Author’s response to reviews

Title: Prevalence of and Factors associated with Sarcopenia among Multi-Ethnic Ambulatory Older Asians with Type 2 Diabetes Mellitus in a primary care setting

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Author’s response to reviews:

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Editor,

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Dear Editor:

Re: Revision of Manuscript entitled “Prevalence of and Factors associated with Sarcopenia among Multi-Ethnic Ambulatory Older Asians with Type 2 Diabetes Mellitus in a primary care setting”

Thank you for the kind review of the manuscript. We have revised the manuscript based on the suggestions and advice by the editor and the reviewer
1. **Editor Comments:**

1.1 Please include a list of abbreviations used in the manuscript and insert after the Conclusion section.

Response: We have added the table of abbreviations after the "Conclusion" section.

1.2 Please describe the role of the funding body in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript.

Response: The funding bodies had no role in the design of the study and collection, analysis, and interpretation of data and in writing the manuscript. The investigators carried out the research independently. We have inserted this information for transparency in the revised manuscript.

1.3 Please remove the figure titles embedded within the figures and re-upload the corrected versions. All figure titles/legends should be placed at the end of the main manuscript, after the References, and not within any of the figure files.

Response: Thank you for pointing out the formatting. We have removed figure title within figure 1 and added it after the references:

Figure 1: Venn diagram showing Proportions of Patients with Low Muscle Mass, Low Muscle Strength and Low Physical Performance

Reviewer’s comments from Dr Ding-Cheng Chan (Reviewer 1):

2.1. The study discussed the prevalence and factors of sarcopenia among type 2 DM patients in Singapore. However, the sample is not population representative, and just from a single clinic. The clinical significance and external validity of such study needed to be addressed. Also, from the literature author reviewed, I am not sure if sarcopenia behave differently in patients with or without DM. The authors need to have a stronger rationale on why to limit study sample on DM patients.

Response: We recognise the limitation of the study due to its method of subject recruitment from a single site, even though the population at the study site does not differ significantly from the Singapore general population. It is not our intent to generalise the results to the Singapore population, which we have already indicated in the study title and under the segment on study limitation in the manuscript. To be more explicit, we have further elaborated in the respective paragraph: “the findings are not generalizable to the wider, heterogeneous population of older
patients with T2DM in Singapore. The data from a single study site would not reflect of the nation-wide prevalence of sarcopenia.”

We have reported recent biochemical evidence correlating the association between T2DM and sarcopenia in the second paragraph under the “Introduction” segment: “Recent biochemical studies have shown growing evidence of an association between T2DM and sarcopenia. Intracellular insulin signalling cascade activates the mTOR pathway and inhibits autophagy, including lysosomal degradation of proteins and organelles, including those in the muscles. Insulin resistance due to T2DM may interfere with this signalling mechanism and contributes to accelerated muscle loss.[7] Suppressing insulin signalling also downregulates the phosphatidylinositol-3-kinase pathway, leading to decreased protein synthesis, which can be detrimental to muscle integrity and function.[8]” As a result, we postulated that the association of T2DM and glycemic control status with the muscle strength and function of the older persons, in comparison with other studies on sarcopenia in the general geriatric population.

2.2 Method: Please explain why limit age to 89 years.

Response: Several study team members had previously conducted a cross-sectional study to establish the normative values of hand grip strength for older Singaporeans aged 60 to 89 years (R Malhotra et al, Normative Values of Hand Grip Strength for Elderly Singaporeans, JAMDA 2016). We are planning a sub-analysis to compare the current set of data with that in the earlier study. Hence, we adopted the same upper age limit in our study population.

