

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Predictors of frailty among Chinese community-dwelling older adults with type 2 diabetes: A cross-sectional survey
<b>AUTHORS</b>	Kong, Linglin; Zhao, Huimin; Fan, Junyao; Wang, Quan; Li, Jie; Bai, Jinbing; Mao, Jing

### VERSION 1 – REVIEW

<b>REVIEWER</b>	Mathieu Maltais University of Sherbrooke, Canada
<b>REVIEW RETURNED</b>	15-Jul-2020

<b>GENERAL COMMENTS</b>	<p>This is an interesting study that wanted to identify the prevalence and predictors of frailty in Chinese T2D individuals.</p> <p>Although this is an interesting study, I have few major comments:</p> <ol style="list-style-type: none"><li>1. I feel that the sample size is not adequate for this type of study. There is only 56 frail participants in the cohort, which seem a bit low to provide conclusions. Especially for some variables tested (alcohol consumption - it may have overestimated the odds ratio in the logistic regressions)</li><li>2. First, before re-submission, I strongly recommend that the paper is proofed by a native-English scientist, because there are important grammatical errors in the paper.</li><li>3. The introduction needs improvement. It does not reflect on the objectives and needs to be more structured and more focused. It is very long (&gt;3 pages) and difficult to follow - especially for an exploratory cross-sectional study.</li><li>4. The sections in the methods section need to be shuffled so the manuscript has a better flow. For example, "Data collection and ethical considerations" should be moved after "study design".</li><li>5. Why did the authors not provide a pre-frail group? It may be helpful in understanding the clinical characteristics of these individuals because of their risk of developing frailty compared to the robust individuals.</li></ol> <p>Significant differences were found between frail and non frail individuals, but both had similar median (table 3). Please elaborate.</p> <p>In table 3: exercise seemed higher in non-frail individuals, which is expected because it is one of the Fried criterias. But the PASE do not have a range of 0-14. What is this range?</p>
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<b>REVIEWER</b>	Tu Nguyen University of Sydney, Australia
<b>REVIEW RETURNED</b>	16-Jul-2020

<b>GENERAL COMMENTS</b>	<p>Thank you for the opportunity to review this paper. In this cross-sectional study in 291 community-dwelling older adults aged <math>\geq 65</math> years with type 2 diabetes, the authors found that frailty was present in 19.2% of the participants. Regarding the predictors of frailty, “non-current alcohol drinker” status, higher level of HbA1c, malnutrition, and more depressive symptoms were risk factors of frailty, while exercise and foot self-care behavior were protective factors of frailty. The findings of this study could facilitate future studies to implement targeted and suitable interventions for frailty among community-dwelling older adults with type 2 diabetes, and also contribute to the epidemiology of diabetes in old and frail people in Asia.</p> <p>Overall, the manuscript was well written. Please see below my specific comments:</p> <ol style="list-style-type: none"> <li>1. Exclusion criteria: in the limitation part, the authors stated that they excluded the older adults who could not walk independently, and with severe vision and hearing problems. This should be added in the Method section as well. The current exclusion criteria in the Methods just included: (1) were unable to communicate with the investigators; (2) had dementia or mental health disorders; and (3) had acute diabetic complications. (Page 8 lines 4-7)</li> <li>2. The relationship between alcohol consumption and frailty: Definition of alcohol consumption: more details needed such as the number of units of alcohol consumed per week for current drinkers. For ex-drinkers, when did they stop drinking, and how much they consumed previously. If this information was not collected, it should be stated in the limitation part. Compared to current drinkers, non-drinkers/ex-drinkers were more likely to be frail: OR = 4.37, 95% CI 1.55 - 12.37. This is an interesting finding and the authors provided a comprehensive explanation of this relationship in the Discussion part. However, did the authors check for collinearity and interaction of the variables that were entered in the multivariate logistic models? More specifically, the interaction between sex-alcohol consumption should be checked. Many studies have shown that women are more likely to be frail than men. The significant impact of alcohol consumption on frailty in this study may be because women were more likely to be non-drinkers. It may be the effect of sex rather than alcohol, as in Table 1, the prevalence of frailty was higher in women compared to men (in women: <math>35/154=22.7\%</math>, in men: <math>21/137=15.3\%</math>). What is the unadjusted odds ratio for univariate analysis of sex on frailty?</li> <li>3. The relationship between HbA1c and frailty: HbA1c: “HbA1c measurement was administered by the laboratory in the community health centers” (lines 38-39 Page 10). The authors should provide more details such as when the blood was collected? All HbA1c measures were obtained after the participants were recruited into the study, or some was obtained from the participants’ health records? Regarding the relationship between HbA1c and frailty, and recommendation of HbA1c in frail older patients with diabetes, the authors can have a reference at the IDF guideline for more</li> </ol>
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	<p>discussion: <a href="https://www.idf.org/e-library/guidelines/78-global-guideline-for-managing-older-people-with-type-2-diabetes.html">https://www.idf.org/e-library/guidelines/78-global-guideline-for-managing-older-people-with-type-2-diabetes.html</a></p> <p>4. The authors should present the results of univariate analyses of potential factors that can be associated with frailty in a Supplementary Table.</p> <p>5. Other minor issues:  Page 3 lines 33-35 in the abstract: the authors should replace “non-current drinker” with “non-drinker/ex-drinker”.  Page 11 line 35: “and median (P25-P75)...”: “P25-P75” should be replaced by “interquartile range”  Page 12 line 33: “The majority of participants were female (52.9%)”: I think the sex ratio was pretty balanced (53% women, 47% men). May be just report that 52.9% of the participants were female.  Table 4: depression, exercise, foot care should be presented as GDS-15 score, PASE score, foot care score (respectively)</p>
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<b>REVIEWER</b>	Prof David Hewson Institute for Health Research University of Bedfordshire United Kingdom
<b>REVIEW RETURNED</b>	28-Aug-2020

