Title: Predictors of lower extremity amputation in patients with diabetic foot ulcer: findings from MEDFUN, a multi-center observational study

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Author’s response to reviews:

RESPONSES TO REVIEWER #3

The authors have done a good job of addressing most of the reviewers’ recommendations. However I still feel they need to add clarity to some of the more significant parts of the manuscript before it is ready for publication.

Firstly, I would like to clarify two of the comments made in my original review that were unclear to the authors (because I failed to insert Line numbers - my apologies).

Comment: In Line 48-49 in the Background section the authors state "The International Diabetes Federation and World Health Organization jointly warn that these complications {the authors are referring to diabetes complications}, if unchecked would threaten the viability of many African nations which are already grappling with many infectious diseases." This needs to be re-worded as it implies, as written, that diabetes is also an infectious disease.

Response: The last part of the sentence “which are already grappling with many infectious diseases” has been expunged to clear the ambiguity.
Comment: In Line 54 in the Background section the authors state "One avoidable complication of diabetes that is associated with huge morbidity and mortality is diabetic foot ulcer (DFU)". As per my initial review, describing DFU as 'avoidable' understates the complexity of this as a complication - if it was truly 'avoidable' we would not see so many of them. My preference would be for the authors to describe these as 'potentially preventable' or similar. Further to this, the term 'huge' is not overly scientific and should be replaced wherever it appears in the manuscript.

Response: The word “avoidable” has been replaced with “potentially preventable”. “huge” morbidity and mortality has been revised to “high” morbidity and mortality.

Comment: The reviewers all identified issues with the same parts of the paper, namely:

- confusion around the second manuscript the authors have published (now listed as reference 18)
- the use of the Wagner classification system as opposed to others available
- the diagnosis of vascular disease within the study population
- the definition used for major and minor amputation
- the way in which the authors distinguished between Type 1 and Type 2 diabetes

Whilst the authors gave reasonable explanations regarding some of these in their responses to reviewer feedback, they also need to make corresponding changes to the manuscript in order to add clarity to the paper. This then ensures a broader readership won't raise the same questions regarding the study methods and reliability of results.

Comment: Use of Wagner Tool

There are multiple classification tools available for grading wound severity, all of which I believe are flawed in some way. I don't have a particular issue with the use of Wagner in this study (except as per one of the reviewers it doesn't include wound area / size). The authors however need to make a statement about why they opted to use the Wagner tool so readers can be sure it was the right choice for this particular study. Shortfalls with the Wagner tool should also be discussed as a limitation.

Response: The following statements have been inserted in lines 102 – 108 to explain the rationale and limitations of using the Wagner grading system in this study: “This widely used DFU grading system, although has some limitations including not taking into account, wound
size and vascular integrity of the foot, has the advantages of simplicity and ease of bedside application compared to newer wound classification systems. It does not require sophisticated laboratory or imaging tests and is therefore especially suitable for developing countries like ours with constrained resources. Besides, the Wagner grading system has been shown to have strong correlations with DFU outcomes in several studies”.

Comment: Diagnosis of Vascular Disease

I do have concern over how the diagnosis of PAD was made for the purposes of this study - some were made on the basis of pulse palpation and others on Doppler US - with US being a much more reliable method. So there is inconsistency in how the participants were diagnosed. The authors need to address this in the manuscript and justify why they used the methods they did. They refer to insufficient resources to allow them to US everyone and an inability to to use ABI / TBI due to infected wounds. Both of these explanations need to be included in the manuscript. The inconsistent diagnostics used also needs to be raised as a potential limitation.

Response: This inconsistency has been included as a limitation in lines 310 - 316 as follows: “Secondly, our inability to conduct vascular imaging of the lower limbs for all the participants constitutes another limitation. Due to financial difficulties, only subjects with clinical suspicion of PAD underwent Doppler ultrasound. This has the potential of under diagnosing the condition due to observer bias. The ankle brachial index (ABI) which is a standard bedside screening tool for PAD could also not be utilized in this study due to technical problems associated with applying pressure cuffs on infected wounds and inflamed surrounding skin.”

Comment: Definition of Level of Amputation

I agree with the authors response that there is no agreed definition for level of amputation, however use of 'major' to describe anything above the ankle and 'minor' to describe anything below is fairly universally accepted. If the authors wish to use something different then I have no issue with that but I would suggest they state that this is their own definition 'for the purposes of this study' and perhaps explain the use of it.

Response: Lines 130 – 134 now reads: “We defined amputation above the mid-tarsal bone or involving the big toe as major amputation, otherwise it was considered as minor amputation. There are no generally accepted criteria for classifying amputation as major or minor. Our definition was therefore arbitrary and based on the potential physical limitations imposed by amputation of or above the big toe as the latter is responsible for 40% of weight bearing on the toes, and also the last part of the foot to push off the ground during walking.”
Comment: Type 1 Versus Type 2 Diabetes

Similarly to the amputation definition, the way the authors have differentiated between type 1 and type 2 diabetes is outside of the internationally accepted clinical 'norm'. If there is variation in how this is done in Nigeria then again, the authors need to provide an explanation in the paper.

Response: This has been included as a limitation in lines 307 – 310 which now reads: “The limitations of this study however need to be highlighted. Firstly, distinction between type I and type II DM was made clinically as commonly practiced in most hospitals in Nigeria due to absence of facilities for routine anti-GAD 65 and plasma C-peptide assays. This may lead to misclassification of subjects by diabetes type.”

Comment: Confusion around the other MEDFUN study

My issue with discussion about the original MEDFUN publication in this manuscript was about readers being able to discern between the two studies. I did not assume this paper was a duplicate or had been submitted elsewhere. This has been clarified somewhat following publication of the original study and the authors ability to now reference it. There are still a few sections where I think there is too much cross over but overall its not a major issue.

Response: The authors are very grateful for the time and efforts spent in reviewing this paper. Your contributions have greatly improved the quality of this manuscript.