## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | What factors mediate the interrelationship between frailty and pain in cognitively and functionally sound older adults? A prospective longitudinal aging cohort study in Taiwan |
| **AUTHORS** | Chiou, Jing-Hui; Liu, Li-Kuo; Lee, Wei-Ju; Peng, Li-Ning; Chen, Liang-Kung |

## VERSION 1 – REVIEW

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| **REVIEWER** | Reshma A Merchant<br>Division of Geriatric Medicine<br>Department of Medicine<br>Yong Loo Lin School of Medicine<br>National University of Singapore,<br>Singapore. |
| **REVIEW RETURNED** | 09-Aug-2017 |

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| **GENERAL COMMENTS** | The author has mentioned about functional assessment using Functional Autonomy Measurement System (SMAF) but subsequently did not mention in results. There's some grammatical and spelling error need to be corrected. |

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| **REVIEWER** | Alba Malara<br>National Association of Nursing Home for Third Age (ANASTE) |
| **REVIEW RETURNED** | 31-Aug-2017 |

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| **GENERAL COMMENTS** | Methods: Pain measurement<br>The authors have adapted a question about pain from the Short Form 12 Health Survey – “During the past one month, how severe was your bodily pain?”.<br>It would be useful to know if patients are suffering from chronic pain.<br><br>Cognitive function measurement<br>The authors used the MMSE score below 24 (educated ≥ 6 years) or 14 (educated <6 years) to consider the patients globally cognitively impaired.<br>The MMSE has defined scores and correction factors for age and for 4 education levels. It is not clear why the authors have chosen this score.<br><br>In Introduction please revise:<br>Pg 4 line 26: pain-frailty not fraity; Several not sevral |

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| **REVIEWER** | Cary Reid<br>Cornell Medical College<br>New York, NY<br>USA |
| **REVIEW RETURNED** | 02-Oct-2017 |

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| **GENERAL COMMENTS** | This manuscript focuses on an important issue, i.e., what are the mechanisms that underlie the relationship between pain and frailty. My major concerns about the work as as follows:<br><br>1. The authors have not done an adequate job of providing a rationale for examining the putative mediators of the pain-frailty relationship. I encourage the authors to expand their introduction to provide cogent reasons why the factors examined may in fact operate as mediators in the relationship. This is particularly the case for the examination of various cognitive domains.<br>2. The discussion section appears unfocused at times and meandering. I encourage the authors to revise this section focusing on relevant findings and other published research. For example, the paragraph regarding the neurobiologic perspective on pain and depression does not really help here.<br>3. Seems odd to NOT acknowledge the fact that the relationship between pain and frailty is likely bidirectional. How might that have influenced your findings?<br><br>Other issues<br>1. Methods section, para 2, lines 22-26. It appears as if the authors are leveraging an existing dataset to address their research questions. If that is the case, please state this clearly. Also please add whether you are making use of baseline data from the longitudinal study. Same paragraph: How did you screen for cognitive impairment in prospective participants?<br><br>2. Methods, definition of frailty section. Would be good to add threshold criteria in this paragraph.<br><br>3. Methods, pain measurement. You state that you adapted a question about pain from the SF-12. Does this mean that you assessed participants at some other time point besides the baseline? Please clarify.<br><br>4. Methods, pain measurement section. What was the rationale for dichotomizing the pain scores?<br><br>5. Methods, statistical analysis, para 3, line 4. Please describe the method used to create a composite global cognitive function score. |

## VERSION 1 – AUTHOR RESPONSE

Reviewer: Reshma A Merchant
We appreciated your insightful suggestion. Accordingly, the manuscript has been substantially revised. We have provided the following point by point responses.

Comment 1: The author has mentioned about functional assessment using Functional Autonomy Measurement System (SMAF) but subsequently did not mention in results. There's some grammatical and spelling error need to be corrected.
Reply:
In this study, we wanted to explore the relationship among pain, frailty and their mediators in cognitively and functionally sound community-dwelling older adults. Therefore, we excluded people with either ADL or IADL impairment, ie. SMAF-ADL<0 or SMAF-IADL<0. The means of SMAF-ADL and SMAF-IADL were both zero. We have added it in the text. (page 6 line13-14)
Besides, we have checked and revised these grammatical and spelling errors. Thanks a lot !

Reviewer: Alba Malara
We appreciate your helpful suggestions. Accordingly, the manuscript has been substantially revised. We have provided the following point by point responses.

Comment 1: Methods: Pain measurement
The authors have adapted a question about pain from the Short Form 12 Health Survey – “During the past one month, how severe was your bodily pain?”. It would be useful to know if patients are suffering from chronic pain.
Reply:
In the study, we could not identify whether participants are suffering pain lasting more than 3 months or not due to data limitation. Indeed, this is one of our limitations.

