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Adverse Childhood Experiences and Late Life Cognitive Performance Across Racial/Ethnic Groups: Results from the Kaiser Healthy Aging and Diverse Life Experiences Study

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Abstract (word count=222)

Objectives: Evidence on adverse childhood experiences (ACEs) and late-life cognitive outcomes is inconsistent, with little research among diverse racial/ethnic groups. We investigated whether ACE exposure would predict worse late-life cognition for all racial/ethnic groups, and at different ages of exposure.

Design: Covariate-adjusted mixed-effects linear regression models estimated associations of (1) total number of ACEs experienced, (2) earliest age when ACE occurred, and (3) type of ACE with overall cognition.

Setting: Kaiser Permanente Northern California (KPNC) members aged 65 years and older, living in Northern California.

Participants: Kaiser Healthy Aging and Diverse Life Experiences study baseline participants, aged 65 years and older (n=1,661; including 403 Asian-American, 338 Latino, 427 Black, and 493 White participants).

Results: Most respondents (69%) reported one or more ACE, most frequently family illness (36%), domestic violence (23%), and parental divorce (22%). ACE count was not adversely associated with cognition overall (β=0.01; 95% CI: -0.01 to 0.03), in any racial/ethnic group, or for any age-category of exposure. Pooling across all race/ethnicities, parent's remarriage (β =-0.11; 95% CI: -0.20 to -0.03), mother's death (β =-0.18; 95% CI: -0.30 to -0.07), and father's death (β =-0.11; 95% CI: -0.20 to -0.01) were associated with worse cognition.

Conclusion: Adverse childhood exposures overall did not predict worse cognition in older adults in a diverse sample, although three ACEs were associated with worse cognitive outcomes.

Strengths and limitations of this study

- Evidence on the effect of ACEs on late-life cognitive performance and decline is mixed, with very little research conducted in populations with substantial racial/ethnic diversity.
- In the Kaiser Healthy Aging and Diverse Life Experiences cohort, comprising participants aged 65 years and older identifying as Black, Asian-American, Latino, or White, exposure to Adverse Childhood Experiences (ACE) was not associated with worse late-life cognition in any racial/ethnic group, and associations did not differ by age of ACE exposure
- Only parental remarriage and parental death were consistently associated with worse cognitive outcomes in late life.
- Primary limitations of the present study include reliance on a cross-sectional sample and self-reported ACEs.

Introduction

Adverse childhood experiences (ACEs), such as abuse, violence, and household dysfunction have lasting harmful impacts on adult physical and mental health,[1–3] but evidence on the effect of ACEs on late-life cognitive performance and decline is mixed.[4–6] Prior studies indicate heterogeneities in the association of ACEs and cognitive outcomes by age of exposure, type of ACE, race/ethnicity, and sources of resilience. For example, Ravona-Springer (2012) found that death of a parent during childhood was associated with substantially higher risk of dementia when the experience occurred between the ages of 0 and 6, but the excess dementia risk attenuated the older the age of ACE exposure. Additional findings suggest that while some ACEs appear to adversely affect late-life cognitive functioning, other ACEs predict better cognitive outcomes.[6]

Both exposure to and consequences of ACEs may differ by race/ethnicity. Significant racial and ethnic differences in the prevalence of ACEs as well as between types of adversities have been documented.[8] To date, there has been only one multi-racial study evaluating ACEs and cognition: Barnes et al found no association between early-life adverse events and cognitive decline in Whites, while early-life food deprivation was associated with better cognitive outcomes for African Americans.[4] No other studies have directly compared effects across racial/ethnic groups.

We investigated the association of ACEs with later-life cognitive performance in the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) cohort. We hypothesized that ACE exposure would predict worse late-life cognition for all racial/ethnic groups, with the largest effects associated with experiences when aged 0-6 years.

Methods:

Study participants and data collection

We used baseline data from the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) cohort, which comprises community-dwelling older adults residing in the San Francisco Bay and Sacramento areas of California. KHANDLE aims to evaluate how race/ethnicity and life course health and sociocultural factors influence late-life brain health and cognitive decline. Individuals eligible for KHANDLE: were long-term members of Kaiser Permanente Northern California, an integrated healthcare delivery system; were age 65 years or older on January 1, 2017; spoke English or Spanish; and had previously participated in Kaiser Permanente multiphasic health checkup exams between 1964-1985. Stratified random sampling by race/ethnicity and educational attainment was used with the goal of recruiting approximately equal proportions of Asian, Black, Latino, and White participants and achieving diversity in educational attainment. Exclusion criteria included: electronic medical record diagnosis of dementia or other neurodegenerative disease (frontotemporal dementia, Lewy body disease, Pick's disease, Parkinson's disease with dementia, Huntington's disease); and presence of health conditions that would impede participation in study interviews, defined by hospice activity in the past 12 months, history of severe chronic obstructive pulmonary disease in the past 6 months, congestive heart failure hospitalizations in the past 6 months, and history of end stage renal disease or dialysis in the past 12 months. At baseline, 1,712 individuals were enrolled.

Individuals who self-identified as Native Americans (n=3) or refused to self-identify race/ethnicity (n=1) were dropped from the sample used in this analysis. After excluding 13 individuals who were missing all cognitive measures used in this analysis and 34 individuals missing all ACEs, the final analytic sample size was 1,661. All respondents provided informed consent and completed an interview in English or Spanish either in-home or at a Kaiser Permanente Facility (approximately 40% of baseline interviews were conducted at a facility and 60% in-home).

