PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	What is the association between adverse childhood experiences and late-life cognitive decline? Study of Healthy Aging in African Americans (STAR) Cohort Study
AUTHORS	Lor, Yi; George, Kristen M; Gilsanz, Paola; Meunier, Claire; Peterson, Rachel; Hayes-Larson, Eleanor; Barnes, Lisa; Mungas, Dan; Whitmer, Rachel

VERSION 1 – REVIEW

REVIEWER	Halpin, Amy The University of Maine
REVIEW RETURNED	02-May-2023

GENERAL COMMENTS	Thank you for the opportunity to review the article “What is the association between adverse childhood experiences and late-life cognitive decline? Study of Healthy Aging in African Americans (STAR) Cohort Study.” This study is timely and valuable to the field of neuropsychology. The authors address two important gaps in the literature: a) longitudinal impacts of adverse experiences on cognitive functioning and b) a better understanding of risk/resiliency factors for cognitive decline within diverse, community-dwelling populations. The authors provide relevant and robust theories that subserve their rationale for conducting the study. The authors further used a series of well-studied and appropriate cognitive measures and questionnaires to determine associations between early adversity and mid to late-life cognitive functioning. The comprehensive nature of their evaluation and consideration of multiple key contributors to late-life cognition was appreciated. Furthermore, their statistical approach was elegant and appropriate for investigating these associations. The authors also provided a relevant and rich discussion to support their findings. Despite this, the article would benefit from additional considerations. Specific comments follow. Introduction 1. It is recommended that the authors include more pointed studies that specifically investigate associations between early life adversity and cognition. Right now, the authors do not provide a clear link for why they specifically chose executive function and verbal episodic memory. 2. In the same vein, the introduction would be strengthened by the inclusion of studies that investigate differential outcomes (or similar outcomes) between different types of ACEs and cognition to better support their hypothesis that all types of ACEs will be related to worse cognitive outcomes.

	Methods 1. While the authors referenced a prior study for further detail on their cognitive measures/procedures, a brief but more explicit description of the specific cognitive tests used would be appreciated by the reader. 2. It is unclear what ACE measure was used by reading the methods section. 3. The social factors outlined in the methods section provide an interesting layer to the study design, as investigating both risk and resiliency factors meaningfully contributes to the literature. However, I am curious as to whether the reliability of these scales was examined in the current sample. 4. I recommend the authors provide more rationale and justification for their parent education and participant education groups. To me, it seems like it would make sense to have three groups for parents: 1) both high school, 2) one high school and one more, and 3) both more. Similarly for the participants, 1) high school, 2) some college and 3) college/graduate. There is some evidence to suggest there are meaningful differences between some college and college groups. 5. The terms male and female are more consistent with sex as opposed to gender. Results 1. Perhaps I am misunderstanding how it is written, but I am confused with how 75% of participants only had 2 waves of cognitive data, yet 83% had all 3 waves of cognitive data. These percentages don't add up. Discussion 1. It is recommended that the authors provide more specific directions for future research in the discussion. 2. In the discussion, the authors note that a prior study found that lower SES was associated with faster aging. However, it is unclear what aging refers to here (e.g., worse cognitive functioning? More rapid decline? Greater number of health risk factors?) 3. The authors also mention that "CI theory suggests that the detrimental, cumulative impact of experiencing multiple ACEs may have been modified by other factors, such as human agency or social support." This is a powerful potential reason for the current study's findings; however, it was not examined whether a greater number of ACEs was associated with more protective factors. In order to better align with the theory used to support the study, it is recommended that the authors investigate whether the number of ACEs was positively associated with the number of supportive social factors. Overall 1. The manuscript in totality could benefit from an eye toward grammar. Some examples: • Page 7, line 33 should read "Black" not "Blacks" • Page 9, line 47: ACEs, not ACES • Page 12 line 13 should be changed to "someone close to" instead of "someone to close" • Page 17 line 6 needs a "with" added between "associated" and "faster"

