

Response to reviewers

Dear Professor Andrzej S Tarnawski and *World Journal of Gastroenterology* Editorial Team, and the reviewers,

We sincerely appreciate your valuable advice and comments on the manuscript. We are truly grateful for the potential opportunity to publish the article in the *World Journal of Gastroenterology*, and we are deeply grateful for your time, dedication, and efforts throughout the whole revision process. In order to best answer the comments from the reviewers, additional statistical analyses were performed, and we are more than happy to meet the revision deadline.

Below are the responses to the comments from the reviewers. The modified contents are highlighted in yellow in the revised manuscript. I hope to hear great news from you soon.

Sincerely yours,

Ga Eun Nam, M.D., Ph.D.

Reviewer #1:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Major revision

Specific Comments to Authors: The author collected 17,349 eligible individuals who participated in KNHANES between 2015 and 2018. By analyzing the relationship between different muscle strength quartile groups and the prevalence of MAFLD, they found lower muscle strength was associated with an increased risk of MAFLD and liver fibrosis in patients with MAFLD.

Majors: 1, This nationwide cross-sectional study analyzed 17349 general population who participated in the Korea National Health and Nutrition Examination Survey and measured handgrip strength between 2015 and 2018. The data is slightly old. It also does not specify whether the database is authorized.

Response: Thank you for your comment. The Ministry of Health and Welfare and the Korea Disease Control and Prevention Agency jointly conduct KNHANES to collect national health statistics, which is the primary database used for healthcare policymaking in South Korea. The highly skilled personnel responsible for KNHANES maintain the quality of the database through meticulous data collection and rigorous quality control of procedures, which are reviewed by internal and external experts affiliated with pertinent academic societies. Furthermore, we conducted a data analysis using the KNHANES surveys conducted between 2015 and 2018, to maximize the inclusion of available data for defining MAFLD. These surveys represent the most up-to-date database available at the commencement of our study. We have added the following sentences to the survey description in the Methods section (page 6).

“The Ministry of Health and Welfare and the Korea Disease Control and Prevention Agency jointly conduct the KNHANES to calculate national health statistics, which is the fundamental database for healthcare policymaking in South Korea.

The KNHANES ensures the quality of the data entered into the database through data collection by well-trained staff and quality control of procedures by internal and external professionals.”

2, The inclusion criteria for research subjects are not clearly explained.

Response: Thank you for this suggestion. We have added the following sentence to the survey description in the Methods section (page 6): “Because the KNHANES database includes pediatric and adolescent participants, only Korean citizens aged ≥ 19 years who participated in the KNHANES during 2015–2018 were initially included in the analysis.”

3, As in Materials and Methods "Assessment of muscle strength" mentions that muscle strength is assessed using relative grip strength. However, the relative grip strength of different sexes varies greatly, which will change the data quartile grouping (e. g., the muscle strength of a male is Q1 in men, and Q2 in the total population). It is suggested that different sexes be analyzed and discussed separately. The Q1-Q4 grouping definition shall be described in detail.

Response: Thank you for this comment. We have added the cut-off values for the sex-specific quartiles of muscle strength under “Assessment of muscle strength” in the Methods section as follows (page 7):

“The cutoff values for the quartiles were 1.30, 1.53, and 1.77 in men, and 0.76, 0.94, and 1.11 in women, respectively.”

Minors 1, What is the basis for selecting the adjustment variables in Model 2 and Model 3?

Response: Thank you for your insightful comment. Various factors were considered when selecting the adjustment variables in Models 2 and 3. The following sentence has been added to the statistical analyses section in the Methods section (page 9).

“The adjusted variables were selected from the statistically significant variables in Table 1, the clinical factors that were expected to be associated with muscle strength and MAFLD, and based on the results of the preliminary logistic regression analysis between baseline variables and MAFLD (Supplementary Table 1) and a literature search.”

2, The description of adjusted variables in Table 3 should be all these variables after removing stratified variables.