2.3 Please confirm if the index used is the appendicular skeletal muscle index or other type of skeletal muscle index.

Response: The study is conducted in primary care, which serves the bulk of the geriatric population in Singapore, and that is the case for many countries. The intention is to screen the aging subjects for sarcopenia routinely in primary care setting in the near future. However, unlike specialised geriatric setting in tertiary institutions such as hospital, there are space and resource constraints in primary care clinics, which limits the use of sophisticated equipment to measure muscle mass. We recognise the appendicular skeletal muscle index as the standard for muscle mass measurement, which is not feasible using our device in this study. We have selected the BIA device (OMRON Body composition monitor, Model HBF-375) to measure the muscle mass due to its specifications, portability and ease of use. It measures the total skeletal mass which is a close proxy for the appendicular skeletal muscle index. The skeletal muscle index used is calculated by total skeletal muscle mass (measured with the bio-electrical impedance analysis machine) divided by the square of height in metres. We have added this proxy measurement in the study limitations.
2.4 Results:

The prevalence of low muscle mass (58%) is very high and also the sarcopenia prevalence. In general, DM patients are more obese than general population with more muscle. It is really difficult to imagine more than half of the study population had low muscle mass. In many other Asia studies, prevalence of low muscle mass is usually low.

Response: Based on a Malaysian study by Norshafarina et al in 2015, the prevalence of sarcopenia among community dwelling older people aged 60 years and above in Malaysia, which has a multi-ethnic population similar to Singapore, was reported to be as high as 59.8%. In addition, according to a local study which used a 5-item self-report questionnaire to identify sarcopenia in participants above 65 years and attending medical specialist outpatient clinics at a tertiary hospital, the prevalence of sarcopenia was 44.3% (Tan et al, 2017. http://dx.doi.org/10.1016/j.jamda.2017.01.004). Therefore, our study results are not disparate from these earlier findings.

2.5 Table 1, only 15 participants with severe sarcopenia, probably no need to separate a group.

Response: Our intention is to describe the subset of the study population with “severe sarcopenia””. This is one of the study aims to assess the prevalence of sarcopenia in primary care setting. While the number is small, they are at high risk of sarcopenia–related complications. The study is still in progress to determine the rate of progression of those with “sarcopenia” to “severe sarcopenia” over a period of one year and to determine the outcomes of those with severe sarcopenia. Thus the data is presented as baseline information for the longitudinal study.

For the segment to identify the factors associated with sarcopenia, those with severe sarcopenia is grouped with those with sarcopenia for analysis.

2.6 Table 2: Please check data: difficult to explain why someone can do light house work, worked for pay increased risk of sarcopenia

Response: Sarcopenia is associated with aging and is asymptomatic. The finding that it is present in persons who can do light house work and work for pay is a significant revelation from this study. Sarcopenia will not inhibit anyone to carry out housework or job such as sweeping the floor or cooking or laundry, or work as a cashier or sales promoter. The finding that these persons are unaware of sarcopenia unless they are assessed with the three measures is clinically significant. If we are able to identify these at-risk persons at primary care, the first point of contact with healthcare for most of them, opens up the door for intervention to address their risks of falls and susceptibility to fragility-related fractures.
The study population is targeted at the aging persons. We agree that there is always bias in self-reporting. However, this study is not adequately funded to have the resources to capture objective measurements of lifestyles using sensors and video-recordings. We took a balanced approach to ask history of domiciliary activities within a week that these older persons can remember.

We appreciate the reviewer’s understanding of the challenges in documenting work for pay, which is variable depending on the nature of the work. We agree that physical activity is independent of sedentary behaviour. The senior author has a separate paper which has been accepted for publication in a medical journal, to report on the differentiation of physical activity and sedentary behaviour of the aging population in an estate in Singapore. We report “work for pay” to describe a subset of the study population who have to travel out of their residence to work, which is a proxy for their health, cognitive and intellectual status.

2.7 Discussion:

The discussion on hip circumference and sarcopenia is difficult to comprehend.

Response: We apologise for the confusion. As we review the literature, the biochemical basis for the association between HC and sarcopenia remains uncertain. Hence we have revised this segment and removed the references.

