

PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Physical frailty and health-related quality of life among Chinese rural older adults: A moderated mediation analysis of physical disability and physical activity
AUTHORS	Hao, Wenting; Li, Jie; Fu, Peipei; Zhao, Dan; Jing, Zhengyue; wang, yi; Yu, Caiting; Yuan, Yemin; Zhou, Chengchao

VERSION 1 – REVIEW

REVIEWER	Yili Wu Department of Epidemiology and Health Statistics, Public Health College, Qingdao University
REVIEW RETURNED	17-Aug-2020

GENERAL COMMENTS	<p>Journal: BMJ open Ref: bmjopen-2020-042496 Title: Physical frailty and health-related quality of life among Chinese rural older adults: A moderated mediation analysis of physical disability and physical activity</p> <p>This study examined a moderated mediation model of relations among physical frailty, physical disability (mediator), physical activity (moderator) and quality of life in older Chinese rural elderly. The idea is interesting. The paper is well written, which is generally clear and concise. I have a number of comments and queries, as follows:</p> <p>Abstract 1. Please report the results for role of PA as a moderator in the relationship between physical frailty and quality of life in details. (Line 37-39)</p> <p>Introduction 2. What do you mean when you say “Previous cross-sectional and longitudinal studies have shown that frailty was negatively associated with HRQoL. In addition, the HRQoL in older adults with frailty is poorer than the non-frailty older adults”? Why do you use “in addition”? And sentence of “the HRQoL in older adults with frailty is poorer than the non-frailty older adults” should be rewritten. (Line 80-83)</p> <p>Methods 3. I can’t understand the coding for PA. How do authors transfer PA score to binary variable (low vs. high)? Could you please list the references?</p>
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	<p>Results</p> <p>4. According to Table 1, mean of PA is 3122.346 and standard deviation of PA is 3457.705. PA does not follow normal distribution. Thus, it is not appropriate to use mean \pm SD to describe PA.</p> <p>5. Please mention the correlation coefficient in detail in Table 1, Spearman or Pearson?</p> <p>Discussion</p> <p>6. Limited covariates (age and education) were included in the present analysis and residual confounding may influence the observed association. Authors should discuss this scrupulously.</p> <p>7. The English needs improving.</p>
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REVIEWER	Fiona Stanaway University of Sydney School of Public Health
REVIEW RETURNED	19-Aug-2020

GENERAL COMMENTS	<p>This is an interesting paper examining associations with health related quality of life rural-dwelling older people in China.</p> <p>The biggest concern I have with the paper is that this is cross-sectional data, and hence not well suited to examination of mediation effects. This is particularly an issue in the present study as it would not be possible for the researchers to be clear of the temporal ordering of the variables under consideration in terms of cause and effect. Having this temporal ordering correct is an important assumption when using a statistical mediation model.</p> <p>The conclusions in some sections are also overstated given that this is a/observational and b/cross-sectional. For example, conclusions around the need to screen older people for frailty and disability so that early intervention can be offered are not justified by the results given that the effectiveness of providing such an intervention has not been assessed.</p> <p>As a minor point, in Figure 1 the arrows don't appear to be correct. If physical activity is moderating the effect of physical disability as a mediator then the arrows should go from physical activity towards the line showing the mediation relationship rather than towards physical activity as currently shown. It is also possible that physical activity modifies the direct relationship between physical frailty and HRQoL so an arrow should be drawn from physical activity to this line as well.</p> <p>The English is of a good standard but there are some minor errors throughout the text, particularly with the use of prepositions that could benefit from some editing. For example, in many insta</p>
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VERSION 1 – AUTHOR RESPONSE

-Reviewer: 1

This study examined a moderated mediation model of relations among physical frailty, physical

disability (mediator), physical activity (moderator) and quality of life in older Chinese rural elderly. The idea is interesting. The paper is well written, which is generally clear and concise. I have a number of comments and queries, as follows:

Response: Many thanks to you for your kind words and your helpful comments. We hope we can address all of your comments in this round of revision. Following are the responses to your comments:

Abstract

1. Please report the results for role of PA as a moderator in the relationship between physical frailty and quality of life in details. (Line 37-39)

Response: Thank you for your helpful suggestions, and we are happy to follow. In response, we have added more details in the results for role of PA as a moderator in the relationship between physical frailty and quality of life. The new results now read as follows:

“Results: After controlling for age and education, physical disability partially mediated the effect of physical frailty on HRQoL [indirect effect = -0.143, 95% confidence intervals (CI) = -0.175, -0.113], with the mediating effect accounting for 33.71% of the total effect. PA moderated the relationship between physical frailty and physical disability, as well as the relationship between physical disability and HRQoL. Specifically, the interaction term between physical frailty and PA significantly predicted physical disability ($\beta = -0.120$, $t = -7.058$, $P < 0.001$), and the interaction term between physical disability and PA also had a significant predictive effect on HRQoL ($\beta = 0.115$, $t = 6.104$, $P < 0.001$).”

Introduction

2. What do you mean when you say “Previous cross-sectional and longitudinal studies have shown that frailty was negatively associated with HRQoL. In addition, the HRQoL in older adults with frailty is poorer than the non-frailty older adults”? Why do you use “in addition”? And sentence of “the HRQoL in older adults with frailty is poorer than the non-frailty older adults” should be rewritten. (Line 80-83)

Response: Thank you for this comment. Apologies for any confusion on this issue. In response, we have rewritten the sentences. The new sentences now read as follow :

“Previous cross-sectional and longitudinal studies have shown that frailty was negatively associated with HRQoL^{9, 10}, and frail older adults reported worse HRQoL than those who were not frail¹¹.”

Methods

3. I can't understand the coding for PA. How do authors transfer PA score to binary variable (low vs. high)? Could you please list the references?

Response: Thank you for this comment. Apologies for any confusion on this issue. In response, we have added some sentences to explain the coding for PA in the “Data analysis” in the Methods section to make it clear, and we also listed some references here to support the coding. The new “Data analysis” now reads as follows:

“Data analysis

To analyze the data, categorical variables were expressed using frequency and percentages (%) and continuous data were described using mean (standard deviation). Pearson correlation coefficient was used to analyze the correlation among physical frailty, physical disability, and HRQoL. All these analyses were performed using IBM SPSS 24.0 (IBM Corp., Armonk, NY, USA). All regression coefficients were tested by the bias-corrected percentile Bootstrap method. The theoretical model was tested by estimating the 95% confidence interval (CI) for mediation and moderating effects with 5000 sampled with repetition. If the 95% CI did not include 0, it meant that the statistics was significant. To illuminate the moderating effect, the moderated variable (PA) is divided into two levels of high and low according to one standard deviation above and below the mean ($M+1SD/M-1SD$)⁴²⁻⁴⁴. The Split-Plot analysis method was used to further examine the direction of the moderation effect, and draw a diagram explaining the moderation effect⁴⁵. The mediation model and moderated mediation model were tested with the PROCESS V3.3 macro for SPSS⁴⁶. In the current study, we selected Model 4 and Model 59 to analyze the mediating effect and moderated mediation effect. In addition, through t

test and ANOVA analysis, we found that HRQoL is related to age and education. Previous studies have also found HRQoL was associated with age and education^{47,48}. We controlled age and education in this study. Sampling weights were used in all of the analyses to adjust for the survey design.”