REVIEWER	He, Ping Peking University, China Center for Health Development Studies

REVIEW RETURNED	06-Jun-2023

GENERAL COMMENTS	This study examined the longitudinal association between ACEs and late-life cognitive decline among African Americans. The major concerns are described below: 1. According to the description of the sample in the method, the subjects were long-term members of Kaiser permanent Northern California, which seems not representative for the older Africans in United States. Is there any unique characteristics of this cohort? 2. I have doubts on the idea that focusing on the association between ACEs and cognitive trajectory, since follow-up time was only three years. It is really difficult to examine a cognitive decline in such a short period, the difference of cognitive score across years could result from measurement error. 3.Another concern is the insufficient adjustment. Only years from baseline, baseline age centered at mean, gender/sex, childhood SES, and composite childhood support were included in the model. Other covariates such as marital status, current financial status, employment, education, current health status should all be adjusted. Otherwise, the result were not robust.

REVIEWER	Tzouvara, Vasiliki King's College London
REVIEW RETURNED	06-Jun-2023

GENERAL COMMENTS	Thank you for submitting this very interesting and useful study on ACEs and cognitive decline. Please find my comments below: Introduction: It would be beneficial to explain in detail which ACEs typologies/framework was used, particularly due to the lack of questions related to abuse which is also one of the major limitations of this study. It would be very interesting and more valuable to know how abuse associates with cognitive decline in this population. It would be advantageous to define and discuss cognitive function and episodic memory and to explain why verbal episodic memory and not for example visual imagery? Methods: I am not entirely convinced about the accuracy of covariates adjustments for analysis and why it was decided to go this way and not to do something else. Could you provide some justification for your decision. Results: I think it is important non-significant results to be communicated and reported. Discussion: The structure of the discussion needs a lot of work. The discussion of the findings in relation to the literature and theory should proceed the section on strengths and limitations of the study. The authors do provide an explanation for the non-significant results but this could be stronger and better explained, particularly given the limitations of the study. I think the discussion re episodic memory should be stronger and maybe literature from neuroscience and neuropsychology would be really advantageous here. Overall structure: The paper is well written, however the referencing system doesn't seem to be entirely correct. The dots should be added after the referencing numbers. Needs proof reading.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Comments to the Author:
Thank you for the opportunity to review the article “What is the association between adverse childhood experiences and late-life cognitive decline? Study of Healthy Aging in African Americans (STAR) Cohort Study.” This study is timely and valuable to the field of neuropsychology. The authors address two important gaps in the literature: a) longitudinal impacts of adverse experiences on cognitive functioning and b) a better understanding of risk/resiliency factors for cognitive decline within diverse, community-dwelling populations. The authors provide relevant and robust theories that subserve their rationale for conducting the study. The authors further used a series of well-studied and appropriate cognitive measures and questionnaires to determine associations between early adversity and mid to late-life cognitive functioning. The comprehensive nature of their evaluation and consideration of multiple key contributors to late-life cognition was appreciated. Furthermore, their statistical approach was elegant and appropriate for investigating these associations. The authors also provided a relevant and rich discussion to support their findings. Despite this, the article would benefit from additional considerations. Specific comments follow.
● Response: We thank the reviewer for their kind comments and encouraging feedback. We will address the reviewer’s specific comments below to further strengthen our manuscript.