Comment 2: Cognitive function measurement
The authors used the MMSE score below 24 (educated ≥ 6 years) or 14 (educated <6 years) to consider the patients globally cognitively impaired. The MMSE has defined scores and correction factors for age and for 4 education levels. It is not clear why the authors have chosen this score.
Reply:
The MMSE is a valid tool to evaluate global cognitive function and extensively used in many studies1. In the study, the cognitively sound participants were enrolled, therefore we exclude the severe global cognitive impairment adults according to previous valid cut-off points. (page 7, line 14 and 15)

1. Liu HC; Lin KN; Teng EL; Wang SJ; Fuh JL; Guo NW, et al. Prevalence and subtypes of dementia in Taiwan: a community survey of 5297 individuals. Journal of the American Geriatrics Society. 1995;43(2):144-9.

Comment 3: In Introduction please revise:
Pg 4 line 26: pain-frailty not fraity; Several not sevral
Reply: We have revised these errors as recommend. (page 4, line26)

Reviewer Name: Cary Reid
We appreciate your constructive and detailed suggestions. Accordingly, the manuscript has been substantially revised. We have provided the following point by point responses.

Comment 1: The authors have not done an adequate job of providing a rationale for examining the putative mediators of the pain-frailty relationship. I encourage the authors to expand their introduction to provide cogent reasons why the factors examined may in fact operate as mediators in the relationship. This is particularly the case for the examination of various cognitive domains.
Reply:
We have added on some literatures to explain why the putative mediators and associated mediating effects examined in the study. (page 5, line 1-3 and line 6-8)

Comment 2: The discussion section appears unfocused at times and meandering. I encourage the authors to revise this section focusing on relevant findings and other published research. For example, the paragraph regarding the neurobiologic perspective on pain and depression does not really help here.
Reply: Thank you for your helpful suggestion. We have rewritten the part of discussion. For the paragraph of the neurological perspective, we have deleted as recommend.

Comment 3: Seems odd to NOT acknowledge the fact that the relationship between pain and frailty is likely bidirectional. How might that have influenced your findings?

Reply:
Previous studies proved (1) pain is independently associated with frailty,1-3 and (2) chronic widespread pain is a risk factor of frailty.4 These evidences showed us that pain would cause frailty. They could not tell us whether frailty would result in bodily pain. The pain-frailty relationship would not likely be bidirectional according the present evidence.
In this study, we found that the total effect of pain on frailty was significant, with the coefficient of c=0.1072 (p=0.0077). After controlling the mediation effect of depression (CES-D), the direct effect of pain on frailty still existed, with the coefficient of c'=0.0760 (p=0.0419). Because c>c', p'>p and p'≠0, pain affects frailty partially via the effect of depression. Depression is a mediator of pain and frailty.

1. Blyth FM; Rochat S; Cumming RG; Creasey H; Handelsman DJ; Le Couteur DG, et al. Pain, frailty and comorbidity on older men: the CHAMP study. Pain. 2008;140(1):224-30.
2. Shega JW; Andrew M; Kotwal A; Lau DT; Herr K; Ersek M, et al. Relationship Between Persistent Pain and 5-Year Mortality: A Population-Based Prospective Cohort Study. Journal of the American Geriatrics Society. 2013;61(12):2135-41.
3. Shega JW; Dale W; Andrew M; Paice J; Rockwood K; Weiner DK. Persistent pain and frailty: a case for homeostenosis. Journal of the American Geriatrics Society. 2012;60(1):113-7.
4. Wade KF; Lee DM; McBeth J; Ravindrarajah R; Gielen E; Pye SR, et al. Chronic widespread pain is associated with worsening frailty in European men. Age and ageing. 2015:afv170.

Other issues
Comment 1: Methods section, para 2, lines 22-26. It appears as if the authors are leveraging an existing dataset to address their research questions. If that is the case, please state this clearly. Also please add whether you are making use of baseline data from the longitudinal study. Same paragraph: How did you screen for cognitive impairment in prospective participants?

Reply:
Yes, we used an existing dataset to address the research questions from the baseline data of the I-Lan Longitudinal Aging Study. We had stated in the methods section. (page 5 line24) The Chinese version of MMSE was used to screen participants' global cognitive function.

Comment 2: Methods, definition of frailty section. Would be good to add threshold criteria in this paragraph.

Reply:
We have added add threshold criteria of CHS frailty criteria in the definition of frailty section. (page 6, line 19-25)

Comment 3: Methods, pain measurement. You state that you adapted a question about pain from the SF-12. Does this mean that you assessed participants at some other time point besides the baseline? Please clarify.

Reply:
In the present study, pain measurement was extracted from SF-12, and we assessed the severity of bodily pain at the same time.

Comment 4: Methods, pain measurement section. What was the rationale for dichotomizing the pain scores?

Reply:
We dichotomize pain scores into no to mild pain and moderate to severe pain according to previously similar studies published by Blyth et al.1(page 7, line 6)

1. Blyth FM; Rochat S; Cumming RG; Creasey H; Handelsman DJ; Le Couteur DG, et al. Pain, frailty and comorbidity on older men: the CHAMP study. Pain. 2008;140(1):224-30.