Kaiser Permanente Northern California (KPNC) is a large, integrated healthcare delivery system that provides comprehensive medical care to over 4 million members.[9] Prior work indicated the member population was generally representative of the overall regional population, though individuals at extreme tails of the income distribution were underrepresented.[10–12] The KPNC older adult population (aged 65+) are generally similar to the population of seniors residing in Northern California with respect to medical history of chronic conditions, including diabetes, hypertension, heart disease, and asthma, and lifestyle factors, including smoking, obesity, and sedentary lifestyle.[12]

Measures

Our cognitive outcomes are standardized scores from the following three cognitive domains: verbal episodic memory, semantic memory, and executive functioning. These scores were obtained from the Spanish and English Neuropsychological Assessment Scales (SENAS), which was given to all participants in their preferred language (English or Spanish).[13] The SENAS is a battery of cognitive tests that has previously undergone extensive development for valid comparisons of cognition across racial/ethnic and linguistically diverse groups. Verbal episodic memory composite scores were derived from a multiracial word-list-learning test. Semantic memory composite scores were derived from verbal (object-naming) and nonverbal (picture association) tests. Executive function composite scores were obtained using component tasks of category fluency, phonemic (letter) fluency, and working memory (digit-span backward, visual-span backward, list sorting). Details of the administration procedures, development, and psychometric characteristics have been extensively described in previous publications.[13] Analyses used cognitive data for everyone who had cognitive measures for at least one of the three cognitive domains.

KHANDLE fielded a modified version of the assessment of ACEs used in the Reasons for Geographic and Racial Disparities in Stroke (REGARDS) cohort.[14] Participants were asked aloud by the interviewer if they had experienced each of 9 ACEs when they were age 16 or younger: parents were divorced or separated; parents remarried; witnessed domestic violence; substance abuse by a family member; loss of a job by a parent; parent had to go to jail; serious illness of a family member; death of mother; and death of father. If any ACE was experienced, respondents were asked the youngest age at which they experienced the event. A composite ACE score was constructed as a count of the number ever experienced, with the scores ranging from 0 if no ACE had been experienced to 9 if every ACE had been experienced. For individuals missing one or more ACE item, we imputed the values to the average of the total observed ACEs for that individual (i.e., if the individual responded to 6 ACE items and endorsed 3 of them, the values of the missing 3 items were imputed to 0.5). Since few people reported more than 4 ACEs

(n=161), the count of ACEs was top coded at 4 for our analyses. Age-specific ACEs were constructed as the count of the number of experiences reported as first occurring in specific age categories (0-6, 7-12, and 13-16).

Because ACEs are experienced in early life, there are few plausible confounders that might influence both ACEs and late-life cognitive outcomes. All models were either adjusted for or stratified by race/ethnicity (classified as Black, White, Latino, or Asian). All models were also adjusted for linear and quadratic terms for year of age over 65 at cognitive assessment, sex, and parental education. Parental educational attainment was reported by the respondent as highest level of education completed. Maternal and paternal education for primary and secondary education was coded as number of years of primary or secondary education, ranging from 0 to 12. We additionally adjusted for parental higher education as a continuous predictor: 0=no higher education; 1=some college but no degree or associates degree; 2=bachelor's degree, master's degree or other higher education. If values for parental education were missing (n=276 and n=417 missing for maternal and paternal, respectively) they were coded as 0 (lowest category), and we additionally adjusted for an indicator variable for missingness.

Statistical Analysis:

Baseline variables gender, race/ethnicity, and parental education were tabulated by ACE composite score. The prevalence of each ACE was estimated for the entire sample and stratified by race/ethnicity.

If the effect of ACEs were the same for all three domains of cognition, it would be most efficient to estimate a single mixed model including each individual's three outcome assessments (verbal memory, semantic memory, and executive function) and derive a single effect estimate applicable to all domains. This added efficiency is especially important when estimating race/ethnicity specific effects where sample sizes are smaller. Before estimating such a model, we first had to assess whether it was appropriate to estimate a single effect of ACE exposure on all three cognitive domains within each racial/ethnic group.

In initial models, we therefore tested for domain-specific effects of composite ACE score on cognition for each racial/ethnic group. To do this, we used a mixed-effects linear regression model with the three standardized cognitive domains as outcomes with random intercepts to account for within-person correlation between cognitive domains. All models were controlled for indicators of cognitive domain (e.g., verbal memory or semantic memory, with executive function treated as the reference outcome), allowing for the possibility that average score differs between domains. We also included interactions between race/ethnicity and domain (allowing for the possibility that domain differences vary by race/ethnicity) and interactions between each person's composite ACE score and each race/ethnicity-domain combination (allowing for the possibility that the effect of ACE exposure differs for any combination of race/ethnicity and cognitive domain). An F-test for the null hypothesis that the race/ethnicity-specific ACE associations with cognition varied significantly across domains indicated evidence of heterogeneity (P=0.09). When we evaluated individual comparisons, we found one significant domain-specific difference: the association between ACE score and semantic memory among

Asian American respondents. For both other domains in Asian Americans and for all domains in the other three racial/ethnic groups, the statistical tests indicated estimation of a single parameter for estimated effects of ACEs on cognition was appropriate. In all subsequent models, interactions between Asian American, semantic memory, and the ACE measure were included to estimate the association of ACEs with semantic memory among Asian Americans separately from all other associations. In these models, the coefficient for the ACE measure can be interpreted as the association of ACEs with cognition, averaged across domains (results are very similar to what would be obtained if the different domains were averaged in advance and treated as a single outcome) except excluding the effect of ACEs on semantic memory among Asian Americans. Associations between ACE exposure and semantic memory among Asian American respondents are reported in the Appendix.

We then used covariate-adjusted linear mixed models to estimate the association of composite ACE score with cognition in pooled analyses and in models stratified by race-ethnicity. To evaluate whether differences in coefficients between racial/ethnic groups were statistically significant, we incorporated race/ethnicity by ACE score interactions and used an F-test. Because of limited prior evidence on racial/ethnic specific associations, we present these even when the F-test indicated no evidence of statistically significant heterogeneity.

Covariate adjusted mixed-effects linear regression models were also estimated to evaluate the association between composite ACE scores at specific age categories (0-6, 7-12, and 13-16) and cognition for the full sample and in models stratified by race/ethnicity.

Finally, we evaluated the association of each of the 9 individual ACEs and standardized cognitive score and whether these associations differed by race/ethnicity or by age ranges of exposure (0-6; 7-12; 13-16). Results for age-specific associations with individual ACE exposures are given in the Appendix.