Introduction
1. It is recommended that the authors include more pointed studies that specifically investigate associations between early life adversity and cognition. Right now, the authors do not provide a clear link for why they specifically chose executive function and verbal episodic memory.
● Response: Thank you for this point. We have provided more discussion and included additional studies of why examining executive function and verbal episodic memory is warranted. To further strengthen this point, we added two review studies (Lund et al., 2020, 2022) examining the association between early life adversity and executive function specifically.
● Changes in manuscript:
○ “Cognitive decline and decreased cognitive function are early indicators of Alzheimer’s disease and related dementias(4). Signs of these cognitive deficits often includes loss of memory and/or loss of the ability to perform high-level mental skills (executive function) such as planning, and management of thoughts and emotions. Therefore, many studies administering cognitive assessments will include some form of memory and executive function assessment(5,6).” (Introduction, page 6, lines 9-10)
○ “Moreover, two systematic reviews found that abuse and neglect were associated with worse executive function(11,12).” (Introduction, page 6, 18-20)
● References:
Lund, J. I., Boles, K., Radford, A., Toombs, E., & Mushquash, C. J. (2022). A Systematic Review of Childhood Adversity and Executive Functions Outcomes among Adults. Archives of Clinical Neuropsychology: The Official Journal of the National Academy of Neuropsychologists, 37(6), 1118–1132. https://doi.org/10.1093/arclin/acac013
Lund, J. I., Toombs, E., Radford, A., Boles, K., & Mushquash, C. (2020). Adverse Childhood Experiences and Executive Function Difficulties in Children: A Systematic Review. Child Abuse & Neglect, 106, 104485. https://doi.org/10.1016/j.chiabu.2020.104485

2. In the same vein, the introduction would be strengthened by the inclusion of studies that investigate differential outcomes (or similar outcomes) between different types of ACEs and cognition to better support their hypothesis that all types of ACEs will be related to worse cognitive outcomes.
● Response: We thank the reviewer for this suggestion to strengthen our manuscript. We included these studies which all examined different types of ACEs and cognition (Barnes et al., 2012; Gold et al., 2021; Kobayashi et al., 2020; O’Shea et al., 2021; Ritchie et al., 2011; Yang & Wang, 2020). We

have added details on how different types of ACEs in these studies were found to be associated with memory.
● Changes in manuscript: “These studies examining the specific types of ACEs have reported associations between of the death of a parent, parental excess alcohol and drug use, mental health problems, physical neglect, and emotional abuse experienced during childhood with worse memory later in life.” (Introduction, page 6, lines 15-18)
● References:
Barnes, L. L., Wilson, R. S., Everson-Rose, S. A., Hayward, M. D., Evans, D. A., & Mendes de Leon, C. F. (2012). Effects of early-life adversity on cognitive decline in older African Americans and whites. Neurology, 79(24), Article 24. https://doi.org/10.1212/WNL.0b013e318278b607
Gold, A. L., Meza, E., Ackley, S. F., Mungas, D. M., Whitmer, R. A., Mayeda, E. R., Miles, S., Eng, C. W., Gilsanz, P., & Glymour, M. M. (2021). 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. BMJ Open, 11(2), Article 2. https://doi.org/10.1136/bmjopen-2020-042125
Kobayashi, L. C., Farrell, M. T., Payne, C. F., Mall, S., Montana, L., Wagner, R. G., Kahn, K., Tollman, S., & Berkman, L. F. (2020). Adverse childhood experiences and domain-specific cognitive function in a population-based study of older adults in rural South Africa. Psychology and Aging, 35(6), Article 6. https://doi.org/10.1037/pag0000552
O’Shea, B. Q., Demakakos, P., Cadar, D., & Kobayashi, L. C. (2021). Adverse Childhood Experiences and Rate of Memory Decline From Mid to Later Life: Evidence From the English Longitudinal Study of Ageing. American Journal of Epidemiology, 190(7), Article 7. https://doi.org/10.1093/aje/kwab019
Ritchie, K., Jaussent, I., Stewart, R., Dupuy, A.-M., Courtet, P., Malafosse, A., & Ancelin, M.-L. (2011). Adverse childhood environment and late-life cognitive functioning. International Journal of Geriatric Psychiatry, 26(5), Article 5. https://doi.org/10.1002/gps.2553
Yang, L., & Wang, Z. (2020). Early-Life Conditions and Cognitive Function in Middle-and Old-Aged Chinese Adults: A Longitudinal Study. International Journal of Environmental Research and Public Health, 17(10), Article 10. https://doi.org/10.3390/ijerph17103451