Additional references:

42. Ng KY, Ang S, Chan KY. Personality and leader effectiveness: a moderated mediation model of leadership self-efficacy, job demands, and job autonomy. *J Appl Psychol* 2008;93(4):733-43. doi: 10.1037/0021-9010.93.4.733 [published Online First: 2008/07/23]

43. Preacher KJ, Rucker DD, Hayes AF. Addressing Moderated Mediation Hypotheses: Theory, Methods, and Prescriptions. *Multivariate behavioral research* 2007;42(1):185-227. doi: 10.1080/00273170701341316 [published Online First: 2007/01/01]

44. Holmbeck GN. Toward terminological, conceptual, and statistical clarity in the study of mediators and moderators: examples from the child-clinical and pediatric psychology literatures. *Journal of consulting and clinical psychology* 1997;65(4):599-610. doi: 10.1037//0022-006x.65.4.599 [published Online First: 1997/08/01]

45. Cohen J, Cohen P, West SG, et al. *Applied multiple regression/correlation analysis for the behavioral sciences*: Routledge 2013.

Results

4. According to Table 1, mean of PA is 3122.346 and standard deviation of PA is 3457.705. PA does not follow normal distribution. Thus, it is not appropriate to use mean SD to describe PA.

Response: Many thanks for this comment. In response, we have made the following modifications in Table 1 and used Median (Quartile1, Quartile3) to describe PA. The new Table 1 is presented in the revised version of the manuscript, and the description of its results now read as follows:

“3.3 Bivariate correlations of main variables

The mean, standard deviation/ Median (Quartile1, Quartile3) and correlation coefficient of each variable were shown in Table 1. Physical frailty was positively correlated with physical disability (= 0.283, $P < 0.01$), physical frailty was negatively correlated with HRQoL (= -0.429, $P < 0.01$) and PA (= -0.378, $P < 0.01$). Physical disability was negatively correlated with HRQoL (= -0.378, $P < 0.01$) and PA (= -0.194, $P < 0.01$). PA was positively correlated with HRQoL (= 0.258, $p < 0.01$).”

5. Please mention the correlation coefficient in detail in Table 1, Spearman or Pearson?

Response: Many thanks for this comment. We have added the Spearman correlation coefficient in Table 1. The new header of the Table 1 now reads as follows:

“Table 1 Spearman correlations coefficients of main variables among the participants in Shandong, China, 2019(N=3243).”

Discussion

6. Limited covariates (age and education) were included in the present analysis and residual confounding may influence the observed association. Authors should discuss this scrupulously.

Response: Many thanks for your comment. This is also a limitation of this study. In response, we added this to the limitations section in the discussion. The new the limitations section in the discussion now read as follows:

“There are several limitations in this study. First, our study was based on a cross-sectional study, which could not provide strong evidence of causation. Future research could adopt a longitudinal design or experiments to explore the causal relationship between physical frailty and HRQoL. Secondly, the data in this study comes from the participants’ self-report information, which might result in recall bias. Thirdly, this study only included age and education as control variables. The study may also be affected by other confounding factors. In the future, we will include more confounding factors related to quality of life to verify our findings. Fourthly, physical disability has a partly mediating effect on the relationship between physical frailty and HRQoL, which indicates that there are other mediating variables in this relationship. More potential mechanisms related to physical frailty and

HRQoL among older adults need to be explored in the future.”

7. The English needs improving.

Response: Thank you so much for your kind words and also the comments. Both of the corresponding author, Prof. Chengchao Zhou (a visiting scholar in Stanford University during 2004-2005), and a co-author, Dr. Peipei Fu (a master student in applied economics in Bowling Green State University during 2006-2008) have carefully edited the manuscript again to make it more academic and scientific, and also more readable.

-Reviewer: 2

This is an interesting paper examining associations with health related quality of life rural-dwelling older people in China.

Response: Many thanks to you for your kind words. We hope we can address all of your concerns in this round of revision. Following are the responses to your comments:

1. The biggest concern I have with the paper is that this is cross-sectional data, and hence not well suited to examination of mediation effects. This is particularly an issue in the present study as it would not be possible for the researchers to be clear of the temporal ordering of the variables under consideration in terms of cause and effect. Having this temporal ordering correct is an important assumption when using a statistical mediation model.