<b>GENERAL COMMENTS</b>	<p>General comments</p> <p>This is an interesting paper that could be improved with a stronger rationale, compared to previous work to make clear the added value of this study. In addition, the use of all three categories of the frailty phenotype as well as using three categories of alcohol and smoking behaviour would strengthen the study.</p> <p>Specific comments</p> <p>Introduction</p> <ul style="list-style-type: none"> <li>- The introduction is clear and well-written, including a good rationale for the study and the identification of the relevant risk factors for the study. However, the authors make a clear point at the end of the introduction the authors that little is known about the frailty status of older adults with type 2 diabetes in China. However, there are several studies in which this population has been studied, one of which is cited in the article itself (reference 5). The authors should revisit their rationale to include the presence of previous studies in this area and identify the originality of their study.</li> </ul> <p>Methods</p> <ul style="list-style-type: none"> <li>- The reference for ethical approval should be reported in the text as well as at the article.</li> <li>- Why was frailty classified as frail and non-frail, with the pre-frail category not used in the analysis? There are marked differences between someone non-frail with no criteria meeting the threshold for frailty and someone who fails on two of the frailty criteria.</li> <li>- Similarly, were any analyses carried out on the smoking and drinking variables to look at non-smoker vs ex-smoker and non-drinker vs ex-drinker. If there were no differences when using three levels, this could be used to justify grouping two of the levels together for subsequent analyses.</li> </ul> <p>Results</p> <ul style="list-style-type: none"> <li>- The results are presented clearly, with appropriate statistics reported.</li> </ul> <p>Discussion</p>
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	<p>- The discussion begins by suggesting that this is the first article to explore predictors of frailty in older adults with type 2 diabetes in China, however, several other studies have looked at this population. One of these studies is then cited in the subsequent paragraph. This needs to be modified to provide a better comparison with previous work.</p> <p>- The discussion about current drinkers and former drinkers is interesting and would be helped by an analysis of three groups of drinkers, as mentioned in the feedback on the methods section.</p>
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## VERSION 1 – AUTHOR RESPONSE

Responses to reviewer 1

General comments: This is an interesting study that wanted to identify the prevalence and predictors of frailty in Chinese T2D individuals.

Response: Thank you so much for this comment.

