

## PEER REVIEW HISTORY

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### ARTICLE DETAILS

<b>TITLE (PROVISIONAL)</b>	Are adverse childhood experiences associated with late life cognitive performance across racial/ethnic groups: Results from the Kaiser Healthy Aging and Diverse Life Experiences Study Baseline
<b>AUTHORS</b>	Gold, Audra; Meza, Erika; Ackley, Sarah; Mungas, Dan; Whitmer, Rachel; Mayeda, Elizabeth Rose; Miles, Sunita; Eng, Chloe; Gilsanz, Paola; Glymour, M

### VERSION 1 – REVIEW

<b>REVIEWER</b>	C Comacchio AOUI Verona
<b>REVIEW RETURNED</b>	16-Sep-2020

<b>GENERAL COMMENTS</b>	<p>This is a paper on the impact of adverse childhood experiences (ACE) on cognition in later life. It is well written and interesting.</p> <p>However, I have the following observations:</p> <ul style="list-style-type: none"><li>-physical abuse and sexual abuse were not included in the screening tool. This is quite weird because these types of ACEs are frequent in the general population. This issue has been briefly discussed in the limitation section but you should explain better why physical and sexual abuse were not included in your analyses and how this may have affected the results (i.e. gender differences in cognition due to gender differences in rates of ACEs)</li><li>-the impact of number and severity of ACEs on cognition was not taken into account, but this should be discussed</li></ul>
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<b>REVIEWER</b>	Gary Donohoe NUI Galway Ireland
<b>REVIEW RETURNED</b>	25-Sep-2020

<b>GENERAL COMMENTS</b>	<p>This interesting study examines the effects of adverse childhood experience on cognitive function in later life (65+ years) based on a large sample of n=1661 health participants. Strengths of the manuscript include that it is well written, involves analysis of not just different types of adversity but also the age at which they first occurred, and well established measures of cognition, including memory (word learning) and semantic memory and executive function (fluency and digit span). The authors report, based on their analyses, that later life cognitive function is relatively resilient to (i.e. not associated with) early life adversity.</p> <p>There were a number of ways in which I felt the impact of the manuscript could be strengthened. Firstly, given that the manuscript is being considered by the BMJ, there was scant attention paid to how</p>
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	<p>this subject is related to health. The authors make the obvious comment that cognitive changes may related to later experience of Alzheimer's disease. However, this is a healthy sample and consideration other ways in which cognition is related to health was warranted (e.g. Davies NM et al, 2019; PMID 31526476).</p> <p>A second comment was regarding the absence of linkage between this study and recent studies of the effects of adversity on cognition in children and young adults (CF several studies based on the ALSPAC dataset). This is etiologically important: it is well established that intelligence in childhood is strongly influences by environment but that with development environment appears to matters less and genetics appears to matter more. This provides important context for discussing the findings of the study.</p> <p>A final point is regarding the measures of adversity used. These are somewhat constrained to issues of illness, witnessing intimate partner violence and divorce. Other frequently measured measures (e.g. neglect) are not by comparison including and this limitation should be noted.</p>
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**VERSION 1 – AUTHOR RESPONSE**

Reviewer 1:

Reviewer Name: C Comacchio

Institution and Country: AOUI Verona

Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below

This is a paper on the impact of adverse childhood experiences (ACE) on cognition in later life. It is well written and interesting.

Thank you for the positive feedback.

However, I have the following observations:

-physical abuse and sexual abuse were not included in the screening tool. This is quite weird because these types of ACEs are frequent in the general population. This issue has been briefly discussed in the limitation section but you should explain better why physical and sexual abuse were not included in your analyses and how this may have affected the results (i.e. gender differences in cognition due to gender differences in rates of ACEs)

This is a great point and we agree with your assessment. Physical and sexual abuse were unfortunately not included in the ACE questions asked to the KHANDLE participants at baseline. When the baseline survey was being planned, it was felt that interviewers would need a great deal of rapport with these older participants before asking about sexual and physical abuse in the face-to-face interview and these items should be deferred until a subsequent KHANDLE wave. Thus, we could not incorporate these important domains of abuse into our analysis. We have discussed the importance of this point in the manuscript (see text below), flagging that our results do not rule out the relevance of more severe ACEs such as sexual abuse.