Methods
1. While the authors referenced a prior study for further detail on their cognitive measures/procedures, a brief but more explicit description of the specific cognitive tests used would be appreciated by the reader.
● Response: Thank you for this suggestion. We agree more information regarding the cognitive assessment used would be helpful to readers and now include additional details on how the Spanish and English Neuropsychological Assessment Scale assesses executive function and verbal episodic memory along with an additional citation.
● Changes in manuscript: “Executive function is a composite constructed from components of category fluency, phonemic/letter fluency, and working memory (digit span backward, and two list sorting). Verbal episodic memory was derived from two Word List Learning test. Each domain was z-standardized to the full baseline sample Moreover, neither cognitive domain is limited by any ceiling or floor effect(32).” (Methods, page 9, lines 15-18)

2. It is unclear what ACE measure was used by reading the methods section.
● Response: We’ve included the ACEs measure that were used in our study, which was part of the REason for Geographic and Racial Disparities in Stroke (REGARDS) Study and cited that study in our manuscript.
● Changes in manuscript: “STAR fielded a modified version of the ACEs assessment from the REason for Geographic and Racial Disparities in Stroke (REGARDS) cohort(36–38).” (Methods, page 10, lines 2-3)

3. The social factors outlined in the methods section provide an interesting layer to the study design, as investigating both risk and resiliency factors meaningfully contributes to the literature. However, I am curious as to whether the reliability of these scales was examined in the current sample.
● Response: We thank the reviewer for their inquiry. We performed a Cronbach's Alpha test on our social support variables and found good internal reliability (0.8).

4. I recommend the authors provide more rationale and justification for their parent education and participant education groups. To me, it seems like it would make sense to have three groups for parents: 1) both high school, 2) one high school and one more, and 3) both more. Similarly for the participants, 1) high school, 2) some college and 3) college/graduate. There is some evidence to suggest there are meaningful differences between some college and college groups.
● Response: We thank the reviewer for the suggested change to education categorization. We justified the operationalization of parental education based on the relatively small number of participants with parental education higher than high school level (38%). If categorized as the reviewer suggested, participants with parents who both had more than high school would only account for a small proportion (13%). We have since updated this in the manuscript to reflect our rationale. For participants' own education, we did not include this variable in the statistical analyses because we hypothesize it as a mediator on the causal pathway between ACEs and late-life cognition and used it for cohort descriptive purposes only. We modified participant's education breakdown as the reviewer suggested and showed it in Table 1.
● Changes in manuscript: "Due to the small number of either one or both parents obtaining higher than high school diploma (38%), we operationalize parent education at the high school level cutoff." (Methods, page 11, lines 11-13)

5. The terms male and female are more consistent with sex as opposed to gender.
● Response: We acknowledge the confusion on the use of the male and female terms. We have clarified this by identifying participants' sex as opposed to gender and explain how this variable was obtained in our cohort.
● Changes in manuscript: "Other covariates included age at baseline interview centered at the mean baseline age, sex (men or women) which was derived from self-report or participant medical records and likely reflected a mixture of sex assigned at birth and gender identity, …" (Methods, page 11, lines 20-22)

Results
1. Perhaps I am misunderstanding how it is written, but I am confused with how 75% of participants only had 2 waves of cognitive data, yet 83% had all 3 waves of cognitive data. These percentages don't add up.
● Response: We thank the reviewer for pointing out this error. The percentage was actually the opposite in that 83% of participants had at least 2 waves of cognitive data, while only about 75% of participants had all three waves of data.
● Changes in manuscript: "About 83% of our baseline cohort had two waves of cognitive measures, and over 75% of participants had all three waves of cognitive measures." (Results, page 13, lines 8-9)

Discussion
1. It is recommended that the authors provide more specific directions for future research in the discussion.
● Response: We have considered the reviewers suggestion and made an addition to the last paragraph of our Discussion section. We provided a specific suggestion for future studies to examine resiliency in ACEs and late-life cognition.

