ARTICLE DETAILS

TITLE (PROVISIONAL)	The Association between Allostatic Load and Mortality among Chinese Older Adults: The Chinese Longitudinal Health and Longevity Study
AUTHORS	Zhang, Tianhang; Yan, Lijing L; Chen, Hua-Shuai; Jin, Hai-Yu; wu, chenkai

VERSION 1 – REVIEW

| REVIEWER | Douglas Crews
The Ohio State University |
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| REVIEW RETURNED | 15-Dec-2020 |

| GENERAL COMMENTS | This is an interesting application of AL to older Chinese sampled during the 1998 Chinese Longitudinal Healthy Longevity Survey, and its multiple follow-ups. Data are from a 2011-2012 ancillary study, where blood was obtained for biomarker typing among 2,439 original participants, and reported mortality. Of these, the sample included 1,519 participants, 53% women averaging 90+ years, and men averaging 80+ years at follow-up. Results confirmed mortality of men was associated significantly with AL burden, but not significantly associated with mortality among females.

Title: Suggest dropping "The Association between". Your analyses are obvious from rest of title.

Keywords: "Allostatic load; Mortality; China; Older adults". All your keywords duplicate those in the title. Keywords are used to index publications. The more they differ from the title words the more likely they are to be found. Can you add new non-repetitious terms?

Text: Authors acknowledge they do not have measures of stress hormones to include in their estimated allostatic load index (ALI), but do have one immune system biomarker, CRP. Recent theory and recommendations for compiling biomarkers into ALIs suggest, such indices should include at least 1 immune and 1 stress biomarker. Most biomarkers included here are measures of cardiovascular function, lipid metabolism, and body habitus. This makes a weaker ALI than the ideal, but still produces a useful estimate in this sample. This estimated ALI associated significantly with mortal outcomes in men, but not women with adjustments. Lack of association of the ALI with mortality among women may reflect the related lack of stress hormones.

Authors have control for many possible covariates, a strength.

RESULTS: The sum of: "For males, 25.5%, 65.3%, and 10.3%" = 100.1? For females, 28.5%, 65.9%, and 5.6% = 100.0.

A few editorial suggestions: "…had a more than three-fold higher hazard of death than those with a lower AL burden…" Add higher.

Same: Add higher: "(score: 5-9) had a more than two-fold higher |

	hazar d of death

An effective what? Drop "an" and add effective: "Social support is effective in relieving stress [40]."

Table 1: Pleas indicate units for all biomarkers. Otherwise, Tables appear appropriate to data. |

| REVIEWER | John Taylor
Florida State University |
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| REVIEW RETURNED | 29-Dec-2020 |

| GENERAL COMMENTS | Manuscript number bmjopen-2020-045369 entitled "The Association between Allostatic Load and Mortality among Chinese Older Adults: The Chinese Longitudinal Health and Longevity Study" examines linkages between allostatic load and mortality within a sample of elderly Chinese study participants. The authors found that higher levels of allostatic load (AL) was associated with higher levels of all-cause mortality among men. No such pattern was observed among women.

This study is one of many documenting the positive association between AL burden and a wide array of health outcomes. According to the authors, the major contribution of this paper is that it was the first study of its kind that employed a sample of Chinese study participants. The findings, for males at least, are consistent with previous studies on this topic.

General Comments:

1.There are several grammatical errors throughout the paper. A detailed copy editing is needed before this paper will be ready for publication.

2.How unique is it that observed associations were limited to male study participants? A brief review of the literature is needed to place these findings in context.

3.Also, some mention should be made of the fact that the sample was extremely old and what, if any way this may have influenced the findings presented here.

Specific Comments:

4.Pg. 12. Was the sample composed of medical patients? If not, they should be referred to as study participants.

5.Table 3. The authors may want to mention that, although no significant associations were observed among females, the findings are trending in in the expected direction. |
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VERSION 1 – AUTHOR RESPONSE

Reviewers' comments:

Reviewer#1: Dr. Douglas Crews, The Ohio State University Comments to the Author:

This is an interesting application of AL to older Chinese sampled during the 1998 Chinese Longitudinal Healthy Longevity Survey, and its multiple follow-ups. Data are from a 2011-2012 ancillary study, where blood was obtained for biomarker typing among 2,439 original participants, and reported mortality. Of these, the sample included 1,519 participants, 53% women averaging 90+ years, and men averaging 80+ years at follow-up. Results confirmed mortality of men was associated significantly with AL burden, but not significantly associated with mortality among females.

1.Title: Suggest dropping "The Association between". Your analyses are obvious from rest of title.

RESPONSE: Thanks for this suggestion. We have corrected this in the title page.

2.Keywords: "Allostatic load; Mortality; China; Older adults". All your keywords duplicate those in the title. Keywords are used to index publications. The more they differ from the title words the more likely they are to be found. Can you add new non-repetitious terms?

RESPONSE: Thanks for this suggestion. We have added three new keywords: *Chinese, cohort study, disease burden*.