Response: We appreciate your valuable feedback and wish to address any confusion. In Table 3, certain stratified variables are excluded from the list of adjusted variables during the subgroup analysis. For instance, age was removed as an adjusted variable during subgroup analysis related to age. We have added the following sentences to Table 3 (page 28):

“Stratified variables (sex, age, obesity, and diabetes mellitus) were omitted from the adjusted variables during the respective subgroup analyses.”

At Page 9, line14, the diagnostic criteria of the disease should be marked with references.

Response: Thank you for this comment. We have now added references (27~30) for the diagnostic criteria of the respective diseases (hypertension, diabetes, dyslipidemia, and obesity) under measurements and covariates in the Methods section (page 8-9).

3, In Figure 1A, it was not indicated whether the differences among the four groups were statistically significant (***, $P < 0.001$). In Figure 1B and 1C, the meaning of “* ” should be indicated in the figure legend, $P < 0.05$.

Response: Thank you for this suggestion. The differences between the four groups (Figure 1A) were statistically significant ($P < 0.001$). We added the symbol “*” to the figures to highlight this difference. We have also provided an explanation for the symbol “*” in the legends of Figures 1A, 1B, and 1C as follows (page 23):

* indicates statistical significance ($P < 0.001$)

4, Please check the moderate-intensity and high-intensity activity time on Page 8.

Response: Thank you for your suggestion. In this manuscript, the descriptions of moderate-intensity and high-intensity activity times are consistent with the World Health Organization 2020 guidelines on physical activity and sedentary behavior. (Bull FC, Al-Ansari SS, Biddle S, et al. *Br J Sports Med* 2020;54:1451–1462.). In response to your feedback, we have added a citation (reference 26) in the manuscript (page 8).

5, The reference format should be consistent.

Response: Thank you for your comment. The reference format has been updated and is now consistent throughout the manuscript.

Reviewer #2:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: This study investigated the association between muscle strength and MAFLD in the general population, who participated in the Korea National Health and Nutrition Examination Survey between 2015 and 2018. They found that the lower muscle strength was associated with an increased risk of MAFLD and liver fibrosis in patients with MAFLD. It has some reference value to the clinical practice. However, there are two queries that need to be answered.

1.The author did not describe whether the participants took any medications, such as antihypertensive drugs, anti-hyperlipidemic drug, hypoglycemic drugs, or other drugs that affect liver steatosis. As is well known, these drugs will affect the data used and the results obtained in the analysis of this study.

Response: Thank you for your insightful comment. Unfortunately, the KNHANES database does not contain the medication history of the participants, which is precisely why we chose to diagnose hypertension, diabetes mellitus, and dyslipidemia using a combination of prior records of physician diagnosis and laboratory blood tests. We have included this as a noteworthy limitation of the present study (page 14).

“Fourth, the lack of data on medications for chronic diseases and those potentially affecting liver steatosis is a limitation. Thus, we defined hypertension, DM, and dyslipidemia using a combination of prior physician diagnoses and laboratory blood tests.”

2.Model 2 = adjusted for age, sex, income, education, smoking status, and physical activity I wonder how you made the adjustments.

Response: Thank you for your comment. There were several considerations when selecting the variables for adjustment in Models 2 and 3. This sentence has been added under the statistical analyses section in the Methods section (page 9). “The adjusted variables were selected from the statistically significant variables in Table 1, the clinical factors that were expected to be associated with muscle strength and MAFLD, and based on the results of the preliminary logistic regression analysis between baseline variables and MAFLD (Supplementary Table 1) and a literature search.”

Reviewer #3:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The authors conducted a nationwide study to investigate the association between muscle strength and MAFLD. The work is good and important. However, similar reports have been published. My concerns are as follows:

1. Please update the references. The introduction and discussion sections were not well organized, many literatures (PMIDs: 37024207, 36959316, 36673611, 36520009, 36499438, 36157867, 36157861, 36017777, 35887915, 35692671, 35343663, 35162699, etc) were not cited.