● Changes in manuscript: “Specifically, mediation and moderation analyses of these protective factors will be needed to determine their effects on ACEs with late-life cognition and explain potential resiliency observed in Black Americans.” (Discussion, page 19, lines 18-20)

2. In the discussion, the authors note that a prior study found that lower SES was associated with faster aging. However, it is unclear what aging refers to here (e.g., worse cognitive functioning? More rapid decline? Greater number of health risk factors?)
● Response: We thank the reviewer for pointing out how this term was unclear. We clarified that we were referring to studies examining biological aging and memory problems.
● Changes in manuscript: “In a literature review of Black Americans, multiple studies found that lower SES was associated with faster cellular markers of biological aging and earlier development of memory problems(3). The STAR cohort, on average, has higher SES which may mitigate the impact of ACEs on cognition.” (Discussion, page 17, line 17-19)

3. The authors also mention that “CI theory suggests that the detrimental, cumulative impact of experiencing multiple ACEs may have been modified by other factors, such as human agency or social support.” This is a powerful potential reason for the current study’s findings; however, it was not examined whether a greater number of ACEs was associated with more protective factors. In order to better align with the theory used to support the study, it is recommended that the authors investigate whether the number of ACEs was positively associated with the number of supportive social factors.
● Response: We thank the reviewer for this recommendation. Although we did not report any formal association of social support and ACEs, we have shown, in absolute numbers, the levels of social support with each composite ACEs category in Table 1. Our table indicates that a high percentage of social support (someone to trust and confide in, someone to love, someone to help with homework, someone to motivate in school, and having contact with someone you felt close to) is present regardless of number of ACES. While social support was highest in those without any ACEs, those who experienced 2 or more ACEs all had nearly identical social support scores, indicating perhaps high social support as a possible protective mechanism in the face of increasing ACEs exposure (Table 1).

Overall
1. The manuscript in totality could benefit from an eye toward grammar. Some examples:
• Page 7, line 33 should read “Black” not “Blacks”
• Page 9, line 47: ACEs, not ACES
• Page 12 line 13 should be changed to “someone close to” instead of “someone to close”
• Page 17 line 6 needs a “with” added between “associated” and “faster”
● Response: We thank the reviewer for pointing out these errors. We have proofread the manuscript to correct grammatical errors and made other minor modifications to meet the page limitation (shown in track changes throughout). We also made changes to our Table 1 to clarify our variable labels.

Reviewer 2
Comments to the Author:
This study examined the longitudinal association between ACEs and late-life cognitive decline among African Americans. The major concerns are described below:
● Response: We thank the reviewer for their feedback. We address the reviewer’s major concerns below.

1. According to the description of the sample in the method, the subjects were long-term members of Kaiser permanent Northern California, which seems not representative for the older Africans in United States. Is there any unique characteristics of this cohort?
● Response: We thank the reviewer for inquiring more about our cohort. Our cohort is not necessarily representative of older African Americans but do have representative characteristics as well as unique

characteristics. In the STAR cohort, educational attainment is similar to the national U.S. census data on older Black American (50+ years old) educational attainment where about 34% had attained a college education or more, 16% with some college, and 42% with high school education or less(Table 1. Educational Attainment of the Population 18 Years and Over, by Age, Sex, Race, and Hispanic Origin: 2022, 2023, p. 1). Our cohort has a range of education with over one-third (34%) having attained a college education or more, 42% with some college, and 24% with high school education or less. Additionally, although the STAR cohort represents long-term members of Kaiser Permanente Northern California, most of our participants were born and also resided in different states during their early life. About one-third of the cohort were also born in the Southern states. We have added to our cohort description to reflect this representation.

● Changes in manuscript: “Although most participants of STAR resided in California by the 1960s, more than half of the participants (53%) were born outside of California, and about one-third (36%) of these participants were from the Southern states.” (Methods, page 9, lines 4-6)

● Reference:

Table 1. Educational Attainment of the Population 18 Years and Over, by Age, Sex, Race, and Hispanic Origin: 2022. (2023). U.S. Census Bureau. https://www.census.gov/data/tables/2022/demo/educational-attainment/cps-detailed-tables.html

2. I have doubts on the idea that focusing on the association between ACEs and cognitive trajectory, since follow-up time was only three years. It is really difficult to examine a cognitive decline in such a short period, the difference of cognitive score across years could result from measurement error.