“The survey used in KHANDLE does not include questions about neglect, physical, or sexual abuse, rather, it focuses on household dysfunction questions. Our null findings with the 9 ACEs assessed in

KHANDLE do not rule out the relevance of other ACEs that are more severe.” (page 8, lines 307-310)

-the impact of number and severity of ACEs on cognition was not taken into account, but this should be discussed

The count of ACEs and cognition was considered in Table 2, with a higher composite score representing increased number of ACEs; thus, the possible number of exposures ranged from 0 (unexposed) to 4+ (exposed to all categories). We made the limit 4 because there were very few who had cumulative exposures over 4. Coefficients for each ACE are shown in Table 3. We did not attempt a priori to rank the severity of these experiences, because we are not sure how to compare for example parental death versus exposure to family violence.

Reviewer 2

Reviewer Name : Gary Donohoe

Institution and Country: NUI Galway, Ireland

Please state any competing interests or state 'None declared': None

Please leave your comments for the authors below

This interesting study examines the effects of adverse childhood experience on cognitive function in later life (65+ years) based on a large sample of n=1661 health participants. Strengths of the manuscript include that it is well written, involves analysis of not just different types of adversity but also the age at which they first occurred, and well established measures of cognition, including memory (word learning) and semantic memory and executive function (fluency and digit span). The authors report, based on their analyses, that later life cognitive function is relatively resilient to (i.e. not associated with) early life adversity.

Thank you for the positive feedback.

There were a number of ways in which I felt the impact of the manuscript could be strengthened. Firstly, given that the manuscript is being considered by the BMJ, there was scant attention paid to how this subject is related to health. The authors make the obvious comment that cognitive changes may be related to later experience of Alzheimer's disease. However, this is a healthy sample and consideration of other ways in which cognition is related to health was warranted (e.g. Davies NM et al, 2019; PMID 31526476).

Thank you for pointing this out. KHANDLE was founded with the aim of understanding cognitive aging, so we sometimes take for granted the importance of late life cognition! But it would be very useful to flag how relevant cognitive function is for countless other health domains. We have added the following text:

Introduction: Understanding the links between ACE exposure and late life cognitive function is critical because low cognitive function, especially memory, is a strong predictor of risk of dementia, mortality, institutionalization, self-rated health, and disability, among other health outcomes.1,4,7–9 (page 3, lines 64-67)

And

Discussion: Understanding early life determinants of cognition in older age is important because cognitive function is predictive of myriad health outcomes, including physical health and functional independence as well as dementia.1,7–9,26 (page 9, lines 323-325)

A second comment was regarding the absence of linkage between this study and recent studies of the effects of adversity on cognition in children and young adults (CF several studies based on the

ALSPAC dataset). This is etiologically important: it is well established that intelligence in childhood is strongly influenced by environment but that with development environment appears to matter less and genetics appears to matter more. This provides important context for discussing the findings of the study.

We have noted the prior evidence on children, although we are hesitant to delve too deeply in this complex and very active research domain within the brief space in this paper.

Discussion: Our finding of no association between overall ACE count and cognition is surprising in light of prior evidence that ACEs influence multiple domains of adult physical health.<sup>1,18</sup> Early life stress predicts both hippocampus and amygdala development in children as well as children's cognitive and affective functioning.<sup>19–21</sup> However, children's responses to such adversity are very heterogeneous, and both social and genetic factors may ameliorate or outweigh the effects of adversity as a child matures.<sup>22</sup> (page 7, lines 265-268)

A final point is regarding the measures of adversity used. These are somewhat constrained to issues of illness, witnessing intimate partner violence and divorce. Other frequently measured measures (e.g. neglect) are not by comparison including and this limitation should be noted.

We agree with the reviewer's suggestion and have added more details in the limitations section about our ACE instrument being more attuned to household dysfunction versus the more severe ACEs including, physical/sexual abuse and neglect. The text now reads as below:

"The survey used in KHANDLE does not include questions about neglect, physical, or sexual abuse, rather, it focuses on household dysfunction questions. Our null findings with the 9 ACEs assessed in KHANDLE do not rule out the relevance of other ACEs that are more severe." (page 8, lines 307-310)

#### VERSION 2 – REVIEW

<b>REVIEWER</b>	Gary Donohoe NUI Galway Ireland
<b>REVIEW RETURNED</b>	02-Dec-2020
<b>GENERAL COMMENTS</b>	The authors have addressed my recommendations.