Author’s response to reviews

Title: Peripheral Artery Disease and Exertional Leg Symptoms in Diabetes Patients in Ghana.

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POST OFFICE BOX KB 143
ACCRA. GHANA.
The Editor,

BMC Cardiovascular Disorders.
Dear Dr. Kim Smolderen

Re: Manuscript MS: BCAR-D-15-00086R1

Peripheral Artery Disease in Diabetes Patients in Ghana: Comparison of Ankle Brachial Index and the Edinburgh Claudication Questionnaire. (Title has been changed in the revision)

We appreciate the Editorials’ constructive comments and feel that our responses have helped improve the quality and presentation of our manuscript. We dearly apologise for our casual previous response. In this response, we provided, below, a detailed point-by-point response to each of the editors’ queries.

We have also highlighted (yellow) in the revised manuscript the appropriate sections that the changes were applied.

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Reviewer #1: This study adopted a case-control study design and enrolled 485 patients with type II diabetes and 330 non-diabetes patients. In both groups, assessments were performed to detect the presence of intermittent claudication using 2 methods: the Edinburgh Claudication questionnaire (ECQ) and the ankle-brachial index measurement. The authors looked at prevalence numbers using these criteria, evaluated the correlation between these 2 methods and looked at predictors of a low ABI. They recruited patients from Ghana.

Major points:

* Overall, I think it is great that data on peripheral arterial disease is available from this region as there is a great shortage of global data on PAD. Perhaps the framing of the paper could have been different. The authors consider the 2 assessment tools as instruments to screen for the presence of intermittent claudication. I would rather frame this paper to evaluate the correlation of these 2 instruments, as they both are measuring different things. The ECQ measures a constellation of symptoms that is consistent with the typical pain patients are experiencing when confronted with arterial obstructions in the leg arteries, whereas the other method is based on a Doppler examination and is providing an objective measure for arterial perfusion of the leg arteries. It is possible that patients' ABI values may indicate that they have a narrowing of the arteries, but at the same time, are not reporting symptoms for PAD. I would highlight these differences throughout the paper, rather than focusing on trying to find overlap between the 2 methods. Each method has its own relative weaknesses and strengths and should be used complementary.

Response:
The authors dearly appreciate the reviewer’s constructive criticism, and hence, we have re-analyzed the ECQ data to categorize the subjects based on their exertional leg symptoms, and emphasized the difference between the two instruments as recommended by the reviewer. The manuscript has therefore, been revised to capture these modifications in the data presentation as follows:

- The authors therefore change the title of the manuscript to reflect the modification to data presentation. The new title is: ‘Peripheral Artery Disease and Exertional Leg Symptoms in Diabetes Patients in Ghana’. (Title page 1)

- Table 1 in the previous write-up has been modified to capture other exertional leg symptoms screened using ECQ, and presented as Table S2 in the supplementary.

- The association between leg symptoms and PAD by ABI has been captured in Table 3 and highlighted throughout the current write-up.

* Also, it is unknown how representative the sample was for the region. What was the catchment area? Were rural or urban populations represented? How were patients referred to the program? This information needs to be known in order to be able to assess the generalizability of the findings.

Response: The study was conducted in an urban community and hence, no urban-rural dynamics was captured in data collection. This limitation has been acknowledged in the discussion. (page 10, line 1-2)

* Can you add a hypothesis to the introduction? Can you also specify your aims more clearly and accurately? Right now, it is formulated in a very broad way.

Response: The aim of the study has been modified accordingly. A hypothesis has been introduced in the introduction. (Page 3, lines 28-30)

* Page 4 - medical history; can you specify what variables?

Response: Variables of personal & medical history have been added to the methods. (Page 4, lines 18-21)

* Page 4: "patients were considered not to have intermittent claudication if pain was reported in hamstrings, ...." Was this a self-imposed definition? Presence of this pain in the absence of calf pain, does not preclude that one has peripheral arterial disease. One can also present with atypical symptoms of PAD.

Response: This section has been removed. Intermittent claudication has been re-defined according to Rose’s definition and indicate accordingly in the methods section. (page 4, line 23 – page 5 line 6)
* Describe psychometric properties of the ECQ; explain the claudication definition that it uses.

Response: a new Table S1, psychometric properties on ECQ is added as supplementary.