1. I feel that the sample size is not adequate for this type of study. There is only 56 frail participants in the cohort, which seem a bit low to provide conclusions. Especially for some variables tested (alcohol consumption - it may have overestimated the odds ratio in the logistic regressions)

Response: Thank you so much for your consideration. As shown in the Figure 1, although we identified 960 older adults with type 2 diabetes ( $\geq 65$  years) from the community health files in the community health centers, we finally recruited 291 participants because of the lack of accessibility. We agree with your comment and it is the limitation for our study. We supplemented the limitations in the discussion section: "Fourth, the data collected from one city would likely not reflect the nation-wide prevalence of frailty. Fifth, information such as the amount of alcohol consumed weekly for current drinkers and the date of drinking cessation, as well as the amount of previous alcohol consumption for ex-drinkers was not collected in this study. Future studies on the relationship between alcohol consumption and frailty in this population are warranted. Finally, future studies should explore the effects of clinical and behavioral factors on frailty among community-dwelling diabetic older adults using a prospective longitudinal design and a larger sample size".

2. First, before re-submission, I strongly recommend that the paper is proofed by a native-English scientist, because there are important grammatical errors in the paper.

Response: Thank you for your advice. We have invited a native-English scientist for our manuscript proofreading and amended the errors before re-submission.

3. The introduction needs improvement. It does not reflect on the objectives and needs to be more structured and more focused. It is very long (>3 pages) and difficult to follow - especially for an exploratory cross-sectional study.

Response: Thank you for this helpful suggestion. We have deleted some sentences and modified the content in introduction to make it more focused and concise (Page 4, lines 16-19; Page 5, lines 1-10, 15-19).

4. The sections in the methods section need to be shuffled so the manuscript has a better flow. For example, "Data collection and ethical considerations" should be moved after "study design".

Response: Thank you for your nice reminding. We have adjusted the order of methods section and moved the "Data collection and ethical considerations" after "study design and setting".

5. Why did the authors did not provide a pre-frail group? It may be helpful in understanding the clinical characteristics of these individuals because of their risk of developing frailty compared to the robust individuals.

Response: Thank you for your professional suggestion. The dependent variable “frailty” has been divided into “robust, pre-frail and frail” groups for re-analysis in this revised manuscript. We have made all the modification in the Methods, Results, Discussion, Tables and Abstract.

6. Significant differences were found between frail and non frail individuals, but both had similar median (table 3). Please elaborate.

Response: Thank you for your question. We found that the median (IQR) of “medication care behavior” were similar for non-frail and frail individuals, and both of them had the median (IQR) with 7 (7-7) (Table 3 in the original manuscript). This can be explained by two reasons: firstly, in this study, the mean (SD) of “medication care behavior” was  $6.54 \pm 1.47$ , and most of the participants (88.7%) scored 7 points on the “medication care behavior”. Therefore, the median (IQR) for the two groups were similar; secondly, although the median score of “medication care behavior” were similar, the mean (SD) for the non-frail and frail group were  $6.63 \pm 1.305$  and  $6.14 \pm 1.986$ , respectively, which showed a subtle difference between two groups. Thus, it was possible to show a significant statistical difference in the Mann-Whitney U test.

7. In table 3: exercise seemed higher in non-frail individuals, which is expected because it is one of the Fried criterias. But the PASE do not have a range of 0-14. What is this range?

Response: Thank you for your question. We are very sorry for the confusion we made. As we stated in the “Survey instrument” section, the PASE (Physical Activity Scale for the Elderly) was used to assess participants’ physical activity level so as to judge the frailty status. The “Exercise” is one dimension of SDSCA (Summary of Diabetes Self-Care Activities), which was used to evaluate the exercise self-care behavior for the diabetic older adults, and the range of the “exercise score” is 0-14.

Responses to reviewer 2

General comments: In this cross-sectional study in 291 community-dwelling older adults aged  $\geq 65$  years with type 2 diabetes, the authors found that frailty was present in 19.2% of the participants. Regarding the predictors of frailty, “non-current alcohol drinker” status, higher level of HbA1c, malnutrition, and more depressive symptoms were risk factors of frailty, while exercise and foot self-care behavior were protective factors of frailty. The findings of this study could facilitate future studies to implement targeted and suitable interventions for frailty among community-dwelling older adults with type 2 diabetes, and also contribute to the epidemiology of diabetes in old and frail people in Asia. Overall, the manuscript was well written.