Analyses were conducted using STATA SE 15 (STATA Corporation, College Station, TX, 2003).

Results

Among the 1,661 participants enrolled in the KHANDLE baseline, 69% reported experiencing at least one ACE prior to age 16: 448 individuals (27%) reported experiencing 1 ACE; 336 (20%) reported 2 ACEs; 203 (12%) reported 3 ACEs, and 161 (10%) reported 4+ ACEs (Table 1). Among the 9 individual ACEs, illness in the family had the highest overall prevalence at 36%, followed by domestic violence (23%), and parental divorce (22%) (Figure 1). Both the distribution of total ACE score and the prevalence of each specific ACE varied by race/ethnicity.

In covariate-adjusted mixed-effects linear regression models, there was no association between the composite ACE score and standardized cognition when considering all racial/ethnic groups in a pooled analysis (β =0.01; 95% CI, -0.01 to 0.03) (Table 2). Age-specific ACE exposures were not significantly associated with cognition (ACE scores ages 0-6, β =0.01; 95% CI, -0.03 to 0.05; ACE scores ages 7-12, β = -0.03; 95% CI, -0.07 to 0.01; or ACE score ages 13-16, β = 0.01; 95% CI, -0.05 to 0.06) (Table 2). When evaluating the association between total ACE score and

cognition for each racial/ethnic group, the only apparent association was for Asian Americans, among whom each unit increase in the composite ACE was associated with better cognitive scores (estimated association based on verbal memory and executive function, β =0.07; 95% CI, 0.01 to 0.14). Although this individual race-specific association was statistically significant, the overall test for differences in the association of ACE composite score and cognition across racial/ethnic groups was not significant (p=0.13) after excluding the single Asian-semantic memory comparison.

Interactions between race/ethnicity and age-specific ACE exposures were also non-significant. There was no evidence of associations between age-specific ACE exposures and cognition overall, although Asian Americans exposed to ACEs age 13-16 averaged worse cognition β =-0.12; 95% CI, -0.24 to 0.00) (Table 2).

Pooling across all race/ethnicities, three types of ACE exposures were associated with worse cognition: parent remarried; death of mother; and death of a father (Table 3). Although there were some differences in the associations of individual ACEs with standardized cognition between racial/ethnic groups, differences were consistent with chance (i.e., the tests of heterogeneity in the ACE associations with cognition across racial/ethnic groups were not statistically significant). Patterns were generally similar when evaluating cognition based on indicator variables for age of first exposure overall and race/ethnicity (Appendix Table 1).

Discussion

Retrospectively reported exposure to childhood ACEs was prevalent in a sample of long-term elderly Kaiser Permanente Northern California (KPNC) members, but ACEs were not associated with cognition in later-life among White, Black, or Latino respondents. Results were similar for total ACE count and ACE exposures during age groups categorized as 0-6, 7-12, and 13-16. Among Asian American respondents, higher ACE count was associated with slightly better cognitive performance. Among the individual ACEs, three experiences were associated with significantly worse cognition when pooling across all racial/ethnic groups, but when examining each racial/ethnic group separately, point estimates indicated adverse associations only for parents remarried and death of a mother (albeit with wide confidence intervals in racial/ethnic group specific estimates). For other ACEs, associations were inconsistent and, in several instances, positive. All racial/ethnic differences in ACE by cognition associations were consistent with chance.

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.[1,15] However, prior findings in early work on ACEs and cognition has been mixed and has been conducted in predominantly White samples. Very few prior studies include multi-racial samples or assessments with both age-specific ACE exposure and late-life cognitive outcomes. This is important to evaluate because race/ethnicity is strongly associated with economic, social, political, and environmental factors that influence cognitive aging.[16,17] These factors may modify the consequences of ACEs for cognition in late life or may create selection processes such that only especially resilient individuals survive to late life. For example, increased exposure to

extreme adversity across the lifecourse may blunt the special relevance of childhood adversity among racial/ethnic minorities in the United States.

Our findings do suggest that parental remarriage and parental death are associated with worse cognitive outcomes in late life. The exposures were common, especially for racial/ethnic minorities. The importance of these experiences over other adversities may imply the special relevance of a child being separated from the parent.

Prior studies have documented significant racial and ethnic differences in the prevalence of total ACEs as well as between types of adversity, such as incarceration of a family member versus domestic violence, in the U.S.[8] ACEs are strongly patterned by socioeconomic status and neighborhood context.[18] Barnes et al reported that in a cohort of 6,105 older African Americans and Whites followed for up to 16 years, there was no association between early life adverse events and rate of cognitive decline in Whites, while food deprivation and being thinner than average in early life were associated with better cognitive outcomes for African Americans.[4] Food deprivation is not commonly used in ACE surveys and was not included in the KHANDLE baseline survey.

Although point estimates for the effects of ACEs among Whites were generally more adverse than for other racial/ethnic groups, only for Asian American did we find evidence of a statistically significant difference. Among Asian Americans, higher ACE count was associated with better overall cognition. It is difficult to theorize how ACEs might enhance later life cognition. The positive association observed among older Asian Americans may be due to chance, selective survival, or differential recall. Especially among Asian Americans in the KHANDLE sample, many of whom were born outside the US, individuals who have migrated, survived to late life, and enrolled in the study may be an extraordinarily resilient group. This type of selection could lead to inverse associations if both ACE exposure and other determinants of late life cognition influence the process that leads to study enrollment. Chance is also a plausible explanation, as indicated by the non-significant F-test for heterogeneity between racial/ethnic groups.

