

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Association between cardio-metabolic risk factors and body mass index, waist circumferences and body fat in a Zanzibari cross-sectional study
AUTHORS	Nyangasa, Maria Adam; Buck, Christoph; Kelm, Soerge; Sheikh, Mohammed Ali; Brackmann, Kim Laura; Hebestreit, Antje

VERSION 1 – REVIEW

REVIEWER	Guang Ji Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China
REVIEW RETURNED	09-Aug-2018

GENERAL COMMENTS	<p>In the manuscript “Association between cardio-metabolic risk factors and body mass index, waist circumferences and body fat in a Zanzibari cross-sectional study”, the authors propose to determine the prevalence of BMI, WC, BF and cardio-metabolic risk factors, and investigate the association between obesity indices and cardio-metabolic risk factors in a Zanzibari population. The paper has merit but needs an improvement. I have some specific comments that may improve the manuscript.</p> <p>Introduction:</p> <ol style="list-style-type: none">1. I would suggest to rewrite the whole introduction, with regards to the scientific English syntaxes.2. The description for epidemiology is too long. The obesity indices should be introduced in a separate paragraph.3. Why BMI, WC and BF? As these obesity indices are numerous. <p>Subjects and Methods:</p> <ol style="list-style-type: none">4. For inclusion criteria, subjects with malignant tumors should be excluded at least.5. “Top 1% was excluded for cardio-metabolic risk and obesity indices variables with high extreme values”, please explain it.6. For statistical analysis, did you check for normality of the data? <p>Results and Discussion:</p> <ol style="list-style-type: none">7. For characteristics of study population, the gender, age, education level (ISCED), area of residence and utilization of medication should be characterized better.8. The results can be of interest but should be better prepared, including a statistical power of the results.9. The biological/clinical significance of the results is not on spotlight. The authors should clearly discuss these topics. The translational nature of the results could be discussed.10. Language revision is mandatory. There are several typo and grammar errors.11. The format of the paper is not in the style of BMJ Open, please read the instructions for authors.
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REVIEWER	Shivananda Nayak The University of The West Indies, Trinidad and Tobago
REVIEW RETURNED	17-Aug-2018

GENERAL COMMENTS	<p>similar type of study done by many researchers in different population and justify what is new in it</p> <p>Abstract:</p> <p>Line 40: (24.5%), low HDL-C (29.4%), high HDL-C (21.3%), is this a typo error</p> <p>It is surprising to see the HbA1c value of 19</p> <p>Justify for the involvement of subjects aged less than 18 and more than 70 and above</p> <p>what about the consent from the parents if the study used subjects of aged less than 18 years?</p> <p>Study subjects</p> <p>page 6: Researchers have mentioned that Patients were not involved in this study but in the same page mentioned that 5.0 ml blood sample collected- explain this</p> <p>The study used subjects of aged 5 to 10 years and it is very difficult to get the required samples and information and explanation required for this inclusion</p> <p>Exclusion criteria needs more explanation: especially about the medication and diet</p>
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REVIEWER	FAILDE Inmaculada University of Cadiz. Spain
REVIEW RETURNED	19-Oct-2018

GENERAL COMMENTS	<p>Authors should express the results of prevalences with their 95% CI.</p> <p>Although they refer to another article published by themselves with the same population, (ref 17) they should briefly describe the sampling procedure and the calculation of the sample size used. The response rate is around 30% quite low for a face to face study.</p> <p>They should better explain the procedure used to calculate the associations between BMI, WC and BF% and the metabolic variables presented in table 4. How were the BMI or Hypertension variables considered, initially with 3 categories? They should also explain the meaning of the AIC index.</p> <p>The authors explain that they constructed a global model with the 3 variables, but how were the 3 BMI, WC and BF% variables considered globally? This is not clear from the information presented in table 5. Why, in addition to the adjustment variables age, sex ... was the treatment of hypertension considered and not treatment of hyperlipemia and / or hyperglycemia? This should be justified.</p> <p>In the summary reference is made to a multilevel model, however nothing is described about this procedure in the methodology of the article. It seems rather that the geographical area has been considered as an adjustment variable in the model</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer(s)' Comments to Author:

Reviewer: 1

Reviewer Name: Guang Ji

Institution and Country: Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai, China

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

In the manuscript “Association between cardio-metabolic risk factors and body mass index, waist circumferences and body fat in a Zanzibari cross-sectional study”, the authors propose to determine the prevalence of BMI, WC, BF and cardio-metabolic risk factors, and investigate the association between obesity indices and cardio-metabolic risk factors in a Zanzibari population. The paper has merit but needs an improvement. I have some specific comments that may improve the manuscript.

Introduction:

1. I would suggest to rewrite the whole introduction, with regards to the scientific English syntaxes.

Thank you for this comment, the Introduction was modified (lines 73-75; 77-98; 100-103; 105-107) as suggested and the manuscript has been edited by an English-speaking native.

2. The description for epidemiology is too long. The obesity indices should be introduced in a separate paragraph.

Thank you for your suggestion, a new paragraph on obesity indices has been added to the introduction part (lines 82-96).

3. Why BMI, WC and BF? As these obesity indices are numerous.

Thank you for this question, all the three measurements are good indicators of health status and well-known predictors of metabolic risk. However, each of them has restrictions in defining adiposity thus can not be used universally across sex and race. Therefore, including several indices adds up information on which indicator fits best for cardio-metabolic risk screening and for which target group. A new sentence answering your question has been added to the introduction part in line (94-96).

Subjects and Methods:

4. For inclusion criteria, subjects with malignant tumours should be excluded at least.

Thank you for your comment, but due to the nature of large-scale epidemiological studies, diagnosis of malignant tumours is difficult and ethically problematic. As population-based observation studies mainly target healthy populations (no patients) it is not foreseen or supported by ethical clearance authorities to scan for malignant tumours. It would be problematic to detect a tumour (which is not the aim of the study) and not provide adequate therapy afterwards. We included a statement in line 148-149: “This observational epidemiological study examined participants in their home environment and did not enrol clinical patients.

5. “Top 1% was excluded for cardio-metabolic risk and obesity indices variables with high extreme values”, please explain it.

Thank you for this comment. We excluded extremely high values in order to reduce bias when estimating mean and SD in the regression analysis. We included a justification to the text (line 246-248).

6. For statistical analysis, did you check for normality of the data?

Thank you for this question. As part of the regression analysis we tested the necessary assumptions in terms of symmetry and normality using residual-plots and Q-Q-Plots. We added this information describing the statistical analyses in line 253-254.

Results and Discussion:

7. For characteristics of study population, the gender, age, education level (ISCED), area of residence and utilization of medication should be characterized better.

We included education level, area of residence and utilization of medication in table 3 (providing characteristics of study population) stratified by age-group according to the reviewers suggestion.

8. The results can be of interest but should be better prepared, including a statistical power of the results.

Thank you for this advice. With respect to the better presentation of the results, we added statements to the discussion section (see examples given in the answer to the comment 9).

A power calculation was conducted previous to the survey. According to our power calculation, our sample size of 1314 individuals would have been enough to reach a statistical power, and did so for other research questions. Due to the individual opt-out option for particular examinations (anthropometric measurements, blood pressure measurement, bio sampling, and questionnaire) and the exclusion of outliers, completeness of variables of interest was reduced in the total sample of 1314. Nonetheless, we believe that detected associations did not reach the significance threshold only because of the small sample and still give important information for public health stakeholders, policy makers and researchers. We included a statement in the limitations section (lines 435-445).

9. The biological/clinical significance of the results is not on spotlight. The authors should clearly discuss these topics. The translational nature of the results could be discussed.