* Also page 4 - was information on other cardiovascular risk factors also collected? What about smoking? Smoking is the #1 risk factor for PAD.

Response: Yes. Data on smoking was collected as current, former and never. Also, possible second-hand smoking was added to the current analysis. (page 4, lines 20-21)

* Were diabetic patients matched with non-diabetic patients based on e.g. demographics?

Response: Diabetes patients were gender and age-decade match with non-diabetes controls. (page 4, lines 6-9). A new Table 1 has been added, comparing diabetes patients to non-diabetes controls in the results section.

* Results - it is very unusual that there were so few patients who reported a history of smoking as the #1 risk factor for PAD is smoking. Can the authors explain and reflect on this?

Response: Yes, we agree with the reviewer. Few participant reported positive for cigarette smoking and in the opinion of the authors, other factors besides smoking may be driving PAD in blacks in Ghana. This has been acknowledge in the discussion. (page 8, lines 31-32)

* Discussion: "However, given that the prevalence of smoking, …" page 6. Can the authors elaborate on the smoking statement and back-up the statement with actual numbers and references? It is unknown to the public that smoking rates in this region of the world are particularly low in comparison with other geographical regions.

Response: Other studies conducted in Ghana and other parts of sub-Saharan Africa have reported similar low prevalence of smoking. This has been referenced accordingly in the discussion. (page 8, lines 31-32)

* Discussion: "more female participants had PAD than their male counterparts" page 7. Can the authors reflect on this statement? In Westernized nations, the opposite is usually seen.

Response: With respect to prevalence of intermittent claudication, we agree with the reviewer that it is higher in males than females. However, we found contrary results in
our study. Future studies may be required to confirm or refute this result. With respect to PAD prevalence by ABI, inconsistent results on gender difference has been reported literature, however, studies like MESA and ARIC studies reported prevalence of ABI≤0.9 to be higher in females than in males. We have reference this in our discussion. (page 9, lines 4-6)

* Discussion, page 7 - the fact that low ABI values were not associated with any macrovascular disease is odd and suggests more a methodological concern than an actual finding. This is a weakness and should be further explored and commented on in the discussion.

Response: We thank the reviewers for this important criticism and hence, we have deleted this section from the results and discussion.

* Table 3 - use 'multivariable' instead of 'multivariate'. Not sure whether the title accurately explains what is represented in the table.

Response: Table 3 has been re-modified to capture association of exertional leg symptoms and PAD. Association between other clinical factors and PAD has been reported in Table S3 in the supplementary.

* How was the variable 'ABI' distributed? Was it normally distributed?

Response: Yes. We used Shapiro-Wilk’s test to test the distribution of ABI and no further transformation was required in regression analysis.

Reviewer #2: The authors have conducted a cross-sectional case-control study whereby all patients in the study underwent the Edinburgh Claudication Questionnaire as well as ankle brachial index testing. The authors conclude that: there is a high burden of PAD in T2DM patient in Ghana. The use of intermittent claudication to screen for PAD was not in agreement with ABI diagnosed PAD. Future studies should investigate the cost-effectiveness of ABI as a diagnostic tool and treatment target of PAD. I have several questions about the design and discussion of the study.

Population: The selection of the control cohort is not completely clear to me. Were controls selected as every third patient to visit "the clinic?" Was any matching undertaken in selecting the controls?

Response: The authors thank the reviewer for this constructive criticism and hence, we have modified the population description. The controls were recruited by invitation to people in the communities around the hospital. (page 4, lines 6-9)

A Consort diagram would also be helpful - how many patients were approached for the study (both diabetics and controls), and how many were actually consented?
Response: A consort diagram has been added to the manuscript as Figure 1.

Study period (over what years did this study take place? Were the controls recruited simultaneously to the PAD patients?

Response: the study period is now stated in the method section as June, 2009 to May, 2010. This has been added to the methods section of the manuscript (page 4, line 3)

Methods:

What were the covariates of adjustment in the multivariate model?

Response: A legend has been added to the table, explaining the covariates included in the regression model.

The authors state in the discussion: "In this study, however, low ABI was not associated with any macrovascular disease, which was assessed retrospectively from case notes and self-report." This assessment is not discussed in the results or methods section and therefore should be removed from the manuscript unless the authors can provide details about how follow-up was conducted, number of patients with follow-up, length of follow-up, etc…

Response: The authors have decided to take out the macrovascular disease from the results due to the weakness in the methodology of assessment.