The limitations of the present study include reliance on a cross-sectional sample and self-reporting ACEs. This precludes evaluating within-person cognitive decline and increases vulnerability to confounding. However, confounding seems unlikely to account for the largely null results reported here. Several different ACE assessment instruments, reflecting different levels of trauma, are currently in use across the field. The survey used in KHANDLE does not include questions about physical or sexual abuse. Our null findings with the 9 ACEs assessed in KHANDLE do not rule out the relevance of other ACEs. Finally, sample size is an important limitation, although for the overall and race-specific estimates of composite ACE score and cognition associations, confidence intervals were fairly narrow and inconsistent with especially large benefits or harms. KHANDLE is, to our knowledge, the only available community-based study with information on the four largest racial/ethnic groups represented in the US and rigorous cognitive assessments in older adults. We have reported finely grained results to facilitate future meta-analyses. This study did not directly address dementia because the participants were screened at baseline to be free of dementia. Differences in cognitive

performance in late life are relevant for anticipating dementia risk, however, because of the established importance of cognitive reserve.[19,20] Our findings, therefore, if taken at face value, suggest these ACEs may not have major relevance for subsequent dementia risk.

Our results suggest that previously reported findings linking ACEs to cognitive outcomes in late life may be over-estimated or may not hold in many communities. These findings should be interpreted cautiously until replicated in additional multi-ethnic samples. Given the robust evidence of early life experiences overall for cognitive reserve and dementia risk, these results would suggest a focus on other aspects of childhood, such as material deprivation or educational experiences.

Figure 1 caption: Grey vertical line segments indicate exact binomial confidence intervals

Competing interests: authors declare no competing interests.

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Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research**.**

Patient consent for publication: Not required.

Ethics Approval: Ethical approval was granted by the Kaiser Permanente Northern California Institutional Review Board (IRB Number: CN-16-2786).

Data availability statement: De-identified data are available to qualified investigators from the KHANDLE Leadership Committee upon approval for the purposes of replicating procedures and results.

Table 1: Descriptive Statistics, KHANDLE Cohort

Variable	Level	Composite ACE Score				
		0	1	2	3	4+
N	1,661	513 (100%)	448 (100%)	336 (100%)	203 (100%)	161 (100%)
Age (years), mean (SD)	76.0 (6.8)	75.7 (6.6)	76.6 (6.9)	76.1 (6.9)	76.0 (6.7)	74.6 (6.4)
Gender	Female	223 (43.5%)	182 (40.6%)	133 (39.6%)	74 (36.5%)	63 (39.1%)
	Male	290 (56.5%)	266 (59.4%)	203 (60.4%)	129 (63.5%)	98 (60.9%)
Race/Ethnicity	Asian	181 (35.3%)	111 (24.8%)	68 (20.2%)	29 (14.3%)	14 (8.7%)
	Black	105 (20.5%)	116 (25.9%)	92 (27.4%)	66 (32.5%)	48 (29.8%)
	Latino	71 (13.8%)	82 (18.3%)	85 (25.3%)	51 (25.1%)	49 (30.4%)
	White	156 (30.4%)	139 (31.0%)	91 (27.1%)	57 (28.1%)	50 (31.1%)
Maternal education	Mean years of education among those with <=12 years, (SD)	8.46 (4.73)	7.76 (4.87)	7.78 (4.74)	7.98 (5.00)	7.83 (4.76)
	Some college but no degree/ associates degree	59 (11.5%)	51 (11.4%)	38 (11.3%)	25 (12.3%)	14 (8.7%)
	Bachelor's or more	63 (12.3%)	34 (7.6%)	32 (9.5%)	18 (8.9%)	10 (6.2%)
Paternal education	Mean years of education among those with <=12 years, (SD)	8.51 (4.75)	7.29 (5.16)	6.82 (5.36)	6.19 (5.21)	6.53 (5.45)
	Some college but no degree/ associates degree	60 (11.7%)	43 (9.6%)	32 (9.5%)	21 (10.3%)	12 (7.5%)
	Bachelor's or more	110 (21.4%)	70 (15.6%)	46 (13.7%)	14 (6.9%)	15 (9.3%)

Table 2. Mixed-effects linear regression coefficients (95% confidence intervals) for the difference in cognitive scores associated with total childhood or age-specific count of ACEs (0 to 4+), overall and stratified by race/ethnicity.

	Total childhood ACEs β (95% CI)	Early childhood (0-6 years) ACEs β (CI)	Middle childhood (7-12 years) ACEs β (CI)	Adolescent (13-16 years) ACEs β (CI)
Full sample	0.01 (-0.01, 0.03)	0.01 (-0.03, 0.05)	-0.03 (-0.07, 0.01)	0.01 (-0.05, 0.06)
White	0.00 (-0.04, 0.05)	0.01 (-0.05, 0.08)	-0.03 (-0.09, 0.03)	0.07 (-0.03, 0.17)
Black	0.01 (-0.03, 0.05)	0.04 (-0.02, 0.10)	-0.03 (-0.09, 0.03)	-0.01 (-0.09, 0.08)
Asian-American	0.07 (0.01, 0.14)	0.06 (-0.05, 0.17)	0.00 (-0.11, 0.10)	-0.12 (-0.24, 0.00)
Latino	-0.01(-0.06, 0.04)	-0.04(-0.10, 0.03)	-0.01 (-0.08, 0.05)	0.03 (-0.06, 0.13)
P-value from an F-test for interaction between ACE composite score and race/ethnicity	0.13	0.17	0.26	0.80

*** All models adjusted for age (linear and quadratic), sex, parental education and race/ethnicity (unless stratified by race/ethnicity).**

**** All models provide a single coefficient for associations with verbal episodic memory, semantic memory, and executive function, with the exception of the coefficients for ACE association with semantic memory among Asian Americans, which are estimated separately and presented in the supplement.**

Table 3. Mixed effects linear regression coefficients (95% confidence intervals) for the difference in memory scores associated with each ACE, overall and stratified by race/ethnicity.

