Author’s response to reviews

Title: The impact of multimorbidity on foot health outcomes in podiatry patients with musculoskeletal foot pain: a prospective observational study

Authors:

Gordon Hendry (gordon.hendry@gcu.ac.uk)
Linda Fenocchi (linda.fenocchi@gcu.ac.uk)
Helen Mason (helen.mason@gcu.ac.uk)
Martijn Steultjens (martijn.steultjens@gcu.ac.uk)

Version: 2 Date: 11 Jun 2019

Author’s response to reviews:

Thanks again to the reviewers for their suggested revisions. We have provided point-by-point responses below.

1. Regarding response rate. I appreciate your detailed answer to the query raised by both reviewers. I am still struggling to see how the original 1329 people targeted aren't relevant to your overall recruitment rate. I can understand if the letters were sent to the general public seeking involvement in the study, but this was a targeted group. As it reads, the target population were those referred with a new episode of foot pain. Once you apply the eligibility criteria, unless they are < 18 years old or don't want to participate, they are going to be eligible. I see this point may be frustrating, but have I missed something?

RESPONSE: We appreciate the concern and welcome further discussion on the issue of generalisability of these data in the context of low response to the initial mail-out invitations, and the potential for non-response bias. We refer the reviewer to the further comments by reviewer 2 below and our subsequent response and revision to the manuscript. In addition, we also provide further clarity below.

As mentioned in our previous point-by-point responses, we were unable to undertake analysis to compare responders and non-responders (response to reviewer 2 point 2). This was because the TrakCare system used for recruitment is not yet ideally set up for extraction of data and as such it
remains cumbersome and time consuming, and we did not have sufficient time/resource in place for this. We would highly recommend that future confirmatory studies undertake planned responder v non-responder analyses. Therefore, all things considered, it seems the best we can do is emphasise in the results and discussions sections of the manuscript that these data may be subject to non-response bias and as such may not be generalizable. This is, to our knowledge the first study specifically looking at multimorbidity in an MSK podiatry context and as such we emphasise that this study is exploratory in nature and the results warrant further investigation.

With regards to the statement concerning the targeted group and eligibility – the reviewer incorrectly assumes that all targeted patients would have been eligible. The key issue here is that patients were eligible if they were attending specifically for a new episode of foot pain. We know from our exclusions at screening that several patients were attending as new patients following discharge and were re-attending as new patients for further consultation/treatment for the same original episode of foot pain. Similarly, patients without foot pain i.e. those with knee/hip/lower back pain, neuropathic patients, or those with (pain free) complex deformity and associated footwear issues, were not eligible.

Nevertheless, we acknowledge that some eligible participants would have not responded to the study invitation and a limitation of this study is that we cannot assume that they were similar to those who participated. We have now added further additional comment to the limitation section to place further emphasis on the issue:

“The implications of this are that those who responded (and those who were eligible and were subsequently enrolled) are not necessarily representative of the invited population who were eligible.”

We believe we have now provided sufficient emphasis in the discussion section to acknowledge this. If the reviewer feels that there is anything else we can do, we would be open to receiving and considering further suggestions.

2. Regarding the between-group comparisons.
a) Given that the three month and six month scores are significantly different between groups in Table 5 (discrete scores), but not Table 6 (change scores), provides a good reason to adjust for baseline scores. I can't see the justification or the basis for comparing between-group scores without adjusting for baseline scores, particularly given the differences at baseline between the multimorbidity group and the other groups. Furthermore, using negative values to indicate improvement with the FHSQ may be confusing for the reader given higher scores mean improvement. I would recommend you reconsider these analyses. Indeed, I think that both of these Tables could be removed.

RESPONSE: Respectfully disagree. A common approach to exploratory analyses such as these is to perform univariate analyses, followed by multivariate analyses including confounders. These analyses represent an iterative approach to the data, where initial univariate analyses appeared to justify 1) interest in multimorbidity group as an independent variable of interest; and 2) the subsequent adjustment in multivariate models for confounding variables. Presentation of both univariate and multivariate analyses provides clarity as to the effect of the covariates on the dependent variable. The story of how we got to our final multivariate model is of importance given the exploratory nature of the study. Given that we have adjusted for baseline scores in our adjusted regression models, it appears this point has now been addressed in full.

b) The new Table xx reports the regression analyses. To me, this is the most interesting and useful data. I assume that 'no conditions' is the referent in these models? I would recommend adding gender to the models and adding confidence intervals so the readers can see your precision. If you are reporting change in foot pain and change in foot function it is not necessary to have the baseline pain and function variables listed in the model.

RESPONSE: Agree, this data (now labelled table 7) is interesting and thank you to both reviewers for suggesting these additional analyses. You are correct in that “no conditions” is the referent in the models, with multimorbidity group and single condition groups modelled as dummy variables. Gender has been added to the adjusted models as a covariate, and confidence intervals are now presented in the results as requested. Note that as a result of inclusion of gender, the p-value for footwear changed from 0.049 to 0.052 and the manuscript has been amended accordingly to reflect this.

In the regression models, we have analysed discrete FHSQ scores at 3 and 6 months and so adjustment for baseline scores in these domains is indeed required (and was conducted as
requested in the reviewer’s initial comments). If we had modelled change scores as the dependent variable, we would have omitted baseline FHSQ domains scores from the model. We opted to focus on discrete scores adjusted for baseline scores instead of change scores.