Response: We gratefully appreciate for your nice comment.

1. Exclusion criteria: in the limitation part, the authors stated that they excluded the older adults who could not walk independently, and with severe vision and hearing problems. This should be added in the Method section as well. The current exclusion criteria in the Methods just included: (1) were unable to communicate with the investigators; (2) had dementia or mental health disorders; and (3) had acute diabetic complications. (Page 8 lines 4-7)

Response: Thank you for your careful review. We have modified the exclusion criteria in the methods section (Page 7, lines 5-8).

2. The relationship between alcohol consumption and frailty:

Definition of alcohol consumption: more details needed such as the number of units of alcohol consumed per week for current drinkers. For ex-drinkers, when did they stop drinking, and how much they consumed previously. If this information was not collected, it should be stated in the limitation part.

Response: Thank you for the helpful suggestion. We have added the definition of current drinker, ex-drinker and non-drinker in the methods section (Page 7, lines 21-22; Page 8, lines 1-5). However, we didn’t collect the information such as the amount of alcohol consumed weekly for current drinkers, and

the date of drinking cessation, as well as the amount of previous alcohol consumption for ex-drinkers. Thus, we supplemented this limitation in the discussion section (Page 17, lines 4-8).

Compared to current drinkers, non-drinkers/ex-drinkers were more likely to be frail: OR = 4.37, 95% CI 1.55 - 12.37. This is an interesting finding and the authors provided a comprehensive explanation of this relationship in the Discussion part. However, did the authors check for collinearity and interaction of the variables that were entered in the multivariate logistic models? More specifically, the interaction between sex-alcohol consumption should be checked. Many studies have shown that women are more likely to be frail than men. The significant impact of alcohol consumption on frailty in this study may be because women were more likely to be non-drinkers. It may be the effect of sex rather than alcohol, as in Table 1, the prevalence of frailty was higher in women compared to men (in women: 35/154=22.7%, in men: 21/137=15.3%). What is the unadjusted odds ratio for univariate analysis of sex on frailty?

Response: Thank you for your helpful suggestion. We had checked for collinearity of the variables that were entered in the multivariate logistic models. Multi-collinearity between the independent variables was assessed by performing variance inflation factor (VIF) test, and all the VIF values were less than 10, which indicated the absence of multi-collinearity in our study. According to your suggestion, we evaluated the interaction between sex-alcohol consumption by performing multiple logistic regression, and there was no interaction between sex-alcohol consumption ( $p > 0.05$ ) in our study. The unadjusted odds ratio for univariate analysis of sex on frailty is 0.616 (95% CI 0.338 to 1.120,  $p > 0.05$ ) in our study.

In order to better understand the relationship between alcohol consumption and frailty, we categorized the "alcohol drinking" into "non-drinker, ex-drinker and current drinker" in this revision. The multivariate logistic regression model indicated that alcohol drinking (ex-drinker) (OR = 4.461, 95% CI 1.079 to 18.438) was the risk factor of frailty in our study, which proved our preliminary hypothesis of "sick quitter" effect. The diabetic older adults in poor health may reduce alcohol consumption or quit drinking, so the ex-drinker group may contain people who were previous alcoholism or with a poor health condition. However, the information such as the amount of alcohol consumed weekly for current drinkers and the date of drinking cessation, as well as the amount of previous alcohol consumption for ex-drinkers was not collected in this study. Therefore, we mentioned that future studies on the relationship between alcohol consumption and frailty in diabetic older population are warranted in the limitation section (Page 17, lines 4-8).

### 3. The relationship between HbA1c and frailty:

HbA1c: "HbA1c measurement was administered by the laboratory in the community health centers" (lines 38-39 Page 10). The authors should provide more details such as when the blood was collected? All HbA1c measures were obtained after the participants were recruited into the study, or some was obtained from the participants' health records?

Response: Thank you for the question and suggestion. In our study, all the HbA1c measures were obtained after the participants were recruited into the study. The blood collection and HbA1c measurements were administered by the community health center laboratories when the participants came to the centers for this survey. We supplemented the details in terms of HbA1c measurement in the methods section (Page 10, lines 3-6).