ACEs	Overall β (95% CI)	White β (95% CI)	Black β (95% CI)	Asian β (95% CI)	Latino β (95% CI)	P-value for interaction with race/ethnicity**
Parents divorced	-0.03 (-0.11, 0.04)	-0.10 (-0.24, 0.04)	-0.03 (-0.15, 0.09)	0.09 (-0.16, 0.35)	-0.00 (-0.14, 0.14)	0.20
Parents remarried	-0.11 (-0.20, -0.03)	-0.10 (-0.26, 0.07)	-0.04 (-0.18, 0.09)	-0.08 (-0.34, 0.19)	-0.18 (-0.34, -0.03)	0.74
Domestic violence	0.01 (-0.06, 0.08)	0.07 (-0.07, 0.21)	-0.00 (-0.12, 0.12)	0.19 (0.00, 0.38)	-0.07 (-0.21, 0.06)	0.11
Witnessed substance abuse	-0.06 (-0.14, 0.01)	-0.08 (-0.21, 0.06)	0.02 (-0.11, 0.15)	0.18 (-0.10, 0.46)	-0.16 (-0.29, -0.02)	0.05
Parent job loss	0.04 (-0.04, 0.11)	0.10 (-0.04, 0.23)	-0.04 (-0.19, 0.10)	0.16 (-0.04, 0.37)	-0.04 (-0.19, 0.12)	0.26
Parent in jail	-0.10 (-0.21, 0.01)	-0.16 (-0.43, 0.10)	-0.09 (-0.27, 0.08)	0.17 (-0.11, 0.45)	-0.13 (-0.32, 0.05)	0.29
Family member illness	0.02 (-0.04, 0.08)	0.06 (-0.06, 0.17)	-0.05 (-0.17, 0.06)	0.11 (-0.04, 0.26)	0.00 (-0.12, 0.13)	0.29
Death of mother	-0.18 (-0.30, -0.07)	-0.10 (-0.34, 0.14)	-0.15 (-0.36, 0.06)	-0.19 (-0.48, 0.10)	-0.29 (-0.49, -0.09)	0.67
Death of father	-0.11 (-0.20, -0.01)	0.05 (-0.15, 0.25)	-0.14 (-0.31, 0.03)	-0.10 (-0.33, 0.12)	-0.21 (-0.39, -0.02)	0.55

*** All models adjusted for age (linear and quadratic), sex, parental education, and race/ethnicity (unless stratified by race/ethnicity).**

****P values reflect the F-test of the interaction between individual ACEs and race/ethnicity**

***** All models provide a single coefficient for associations with verbal episodic memory, semantic memory, and executive function, with the exception that coefficients for ACE association with semantic memory among Asian Americans are estimated separately and presented in the supplement**

References

1. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults. Am J Prev Med. 1998 May;14(4):245–58.

2. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield Ch, Perry BD, et al. The enduring effects of abuse and related adverse experiences in childhood: A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006 Apr;256(3):174–86.

3. Baglivio M, Swartz, Kimberly, Huq, Mona Sayedul, Sheer, Amy, Hardt, Nancy. The Prevalence of Adverse Childhood Experiences (ACE) in the Lives of Juvenile Offenders. 2014;

4. Barnes LL, Wilson RS, Everson-Rose SA, Hayward MD, Evans DA, Mendes de Leon CF. Effects of early-life adversity on cognitive decline in older African Americans and whites. Neurology. 2012 Dec 11;79(24):2321–7.

5. Korten NCM, Penninx BWJH, Pot AM, Deeg DJH, Comijs HC. Adverse Childhood and Recent Negative Life Events: Contrasting Associations With Cognitive Decline in Older Persons. J Geriatr Psychiatry Neurol. 2014 Jun;27(2):128–38.

6. Ritchie K, Jaussent I, Stewart R, Dupuy A-M, Courtet P, Malafosse A, et al. Adverse childhood environment and late-life cognitive functioning: Childhood adversity and late-life cognition. Int J Geriatr Psychiatry. 2011 May;26(5):503–10.

7. Ravona-Springer R, Beeri MS, Goldbourt U. Younger Age at Crisis Following Parental Death in Male Children and Adolescents Is Associated With Higher Risk for Dementia at Old Age: Alzheimer Dis Assoc Disord. 2012;26(1):68–73.

8. Mersky JP, Janczewski CE. Racial and ethnic differences in the prevalence of adverse childhood experiences: Findings from a low-income sample of U.S. women. Child Abuse Negl. 2018 Feb;76:480–7.

9. Klein NP, Fireman B, Goddard K, Zerbo O, Asher J, Zhou J, et al. Vaccine effectiveness of cell-culture relative to egg-based inactivated influenza vaccine during the 2017-18 influenza season. Huber VC, editor. PLOS ONE. 2020 Feb 26;15(2):e0229279.

10. Gordon NP, Kaplan GA. Some evidence refuting the HMO “favorable selection” hypothesis: the case of Kaiser Permanente. Adv Health Econ Health Serv Res. 1991;12:19–39.

11. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992 May;82(5):703–10.

12. Gordon NP. Similarity of the Kaiser Permanente Senior Member Population in Northern California to the Non-Kaiser Permanente Covered and General Population of Seniors in Northern California: Statistics from the 2009 California Health Interview Survey. Kaiser Permanente Northern California Division of Research; 2012.

13. Mungas D, Reed BR, Crane PK, Haan MN, González H. Spanish and English Neuropsychological Assessment Scales (SENAS): Further Development and Psychometric Characteristics. Psychol Assess. 2004 Dec;16(4):347–59.

14. Howard VJ, McClure LA, Glymour MM, Cunningham SA, Kleindorfer DO, Crowe M, et al. Effect of duration and age at exposure to the Stroke Belt on incident stroke in adulthood. Neurology. 2013 Apr 30;80(18):1655–61.

15. Anda RF, Dong M, Brown DW, Felitti VJ, Giles WH, Perry GS, et al. The relationship of adverse childhood experiences to a history of premature death of family members. BMC Public Health. 2009 Dec;9(1):106.

