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Letter to the Editor

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Complex exposures require comprehensive and accurate analysis

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To the editor,

We have read with great interest Rimvall, Meteran and Meteran's commentary on our study on latent factors of adverse childhood experiences (ACEs) and their association with asthma in adulthood. We acknowledge the challenges highlighted by Rimvall, Meteran and Meteran about gathering comprehensive data to answer complex problems. In contrast to the interpretation of our work by Rimvall, Meteran and Meteran, our secondary analysis of the Alberta ACE survey[1] was not aimed at replicating a clearly established association. Hughes *et al.*[2] (cited in our article) have nicely summarized the role of ACEs as major risk factors for many health conditions, including respiratory diseases. The meta-analysis by Hughes *et al.*[2] combined data from eight cross-sectional studies ($n = 72{,}050$ individuals) yielding to a moderate pooled odds ratio for an association between respiratory diseases (not only asthma) and experiencing at least four ACEs (no matter which they were). All studies included in the Hughes *et al.* meta-analysis used survey/cross-sectional designs with self-reported data to ascertain both ACEs exposures and respiratory outcomes, similar to the Alberta ACE study.[1]

We agree with Rimvall, Meteran and Meteran answers to complex problems require comprehensive and accurate data. We would add that complex exposures, such as early-life adversity, also require comprehensive and accurate analytical methods. Our work critically examines the measurement and analytic methods that are used to quantify ACEs. ACEs are multidimensional psychological constructs, which lead to large measurement error, requiring appropriate methods to address their complexity. It is well known that different adverse exposures tend to co-occur within the same individuals. These exposures correlate, as demonstrated in our analysis, which makes including them in traditional regression analyses as independent variables problematic and impossible to tease out their individual association with health outcomes. With our analysis of latent factors of ACE exposures, we attempted to do what Rimvall, Meteran and Meteran call for: presenting an alternative statistical method to tackle these measurement challenges in ACE research.

We expect that results of our study can further inform recent controversies about the use of individual ACEs and cumulative ACE scores as predictors of certain conditions in adulthood. The concept of a critical "dose" of ACEs (a threshold of any four as per the studies in the Hughes *et al.* review[2]) is being increasingly criticized from a population-based perspective,[3–5] in favor of epidemiological approaches that help to address the problem from a broader perspective, allowing for developing more structural and communal interventions rather than being concerned about individual "diagnoses" in ACEs practice. We argue that providing evidence of latent structures underling individual ACEs clarifies the public health implications of adverse exposures because some clusters of exposure have stronger associations with specific disease states. Our methodological approach to the study of the relationships between ACE and asthma in adulthood highlights the importance of specific constellations of adverse experiences rather than focusing on the additive value of independent experiences.

Relevant to the discussion about how ACEs relate with asthma in adulthood, the systematic review by Exley *et al.*[6] (also cited in our article) evaluated observational evidence from 12 studies ($n = 31{,}524$) on the relationship between ACEs and asthma onset. Of interest, the review considered physician asthma diagnosis (the same outcome used by the Alberta ACE study[1]) as one of the methods to evaluate asthma in population-based studies. We agree with Rimvall, Meteran and Meteran that assessing the true prevalence of asthma requires confirmation of diagnosis via spirometry to avoid misclassification and disambiguate the symptoms of asthma from related health conditions. We are not aware of prospective studies evaluating associations between ACEs and respiratory physiological measures on a population level that can help to disambiguate asthma from other related conditions. Such work is needed.

Nevertheless, disambiguating the effects of different ACEs is also needed. The review by Exley *et al.*[6] suggests that future research should expand the evidence base on exposure to

multiple ACEs as having a multiplicative effect on the risk of asthma onset and that concurrent multiple ACEs exposure can increase the risk of asthma to a greater extent than adding together the odds ratios for each ACE.[6] Our secondary analysis of the Alberta ACE survey[1] contributes to that knowledge gap: to explore the complexity of the joint effects of ACEs rather than their individual role as predictors of certain conditions in adulthood.

We acknowledge that our paper cannot achieve the research objectives that Rimvall, Meteran, and Meteran have in mind. Nevertheless, we believe that our work addresses the need to clarify the complexity of ACE exposures and the relations between co-occurring clusters of exposure with physician-diagnosed asthma in adults. We fully agree with Rimvall, Meteran and Meteran that advances in the psychosocial contributions to asthma will require comprehensive and accurate outcome data. We hope that our work highlights the need to also comprehensively and accurately model psychosocial exposures.

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