Response: Thank you so much for your comments and careful read. We do agree with you that cross-sectional data is not well suited to examination of mediation effect. Similar with many previous studies based on cross-sectional data, the biggest limitation is the examination of mediation effects in our study. Some longitudinal studies have shown that frailty had a negative impact on HRQoL, and also increased the risk of disability. Some researchers even believed that frailty might be the precursor and cause of disability. Some other studies have also demonstrated that the quality of life worsened as the degree of disability increased. Based on the literature review, we hypothesize that physical disability plays a mediating role in frailty and quality of life. Using the cross-sectional data, we try to examine the hypothesis in this study. In response, we have added some new sentences in the Background to support the research hypothesis, and also added this point in the Limitation. In addition, our research team have had an in-depth interview about this comment, and decided to conduct a follow-up survey in the same population to explore the causal relationship between physical frailty and HRQoL in the next year.

“Studies have found that physical activity moderated the relationship between chronic illness and functional limitations, and moderated functional disability and body function^{23,24}. PA can alleviate the decline of physical function in older adults and has a beneficial effect on functional limitations, physical frailty, disability and quality of life in older adults²⁵⁻²⁷. Studies indicated the positive effect of physical activity on reducing adverse events caused by frailty in older people. Performing a physical activity of moderate to vigorous intensity would improve physical frailty and prevent the occurrence of disability when compared to the performance of a physical activity of low intensity, ultimately promote older adults' quality of life²⁸⁻³⁰. Therefore, PA may moderate the direct and indirect relationship between physical frailty and HRQoL through physical disability as a mediator. In the present study, we used a cross-sectional study to the relationship between physical frailty and HRQoL, focusing on the mediating role of physical disability and the moderating role of PA in the relationship between physical frailty and HRQoL.”

“There are several limitations in this study. First, our study was based on a cross-sectional study, which could not provide strong evidence of causation. Future research could adopt a longitudinal design or experiments to explore the causal relationship between physical frailty and HRQoL. Secondly, the data in this study comes from the participants' self-report information, which might result in recall bias. Thirdly, this study only included age and education as control variables. The study may also be affected by other confounding factors. In the future, we will include more confounding factors related to quality of life to verify our findings. Fourthly, physical disability has a partly mediating

effect on the relationship between physical frailty and HRQoL, which indicates that there are other mediating variables in this relationship. More potential mechanisms related to physical frailty and HRQoL among older adults need to be explored in the future.”

2. The conclusions in some sections are also overstated given that this is a/observational and b/cross-sectional. For example, conclusions around the need to screen older people for frailty and disability so that early intervention can be offered are not justified by the results given that the effectiveness of providing such an intervention has not been assessed.

Response: Many thanks to your comment and careful read. We have revised those possible overstated conclusions in some sections in the revised manuscript to make them proper, and the new Discussions now reads as follows:.

“4. Discussion

In this study, a moderated mediation model was established with the mediation role of physical disability on the relationship between physical frailty and HRQoL, as well as the role of PA as a moderator in this indirect path between physical frailty and HRQoL. These findings preliminarily elucidate the potential causes of physical frailty on HRQoL and facilitate the development of targeted interventions for individuals so as to improve HRQoL in rural older adults.

Consistent with previous studies⁵⁰⁻⁵¹, we find that physical frailty negatively affect HRQoL of older adults. This suggests that as the degree of physical frailty increases, the quality of life in older adults becomes worse. Although many studies have established a direct relationship between frailty and HRQoL, few have explored the underlying mechanisms of this relationship. Our study demonstrates that the physical disability mediates the physical frailty and HRQoL, with the mediating rate of 33.71%. A study also suggested that physical disability was one of the potential factors underlying the association between frailty and HRQoL, which was similar with our study⁵².