● Response: We agree and acknowledged this limitation in our discussion as part of our limitation on page 18. We further clarified this point by adding to our discussion to indicate that we observed no differences in measurement error due to practice effects from short follow-up even after adjusting for first visit indicators in our statistical models.

● Changes in manuscript: “As a middle-age and older cohort with a relatively shorter follow-up time of approximately 3 years, there could be practice effects impacting cognitive testing. Yet, when we adjusted for practice effects using a first visit indicator in the models, we found estimates to be almost identical(54). Given the short follow-up, it is also possible that participants did not experience substantial decline, and this study cannot examine how ACEs impact long-term cognitive decline yet but this is a future goal.” (Discussion, page 18, lines 21-23)

3. Another concern is the insufficient adjustment. Only years from baseline, baseline age centered at mean, gender/sex, childhood SES, and composite childhood support were included in the model. Other covariates such as marital status, current financial status, employment, education, current health status should all be adjusted. Otherwise, the result were not robust.

● Response: We thank the reviewer for pointing out these important additional factors. Given that these covariates (marital status, current financial status, employment, education, current health status) all occur in mid- or late-life, we believe they are on the causal pathway between ACEs (early life adversity) and late-life cognition/decline. Adjusting for these potential mediators could create bias.(Schisterman et al., 2009; van Zwieten et al., 2022) However, we have provided the possibility of future directions in which we can study the time dependent mediating or moderating effects of these factors on the association of ACEs and cognition.

● Changes in manuscript: “Specifically, mediation and moderation analyses of these protective factors will be needed to determine their effects on ACEs with late-life cognition and explain potential resiliency observed in Black Americans.” (Discussion, page 19, lines 10-12)

● References:

Schisterman, E. F., Cole, S. R., & Platt, R. W. (2009). Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology (Cambridge, Mass.), 20(4), 488–495. https://doi.org/10.1097/EDE.0b013e3181a819a1

van Zwieten, A., Tennant, P. W. G., Kelly-Irving, M., Blyth, F. M., Teixeira-Pinto, A., & Khalatbari-Soltani, S. (2022). Avoiding overadjustment bias in social epidemiology through appropriate covariate selection: A primer. Journal of Clinical Epidemiology, 149, 127–136. https://doi.org/10.1016/j.jclinepi.2022.05.021

Reviewer 3
Comments to the Author:
Thank you for submitting this very interesting and useful study on ACEs and cognitive decline. Please find my comments below:
● Response: We thank the reviewer for their kind words and positive feedback. We address the reviewer's' specific comments below.

Introduction: It would be beneficial to explain in detail which ACEs typologies/framework was used, particularly due to the lack of questions related to abuse which is also one of the major limitations of this study. It would be very interesting and more valuable to know how abuse associates with cognitive decline in this population.
It would be advantageous to define and discuss cognitive function and episodic memory and to explain why verbal episodic memory and not for example visual imagery?
● Response: We thank the reviewer for the in-depth comment. We agree that abuse is a very important ACE to evaluate. Unfortunately, data on abuse was not collected due to IRB feedback when the study was approved. Our ACEs measures focused on household dysfunction (e.g., domestic violence, substance abuse, parent death, etc.), therefore, we discussed and cited other studies that include abuse types of ACEs in other populations that did find an association between abuse and cognition (see Majer et al 2010, Ritchie et al 2011 in Introduction page 6, lines 15-18: "These studies examining the specific types of ACEs have reported associations between of the death of a parent, parental excess alcohol and drug use, mental health problems, physical neglect, and emotional abuse experienced during childhood with worse memory later in life"). We have also made changes in our Introduction section to clarify executive function and memory as markers of Alzheimer's disease and dementia which justify our reason for using these domains (page 6, lines 9-13). Although we acknowledge that visual memory may also be associated with Alzheimer's disease and dementia, our cognitive measures (the Spanish and English Neuropsychological Assessment Scale) were specifically validated and standardized for our two specific domains (executive function and verbal episodic memory).
● Changes in manuscript: "Cognitive decline and decreased cognitive function are early indicators of Alzheimer's disease and dementia(4). Signs of these cognitive deficits often includes loss of memory and/or loss of the ability to perform high-level mental skills (executive function) such as planning, and management of thoughts and emotions. Therefore, many studies administering cognitive assessments will include some form of executive function and memory assessment(5,6)." (Introduction, page 6, lines 9-13)

