Reviewer’s report

Title: Early life adversity and C-reactive protein in diverse populations of older adults: a cross-sectional analysis from the International Mobility in Aging Study (IMIAS)

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Reviewer: Alessandro Ble

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In this multi-country (Canada, Columbia and Brazil) cross-sectional study the authors investigated the association between self-reported health status, economic and social adversities in early life and serum levels of C-reactive protein (CRP) in advanced age (people aged 65 to 74). Results of a stratified analysis showed that social adversity is associated with CRP in Canadian cities and that the association is explained by health-related factors and behaviours. No association was found in the pulled data relevant to the cities of Colombia and Brazil.

While the topic of early determinants of health in older age is of interest, important concerns make this manuscript unsuitable for publications in the present form.

Major Compulsory revisions

1. Introduction: It would be useful to include a paragraph on the relevance of their research, perhaps by clarifying why investigating potentially preventable causes/early predictors of inflammation in older age is of importance (anaemia, sarcopenia etc.). Moreover, while to the general medical audience, CRP is mostly a maker of cardiovascular risk, it has been shown that this protein might also be involved in thrombus formation and take part in the onset of cardiovascular events.

2. Methods: I appreciate that using prevalence rates instead of the more widely used odds ratios can facilitate the clinical interpretation of the results. However, Poisson regression when used to analyse cross-sectional data might lead to overestimation or underestimation of confidence intervals (please see Barros et al. 2003). The authors might want to explain what methods they used to account for this statistical issue in the statistical section of the methods.

3. Results, Table 1 description: please report results in percentages (absolute numbers in brackets) to make the table more readable. Moreover, it is rather hard to follow what is reported in table 1 when read along the result section of the manuscript. The main reason is that estimates of different levels of the same characteristic are often reported in the text as the sum of two or more estimates reported in the table. For instance, the authors say “Childhood social adversity
was more frequent in Kingston where 13.4% reported to have suffered two or more adversities and the lowest in Saint-Hyacinthe (10.2)". In table 1, 9.5% of the sample reported two and 6.8% reported three social adversities in Kingston while 6.9% and 3.3% of the sample reported respectively two and three social adversities in Saint-Hyacinthe. The reader is forced to look for percentages of different levels of adversities in parentheses, sum them up by column and compare them by row. In the specific case the percentage reported in the text for Kingston (13.4%) is also different from the correspondent sum of the percentages reported in the table (=14.4% ???).

4. To justify the pooling of Canadian and Latin American cities based on their similarities of distribution of CRP levels, the authors should statistically test whether or not the distribution is actually similar.

5. Please avoid duplicate information. Results of table 2 are replicated in figure 2, 3 and 4. Please choose one of the others.

6. The overall meaning of the results reported in table 5 is different from that reported in the text. While the authors report that “childhood social adversity was significantly associated with hs-CRP (p=0.011) after adjusting age, sex, marital status… These results did not change after extensive adjustment for health behaviour, obesity etc. (Model 2)”. In reality model 2 shows that results did change after adjustment. In fact, not only the .05 level of significance is no longer met, but more importantly the beta coefficient from positive becomes negative. Healthy behaviour seems to be the mediator of the association tested.

7. The point estimate for social adversities (the main finding) in the multivariate analysis relevant to the Canadian cities looks very similar to that of Latin American cities (Model 2 tables 4 and 5, beta coeff. -.110 vs. -.108). To claim for a different behaviour of the association between social difficulties and CRP in Canadian and Latin American cities (here and in table 6) this should be statistically tested by including an interaction term in the model.

8. The chosen exposures, investigated in this analysis, are childhood economic and social difficulty and poor health. These can be considered statistically significant and discussed accordingly at a level of P<.05. However if the authors want to discuss also the associations between the covariates and CRP as statistically significant they have to account for multiple comparisons by applying appropriate methods of adjustment (e.g. Bonferroni).

Minor essential revisions

9. It is not clear why, in men, a threshold for waist circumference of 104 cm rather than the most used 102 cm has been chosen by the authors. Please provide a reference here.

10. In the “exclusion criteria” section, please reported the real number of people excluded because of severe cognitive impairment as opposed to reporting “less than 5”.

Discretionary revisions

11. General comment: I appreciate that the Authors master the scientific literature supporting their research hypothesis. It is also true that the reader is overwhelmed by a wealthy of information that diverge the attention from the main focus and make the flow of the paper sometime harder to follow. The authors might want to shorten the paper, building the manuscript around the main findings and reducing all non-crucial information and comments, particularly in the methods and results sections.

12. Methods: In line with what advised in the general comments, the authors might want to provide full details only on the study-specific design and characteristics (if not published elsewhere). Referencing the choice of specific covariates, particularly for the most obvious ones (smoking, physical activity etc.), instead of fully explaining the rationale of their use will maintain it scientifically sound as well as will improve the flow of the paper.

13. Results: While results of table 3 (association between confounders and CRP) are definitely useful to build a solid multivariate analysis, most of the association found are already known in the literature and this table (and relevant results) can be safely removed.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**

I declare that I have no competing interests