Regarding the relationship between HbA1c and frailty, and recommendation of HbA1c in frail older patients with diabetes, the authors can have a reference at the IDF guideline for more discussion: <https://www.idf.org/e-library/guidelines/78-global-guideline-for-managing-older-people-with-type-2-diabetes.html>

Response: Thank you for the advice. We supplemented the recommendation of the HbA1c target for the older people with type 2 diabetes by citing the reference (IDF guideline) in the Discussion (Page 14, lines 17-19). In addition, we added another reference (an international position statement) in the

Discussion in terms of HbA1c target for mild to moderate frail and severe frail diabetic older adults (Page 14, lines 19-22).

4. The authors should present the results of univariate analyses of potential factors that can be associated with frailty in a Supplementary Table.

Response: Thank you for your suggestion. We are very sorry for the confusion we made. As we stated in the "Data analysis", the univariate analyses were conducted using chi-square test for categorical variables and Kruskal-Wallis H test for continuous variables in the revised manuscript. The results of univariate analyses of potential factors that can be associated with frailty were presented in the Table 1, Table 2 and Table 3 with P value. In addition, we have modified the titles of tables to make it clearer.

5. Other minor issues:

Page 3 lines 33-35 in the abstract: the authors should replace "non-current drinker" with "non-drinker/ex-drinker".

Response: Thanks for your advice. Because we have categorized the "alcohol drinking" into "non-drinker, ex-drinker and current drinker" groups in this revision, so we made all the modification in the revised manuscript.

Page 11 line 35: "and median (P25-P75)...": "P25-P75" should be replaced by "interquartile range"

Response: Thanks for your careful review. We have made the correction in the revised manuscript (Page 10, line 13).

Page 12 line 33: "The majority of participants were female (52.9%)": I think the sex ratio was pretty balanced (53% women, 47% men). May be just report that 52.9% of the participants were female.

Response: Thanks for your careful review. We have made the modification in the results section of the revised manuscript (Page 11, line 11).

Table 4: depression, exercise, foot care should be presented as GDS-15 score, PASE score, foot care score (respectively)

Response: Thanks for your suggestion. We have changed the "Depression, Diabetes self-care behaviors, General diet, Specific diet, Exercise, Blood-glucose testing, Foot care and Medication care" to "GDS-15 score, SDSCA score, General diet score, Specific diet score, Exercise score, Blood-glucose testing score, Foot care score and Medication care score" in Table 3 and Table 4 in the revised manuscript.

In addition, we apologize for the confusion we made. As we stated in the "Survey instrument" section, the PASE (Physical Activity Scale for the Elderly) was used to assess participants' physical activity level so as to judge the frailty status, and the "Exercise" is one dimension of SDSCA (Summary of Diabetes Self-Care Activities), which was used to evaluate the exercise self-care behavior for the diabetic older adults. Therefore, we just changed the "Exercise" to "Exercise score" in the tables.

Responses to reviewer 3

General comments: This is an interesting paper that could be improved with a stronger rationale, compared to previous work to make clear the added value of this study. In addition, the use of all three categories of the frailty phenotype as well as using three categories of alcohol and smoking behaviour would strengthen the study.

Response: Thank you for your constructive comments.

Introduction

1. The introduction is clear and well-written, including a good rationale for the study and the identification of the relevant risk factors for the study. However, the authors make a clear point at the

end of the introduction the authors that little is known about the frailty status of older adults with type 2 diabetes in China. However, there are several studies in which this population has been studied, one of which is cited in the article itself (reference 5). The authors should revisit their rationale to include the presence of previous studies in this area and identify the originality of their study.

Response: Thank you so much for your suggestion. We are very sorry for our unclear statement in the introduction. We have made the modification to make our statement clearer and more reasonable. We re-summarized the related studies exploring the associated risk factors for frailty, which enrolled the diabetic older adults aged 60 years and above (Page 4 , lines 16-19), and added the sentence “To our knowledge, only one study reported the prevalence of frailty in a community-dwelling diabetic population in mainland China; however, that study included a sample of diabetic people aged 55 years and older, identifying the risk factors of frailty among an elevated blood glucose (pre-diabetes and diabetes) population” to elaborate the necessity of our study (the reference citing in the revised manuscript is the reference 5 in the original manuscript) (Page 5 , lines 15-19).