Methods: I am not entirely convinced about the accuracy of covariates adjustments for analysis and why it was decided to go this way and not to do something else. Could you provide some justification for your decision.
● Response: We thank the reviewer for the commentary. We selected the covariates due to their potential as confounders during early life in the association of ACEs and late-life cognition and cognitive decline. Moreover, other studies have similarly adjusted for early life factors (i.e., childhood socioeconomic status and social support) to account for this potential confounding in their analyses (Barnes et al., 2012; Gold et al., 2021; Kobayashi et al., 2020; O'Shea et al., 2021). We will clarify this in our manuscript for our covariates section. Intentionally not adjusting for covariates on the causal

pathway will allow for unbiased estimation in the association of early life with cognition and cognitive decline.(Schisterman et al., 2009; van Zwieten et al., 2022)
● Changes in manuscript: “As ACEs occurs early in life, we identified potential factors in early life that may cause confounding in the association of ACEs and late-life cognition and cognitive decline(7,10,16–18).” (Methods, page 10, lines 18-19)
● References:
Barnes, L. L., Wilson, R. S., Everson-Rose, S. A., Hayward, M. D., Evans, D. A., & Mendes de Leon, C. F. (2012). Effects of early-life adversity on cognitive decline in older African Americans and whites. Neurology, 79(24), Article 24. https://doi.org/10.1212/WNL.0b013e318278b607
Gold, A. L., Meza, E., Ackley, S. F., Mungas, D. M., Whitmer, R. A., Mayeda, E. R., Miles, S., Eng, C. W., Gilsanz, P., & Glymour, M. M. (2021). 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. BMJ Open, 11(2), Article 2. https://doi.org/10.1136/bmjopen-2020-042125
Kobayashi, L. C., Farrell, M. T., Payne, C. F., Mall, S., Montana, L., Wagner, R. G., Kahn, K., Tollman, S., & Berkman, L. F. (2020). Adverse childhood experiences and domain-specific cognitive function in a population-based study of older adults in rural South Africa. Psychology and Aging, 35(6), Article 6. https://doi.org/10.1037/pag0000552
O’Shea, B. Q., Demakakos, P., Cadar, D., & Kobayashi, L. C. (2021). Adverse Childhood Experiences and Rate of Memory Decline From Mid to Later Life: Evidence From the English Longitudinal Study of Ageing. American Journal of Epidemiology, 190(7), Article 7. https://doi.org/10.1093/aje/kwab019
Schisterman, E. F., Cole, S. R., & Platt, R. W. (2009). Overadjustment Bias and Unnecessary Adjustment in Epidemiologic Studies. Epidemiology (Cambridge, Mass.), 20(4), 488–495. https://doi.org/10.1097/EDE.0b013e3181a819a1
van Zwieten, A., Tennant, P. W. G., Kelly-Irving, M., Blyth, F. M., Teixeira-Pinto, A., & Khalatbari-Soltani, S. (2022). Avoiding overadjustment bias in social epidemiology through appropriate covariate selection: A primer. Journal of Clinical Epidemiology, 149, 127–136. https://doi.org/10.1016/j.jclinepi.2022.05.021