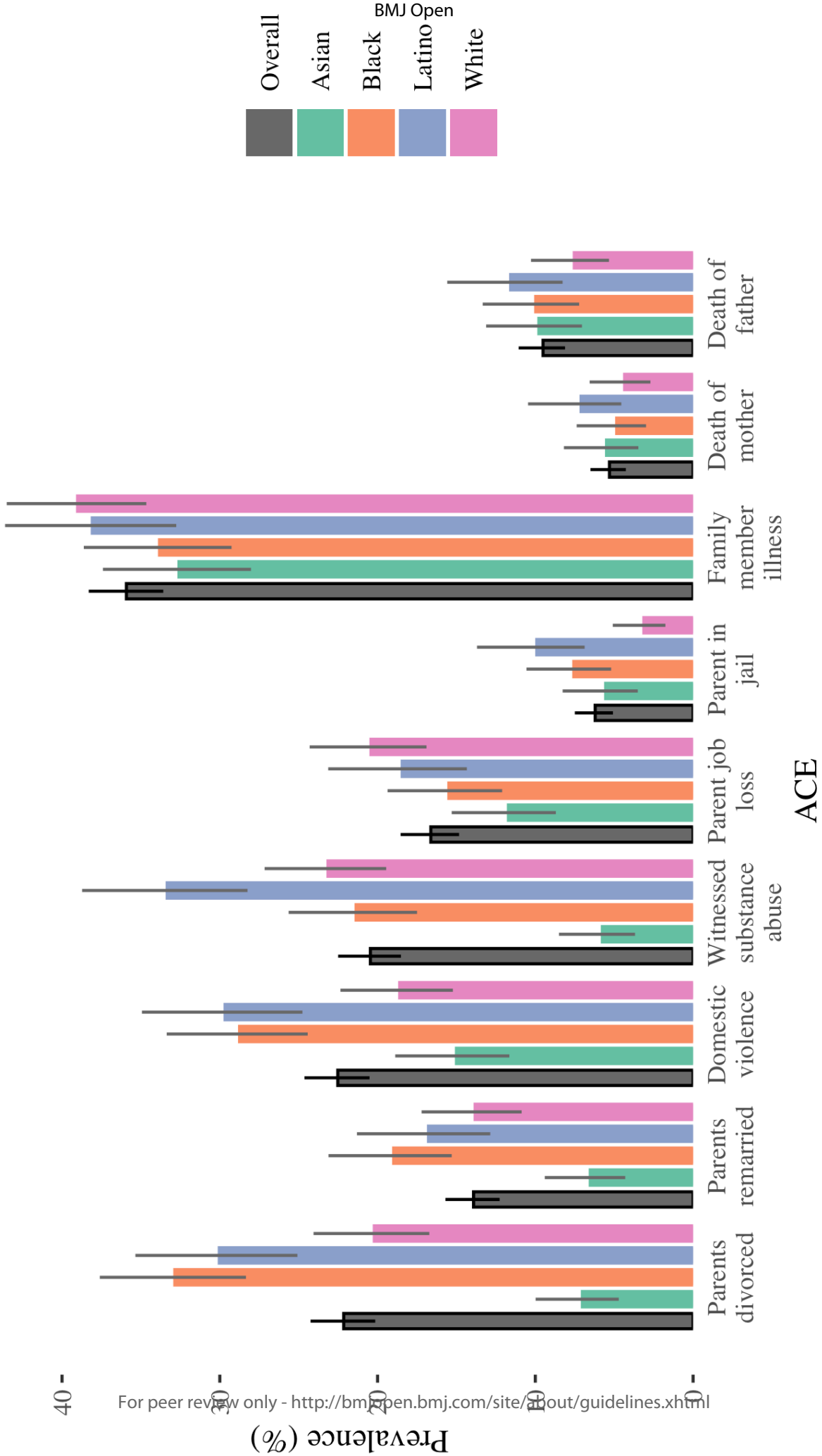
16. Glymour MM, Manly JJ. Lifecourse Social Conditions and Racial and Ethnic Patterns of Cognitive Aging. Neuropsychol Rev. 2008 Sep;18(3):223–54.

17. Mayeda ER, Glymour MM, Quesenberry CP, Whitmer RA. Inequalities in dementia incidence between six racial and ethnic groups over 14 years. Alzheimers Dement. 2016 Mar;12(3):216–24.

18. Walsh D, McCartney G, Smith M, Armour G. Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): a systematic review. J Epidemiol Community Health. 2019 Dec;73(12):1087–93.

19. Scarmeas N, Stern Y. Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. Curr Neurol Neurosci Rep. 2004 Oct;4(5):374–80.

20. Scarmeas N, Stern Y. Cognitive Reserve and Lifestyle. J Clin Exp Neuropsychol. 2003 Aug;25(5):625–33.



Appendix Table 1. Association of ACEs based on interaction terms between race/ethnicity and ages ACE experienced

	Parents divorced	Parents remarried	Domestic violence	Witnessed substance abuse	Parent job loss	Parent in jail	Family member illness	Death of mother	Death of father
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Black, 0-6	0.23 (-0.00, 0.46)	-0.02 (-0.42, 0.37)	0.12 (-0.18, 0.42)	0.07 (-0.27, 0.41)	-0.15 (-0.59, 0.29)	-0.31 (-1.17, 0.54)	0.04 (-0.26, 0.33)	-0.05 (-0.90, 0.80)	0.35 (-0.17, 0.87)
Black, 7-12	-0.13 (-0.45, 0.20)	0.43 (0.11, 0.76)	-0.15 (-0.40, 0.11)	0.09 (-0.19, 0.37)	0.10 (-0.19, 0.40)	0.43 (-0.14, 0.99)	0.00 (-0.22, 0.22)	-0.00 (-0.73, 0.73)	-0.49 (-1.07, 0.08)
Black, 13-16	-0.03 (-0.53, 0.47)	0.04 (-0.41, 0.49)	-0.12 (-0.62, 0.37)	0.30 (-0.08, 0.69)	-0.35* (-0.74, 0.03)	0.43 (-0.52, 1.39)	-0.08 (-0.38, 0.22)	-0.40 (-0.97, 0.18)	-0.17 (-0.59, 0.26)
Latino, 0-6	0.28 (0.02, 0.53)	-0.08 (-0.48, 0.32)	-0.03 (-0.33, 0.26)	-0.10 (-0.40, 0.21)	-0.56 (-0.95, -0.17)	-0.05 (-0.98, 0.87)	-0.17 (-0.47, 0.12)	0.15 (-0.53, 0.82)	0.29 (-0.26, 0.84)
Latino, 7-12	0.14 (-0.21, 0.48)	0.43 (0.07, 0.80)	-0.17 (-0.45, 0.10)	-0.07 (-0.33, 0.20)	0.22 (-0.09, 0.53)	0.18 (-0.38, 0.74)	0.02 (-0.20, 0.24)	0.02 (-0.76, 0.80)	-0.25 (-0.75, 0.26)
Latino, 13-16	-0.04 (-0.55, 0.47)	-0.02 (-0.49, 0.44)	-0.31 (-0.91, 0.28)	-0.11 (-0.50, 0.29)	0.00 (-0.46, 0.46)	0.36 (-0.58, 1.29)	0.19 (-0.13, 0.52)	-0.10 (-0.70, 0.49)	-0.24 (-0.75, 0.28)
Asian,	0.34	-0.10	0.29	0.31	-0.03	0.09	0.06	-0.09	0.25