#### Methods

2. The reference for ethical approval should be reported in the text as well as at the article.

Response: Thanks for your reminding. We have supplemented the ethical approval number obtained from the Medical Ethics Committee of Huazhong University and Science and Technology in the “Data collection and ethical considerations” section.

3. Why was frailty classified as frail and non-frail, with the pre-frail category not used in the analysis?

There are marked differences between someone non-frail with no criteria meeting the threshold for frailty and someone who fails on two of the frailty criteria.

Response: Thank you for your professional suggestion. The dependent variable “frailty” has been divided into “robust, pre-frail and frail” groups for re-analysis in this revised manuscript. We have made all the modification in the Methods, Results, Discussion, Tables and Abstract.

4. Similarly, were any analyses carried out on the smoking and drinking variables to look at non-smoker vs ex-smoker and non-drinker vs ex-drinker. If there were no differences when using three levels, this could be used to justify grouping two of the levels together for subsequent analyses.

Response: Thank you for your professional suggestion. The “smoking” variable and “alcohol drinking” variable were categorized into “non-smoker, ex-smoker and current smoker” and “non-drinker, ex-drinker and current drinker” for univariate analyses and multinomial logistic regression in the revised manuscript. We have made all the modification in the Methods, Results, Discussion, Tables and Abstract.

#### Results

5. The results are presented clearly, with appropriate statistics reported.

Response: Thank you so much for this comment.

#### Discussion

6. The discussion begins by suggesting that this is the first article to explore predictors of frailty in older adults with type 2 diabetes in China, however, several other studies have looked at this population. One of these studies is then cited in the subsequent paragraph. This needs to be modified to provide a better comparison with previous work.

Response: Thank you for your nice advice. We are very sorry for our unclear statements in the discussion. We have made the modification for the comparison of frailty prevalence with previous studies, and we supplemented the interpretation of the wide variation in the prevalence of frailty in the first paragraph of Discussion (Page 13, lines 4-16).

7. The discussion about current drinkers and former drinkers is interesting and would be helped by an analysis of three groups of drinkers, as mentioned in the feedback on the methods section.



Response: Thank you for your nice advice. The “alcohol drinking” variable was categorized into “non-drinker, ex-drinker and current drinker” for univariate analyses and multinomial logistic regression. Accordingly, we have made the modification in the discussion about the association between alcohol drinking and frailty (Page 13, lines 17-22; Page 14, lines 1-6).

### VERSION 2 – REVIEW

<b>REVIEWER</b>	Mathieu Maltais University of Sherbrooke, Canada
<b>REVIEW RETURNED</b>	06-Nov-2020

<b>GENERAL COMMENTS</b>	<p>The paper has improved quite substantially. However, few concerns are present.</p> <p>Major concerns:</p> <p>1) First is regarding alcohol consumption. The authors addressed adequately the concerns of the other reviewers. However, I have a reservation in interpreting these results, because of the low number of participants that were ex-drinkers and drinkers in the frail group (9 vs 6, respectively, table 2). When looking at table 4 the odd ratios are indeed interesting, but the Confidence intervals are way high (1 to 18), which usually indicates low number of participants in some cases. I suggest to the authors to review this issue with a statistician.</p> <p>This comment is also for malnutrition score, with a high confidence interval (2.4 to 26.3, table 4).</p> <p>Please make sure that this is addressed correctly.</p> <p>Minor comments:</p> <p>1) I suggest reviewers to modify the text by using depressive symptoms instead of depression. Depression is not diagnosed with the GDS scale. It measures the amount of depressive symptoms a participant has. This can be modified in the text. Example: Page 12, line 3: "The median score of depression was 3..." This should be "The median score of depressive symptoms was 3..."</p>
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<b>REVIEWER</b>	Tu Nguyen University of Sydney, Australia
<b>REVIEW RETURNED</b>	13-Nov-2020

<b>GENERAL COMMENTS</b>	The revised manuscript looks great. The authors have addressed my comments. I have nothing to add.
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### VERSION 2 – AUTHOR RESPONSE

Responses to reviewer 1

General comments: The paper has improved quite substantially. However, few concerns are present.