Ellen Freiberger (Reviewer 2):

The authors investigated with a cross-sectional design first the prevalence of sarcopenia in Typ 2 diabetes Asian population, and second the identification of mediating factors for sarcopenia. Although this topic is of interest as sarcopenia is a relatively new research field and many interactions are not well understood there are major comments to be addressed before the manuscript can be considered for publication.

Major comments:

3.1 Key words: Please change "elderly" to aging as elderly is no longer appropriate. Furthermore, the reviewer would suggest highlighting more the first objective "prevalence", and seconding "risk factors". For the reviewer it is not clear why chronic kidney disease would be a key word.
Response: Thank you for the suggestions. We have revised the keywords revised accordingly and replaced ‘elderly’ with ‘aging’.

3.2 Background: Please provide information if the AWGS also include the different stages of sarcopenia. For the future reader it may be confusing switching between the different definitions. Please provide a rational to look at the different stages of sarcopenia. The reviewer fully understands, that to look at the different stages is important, but would like to see a rational behind it (p 4 line 10-14).

Response: We apologise for the confusion. AWGS criteria does not include the different stages of sarcopenia. The intention of classifying the different stages of sarcopenia (reference to EWGSOP) is to stratify the risk of the study population. As healthcare providers with limited resources, we will pay attention to those with sarcopenia and severe sarcopenia, with the intention to intervene and assess if the intervention is effective in addressing their muscle health. The next target group will be those with pre-sarcopenia and to leverage on research to determine if there is remedial measure to retard their progression to sarcopenia. The study opens the door to further research to support the health and mobility of the aging population in Singapore.

We have revised the Methods section to clarify this aspect.

Method

3.3 Please provide information why the authors choose the ambulatory primary care setting (is this a GP setting or special care settings for T2DM. The reviewer is coming out of health care system in which T2 DM would have a special care system so please specify.

Response: In Singapore, the majority of the patients (45% to 60%) with T2DM are managed at the public primary care clinics (polyclinics) due to healthcare finance policy and infrastructure set-up. These polyclinics are located within easy reach of the general population, and accessible within 30 min of public transport time. They provide a one-stop primary care services to outpatients, ranging from consultation with primary healthcare teams (physicians, nurses, pharmacists, allied health, medical social workers). They are thus suitable platform for the screening of sarcopenia in the near future, with the setting up of fall prevention clinics within these polyclinics. Thus the study was conducted in one such polyclinic, which also provides opportunity to assess the potential for scaling up of the sarcopenia screening.

3.4 Please provide information why there is a cut-off on age (89 years) as especially higher age is prevalent in older population (above 85 y).
Response: The senior author is part of the study team who had previously conducted a cross-sectional study to establish the normative values of hand grip strength for elderly Singaporeans aged 60 to 89 years (Malhotra R et al, JAMDA 2016). There is potential for a sub-study to compare this study’s results with that in the earlier study. Thus, we adopted the same age group in this study population.

3.5 The sample size estimation is very well explained (p 6 line 68-76).
Response: Thank you. The biostatistician in the team has done a fine job.

3.6 Please provide information about the possible period for the "latest Hb1C" values (p 8 line 110-111) as the authors mention earlier that the participants would come only one-two times into the clinic. Therefore, the reviewer wonders if this value could be a year old.
Response: The latest HbA1C value could be up to 6 months ago, as these participants visit the clinic at least twice over the past one year. The majority of patients visit the study site once every 3-4 months, or sooner if their glycaemic control are poor. We have added information in the “Results” section for clarity: “The recent glycemic control index (up to 6 months ago), HbA1C (OR=0.81, 95%CI=0.63-1.04, p=0.093) and lipid profiles were not associated with sarcopenia.”

Results:

3.7 The reviewer would like to suggest analyzing the data by creating two age groups. From table 1 it is clear that the prevalence of sarcopenia is increasing, and it may be that there are other factors are more important in the different age groups e.g. hospitalization.
Response: We have revised Table 1 by collapsing the 5 age bands to two age groups: from 60-69 years and those 70 year and older.