Comment 5: Methods, statistical analysis, para 3, line 4. Please describe the method used to create a composite global cognitive function score.

Reply:
The composite cognitive function score neuropsychological performance: “NP” was the sum of CVVLT, BNT, VFT, CFT, DB and CDT scores. It was also a continuous variable. Therefore, we revised the manuscript. (page8 line10 )

**VERSION 2 – REVIEW**

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| **REVIEWER** | Reshma A Merchant<br>Yong Loo Lin School of Medicine,<br>Singapore |
| **REVIEW RETURNED** | 16-Nov-2017 |

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| **GENERAL COMMENTS** | For abstract, under primary / secondary outcome, what is your definition of less aged? Should it be middle aged and older adults? Similar term under results.<br><br>Line 19 - "People with either ADL or IADL impairment, ie. SMAF-ADL<0 or SMAF-IADL<0, were excluded. The means of SMAF-ADL and SMAF-IADL were both zero". Did you mean >0 excluded? |

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| **REVIEWER** | Alba Malara<br>Scientific Committee of National Association of Third Age Residences (ANASTE), Italy |
| **REVIEW RETURNED** | 11-Nov-2017 |

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| **GENERAL COMMENTS** | Thank you for the opportunity to review this revised manuscript. My comments were adequately addressed. I have no further comments. |

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| **REVIEWER** | Cary Reid<br>Weill Cornell Medical College |
| **REVIEW RETURNED** | 20-Nov-2017 |

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| **GENERAL COMMENTS** | The revised manuscript is improved but could still be improved in the following ways.<br>1. While the English translation is very good, there are still sections that reflect incorrect translation and require attention, page 5, line 24. "This cross-sectional study retrieved from the baseline data...." is an example of this problem.<br><br>2. Why were individuals with functional (ADL) impairments excluded from the study?<br><br>3. What cut-off on the Chinese MMSE was used to exclude participants from this study?<br><br>4. Table 1. Note in the data for participants ages 65+ you report sex data for male sex only while in the lower panel of the Table (those ages 50-64) you report data for both men and women.<br><br>5. Table 3. Please change moderate pain to moderate-to-severe pain in the rows. |

## VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Reshma A Merchant
Institution and Country: Yong Loo Lin School of Medicine, Singapore

We appreciate your constructive and detailed suggestions. Accordingly, the manuscript has been substantially revised. We have provided the following point by point responses.

Comment 1: For abstract, under primary / secondary outcome, what is your definition of less aged? Should it be middle aged and older adults? Similar term under results.
Reply: Yes, the definition of less aged was 50–64 years. They were middle-aged adults. To avoid misunderstanding, we have replaced “less-aged” with “middle-aged” as recommend.

Comment 2: Line 19 - "People with either ADL or IADL impairment, ie. SMAF-ADL<0 or SMAF-IADL<0, were excluded. The means of SMAF-ADL and SMAF-IADL were both zero". Did you mean >0 excluded?
Reply: The scores of SMAF-ADL<0 and SMAF-IADL <0 , which indicated functional dependent, were all excluded. Therefore, the highest score and mean scores of both SMAF-ADL and SMAF-IADL were zero.

Reviewer: 2
Reviewer Name: Alba Malara
Institution and Country: Scientific Committee of National Association of Third Age Residences (ANASTE), Italy
Please leave your comments for the authors below

Thank you for the opportunity to review this revised manuscript. My comments were adequately addressed. I have no further comments.

Reply: We thank for your constructive inputs and appreciate for your efforts for reviewing our manuscript.

Reviewer: 3
Reviewer Name: Reshma A Merchant
Institution and Country: Yong Loo Lin School of Medicine, Singapore

Comment 1: While the English translation is very good, there are still sections that reflect incorrect translation and require attention, page 5, line 24. "This cross-sectional study retrieved from the baseline data...." is an example of this problem.
Reply: We have rewritten the sentence and the manuscript have been polished by a native English speaker.

Comment 2: Why were individuals with functional (ADL) impairments excluded from the study?
Reply: In this study, we wanted to explore the relationship between pain (as a medical condition) and frailty. As we know, frailty has been taken regards as a state of pre-disability. Therefore, we excluded functionally impaired participants to avoid potential confounding effects.

Comment 3: What cut-off on the Chinese MMSE was used to exclude participants from this study?

Reply: The cut-off on the Chinese MMSE was 24 for educated ≥ 6 years, or 14 for educated < 6 years. As mentioned on page 7, line 14-15. Participants' MMSE score less than the criteria were excluded.

Comment 4: Table 1. Note in the data for participants ages 65+ you report sex data for male sex only while in the lower panel of the Table (those ages 50-64) you report data for both men and women.
Reply: We have corrected the erratum.

Comment 5: Table 3. Please change moderate pain to moderate-to-severe pain in the rows.
Reply: We have changed it to moderate-to-severe pain as recommend.