1. Major concerns: First is regarding alcohol consumption. The authors addressed adequately the concerns of the other reviewers. However, I have a reservation in interpreting these results, because

of the low number of participants that were ex-drinkers and drinkers in the frail group (9 vs 6, respectively, table 2). When looking at table 4 the odd ratios are indeed interesting, but the Confidence intervals are way high (1 to 18), which usually indicates low number of participants in some cases. I suggest to the authors to review this issue with a statistician.

This comment is also for malnutrition score, with a high confidence interval (2.4 to 26.3, table 4).

Please make sure that this is addressed correctly.

Response: We deeply appreciate your professional suggestion. According to your suggestion, we have consulted a statistician on this issue in our medical school. The statistician has given us some advice to address the issue of wide confidence interval (CI): for one thing, the CI could be improved by combining groups with low number of cases; for another, the CI may be improved by using the Bootstrap method, 1 2 which can enlarge the sample size.

We carefully considered the statistician's suggestions and re-analyzed the data. Firstly, in this study, there were 96, 6 and 189 participants were "at risk of malnutrition", "malnourished" and "nourished", respectively. Considering low number of cases in the "malnourished" group, we combined the group of "at risk of malnutrition" with the group of "malnourished" for data analysis, so all participants were categorized into two groups: "malnutrition risk/malnutrition" (n=102) and "nourished" (n=189); In addition, the results of multiple logistic regression based on Bootstrap method revealed that "malnutrition risk/malnutrition" was the risk factor for frailty (odds ratio [OR] = 8.061, 95% CI 1.482 to 43.835, p = 0.004). Although the OR is consistent with our previous results (OR = 8.062, 95% CI 2.470 to 26.317, p = 0.001), the 95% CI has become wider than our previous results. Secondly, we also adopted multiple logistic regression based on the Bootstrap method to re-analyzed the association between frailty and alcohol drinking. However, we tried several times and found that the parameter estimates varied widely, indicating the results based on the Bootstrap method were not reliable and this method may not applicable to our study.

Therefore, we still choose the previous statistical method for our study. Although the confidence intervals are a bit wide, they are still acceptable and statistically significant. We have to admit that it is one of limitations in the present study, and we included the limitations in the discussion section: "Fifth, information such as the amount of alcohol consumed weekly for current drinkers and the date of drinking cessation, as well as the amount of previous alcohol consumption for ex-drinkers was not collected in this study. Future studies on the relationship between alcohol consumption and frailty in this population are warranted. Finally, future studies should explore the effects of clinical and behavioral factors on frailty among community-dwelling diabetic older adults using a prospective longitudinal design and a larger sample size" (Page 17, lines 7-13).

## References

1. Bland JM, Altman DG. Statistics Notes: Bootstrap resampling methods. *Bmj* 2015;350:h2622.
2. Bland JM, Altman DG. Statistics Notes: Bootstrap resampling methods (In Chinese). *Bmj Chinese Edition* 2016;19:154-155.

2. Minor comments: I suggest reviewers to modify the text by using depressive symptoms instead of depression. Depression is not diagnosed with the GDS scale. It measures the amount of depressive symptoms a participant has. This can be modified in the text.

Example: Page 12, line 3: "The median score of depression was 3..." This should be "The median score of depressive symptoms was 3..."

Response: Thank you so much for this suggestion and we agree with your comment. We have modified the text by using depressive symptoms instead of depression in the revised manuscript.

Responses to reviewer 2

General comments: The revised manuscript looks great. The authors have addressed my comments. I have nothing to add.

Response: We appreciate your positive evaluation of our work.

### VERSION 3 – REVIEW

<b>REVIEWER</b>	Mathieu Maltais University of Sherbrooke, Canada
<b>REVIEW RETURNED</b>	23-Dec-2020

<b>GENERAL COMMENTS</b>	I thank the authors for replying to my comments. It is now suitable for publication.
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<b>REVIEWER</b>	Tu Nguyen University of Sydney, Australia
<b>REVIEW RETURNED</b>	29-Dec-2020

<b>GENERAL COMMENTS</b>	I have nothing to add.
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