Thank you for this comment, few paragraphs have been added to the discussion section; see lines: 368-372; 388-396; 398-400; 408-412; 420-426;

10. Language revision is mandatory. There are several typo and grammar errors.

An English native speaker proofed the manuscript as suggested, changes were made where necessary.

11. The format of the paper is not in the style of BMJ Open, please read the instructions for authors. Thank you for your comment, the style has been adapted to that of BMJ Open.

Reviewer: #2

Reviewer Name: Shivananda Nayak

Institution and Country: The University of The West Indies Trinidad and Tobago

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

1. Similar type of study done by many researchers in different population and justify what is new in it This is the first observational research study providing information on the prevalence and risk of NCDs with particular focus on identifying vulnerable age-groups in Zanzibar. The results may be used for the development of interventions or policies. Researchers, stakeholders and government officials supported and still support this study as evidence is needed for public health actions on Zanzibar. We included a statement in line 442-445.

Abstract:

2. Line 40: (24.5%), low HDL-C (29.4%), high HDL-C (21.3%), is this a typo error. It is surprising to see the HbA1c value of 19.

Thank you; we corrected the error (high LDL-C).

You are right; in particular participants from 45 years and above were categorized with HbA1c values above the cut-off (see Table 3).

3. Justify for the involvement of subjects aged less than 18 and more than 70 and above.

One aim of the study was to identify vulnerable groups in the Zanzibari population with respect to cardio-metabolic risk. We presumed that particularly in polygamous families, young children and elderly who depend on the family food environment were under risk. We therefore examined all members of the same household. We included a statement in line 106-107 and 117-119.

4. What about the consent from the parents if the study used subjects of aged less than 18 years?

Thank you for your question; all adult members signed inform consent for themselves and parents/guardian signed for the minors who were also verbally asked for their consent before each examination. We clarified this in line 129-130.

Study subjects

5. page 6: Researchers have mentioned that Patients were not involved in this study but in the same page mentioned that 5.0 ml blood sample collected- explain this

For the purpose of this study we received ethical clearance for the collection biosamples. For the analysis of cardio-metabolic risk factors venous blood samples were collected from all participants above 5 years of age. This has been described in detail in our publication (Nyangasa et al., 2016): Nyangasa MA, Kelm S, Sheikh MA, et al. Design, Response Rates, and Population Characteristics of a Cross-Sectional Study in Zanzibar, Tanzania. JMIR research protocols 2016;5(4):e235. doi: 10.2196/resprot.6621

6. The study used subjects of aged 5 to 10 years and it is very difficult to get the required samples and information and explanation required for this inclusion.

For this study analysis we included all participants above 5 years since they were eligible for blood drawing. Children from 5 years and above were given local anaesthetics plaster before blood drawing to reduce pain on the arm which motivated children to participate. Parents/guardians were informed before each examination and they signed consents for their minors. Previous to the blood drawing (and any other examination) procedures were explained in easy language to the child and it had the option to refuse participation. We included this explanation in line 192-194.

7. Exclusion criteria need more explanation: especially about the medication and diet.

Thank you for your suggestion. For this particular analysis we investigated the association between obesity indices and cardio-metabolic risk factors thus diets and other eating behaviours were - this time - not taken into consideration. The variable "utilization of medication" was used as an adjustment variable (confounder) in the regression models (see line 270).

Utilization of medication was explained better now in the text (line 161-165):

"Utilization of medication was also documented in the questionnaire. Regarding medication for obesity-related conditions, participants reported use of hypertension medication but not of diabetes or dyslipoproteinemia medication. Hence, the variable was later categorized as "hypertension medication" and "other medication" (e.g. anti-Malaria therapy or antipyretic products)."

