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Critiquing a study or a paradigm?

In response to: The Promise of Allostatic Load Rests Upon Strategic Operationalization, Scoring, and Targeted Interventions

To the editor

We are thankful to Li and Rosemberg for their commentary on our study and for giving us the opportunity to respond. Firstly, it should be acknowledged that we agree with many of the points raised as their commentary reads more like a critique of the general Allostatic Load literature rather than a specific commentary on our paper. To briefly recap, our study was designed to compare the explanatory utility of a variety of different Allostatic Load scoring algorithms for predicting health outcomes using a panel of 12 biomarkers across 4 physiological systems using a large nationally representative sample of community-dwelling older people. Our results suggested that the choice of Allostatic Load scoring algorithm exerts a relatively modest influence in predicting several important age-related health outcomes, including walking speed and self-reported health.

Nevertheless, Li and Rosemberg seem to use our study as a springboard to underscore several common and recurring theoretical and empirical issues in the field of Allostatic Load, which arguably no single study can address. Perhaps most notably, the absence of a clear consensus about which biomarkers should be used to define an optimal measure of Allostatic Load. Such concerns have been highlighted extensively in previous reviews (Beckie, 2012; Johnson et al., 2017; Juster et al., 2010), with our own study concluding that any impact from the choice of biomarkers employed to reflect physiological dysregulation remains to be elucidated (McLoughlin et al., 2020; pg 8). This study, the first from my proposed plan of doctoral research, was not designed to directly test the impact of including/ excluding specific biomarkers/ biological systems when generating an Allostatic Load index. In fact, we believe that no singular study is optimized for doing so. We are currently working on a paper that attempts to move towards a consensus statement concerning which biomarkers are integral to Allostatic Load using multi-cohort data (including the NHANES data which Li. et al. used in their own study (Li et al., 2019)) to try to bring some clarity to this issue. The primary contribution of our study is the suggestion that the scoring method is not a major cause of concern for researchers, albeit with the proviso that future studies may wish to consider using sex-specific cut-offs and include medications when determining the overall score.

Does the non-inclusion of neuroendocrine markers invalidate the results of our study? We think not. Whilst the large heterogeneity of biomarkers employed across Allostatic Load studies limits direct comparisons, Johnson et al. (2017) noted that approximately half of the studies examined in their systematic review on socioeconomic position (SEP) and Allostatic Load similarly excluded markers of the HPA axis. The direction of the SEP-Allostatic Load relationship did not vary across these studies (Johnson et al., 2017), suggesting any impact of their inclusion is minimal. A second and related issue highlighted by Li and Rosemberg was whether an uneven number of biomarkers across physiological systems is a cause for concern. We refer readers to our original study, as this issue was addressed comprehensively; to account for inconsistencies in representation of indicators across systems, each dysregulated biomarker was weighted according to the number of biomarkers in the system (see "*system weighted*" scoring algorithm). Results did not suggest that the inclusion of varying quantities of indicators per system impaired the utility of the predictions. Similarly, others have reported no substantive difference in results when comparing system weighted scores with the "classic" count-based method of high risk biomarkers (Barboza Solís et al., 2016; Seeman et al., 1997).

The final issue raised by Li and Rosemberg calls attention to the need for additional prospective and longitudinal research in the field of Allostatic Load. We agree and would also welcome more research in this vein, particularly studies that explore how Allostatic Load develops over time given the growing evidence that the physiological response to stress varies by development stage, and that early childhood may represent a critical / sensitive period for the embedding of disease. A major limitation of many current epidemiologic studies is that biomarkers of Allostatic Load are collected at only one time point, which means we have little understanding of how Allostatic Load develops over time and whether changes in Allostatic Load modify disease risk. This reinforces the need to move beyond simple point in time measures. A major advantage of TILDA is that it has repeat biological measures on the same panel of individuals at each health wave sweep (although not yet available for analysis) which means that we will be able to model the functional form of change in Allostatic Load over time and examine how different Allostatic Load trajectories are related to incident disease states and cause-specific mortality, helping to provide some of the responses to concerns that Li & Rosemberg articulate in their letter.

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