The current study indicates that physical frailty is associated with disability, which is consistent with a study by Kojuma G⁵³. Frail older adults are very vulnerable to adverse health effects. A study indicated the risk of disability in the frail older adults was 12- to 13-fold increased than that in the non-frail older adults⁵⁴. Meanwhile, this study also demonstrates that the negative predictive effect of disability on individual HRQoL, which was consistent with previous studies⁵⁵⁻⁵⁶. The possible explanation is that disabled older adults' poor self-care ability deteriorates their health, such as their normal physiological activities are restricted, physiological function is declined, social interaction is reduced, which adversely affect their physical and mental health and ultimately reduce HRQoL. One study found that disability was the most important health problem for older adults, which seriously affected their quality of life in old adults' later years⁵⁷. The disability was the most important factor that contributed to decreasing quality of life in older adults. Physical disability has been shown to be associated with increased chronic diseases, and premature mortality⁵⁸⁻⁵⁹, all of which could adversely affect the quality of life of older adults⁶⁰. Therefore, physical frailty may reduce HRQoL of rural older adults by increasing their disability.

In the present study, we also find that PA plays a moderating role in the indirect effect between physical frailty and HRQoL. A larger indirect effect is observed among rural older adults with low-level of PA than among those with average or high-level of PA. Specifically, PA moderates the relationship between physical frailty and physical disability, and between physical disability and HRQoL. For older adults with low-level PA, the impact of physical frailty on physical disability is stronger than older adults with high-level PA. This finding indicates that PA moderates the relation between physical frailty and physical disability. We speculate that older adults with low-level PA may have a decline in their physiological system reserves, leading to a deterioration of their functional status and ultimately increasing the possibility of physical frailty and disability⁶¹. A systematic review showed that older adults without exercise habits were at greater risk of developing frailty. Taichi, resistance sports and other physical activities might effectively improve the health of older adults, reduce the symptoms of physical weakness, and prevent the occurrence of physical disability⁶². Compared with older adults with high-level PA, older adults with low-level PA are more vulnerable to the negative effects of physical frailty. As a result, physical frailty may cause more interference in older adults with low-level

PA and increase the risk of physical disability.

We also find that physical disability has a significant impact on quality of life at both high and low-level of PA. Compared with older adults with high levels of PA, physical disability is more likely to adversely affect HRQoL of older adults with low-level PA. A study showed that low-level PA was a major contributing factor for older adults disability⁶³. As the level of disability increases, the individuals with low-level of PA experience a more serious functional decline and become more worried about the health status, thus further negatively affect the HRQoL⁶⁴. In addition, physical disability has a greater effect on individuals with low-level PA than high-level PA, which indicates that PA plays a moderating role between physical disability and HRQoL. One study found that PA could improve the physical function and daily life activities of disabled older adults, and ultimately improved the life of older adults quality⁶⁵. Therefore, a low-level of PA might be associated with poor quality of life in rural older adults with high disability.

However, physical activity does not moderate the direct relationship between physical frailty and HRQoL. Physical frailty may lead to a decline in physical function, muscle strength and physical activity in older adults, which may increase the risk of adverse health outcomes and ultimately affects HRQoL of older adults. Currently, there are few studies on the moderating role of physical activity between physical frailty and HRQoL. Further research is needed to explore the underlying reasons for such findings.

Based on our findings, we recommended that community health managers should focus on ensuring the medical assistance, life care of older adults with physical frailty or physical disability. Besides, rural communities should establish some public facilities or organize some public activities to encourage older adults to participate in sports activities, and ultimately improve health and promote their HRQoL. There are several limitations in this study. First, our study was based on a cross-sectional study, which could not provide strong evidence of causation. Future research could adopt a longitudinal design or experiments to explore the causal relationship between physical frailty and HRQoL. Secondly, the data in this study comes from the participants' self-report information, which might result in recall bias. Thirdly, this study only included age and education as control variables. The study may also be affected by other confounding factors. In the future, we will include more confounding factors related to quality of life to verify our findings. Fourthly, physical disability has a partly mediating effect on the relationship between physical frailty and HRQoL, which indicates that there are other mediating variables in this relationship. More potential mechanisms related to physical frailty and HRQoL among older adults need to be explored in the future."