Reviewer: #3

Reviewer Name: FAILDE Inmaculada

Institution and Country: University of Cadiz. Spain

Please state any competing interests or state 'None declared': "None declared"

Please leave your comments for the authors below

1. Authors should express the results of prevalence with their 95% CI.

Thank you for this suggestion. Presenting the prevalence is part of the description of the examined study sample in this observational epidemiological study. The prevalence was not derived as an estimation of the overall Zanzibari population prevalence. As no estimated variation needs to be presented, the provision of confidence limits is not necessary. We hope you agree.

2. Although they refer to another article published by themselves with the same population, (ref 17) they should briefly describe the sampling procedure and the calculation of the sample size used. The response rate is around 30% quite low for a face to face study.

Thank you for your comment; we included a detailed description of the enrolment in line 119-122. The overall response rate for participation was higher (97,9%). But due to the opportunity for participants to refuse particular examinations (anthropometric and physiological measurements, bio sampling, and questionnaire), completeness of the participant examination modules varied individually. This led to a response rate for this study sample of 46%; this includes all members eligible for blood draw (1234 participants), about 570 participants gave complete blood sample. Unfortunately, we were not able to analyse all provided blood samples, due a broken centrifuge that could not be fixed directly (in Zanzibar). We included a more detailed description in line 435-441.

3. They should better explain the procedure used to calculate the associations between BMI, WC and BF% and the metabolic variables presented in table 4.

We clarified the use of regression models in the statistical analysis section as follows (lines 250 and following).

4. How were the BMI or Hypertension variables considered, initially with 3 categories? They should also explain the meaning of the AIC index.

For a better description of the study characteristics, we used three categories. For the regression analysis later, all variables included in the models were binary which was classified as normal/low for those below the given cut-off and overweight/obese or high for those above the cut-off, a sentence has been added in the methods in line 180-183. Also a detailed description of the cut offs is given in Table 1.

A sentence on AIC has been added in line 333-334.

5. The authors explain that they constructed a global model with the 3 variables, but how were the 3 BMI, WC and BF% variables considered globally? This is not clear from the information presented in table 5.

We analysed associations between obesity indicators (BMI, WC and BF %) individually and each the eight risk factor (hypertension, TC, TG, HDL-C, LDL-C, HbA1c, FPG and HOMA-IR). This approach was useful to understand how the single parameters relate individually. But since BMI, WC and BF% are interrelated their predictive power on cardio-metabolic risk factors was investigated by including them together in the logistic regression models. This is described in detail in the statistical analysis (lines 265-268). We hope this clarifies the question.

6. Why, in addition to the adjustment variables age, sex ... was the treatment of hypertension considered and not treatment of hyperlipemia and / or hyperglycemia? This should be justified.

Thank you for this question; we clarified this in the text (161-165):

“Utilization of medication was also documented in the questionnaire. Regarding medication for obesity-related conditions, participants reported use of hypertension medication but not of diabetes or dyslipoproteinemia medication. Hence, the variable was later categorized as “hypertension medication” and “other medication” (e.g. anti-Malaria therapy or antipyretic products).”

7. In the summary reference is made to a multilevel model, however nothing is described about this procedure in the methodology of the article. It seems rather that the geographical area has been considered as an adjustment variable in the model.

Thank you for this comment. First, we considered cluster effects by Shehia, as they may provide comparable economic, food supply and infrastructural conditions for households of the same Shehia. But a sensitivity analysis revealed no substantial differences between using Shehia or household as random intercept, so that we decided to use household for the multilevel model. See lines 256-261.