0-6	(-0.03, 0.71)	(-0.68, 0.48)	(-0.06, 0.64)	(-0.15, 0.78)	(-0.50, 0.44)	(-0.70, 0.88)	(-0.23, 0.34)	(-0.74, 0.57)	(-0.25, 0.75)
Asian,									
	-0.05	0.28	0.05	0.34	0.31	0.40	0.08	-0.10	-0.45
7-12	(-0.53, 0.43)	(-0.16, 0.72)	(-0.26, 0.35)	(-0.19, 0.86)	(-0.02, 0.64)	(-0.25, 1.06)	(-0.14, 0.30)	(-1.15, 0.95)	(-1.05, 0.14)
Asian,									
	0.17	-0.37	-0.59	-0.13	-0.25	-0.18	0.15	-0.10	-0.16
13-16	(-0.63, 0.97)	(-0.95, 0.22)	(-1.18, -0.00)	(-0.66, 0.40)	(-0.72, 0.21)	(-1.22, 0.87)	(-0.17, 0.48)	(-0.51, 0.30)	(-0.61, 0.29)
White,									
	-0.15	-0.02	0.02	0.02	0.26	0.26	0.06	-0.29	-0.36
0-6	(-0.32, 0.02)	(-0.31, 0.28)	(-0.19, 0.24)	(-0.22, 0.25)	(0.02, 0.50)	(-0.44, 0.95)	(-0.12, 0.23)	(-0.79, 0.20)	(-0.73, 0.01)
White,									
	-0.01	-0.41	0.07	-0.09	-0.02	-0.37	0.02	0.15	0.27
7-12	0.95	(-0.65, -0.17)	(-0.12, 0.27)	(-0.27, 0.09)	(-0.22, 0.17)	(-0.83, 0.09)	(-0.12, 0.16)	(-0.46, 0.76)	(-0.13, 0.68)
White,									
	0.15	0.04	0.03	-0.12	0.27	-0.27	-0.02	-0.32	0.10
13-16	(-0.23, 0.54)	(-0.28, 0.36)	(-0.33, 0.40)	(-0.38, 0.15)	(0.01, 0.53)	(-1.12, 0.59)	(-0.25, 0.20)	(-0.91, 0.27)	(-0.22, 0.42)

*** All models adjusted for age (linear and quadratic), sex, parental education and race/ethnicity (unless stratified by race/ethnicity).**

**** All models provide a single coefficient for associations with verbal episodic memory, semantic memory, and executive function, with the exception that coefficients for ACE association with semantic memory among Asian Americans are estimated separately and presented in the supplement.**

Results from Asian and semantic memory omnibus testing

Appendix Table 2. Regression estimates for the interaction of composite ACE score, race/ethnicity, and the domain of the cognitive measure.

Variable	Beta Coef.	Confidence intervals	P-value
Composite ACE score*	0.01	(-0.06, 0.08)	0.81
Asian executive	ref	ref	
Asian semantic by ACE score	0.13	(0.04 , 0.21)	0.00
Asian verbal by ACE score	0.00	(-0.08 , 0.08)	0.99
Black executive by ACE score	0.02	(-0.08 , 0.11)	0.71
Black semantic by ACE score	-0.01	(-0.10 , 0.09)	0.92
Black verbal by ACE score	-0.002	(-0.10 , 0.09)	0.97
Latino executive by ACE score	-0.03	(-0.12 , 0.07)	0.61
Latino semantic by ACE score	-0.00	(-0.10 , 0.10)	0.99
Latino verbal by ACE score	-0.01	(-0.11 , 0.09)	0.90
White executive by ACE score	-0.04	(-0.13 , 0.05)	0.40
White semantic by ACE score	-0.02	(-0.11 , 0.07)	0.67
White verbal by ACE score	-0.01	(-0.10 , 0.08)	0.87
F-test	**0.10**		

* The main effect of for Composite ACE score refers to the estimate for executive function among Asian American respondents. All other terms refer to the deviation from that effect for the specified racial/ethnic group in the specified cognitive domain. The P-value tests whether that deviation is consistent with the null.

Appendix Table 3. Final regression model results estimating one effect of composite ACE score on semantic memory among Asian American respondents and another effect for all other racial/ethnic group and cognitive domain combinations.

