Author's response to reviews

Title: The associations of leg lean mass with foot pain, posture and function in the Framingham Foot Study

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Editor
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RE: Manuscript 1158426290128430: The associations of leg lean mass with foot pain, posture and function in the Framingham Foot Study

Dear Editor and Reviewers:

Thank you for reviewing the above referenced manuscript and for inviting resubmission of a revised paper. We wish to thank the reviewers for their valuable suggestions, and we have addressed each of the reviewers’ comments and concerns with a point-by-point description of the changes made attached to this cover letter. All authors have reviewed the revised manuscript and approved the manuscript as submitted. Furthermore, no portion of this work has been or is currently under consideration for publication elsewhere, and no part of this manuscript has been published or posted on the Internet. We hope the revised manuscript submission is acceptable for publication in The Journal of Foot and Ankle Research.

Please contact me if any additional information concerning the manuscript is required. We look forward to hearing from you, and would like to thank you for considering the revised paper for publication.

Sincerely yours,

Robert R. McLean, DSc, MPH
1. The research is well executed and well described. However, several parts of the manuscript imply a possible causal relation between lower lean leg mass and the occurrence of foot pain, abnormal foot posture or function. The chosen study design (a cross-sectional study) is incapable to assess causality, it can only assess a relation. Since the study design prevents assessment of causality, the clinical relevance of the research question is debatable. The limitation section of the discussion does mention the inability to assess for causality but the entire manuscript suggests otherwise.

We did not intend to imply that our study would assess the causal relation between leg lean mass and foot outcomes, and throughout the manuscript we consistently refer to any effect measures only as estimates of association. While we agree that our study design precludes any conclusions of causal relations, we contend that our research question has important clinical relevance as it should be considered as a “first step” in determining the influence of leg lean mass on foot problems. All research investigating an exposure and an outcome begins with general clinical observation, followed by studies of readily available data that establish statistical associations, which is what we have begun to do here with the current manuscript. Once associations are replicated and established, additional studies are then conducted to derive causal inferences. The goal of our current study is to support the essential step that bridges the gap from clinical observations to studies of causal inference. Causality can perhaps only be implied from randomized trials; even longitudinal observational studies cannot truly establish causality. Yet, observational studies, both cross-sectional and longitudinal, are an important step that cannot be ignored. Thus, we contend that our study does hold clinical relevance, particularly since it is among the first to address this scientific question in a large, population-based cohort.

2. The content of the introduction is questionable in my opinion. It describes causality where foot pain or problems could be caused by lower muscle strength. As a cross-sectional study is unable to assess causality the content of the introduction is misleading. The possibility of declining muscle strength due to foot pain is not explored while this addition would correspond with the study design.

While this paper is based on an overarching hypothesis that lean mass deficits are a causal mechanism for foot problems, the current study was not conducted to determine a final inference regarding the relation between lean mass and foot problems. As stated above in our response to Comment 1, this study represents an intermediate but necessary phase in research into causal inference that is to establish associations between an exposure and an outcome. The introduction is meant to build a case for the larger causal hypothesis, presenting plausible biologic relations between lean mass and foot problems, and demonstrate that there is limited data to support even an association, let alone a causal relation. Thus, we do not feel the introduction misleads the reader into thinking that our study will prove causality. At the end of the introduction we clearly state that our hypothesis is one of association, and not causality. In the previously submitted manuscript, we acknowledged in the discussion section that we were “unable to determine whether foot pain, posture or function preceded loss of muscle mass, or vice versa.”

3. The hypothesis includes all foot deformities; it seems unlikely that lower lean leg mass could be associated with both supinated and pronated feet and with both pes planus and pes cavus.
As the current state of knowledge regarding the causal relation between lean mass and foot problems is very limited, and because there was no evidence to support the hypothesis that lean mass would be associated with supination over pronation, or pes planus over pes cavus, we conducted our analysis to allow for the possibility of all associations.

4. The foot pain questions were able to differentiate between left and right foot and bilateral pain. Isn’t it possible to assess lean leg mass per leg? A differentiation and correlation for a single leg would increase the power and the specificity of the analysis.