3. As a minor point, in Figure 1 the arrows don't appear to be correct. If physical activity is moderating the effect of physical disability as a mediator then the arrows should go from physical activity towards the line showing the mediation relationship rather than towards physical activity as currently shown. It is also possible that physical activity modifies the direct relationship between physical frailty and HRQoL so an arrow should be drawn from physical activity to this line as well.

Response: Thank you very much for your comments and careful read. We have made modifications to Figure 1 according to the suggestions you provided.

We have added the hypothesis that physical activity may have a moderating effect on physical frailty and HRQoL in the introduction section. According to the model diagram, we used SPSS process V3.3 model 59 to verify the moderated mediation model. Then we found physical activity moderated the relationship between physical frailty and physical disability, and the relationship between physical disability and HRQoL. However, physical activity did not moderate physical frailty and HRQoL. We have modified the data of Table 4, Table 5, Fig 2, Fig 3, and have modified the description of the results. We have made some modifications in the discussion section accordingly.

4. The English is of a good standard but there are some minor errors throughout the text, particularly with the use of prepositions that could benefit from some editing. For example, in many instances where 'the older adults' is written, just 'older adults' would be more appropriate.

Response: Thank you so much for your kind words and also the comments. We have revised 'the

older adults' to 'older adults' throughout the manuscript. In addition, both of the corresponding author, Prof. Chengchao Zhou (a visiting scholar in Stanford University during 2004-2005), and a co-author, Dr. Peipei Fu (a master student in applied economics in Bowling Green State University during 2006-2008) have carefully edited the manuscript again to make it more academic and scientific, and also more readable.

VERSION 2 – REVIEW

REVIEWER	Yili Wu Qingdao University, China
REVIEW RETURNED	19-Nov-2020

GENERAL COMMENTS	I have no further question
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REVIEWER	Fiona Stanaway University of Sydney, Australia
REVIEW RETURNED	03-Dec-2020

GENERAL COMMENTS	<p>The authors have responded well to the comments, but I still have some concerns about the strength of the conclusions given the cross-sectional nature of the data. I would suggest the following edits:</p> <p>Abstract Conclusion: Change 'PA can moderate' to 'PA appears to moderate'. Change 'this study helps to understand the mechanism' to 'this study provides support for potential mechanisms'</p> <p>Strengths and Limitations Point 3: Add 'and may result in biased estimates of mediation effects'</p> <p>Main text Discussion Line 271. Please change to 'we find that physical frailty has a negative association with HRQoL' Line 275. Please change to 'Our study suggests that physical disability mediates the association between physical frailty and HRQoL' Line 294. Please change to 'find that PA appears to play a moderating role' Line 297. Please change to 'appears to moderate the relationship' Line 321. Please change to 'does not appear to moderate' Line 337. Please also add after 'evidence of causation.' 'In addition, using cross-sectional data to examine longitudinal mediation effects can lead to substantially biased estimates of mediation effects.'</p> <p>For this additional comment you can add the reference: Maxwell SE, Cole DA, Mitchell MA. Bias in cross-sectional analyses of longitudinal mediation: partial and complete mediation under an autoregressive model. <i>Multivariate Behavioral Research</i>. 2011; 46(5): 816-841. DOI: 10.1080/00273171.2011.606716</p> <p>General comment Unfortunately, there are still multiple minor English errors that need to be corrected. I would suggest using a professional editor rather than relying on co-authors. For example, line 83 on page 41 in the</p>
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	<p>marked up version, it should be 'falls' not fall. And line 89 on the same page, it should be 'among frail older adults' not 'among the frail older adults.' In contrast, in line 91 of the next page it should be 'the US' not 'US'. On line 112, page 43, it should be 'to examine the relationship' not 'to the relationship.' These are just a few examples and not an extensive list.</p>
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VERSION 2 – AUTHOR RESPONSE

