 54,7 years which include age for both sexes. They don’t give the mean of age for males. Furthermore the age of diabetics and controls were different (54 vs 38 years respectively) and the authors compared all the reported variables between these groups. I’m wondering if for all the variables studied, the differences of the results found between diabetic patients and controls were only related to the effect of age. More deep statistical analyses could raise the determining factor.
Response: We have added a Supplementary Table 1 showing the effects of gender and age for all variables in Tab. 1. The mean age for males and females is included. The age difference between controls and diabetic patients also reflects the higher risk of type 2 diabetes mellitus with increasing age, for which final analyses are adjusted (Tab. 2). Clearly, an age-matched study design would have been optimal but was not feasible. We acknowledge these limitations in the discussion section (P. 13).

2- How the authors could explain the higher energy expenditure associated with the higher obesity in diabetics than in controls?
Response: The formula of energy expenditure takes the weight of patients into account. Obese patients yield higher daily expenditure than non-obese patients. In addition, overweight or obese individuals tend to report longer periods of physical activity than lean persons. Further analyses regarding anthropometry, nutrition and physical activity will be performed and presented in future publications. No changes.

Minor Comments

• In the Discussion section:

Page 14, 1st paragraph:

1- Could the authors give more information and clarify the 2nd sentence: However, replication of risk alleles established in Caucasians not rarely has failed in African …………………………….[41].

Response: As stated, genetic markers known among Caucasians to be associated with an increased risk of diabetes do not necessarily associate with diabetes in Africans. In the revised manuscript, we emphasize this (P.14, Ll.18): “Because of this, validated genetic markers of an increased risk of DM2 in Africans are rare.

Page 14, 2nd paragraph, Line 5:

2- Could the authors give more information and clarify the sentence : Clearly, more research into the traditional cognitive imagery is needed to………

Response: This notion relates to the concept of knowledge, attitudes, and practise which is further explained now (P.15, Ll.1): “Clearly, more research into the traditional cognitive imagery as well as into DM2-related knowledge, attitudes and behaviour is needed to be able to implement socio-culturally appropriate health promotion campaigns”