Unfortunately the LUNAR DPX-L bone densitometer and accompanying software only measures lean mass of both legs combined, with no means to separate individual legs. We have added this as a limitation to the Discussion section.

5. The division into sex groups seems like a good idea since there are many differences in outcome measures between men and woman (table 1). Unfortunately effect modification is not tested by adding an interaction term to the models. Therefore the choice to divide based on sex is not substantiated.

Effect modification and interaction do not necessarily mean the same thing. An interaction term in our regression model would test for statistical interaction, which in our case would test whether the joint effect of lean mass and sex differs from that which would be expected based on the independent effects of lean mass and sex. Our goal was not to describe the joint effects of lean mass and sex, but was instead to assess whether the association between lean mass and foot problems differs between the two sexes. This is more appropriately termed effect modification, which is most straightforwardly conducted and interpreted by the reader using stratified analyses, thus our choice to stratify is substantiated [1].

6. Without results of testing sex as effect modifier, the reader is not able to sufficiently interpret the models 1, 2 and 3. In these models sex is treated as respectively an effect modifier and a confounder and it does not become clear which model is statistically sound.

It is possible for a variable to be both a confounder and an effect modifier [2], and in our analyses we conducted separate analyses to determine whether this was true of sex. We evaluated potential confounding by sex in model 3 among all participants by including sex in the regression model. To evaluate sex as an effect modifier, we then conducted sex-stratified analyses of models 1 and 2. For all analyses, model 1 was the crude (unadjusted) analysis, and model 2 adjusted only for age and BMI. We present all 3 models so that the reader may easily interpret the incremental building of the multivariable model and how adjustment for each of the variables influences the association between lean mass and foot problems. Whether sex is an effect modifier does not impact the validity of the statistical model.

7. In the first paragraph (of the Discussion) the association between a pes cavus and lower lean leg mass is incorrectly interpreted as a causal relation. As said before; causality is not able to be assessed with a cross-sectional study. Due to this I do not agree with the content of most of the discussion. In my opinion it could very well be that a lower lean leg mass is a consequence of the smaller range of motion that is associated with a pes cavus (Buldt et al; Gait & Posture 38 (2013) 363–372). This possibility is insufficiently explored in my opinion.

On page 15, 1st paragraph of the manuscript (Discussion), we now highlight the cross-sectional nature of our study as the primary limitation of our study in terms of establishing causality, and have added the
reviewer’s statement and reference as an example of a possibility that foot problems may actually precede loss of lean mass. The paragraph now reads:

“It is also important to interpret our findings in light of other limitations of our study. First, we were unable to establish a causal relation between lean mass and foot problems because our study was cross-sectional and could not determine whether loss of lean mass preceded foot pain, posture or function, or vice versa. For example, it may be that lower leg lean mass and weakness are a consequence of the smaller range of motion associated with pes cavus [54].”

8. The mention of sex to be a confounding variable is not necessarily right, it could still be an effect modifier.

Please see comment 6 above regarding sex as potentially being both a confounder and an effect modifier.

9. A study design that assesses possible causality between the occurrence of lower muscle mass and the development of foot pain, abnormal foot posture or function would be highly relevant as mentioned in the introduction and discussion. The clinical relevance of a relationship between those variables assessable with the current study design is debatable in my opinion.

Please see above comments regarding causality.

Reviewer 2

10. This paper aimed to determine whether there is any association between the lean mass of the leg and the presence of foot pain, foot posture and foot function. The time difference between the DXA scans and the foot assessment is a major limitation. It is plausible individuals with foot pain are less active which may mean that muscle mass decline with aging may be greater than average. Although mentioned in the methods section, this needs to be raised in the limitation section of the discussion.

