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Editorial

Adverse Childhood Experiences and Later-Life Cognitive Aging: Persistent Methodological Challenges Limit the Evidence Base

Lindsay C. Kobayashi, PhD[1,2,*]

[1]Department of Epidemiology, Center for Social Epidemiology and Population Health, University of Michigan School of Public Health, Ann Arbor, Michigan, USA.
[2]Survey Research Center, Institute for Social Research, University of Michigan, Ann Arbor, Michigan, USA.
*Address correspondence to: Lindsay C. Kobayashi, PhD. E-mail: lkob@umich.edu

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Adverse childhood experiences (ACEs) are stressful or traumatic events that occur during childhood, such as neglect, abuse, exposure to violence or substance abuse, parental divorce, or parental death (1). There is strong biological plausibility for ACEs to have a negative impact on both brain development in early life and neurodegeneration later in life (2,3). Indeed, a body of epidemiological literature from diverse populations indicates that exposure to ACEs may be associated with worse later-life cognitive outcomes (4–9). However, results from this literature are inconsistent. Null results are common, and results tend to vary according to the type of ACE exposure as well as the cognitive outcome under study (4). The inconsistency of this body of literature precludes firm conclusions, and the development of evidence-based interventions to reduce or eliminate ACEs and their potential effects on long-term cognitive health.

In this issue, Hu et al. contribute to this literature by using data from the UK Biobank to demonstrate the associations between 4 types of childhood adversity and risk of dementia among 150 152 adults with a mean age of 55.9 years at baseline from 2006 to 2010, over a mean 13.5-year follow-up period until 2022 (10). Their main finding was a hazards ratio of 1.300 (95% confidence interval: 1.129–1.496) for incident dementia among those with any versus no experience of childhood adversity, adjusting for a range of adulthood sociodemographic factors and health conditions. Their results appeared to be driven by ACEs in the domains of physical neglect and emotional neglect, which were the most common domains experienced by the UK Biobank sample and assessed by questions assessing having "someone to take to doctor when needed as a child" (physical neglect) and "felt loved as a child" (emotional neglect) (10).

The Hu et al. study is a valuable contribution, as it provides new evidence using high-quality data on dementia diagnoses as the outcome, it leverages a large sample size, it examines multiple domains of ACEs, and it considers a variety of behavioral, physiological, and biological mediators (10). However, this study also highlights the methodological challenges involved in studying the association between ACEs and later-life cognitive aging. A key limitation of the Hu et al. study corresponds with a likely key contributor to why this evidence base is inconsistent: the challenge of measuring ACEs in studies of cognitive aging. The Hu. et al study used UK Biobank questionnaire measures that captured being "physically abused by family as a child," "felt hated by family member as a child," "sexually molested as a child," having "someone to take to doctor when needed as a child," and "felt loved as a child," all with Likert-style response options ranging from "never true" to "often true" (10).

Although these are incredibly important early-life experiences to capture in relation to their consequences for later-life health, these questions exemplify the difficulty in capturing their complex, dynamic, and highly personal nature in quantitative research studies. Further, due to their retrospective and self-reported nature, recall error and bias are highly likely. Indeed, in a systematic review and meta-analysis of 16 longitudinal studies, Baldwin et al. found that 52% of individuals who prospectively reported childhood maltreatment did not retrospectively report it, and conversely, that 56% of individuals retrospectively reporting childhood maltreatment did not have concordant prospective reports (11). This high degree of misclassification, if nondifferential according to cognitive outcomes, could help explain the null and small/small-to-medium effect sizes typically observed in studies of ACEs and cognitive aging (4), including in the Hu et al. study.

However, differential recall of ACEs is likely in studies of cognitive aging, as older adults experiencing cognitive impairment may have difficulty in accurately recalling and reporting ACEs. In 2020, we conducted a quantitative bias analysis to evaluate this possibility, as part of a study on ACEs and cognitive function among older, Black South African adults who grew up during South African Apartheid (6). Using a range of plausible sensitivity and specificity values for the accuracy of retrospectively reported ACEs, we found that differential

under-reporting of ACEs by older adults with cognitive impairment would result in the observed associations between ACEs and cognitive function being substantial underestimates of the truth (6). These findings imply that if there are differential under-reporting patterns in the UK Biobank sample like those of our study population in South Africa, the results of the Hu et al. study would again underestimate the truth. Hence, situations of both nondifferential and differential under-reporting of ACEs according to cognitive impairment status would likely have the effect of biasing estimates to the null.

An alternative explanation for inconsistent findings in the literature is true heterogeneity in the effect of ACEs on later-life cognitive outcomes across populations. This possibility is scientifically exciting, as it suggests that a triangulation of results across populations may illuminate certain circumstances that lead to resilience against or vulnerability to the potential cognitive aging impact of ACEs (12,13). Very few studies have examined the modifying roles of potential resilience or vulnerability factors, such as access to mental health services, social support, government social safety nets, or continued adversity across the life course. In addition, subpopulation effects across groups defined by sex/gender, race/ethnicity, and socioeconomic status are not well understood, further limiting our understanding of resilience and vulnerability. High-quality triangulation studies that use harmonized measures across diverse populations that differ in their prevalence and distribution of factors that may modify the effect of ACEs on cognitive outcomes would be valuable to push the evidence base forward.

Finally, the Hu et al. paper included additional limitations that also warrant caution when interpreting its results. The low and selective response to the online mental health questionnaire that included childhood adversity suggests that selection bias may be a concern. This questionnaire was administered between 2016 and 2017, whereas the measures of model covariates and mediators were taken from the UK Biobank baseline from 2006 to 2010. More concerningly, the authors initiated their follow-up for dementia incidence starting from the UK Biobank baseline, rather than when the ACEs were assessed 6–10 years later. These design elements indicate that reverse causality is a concern not only for the main associations but also for their mediation analyses. Cognitive decline in the years preceding a dementia diagnosis could plausibly affect the accuracy of reporting of ACEs in an online questionnaire, which could exaggerate the types of reporting bias described earlier.

In conclusion, the Hu et al. study provides data on a particular subset of the UK population (14), and further longitudinal studies with rigorous measurement and modeling are needed. Triangulation studies with consistent and high-quality measures can give insight into the consistency of associations across diverse populations and subpopulations with different prevalence, vulnerability, and resilience to ACEs. Imaginative approaches would also be valuable to overcome the persistent measurement issues in this area, such as those using qualitative, mixed methods, and life-course designs.

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Conflict of Interest

None.

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