-Reviewer 2

The authors have responded well to the comments, but I still have some concerns about the strength of the conclusions given the cross-sectional nature of the data. I would suggest the following edits:

Response: Many thanks to you for your kind words and your helpful suggestion. We hope we can address all of your comments in this round of revision. Following are the responses to your comments:

1. Abstract

Conclusion: Change 'PA can moderate' to 'PA appears to moderate'. Change 'this study helps to understand the mechanism' to 'this study provides support for potential mechanisms'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new Conclusion reads as follow:

"Conclusions: PA appears to moderate the indirect effect of physical disability on the association between physical frailty and HRQoL. This study provides support for potential mechanisms underlying the association between physical frailty and HRQoL. Encouraging rural older adults to increase PA appropriately might improve HRQoL for older adults with physical frailty and physical disability problems."

2. Strengths and Limitations

Point 3: Add 'and may result in biased estimates of mediation effects'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new Point 3 reads as follow:

"3. Cross-sectional data could not provide strong evidence of causation and may result in biased estimates of mediation effects."

3. Main text

3.1 Discussion

3.1.1 Line 271. Please change to 'we find that physical frailty has a negative association with HRQoL'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new sentence reads as follow:

"Consistent with previous studies^{50 51}, we find that physical frailty has a negative association with HRQoL."

3.1.2 Line 275. Please change to 'Our study suggests that physical disability mediates the association between physical frailty and HRQoL'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new sentence reads as follow:

"Our study suggests that physical disability mediates the association between physical frailty and HRQoL, with the mediating rate of 33.71%."

3.1.3 Line 294. Please change to 'find that PA appears to play a moderating role'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new sentence reads as follow:

"In the present study, we also find that PA appears to play a moderating role in the indirect effect between physical frailty and HRQoL."

3.1.4 Line 297. Please change to 'appears to moderate the relationship'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new sentence reads as follow:

"Specifically, PA appears to moderate the relationship between physical frailty and physical disability, and between physical disability and HRQoL."

3.1.5 Line 321. Please change to 'does not appear to moderate'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new sentence reads as follow:

"However, physical activity does not appear to moderate the direct relationship between physical frailty and HRQoL."

3.1.6 Line 337. Please also add after 'evidence of causation.' 'In addition, using cross-sectional data to examine longitudinal mediation effects can lead to substantially biased estimates of mediation effects.'

Response: Thank you for your helpful suggestions, and we are happy to follow. Now the new sentence reads as follow:

"First, our study was based on a cross-sectional study, which could not provide strong evidence of causation. In addition, using cross-sectional data to examine longitudinal mediation effects can lead to substantially biased estimates of mediation effects⁶⁶."

Reference :

66. Panza F, Capurso C, D'Introno A, et al. Mild cognitive impairment: risk of Alzheimer disease and rate of cognitive decline. *Neurology* 2007;68(12):964; author reply 64-5. doi: 10.1212/01.wnl.0000259691.26674.d3 [published Online First: 2007/03/21]

4. General comment

Unfortunately, there are still multiple minor English errors that need to be corrected. I would suggest using a professional editor rather than relying on co-authors. For example, line 83 on page 41 in the marked up version, it should be 'falls' not fall. And line 89 on the same page, it should be 'among frail older adults' not 'among the frail older adults.' In contrast, in line 91 of the next page it should be 'the US' not 'US'. On line 112, page 43, it should be 'to examine the relationship' not 'to the relationship.' These are just a few examples and not an extensive list.

Response: Many thanks for your careful read and your comments on the English errors. We have revised all of the errors you pointed out in the comment. We also invited a professional editor, Jason Li, from FSI, Stanford University to edit our manuscript again.

VERSION 3 – REVIEW

REVIEWER	Fiona Stanaway Sydney School of Public Health, Faculty of Medicine and Health, University of Sydney, Australia
REVIEW RETURNED	14-Dec-2020
GENERAL COMMENTS	The authors have responded well to the comments and the manuscript is much improved.