3.Text: Authors acknowledge they do not have measures of stress hormones to include in their estimated allostatic load index (ALI), but do have one immune system biomarker, CRP. Recent theory and recommendations for compiling biomarkers into ALIs suggest, such indices should include at least 1 immune and 1 stress biomarker. Most biomarkers included here are measures of cardiovascular function, lipid metabolism, and body habitus. This makes a weaker ALI than the ideal, but still produces a useful estimate in this sample. This estimated ALI associated significantly with mortal outcomes in men, but not women with adjustments. Lack of association of the ALI with mortality among women may reflect the related lack of stress hormones. Authors have control for many possible covariates, a strength.

RESPONSE: We greatly appreciate reviewer's positive feedback. We added in the Discussion section as suggested, "*First, we did not include any primary neuroendocrine biomarkers such as cortisol in constructing the AL score due to data unavailability; this might partially explain the null finding regarding the association between AL and mortality among women.*" (pp. 14, lines 320-323)

4.RESULTS: The sum of: "For males, 25.5%, 65.3%, and 10.3%" = 100.1? For females, 28.5%, 65.9%, and 5.6% = 100.0. A few editorial suggestions: "…had a more than three-fold higher hazard of death than those with a lower AL burden…" Add higher. Same: Add higher: "(score: 5-9) had a more than two-fold higher hazard of death.

RESPONSE: Thanks for catching up these issues. We have corrected this, "*For males, 25.5%, 64.2%, and 10.3% had an AL score of 0-1, 2-4, and 5-9, respectively.*" (pp. 9, lines 168-169)

We have also added the word "higher" in the places as suggested. (pp. 10, lines 204-208)

5.An effective what? Drop "an" and add effective: "Social support is effective in relieving stress [40]."

Table 1: Pleas indicate units for all biomarkers. Otherwise, Tables appear appropriate to data.

> **RESPONSE**: Thanks for this suggestion. We have revised the sentence as suggested, "*Social support is effective in relieving stress*." (pp. 12, lines 255)

> We have added units of all biomarkers in *Table 1*.

Reviewer#2:

Dr. John Taylor, Florida State University

Comments to the Author:

Manuscript number bmjopen-2020-045369 entitled "The Association between Allostatic Load and Mortality among Chinese Older Adults: The Chinese Longitudinal Health and Longevity Study" examines linkages between allostatic load and mortality within a sample of elderly Chinese study participants. The authors found that higher levels of allostatic load (AL) was associated with higher levels of all-cause mortality among men. No such pattern was observed among women.

This study is one of many documenting the positive association between AL burden and a wide array of health outcomes. According to the authors, the major contribution of this paper is that it was the first study of its kind that employed a sample of Chinese study participants. The findings, for males at least, are consistent with previous studies on this topic.

General Comments:

1. There are several grammatical errors throughout the paper. A detailed copy editing is needed before this paper will be ready for publication.

> **RESPONSE**: Thanks for this suggestion. We have corrected the grammatical errors. For example, "*Examples of biomarkers are blood pressure (BP), cholesterol, and the waist-hip ratio*" (pp.3, lines 12-13) and "*Understanding the relationship between AL and mortality in less developed countries is beneficial for leading to interventions, which could be helpful to change unhealthy lifestyles, decrease morbidity and mortality among the older population*." (pp.4, lines 38-40)

2. How unique is it that observed associations were limited to male study participants? A brief review of the literature is needed to place these findings in context.

RESPONSE: Thanks for this suggestion. We have elaborated in Discussion, "*This finding is somewhat consistent with previous evidence suggesting that AL may be predictor of all-cause mortality later in life.*" (pp. 11, lines 233-235)

We have added, "*To our knowledge, our study was the first to reveal a significant association between AL and mortality among male participants only. However, we need to interpret these results with caution because the findings regarding the association between AL and mortality among females were trending in the expected direction. A study with more female participants is needed to provide a more definite conclusion.*" (pp. 12, lines 261-265)

We have also added, *"Furthermore, different choices of model covariates may influence the strength of observed associations. Hwang et al.'s research only adjusted for age and sex."* (pp. 13, lines 281-282)

3. Also, some mention should be made of the fact that the sample was extremely old and what if any way this may have influenced the findings presented here.

> **RESPONSE:** This is a good suggestion. We added a sentence in the discussion section mentioning this point,*" Lastly, it is important to notice that the sample was extremely old, which may influence which may influence findings presented.*" (pp. 15, lines 338-339)

Specific Comments:

4. Pg. 12. Was the sample composed of medical patients? If not, they should be referred to as study participants.

> **RESPONSE:** This is a statement required by the BMJ Open. We have replaced patients with study participants in the statement. (pp. 9, lines 157-161)

5. Table 3. The authors may want to mention that, although no significant associations were observed among females, the findings are trending in in the expected direction.

> **RESPONSE:** We appreciate for your suggestion. We have added THE following sentence in Discussion," *There is no significant associations observing among females, but the findings are trending in the expected direction."* (pp. 11, lines 236-237)

VERSION 2 – REVIEW

REVIEWER	John Taylor Florida State University
REVIEW RETURNED	12-Apr-2021

GENERAL COMMENTS	The authors have done a very good job of responding to my initial set of critiques.