We now acknowledge the time difference as an important limitation in the Discussion section. In the 1st full paragraph on page 15 of the manuscript we have added the following text:

“Second, the time difference between our lean mass assessment and foot exam must be acknowledged. Although we repeated all analyses after adjusting lean mass measures for age-related loss of lean mass, we assumed a constant rate of loss over time that was identical across all individuals. It is possible that participants with foot problems may have been less active, which could contribute to an accelerated loss of muscle mass in this group. Thus, we may have underestimated lean mass in those with foot problems, potentially masking any associations in our cohort.”

11. My other concern is the use of the terms planus/cavus foot types. These have been defined using quintiles from the population based sample, however, there is no clinical association with these terms (i.e. they may not be pathological). The clearest example of this is the extremely high proportion of participants classified as having a cavus foot type (30%), when this a fairly uncommon pathology in the general population. Therefore I feel that this explains some of the lack of associations with leg mass and foot types.
While we acknowledge that our terminology of planus/cavus foot types is not clinically based, we have used this identical nomenclature in several previous publications [3-6]. In order to be consistent with our published work using the Framingham Foot Study, we have chosen to keep this terminology and have added references to our prior papers on page 8 of the manuscript.

12. **In the 2nd paragraph of the introduction, reference is made to the “long muscles of the leg”.**
   This is not a typical anatomical reference, and I am assuming that the authors mean long muscles of the foot i.e. muscles that control the foot, but originate in the lower leg.

Thank you for suggesting the correct language. We have changed the language on page 5 to read “muscles that control the foot, but originate in the lower leg.”

13. **In the 2nd sentence of the results, please remove the word “marginally” (p value is very small).**

We have removed the word “marginally” from the text.

14. **Please clarify the definition of the leg for the DXA scans. Is just the lower leg (below the knee), does it include the foot?**

The “legs” region of interest for the DXA scan includes the entire lower extremities. We have changed the text to include this language.

15. **It is not clear why the models were adjusted for BMI. Leg mass was already normalised to height.**

While normalizing to height accounts for stature, it does not fully account for the association of adiposity with lean mass [7]. Thus, measures of lean mass must also account for some measure of overall body size, such as BMI. Further, BMI is associated with foot pain [8], thus we consider BMI a potential confounder of the relation between lean mass and foot problems. We have edited the text on page 10 of the manuscript to read:

“Regression models were first unadjusted for covariates, followed by adjustment for age, and for BMI to account for adiposity, which is associated both with lean mass [38] and with foot pain [39].”

16. **The Authors should also include the study by Angin [Angin, Gait Posture, 2014], who found an association between muscle size of the foot/leg and pes planus foot types.**

We have added the reference and the following text to page 13 of the manuscript:

“Additionally, young adults with pes planus demonstrated different sizes and thicknesses of the intrinsic and extrinsic muscles of the foot on ultrasound compared with normal controls [42].”

17. **Please confirm what pressure variable was used to calculate MAI: i.e. mean?**

Total force was used to calculate MAI. This has been added to the text on page 8.
18. Please include the sample size for which the MAI quintile cut-points are based. Please report the age range of the participants.

We have edited the text on page 8 to read:

“Participants’ foot posture was classified based on quintile cut-points from the distribution of MAI values from all Framingham Foot Study participants (3,100 participants yielding 6,153 feet; age range 36-100 years), including those not included in the current analysis [32-33].”

19. The authors should refer to the articles by Wearing [Wearing, Foot Ankle Int, 2004; Wearing, J Orthop Res, 2012] about the influence of body composition on footprint parameters in the discussion. Were there any associations between BMI and foot type in the current study?

We acknowledge that an investigation of the influence of BMI or fat mass would be informative for the relation of overall body composition to foot problems, however the focus of our current manuscript is on muscle. Examining the relation of BMI to foot problems was not an aim of our study and thus outside the scope of this manuscript.

20. In the opening sentences of each results section, insert the 1SD leg mass value in parentheses.

We now include the standard deviations for height-adjusted lean mass in this sentence.

Reviewer 3

21. Recommend changing conclusion in the abstract. While the conclusion is not technically incorrect, I don’t think it summarizes the findings of the study. Also, conclusion is mis-spelled.

We have edited the conclusion of the abstract and corrected the spelling error.

References