VERSION 2 – REVIEW

REVIEWER	Guang Ji Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine
REVIEW RETURNED	12-Dec-2018

GENERAL COMMENTS	This manuscript has been much improved. I am still concerned by the language and some typos. But overall, this version is improved. 1. The article is too long and some unnecessary content could be trimmed or performed in the supplementary materials. 2. In the manuscript, the authors stated the predictive power of the obesity indices on cardio-metabolic risk factors, but why not use ROC approach? The objectives stated in the paper do not support the use of logistic regression analyses. 3. The sample size is small. Is it power enough to validate the final result? This can be a limitation.
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REVIEWER	Shivananda Nayak The University of the West Indies, Trinidad and Tobago
REVIEW RETURNED	26-Dec-2018

GENERAL COMMENTS	It is an interesting article Why the age group 5- 95 selected What about the consent from parents or caregivers in case of children selected for the study Did you validate the questionnaire?
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REVIEWER	Failde Inmaculada University of Cadiz
REVIEW RETURNED	12-Dec-2018

GENERAL COMMENTS	The authors have adequately included the recommendations and comments made in the revision of the manuscript
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VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Guang Ji

Institution: Institute of Digestive Diseases, Longhua Hospital, Shanghai University of Traditional Chinese Medicine

Please state any competing interests or state 'None declared': There is no competing interests exist.

This manuscript has been much improved. I am still concerned by the language and some typos. But overall, this version is improved.

1. The article is too long and some unnecessary content could be trimmed or performed in the supplementary materials.

Thank you for your suggestion, the manuscript has been trimmed from 4839 words to 4736 words (including abstract and strengths and limitations of the study). We additionally removed further typos or unusual language and hope this improved reading.

2. In the manuscript, the authors stated the predictive power of the obesity indices on cardio-metabolic risk factors, but why not use ROC approach? The objectives stated in the paper do not support the use of logistic regression analyses.

We agree with the reviewer that calculating ROC curves may be another interesting approach to exploit the data. In this particular study we aimed at quantifying associations between obesity indices and cardio-metabolic risk factors rather than identifying thresholds for obesity indices. In order to provide easily interpretable results that will be used by local stakeholders of the health system to inform the development of interventions and health policies, we preferred using nominal variables that facilitate interpretation. Thus, we hope the reviewer agrees that our approach is viable for our research aim. We further rephrased the term "predictive power" to "stronger/strongest relationship", see lines (260 and 330) in order to state more clearly our objectives.

3. The sample size is small. Is it power enough to validate the final result? This can be a limitation.

Thank you for your comment; this has already been discussed as one of the limitation of our study. Please refer to line 426-432. "According to our power calculation, our sample size of 1,314 individuals would have been enough to reach a statistical power. However, our study sample decreased to 470 due to the individual opt-out option for particular examinations as well as the exclusion of outliers and the requirement of completeness of variables of interest. We nevertheless believe that our findings provide important information for public health stakeholders, policy makers and researchers, despite the fact that some of the detected associations did not reach the significance threshold due to the small sample size"

Reviewer: 2

Reviewer Name: Shivananda Nayak

Institution and Country: The University of the West Indies, Trinidad and Tobago

Please state any competing interests or state 'None declared': None declared

It is an interesting article

1. Why the age group 5- 95 selected

Thank you for this question, the aim of the study was also to identify vulnerable groups within the families; we therefore randomly selected participated households and examined all members of the same household irrespective of their age. However, for this analysis, we included all members above 5 years since blood was drawn only from children above 5 years. This has been explained in the manuscript; refer to line 117-119.

2. What about the consent from parents or caregivers in case of children selected for the study

Thank you for this question, parents/guardians signed for their children who were also verbally asked for their consent prior each examination, we revised the statement on informed consent (see line 129-130). "All participants gave written informed consent and parents/guardians consented on behalf of their children in writing". We hope it is clearer now.

3. Did you validate the questionnaire?

Thank you for this question. Most of the data collected for this analysis were objectively measured, thus we believe that no further validation was required. We however, used the International Standard Classification of Education (ISCED) as standard classification for education level which is recommended as an established tool by United Nations Educational Scientific and Cultural Organization (UNESCO).

Reviewer: 3

Reviewer Name: Failde Inmaculada

Institution: University of Cadiz

Please state any competing interests or state 'None declared': None declare

The authors have adequately included the recommendations and comments made in the revision of the manuscript

Thank you, we appreciate your feedback