Results: I think it is important non-significant results to be communicated and reported.
● Response: Thank you for the suggestion. We have extended our discussion on the non-significant results in our Discussion section.
● Changes in manuscript: “Our estimates of the association between individual ACEs and domain-specific baseline cognition and cognitive decline were not statistically significant. The association between composite ACEs and verbal episodic memory were also not statistically significant. However, point estimates and borderline confidence intervals in our study suggests that composite ACEs (two and three ACEs) may be associated with slower verbal episodic memory decline. These findings are consistent with other studies finding that individual household-related ACEs were not associated with cognition(7,9,10,16–19).” (Discussion, page 15, lines 18-21)

Discussion: The structure of the discussion needs a lot of work. The discussion of the findings in relation to the literature and theory should proceed the section on strengths and limitations of the study. The authors do provide an explanation for the non-significant results but this could be stronger and better explained, particularly given the limitations of the study. I think the discussion re episodic memory should be stronger and maybe literature from neuroscience and neuropsychology would be really advantageous here.
● Response: We thank the reviewer for their suggestions to improve our discussion structure. We formatted our discussion section in accordance with the journal (BMJ Open) as stated on their website (https://bmjopen.bmj.com/pages/authors) and made changes to reflect the reviewer’s suggestions. Next, we further strengthened our discussion on the non-significant results in our

Discussion section by providing a more detailed explanation of the results observed. We included discussion on how other studies found significant results for ACEs with episodic memory.
● Changes in manuscript: We moved the “Strength” and “Limitation” paragraph to near the end of the paper (page 18, lines 6, and 15).
● We added to the Discussion:
○ “Our estimates of the association between individual ACEs and domain-specific baseline cognition and cognitive decline were not statistically significant. The association between composite ACEs and verbal episodic memory were also not statistically significant. However, point estimates and borderline confidence intervals in our study suggests that composite ACEs (two and three ACEs) may be associated with slower verbal episodic memory decline. These findings are consistent with other studies finding that individual household-related ACEs were not associated with cognition(7,9,10,16–19).” (page 15, lines 18-21)
○ “A review also found that ACEs (emotional and sexual abuse) were associated with better executive function(12), while other studies found that ACEs were associated with worse memory and not executive functioning(7,8,10). One study examining a Chinese cohort found that experiencing at least two ACEs and three types of ACEs (childhood SES disadvantage, parental trauma, maladaptive parental trauma) were associated with decreased episodic memory(42,43), which was supported by a study that found depressive symptoms during early life to be associated with episodic memory deficit(43).” (page 16, lines 7-10)

Overall structure: The paper is well written, however the referencing system doesn't seem to be entirely correct. The dots should be added after the referencing numbers. Needs proof reading.
● Response: We thank the reviewer for their compliment and suggestion. We followed the referencing system for the Vancouver style as set by the BMJ’s guideline: https://authors.bmj.com/writing-and-formatting/formatting-your-paper/, where it is stated “BMJ formats references using Vancouver style; references are sequentially numbered within the text of the main document and match the reference list at the end of the article.” Given the assumption that the reviewer’s comment on “dot” means the “period” punctuation, the BMJ guidelines does not specifically state to add reference numbers before or after the dot (period), so we made changes as the reviewer’s suggested. We acknowledge grammatical errors in our manuscript and have conducted a thorough proofreading to correct any additional errors. We also made changes to our Table 1 to clarify our variable labels and meaning. We additionally made changes in the manuscript to meet the word limits of the journal.
● Changes in manuscript: We have proofread the manuscript to correct grammatical errors and made other minor modifications to meet the page limitation (shown in track changes throughout). We also made changes to our Table 1 to clarify our variable labels.

Author’s Closing Statement
We thank the reviewers for taking their time to provide us with their detailed review and feedback on our manuscript. We appreciate the editors and editorial team for providing us the opportunity to improve our manuscript for resubmission.

VERSION 2 – REVIEW

REVIEWER	Halpin, Amy The University of Maine
REVIEW RETURNED	01-Oct-2023

GENERAL COMMENTS	Thank you to the authors for making the changes I suggested. I am satisfied with the authors edits and changes to the manuscript and believe it is suitable for publication.

VERSION 2 – AUTHOR RESPONSE