3. Regarding a primary outcome measure. Granted it wasn't explicitly stated that you have reported four primary outcome measures, but your primary outcome of interest was 'foot health', a measure that isn't defined beyond the four domains you have reported. It is important to have a primary outcome measure and this should be determined a priori, even in observational studies. One reason it is important to list a primary outcome measure, is that having multiple outcomes risks obtaining and reporting a false-positive result. Are you able to explain why this may not be relevant for your paper?

RESPONSE: We emphasise again that this is an exploratory observational study and it should be considered in that context. We are well aware of the issue of multiplicity with regards to multiple testing and the probability of type 1 error. We understand that procedures for multiple testing are strictly required for confirmatory epidemiological studies, and especially in randomised controlled trials where results would be used for clinical decision making. However, whilst we acknowledge that there is ongoing debate on the subject, our understanding is that they are not strictly required for exploratory studies such as this. The data presented are largely descriptive, highlighting that poorer foot pain and function outcomes may be associated with multimorbidity (presented in the context of limitations of the study) and at least, that these results could be important and are probably worthy of further investigation. We are not presenting our results to inform clinical decision making.

We cannot now retrospectively select a primary outcome measure as this would be vulnerable to bias. This would have needed to have been specified a priori. As such, an alternative approach would be to consider correction for multiple testing using something like Bonferroni to correct α. Correction to account for 4 tests would mean revised $\alpha = 0.0125$. We note that 3 of our 4 significant findings in table 7 are significant at the $p<0.01$ level and so the results and conclusions would effectively remain the same. Given that 1) there is doubt about the need for multiple testing in this exploratory study, and 2) there is controversy surrounding methods of correction which increase the risk of type 2 error, we do not believe it is necessary to take any further action.
4. Regarding the use of p-values in text without context. Tables and in-text data should be able to be read in isolation. I would recommend that you (re)consider listing p-values in-text without contextualising them with the relevant data.

RESPONSE: Respectfully disagree. Context is provided by the tables and figures. We will seek editorial advice on this point, but reviewer personal preference concerning layout/presentation of data should not be considered a major revision, nor a pre-requisite of acceptance for publication. Our view is that duplication of results in text renders the tables redundant and potentially impacts on readability of the manuscript.

5. Regarding the heterogeneity of diagnoses and treatments provided to the participants. I appreciate your response, however, I do think it remains a limitation. Future studies would be best to test the significance of multimorbidity in a group of patients with at the very least the same diagnosis.

RESPONSE: Respectfully disagree. Several articles focusing on correlates of foot pain do not report specific diagnoses. All our participants had foot pain as a common feature. Given the exploratory nature of this study, it is unclear whether or not specific diagnoses would have enhanced the analyses or the results. Therefore, it remains unclear as to whether or not this could or should be perceived as a limitation.

6. The use of IQR as both a single value and a range persists throughout the manuscript. I would recommend selecting one and making it consistent. For example, Table 1 has a fixed value, while on most occasions in-text it is listed as a range.

RESPONSE: All IQR values now appear as a fixed value instead of a range from IQR 1-3.

7. Tables should be able to be read in isolation and therefore I think it would be worth considered providing all initialisms in the relevant captions. A few other comments about your Tables

* Table 1: a) can you report female/male ratios?, b) in the employment status these numbers would benefit from defining, I assume they are n (%)?
Table 3: a) The title could be made clearer that these are baseline characteristics, b) suggest change >1 conditions to >1 condition

Table 4: a) The title could be made clearer. I suggest using the text similar to that in the first column as the title 'Podiatry treatments received over the previous six-months' b) Should be number of participants n (%)

RESPONSE: We have now made these changes to the manuscript.

Reviewer #2: The authors have carefully and thoughtfully responded to the reviewers' comments and the manuscript has improved as a result. Although there are several inherent limitations with these data, these shortcomings have been acknowledged in an open and transparent manner and I think the paper is of value to the readership of JFAR.

I still have some mild residual concern regarding the reporting of the response rate/recruitment rate. I agree with the authors that in the context of this study design, a standard 'response rate' might not be an appropriate measure of response as we do not know how many of these individuals were eligible. However, I also think that the 'recruitment rate' of 74.7% (although technically correct) may provide an (unintentionally) inaccurate impression of how representative the participants are, for the same reason. That is, we do not know what proportion of the invited population were eligible, but we cannot assume that those who responded (and were eligible) are necessarily representative of the invited population who were eligible, as a range of factors may have influenced participants' decision to participate (in surveys such as these, participants are generally healthier and of higher socioeconomic status than those who decline to participate).

I think the authors have done a good job in reporting the response in the flowchart In Figure 1. However, I think something like the following statement needs to be included in the results: "Of the 1,329 invitations sent, 193 individuals responded (14.5%). Of these, 154 (79.8%) were eligible, and of these 115 (74.7%) were enrolled". This will help the reader understand that while the recruitment rate of eligible responders was high (75%), the overall response from the initial mail-out was low (14.5%).
RESPONSE: We thank the reviewer for the suggested revision and agree entirely with these statements. We also acknowledge that reviewer 1 (comment 1) has identified a similar concern. We have made the suggested revision to the manuscript.