3.8 Please also provide some information about the medical condition in Table 1.
Response: We have added in the medical conditions in Table 1.

3.9 Please review if sitting is associated with lower risk of sarcopenia, which is in contrast to the presented data (p 10 line 155-156).
Response: Sitting was associated with lower risk of sarcopenia (OR=0.998, 95%CI=0.997-0.999; p=0.005). However, this factor is no longer significant after multivariable regression analysis.

3.10 Please provide information about the time period of the existing T2 DM diagnosis in all participants as this will have an impact on the association (in Table 1 as well as in the result section). This is an important missing information.

Response: The duration of T2DM in the participants ranged from one year to fifty years. Table 1 displayed the non-medical characteristics of the study population hence this was not included. However, when analysing the factors associated with sarcopenia using univariate analysis, we looked at the “years of diabetes” and as shown in Table 2 (Page 18), the OR was 1.04, 95%CI 1.01-1.07, p=0.013. However, this factor was no longer significant after adjustment, therefore not shown in Table 3 (Page 19). We have added the information in the “Results” section: “The duration of T2DM in the participants ranged from one year to fifty years.”

3.11 Also, information on the therapeutic intervention should be given. The T2 DM participants are actually -at least in our medical systems- by medications having a "normal" HbA1C. For the reviewer it is not clear if the participants were on medication for T2DM or newly diagnosed. Please clarify.

Response: Thanks for the suggestion. We have added the information in the “Method” section: “The participants can be treated by any therapeutic options compatible with their glycaemic control, ranging from diet control alone, oral hypoglycaemic agents alone, or a combination of oral hypoglycaemic agents with insulin injections.”

Discussion

3.12 For the reviewer it is not clear if the participants in this study are sampled, and weighted to represent the general older population in Singapore. To the understanding of the reviewer, this study population was recruited in one Center. Please comment.

Response: Yes, the participants were recruited from a single center due to funding limitation and manpower constraint. However, the study site is a typical public primary care clinic within one of three public primary healthcare institutions (SingHealth Polyclinics SHP) in Singapore. SHP managed over 1.8 million patient-visits in its 8 clinics in 2018, with 80,000 patients in its T2DM Registry. The attendees at the study site are representative of the major ethnic groups with the varied socioeconomic background of the Singaporean population.
3.13. For the future reader it is not clear that the variable "number of policlinic visits" (Table 2 p.18) is higher numbers of visits as explained on p 12 line 220-225. Could another explanation be that the medical doctor closely supervised their T2DM. For the reviewer -again- it is not clear how the "normal" T2DM procedure is in Singapore. In the culture of the reviewer, older persons with severe T2DM would have to see their medical doctor on a regular basis. Therefore, more visits would be related to the severity to the T2DM disease, and not necessarily to health behavior aspects.

Response: We agree that there could be other reasons for the more frequent polyclinic visits associated with lower risks of sarcopenia. We have added more information in the “Discussion” section: “On the other hand, those with overall poorer health, multiple morbidities and complications such as chronic kidney disease, will also require more frequent consultations.” There is a need for prospective study to understand the reason for polyclinic visit in association with sarcopenia risk.

Minor comments:

3.14 Please change throughout the manuscript the term "elderly" (e.g. p 4 line 3) as this term is international not recommended having in many western cultures a negative touch. Please also change the wording "subjects" to "participants" for the same reason.

Response: We have revised the terms as per reviewer’s comments.

3.15 Please provide references for the sentence p4 line 23 as the authors mention "studies" but provide later on only one reference.

Response: Both References 7 and 8 provided information on the biochemical background about T2DM and sarcopenia.

3.16 Please provide for reference 5 Lee et al. the doi or internet link.

Response: Reference 5 has been revised accordingly. There was a typo error, should be Chen et al instead of Lee et al. DOI: http://dx.doi.org/10.1016/j.jamda.2013.11.025