Results and Discussion:

The paper is initially setup as a comparison between those with and without diabetes (patients were recruited from the diabetes clinic and non-diabetic controls were recruited). However, we are never given a table of baseline characteristics between those with and without diabetes. In general, I find a number of comparisons being made in this manuscript - diabetics vs. non diabetics, claudication vs. no claudication, hypertensive diabetics vs. non-hypertensive diabetics, etc… and am having difficulty following the main point of the manuscript.

Response: The author have provided the baseline characteristics between diabetes and non-diabetes participants as Table 1.

Additionally, the authors present data in the discussion that is not given in the results section: The findings of this study showed that the prevalence of falsely elevated ABI (ABI > 1.3) is 6%, more in diabetes patients (5.1% vs. 0.9%, p < 0.001) than non-diabetes participants.

Response: The authors have now provided this data in the results section. (page 6, line 6)
Discussion:

The authors make a comment that because both high and low ABIs have been associated with coronary heart disease, stroke, and cardiovascular mortality, that the ABI must be important in CVD risk prediction. However, it is not the association between the ABI and outcomes that accounts for the ABIs potential place in risk assessment but the additive value or net reclassification afforded by the ABI. The authors' statement should be modified to take this into account or deleted.

Response: The authors have deleted this statement accordingly.

One of the authors' main discussion point that the Edinburg Claudicaiton Questionnaire is not sensitive for PAD when compared to ABI screening is not surprising given that it is well known that the vast majority of patients with PAD are either asymptomatic or have atypical symptoms (which may not be picked up with the ECQ)

Response: The authors accept the weakness of this inference and, as suggested by the other reviewer, the manuscript has been revised to focus on the relationship between exertional leg symptoms and PAD, rather than comparison between the methods of screening PAD.

The baseline characteristics of those with and without intermittent claudication are quite different from those reported in most studies presently available in the literature. Classic claudication symptoms are generally found more often in males than females and PAD (even if the overall burden of PAD is greater in females) is generally found more often in smokers, however, the authors found classic claudicaiton symptoms more frequently in females and PAD (as diagnosed by ABI) was not associated with smoking. These findings need to be addressed more completely in the discussion.

Response: We agree with the reviewer that the prevalence of intermittent claudication has been reported to be higher in males than females. However, we surprisingly found high prevalence in female than males. With absence of comparable studies in this region of the world, future studies may confirm or refute this results. (page 9, lines 4-6)

Minor comments:

p. 4 lines 46/47 - the definition of a "normal" ABI is wrong as written: (normal (0.9 ≥ ABI > 1.3)

Response: This comment has been rectified.

Editorial Requests

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Please note that all submissions to BMC Cardiovascular Disorders must comply with our editorial policies. Please read the following information and revise your manuscript as necessary. If your manuscript does not adhere to our editorial requirements this will cause a delay whilst the issue is addressed. Failure to adhere to our policies may result in rejection of your manuscript.

Ethics:

If your study involves humans, human data or animals, then your article should contain an ethics statement which includes the name of the committee that approved your study.

If ethics was not required for your study, then this should be clearly stated and a rationale provided.

Response: Ethic statement has been made at page 4, lines 14-16

Consent:

If your article is a prospective study involving human participants then your article should include a statement detailing consent for participation.

If individual clinical data is presented in your article, then you must clarify whether consent for publication of these data was obtained.

Response: Statement detailing voluntary informed consent has been included at page 4 line 16-17

Availability of supporting data:

BioMed Central strongly encourages all data sets on which the conclusions of the paper rely be either deposited in publicly available repositories (where available and appropriate) or presented in the main papers or additional supporting files, in machine-readable format whenever possible. Authors must include an Availability of Data and Materials section in their article detailing where the data supporting their findings can be found. The Accession Numbers of any nucleic acid sequences, protein sequences or atomic coordinates cited in the manuscript must be provided and include the corresponding database name.

Response: Not applicable

Authors Contributions:

Your 'Authors Contributions' section must detail the individual contribution for each individual author listed on your manuscript.
Response: Contribution of various authors have been detailed at page 10 line 19 – page 11 line 3.