Reviewer’s report

Title: Allostatic load modifies the effect of blood lead levels on elevated blood pressure among middle-aged U.S. adults: a cross-sectional study

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Reviewer: Jane Clougherty

Reviewer’s report:

Thank you for the opportunity to review this manuscript. The topic of social-environmental interactions is certainly timely and important, and the paper may be a very nice contribution to that growing literature. The analysis is very capably done. Nonetheless, there are some items I would like to see better addressed:

1) The central hypothesis needs better motivation in the abstract and introduction. It should be easy to enrich this background, given ample recent EPA workshops on the topic, growing interest among the cumulative risk community, and a few very good reviews in recent years.

2) More attention to plausible mechanistic pathways for combined effects would be useful in the Introduction (perhaps from the toxicological evidence on combined effects).

3) A mean BP was used except where only one was available – suggesting greater misclassification in these individuals. A nice sensitivity test is to re-run the main analyses excluding these individuals with greater expected misclassification, to observe whether EM magnifies in expected direction.

4) Using blood (rather than bone) Pb may be a problem in regards to short retention time and consequent problems in the relative temporality of exposures. The authors need to somehow establish that stressor exposures plausibly occurred prior to physical exposures, so as to have heightened susceptibility to subsequent Pb exposures – else the directionality is quite difficult to interpret, and observed effect modification (EM) may be due to other factors. This issue is discussed in the Clougherty & Kubzansky review.

5) The Allostatic load model has been criticized in that it is actually a composite measure of metabolic and systemic dysregulation – it is not, inherently, a measure of stress. As such, using AL as a marker of stress, and showing an association with a systemic illness (e.g., hypertension) is, well, ... expected. The ‘exposure’ marker here is actually inherently more similar to the outcome under study (hypertension) than to the true exposure from which it is posited to arise (stress). (Indeed, one might wonder why BP was not an original component of the AL model....) For this reason, the authors really need to find some way of establishing that AL is actually associated with some measures of ‘stress’ (a construct of perception which requires questionnaire data or similar) or, less convincingly, with some measure of ‘stressors’ (e.g., census data on poverty,
SEP). The latter is much less satisfying (and spatial misclassification rampant), but may be all that is currently possible with the existing data.

6) Relatedly, once the authors have established that AL is associated with some important ‘stressors,’ they must also somehow justify their assumption that is it the stress associated with say, living in a low-income census tract -- and not the myriad facets of material deprivation (e.g., poor diet, poor housing …) – which is responsible for the observed EM.

7) I wonder what other, more distal, outcomes the authors may have chosen from NHANES? are corroboratory analyses possible with other outcomes?)

8) There is ample risk here of over-controlling by including individual-level covariates on sex, race/ ethnicity, education, marital status…. There is a need for more sensitivity testing to establish the robustness of the central EM, and some indication of variance in this effect.

9) Why is the “High AL” group larger than the “Low AL” group? Can this really be interpreted as “High AL” when many below the median are included? Again the construct of “high stress” needs be better conceptualized & applied. (In general, better conceptualization and activation of the stress chain would be useful in the manuscript.)

Again, thank you for the opportunity to review this interesting manuscript. I wish the authors great success in further developing & validating the work.

**Level of interest:** An article of importance in its field

**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.