Response: Thank you for your insightful suggestion. They were truly helpful in organizing the introduction and discussion. We have thoroughly reviewed and cited all suggested citations (References 5, 6, 7, 10, 14, 17, 31, 50, 51, 52, 54, 55). The newly added references have been highlighted in the manuscript. We have also added the following limitations based on the literature review (page 14):

“Fifth, handgrip strength was used to diagnose probable sarcopenia in the present study. The prevalence of probable sarcopenia can vary depending on the diagnostic methods, especially in liver steatosis.^[55] Nonetheless, handgrip strength is easy to incorporate into clinical settings and is also a well-studied parameter of sarcopenia in many studies.”

2. The cut-off value or criteria of muscle strength Q1 to Q4 should be described in details.

Response: Thank you for your comment. We added the cut-off values for the sex-specific quartiles of muscle strength under “Assessment of muscle strength” in Methods section as follows (page 7):

"The cutoff values for the quartiles were 1.30, 1.53, and 1.77 in men, and 0.76, 0.94, and 1.11 in women, respectively."

3. The pairwise comparison should be considered for the prevalence of MAFLD according to the muscle strength in figure 1A.

Response: Thank you for this comment. Pairwise comparisons were performed in our statistical analysis conducted using IBM SPSS Statistics ver. 22.0. Additionally, the KNHANES is based on a complex sampling design; thus, we performed the Rao-Scott chi-square test for categorized variables. The manuscript has been edited with the following sentences under statistical analysis in the Methods section (page 9):

"Continuous variables were summarized as mean $\pm$ standard error and categorical variables as percentages, and they were compared using analysis of variance and Rao-Scott chi-square test, respectively. Statistical analyses, including pairwise comparison, were performed using IBM SPSS Statistics ver. 22.0 (IBM Corp., Armonk, NY, USA). Complex sample procedures were performed based on the survey design."

The prevalence of MAFLD of Q2, Q3 and Q4 in the subgroup analysis based on gender and age should be described and compared separately in Figure 1B and 1C.

Response: Thank you for your suggestion. We have modified Figure 1 and the related portions in the Results section as follows:

Results: (page 10)

"Among all participants, including within various sex and age groups, the prevalence of MAFLD was significantly higher in the lower muscle strength quartile groups ($P < 0.001$ in Figures 1A, 1B, and 1C). Additionally, regardless of sex and age group, the prevalence was higher in the lowest quartile (Q1) group of muscle strength than in the remaining quartile (Q2-Q4) groups ($P < 0.001$ in Figure 1B and 1C)."

Figure 1 (page 22-23):

“Figure 1. Prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) by muscle strength in the total participants (A), sex (B), and age (C) groups; The prevalence was higher in the lower muscle strength quartile groups in total participants and age and sex groups. Prevalence was higher in the lowest muscle strength quartile (Q1) group than in the remaining groups (Q2–Q4) in both sexes and all age groups. A dose-response relationship between lower muscle strength quartile and MAFLD was also observed; * indicates statistical significance ($P < 0.001$); Q, Quartile; yrs, years.

4. Since the baseline features were uneven distributed among the four groups in table 1, the variables should be entered in the preliminary logistic analysis. And the results should be presented.

Response: Thank you for this suggestion. We conducted a preliminary logistic analysis between the variables listed in Table 1 and MAFLD; the results are included in Supplementary Table 1. This information has been incorporated into the following sentence within the Statistical Analysis section of the Methods section (page 9).

“The adjusted variables were selected from the statistically significant variables in Table 1, the clinical factors that were expected to be associated with muscle strength and MAFLD, and based on the results of the preliminary logistic regression analysis between baseline variables and MAFLD (Supplementary Table 1) and a literature search.”

5. ROC and Decision Curve Analysis (DCA) methods should be used for the presentation of the results.

Response: Thank you for your suggestion. We have performed ROC analysis between muscle strength and prevalence of MAFLD and have presented the results in Supplementary Figure 1 and the following sentence in the Results section (page 10-11):

“Furthermore, the receiver operating characteristic (ROC) analysis to assess the relationship between muscle strength and prevalence of MAFLD revealed that the area under the curve (AUC) for the entire participant group, as well as for men and women separately, were 0.764, 0.701, and 0.740, respectively. (all $P < 0.001$, Supplementary Figure 1).”