Variables	Beta Coef.	Confidence intervals	P-value
Composite score main effect	0.01	(-0.01 , 0.03)	0.42
Composite score by indicator for Asian respondents predicting semantic memory domain	-0.03	(-0.10 , 0.03)	0.34
Asian semantic	-0.11	(-0.21 , -0.02)	0.02
Asian verbal	0.34	(0.23 , 0.46)	<0.00
Black executive	-0.31	(-0.43 , -0.19)	<0.00
Black semantic	-0.56	(-0.68 , -0.44)	<0.00
Black verbal	-0.20	(-0.32 , -0.08)	<0.00
Latino executive	-0.06	(-0.18 , 0.06)	0.32
Latino semantic	0.23	(0.10 , 0.35)	0.00
Latino verbal	0.01	(-0.11 , 0.13)	0.89
White executive	0.51	(0.40 , 0.62)	<0.01
White semantic	0.61	(0.50 , 0.72)	<0.01
White verbal	0.09	(-0.02 , 0.20)	0.11

Appendix Table 4. Mixed effects linear regression coefficients (95% confidence intervals) for the difference in cognitive scores associated with total childhood or age-specific count of ACEs (0 to 4+), overall and stratified by race/ethnicity. [with Asian Semantic Memory]

	Total childhood ACEs Beta (95% CI)	Early childhood (0-6 years) ACEs Beta (CI)	Middle childhood (7-12 years) ACEs Beta (CI)	Adolescent (13-16 years) ACEs Beta (CI)
Full sample	0.01 (-0.01, 0.03)	0.01 (-0.03, 0.05)	-0.03 (-0.07, 0.01)	0.01 (-0.05, 0.06)
White	0.00 (-0.04, 0.05)	0.01 (-0.05, 0.08)	-0.03 (-0.09, 0.03)	0.07 (-0.03, 0.17)
Black	0.01 (-0.03, 0.05)	0.04 (-0.02, 0.10)	-0.03 (-0.09, 0.03)	-0.01 (-0.09, 0.08)
Asian-American	0.07 (0.01, 0.14)	0.06 (-0.05, 0.17)	0.00 (-0.11, .10)	-0.12 (-0.24, 0.00)
Asian American, Semantic memory	0.01(-0.06, 0.08)	0.05 (-0.06, 0.15)	0.01 (-.09, 0.11)	-0.08 (-0.21, 0.04)
Latino	-0.01(-0.06, 0.04)	-0.04(-0.10, 0.03)	-0.01 (-0.08, 0.05)	0.03 (-0.06, 0.13)

*** All models adjusted for age (linear and quadratic), sex, parental education and race/ethnicity (unless stratified by race/ethnicity).**

**** This table matches Table 2 in the manuscript, with the addition of the coefficients for ACE association with semantic memory among Asian American**

Table 5. Mixed effects linear regression coefficients (95% confidence intervals) for the difference in memory scores associated with each ACE, overall and stratified by race/ethnicity.

ACEs	Overall	White	Black	Asian	Asian, semantic	Latino
Parents divorced	-0.03 (-0.11,0.04)	-0.10 (-0.24,0.04)	-0.03 (-0.15,0.09)	0.09 (-0.16,0.35)	0.20 (-0.11, 0.52)	-0.00 (-0.14,0.14)
Parents remarried	-0.11 (-0.20,-0.03)	-0.10 (-0.26,0.07)	-0.04 (-0.18,0.09)	-0.08 (-0.34,0.19)	-0.24 (-0.57, 0.08)	-0.18 (-0.34,-0.03)
Domestic violence	0.01 (-0.06,0.08)	0.07 (-0.07,0.21)	-0.00 (-0.12,0.12)	0.19 (0.00,0.38)	-0.02 (-0.25, 0.21)	-0.07 (-0.21,0.06)
Witnessed substance abuse	-0.06 (-0.14,0.01)	-0.08 (-0.21,0.06)	0.02 (-0.11,0.15)	0.18 (-0.10,0.46)	-0.04 (-0.39, 0.30)	-0.16 (-0.29,-0.02)
Parent job loss	0.04 (-0.04,0.11)	0.10 (-0.04,0.23)	-0.04 (-0.19,0.10)	0.16 (-0.04,0.37)	0.08 (-0.17, 0.34)	-0.04 (-0.19,0.12)
Parent in jail	-0.10 (-0.21,0.01)	-0.16 (-0.43,0.10)	-0.09 (-0.27,0.08)	0.17 (-0.11,0.45)	-0.16 (-0.51, 0.19)	-0.13 (-0.32,0.05)
Family member illness	0.02 (-0.04,0.08)	0.06 (-0.06,0.17)	-0.05 (-0.17,0.06)	0.11 (-0.04,0.26)	0.04 (-0.14, 0.22)	0.00 (-0.12,0.13)
Death of mother	-0.18 (-0.30,-0.07)	-0.10 (-0.34,0.14)	-0.15 (-0.36,0.06)	-0.19 (-0.48,0.10)	-0.54 (-0.89,,-0.18)	-0.29 (-0.49,-0.09)
Death of father	-0.11 (-0.20,-0.01)	0.05 (-0.15,0.25)	-0.14 (-0.31,0.03)	-0.10 (-0.33,0.12)	-0.08 (-0.36, 0.20)	-0.21 (-0.39,-0.02)

All models adjusted for age (linear and quadratic), sex, parental education, and race/ethnicity (unless stratified by race/ethnicity). ** This table matches Table 3 in the manuscript, with the addition of the coefficients for ACE association with semantic memory among Asian American

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7-8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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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

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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

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Abstract (word count=222)

Objectives: Evidence on adverse childhood experiences (ACEs) and late-life cognitive outcomes is inconsistent, with little research among diverse racial/ethnic groups. We investigated whether ACE exposures were associated with worse late-life cognition for all racial/ethnic groups, and at different ages of exposure.

Design: Covariate-adjusted mixed-effects linear regression models estimated associations of (1) total number of ACEs experienced, (2) earliest age when ACE occurred, and (3) type of ACE with overall cognition.

Setting: Kaiser Permanente Northern California (KPNC) members aged 65 years and older, living in Northern California.

Participants: Kaiser Healthy Aging and Diverse Life Experiences study baseline participants, aged 65 years and older (n=1,661; including 403 Asian-American, 338 Latino, 427 Black, and 493 White participants).

Results: Most respondents (69%) reported one or more ACE, most frequently family illness (36%), domestic violence (23%), and parental divorce (22%). ACE count was not adversely associated with cognition overall (β=0.01; 95% CI: -0.01 to 0.03), in any racial/ethnic group, or for any age-category of exposure. Pooling across all race/ethnicities, parent's remarriage (β =-0.11; 95% CI: -0.20 to -0.03), mother's death (β =-0.18; 95% CI: -0.30 to -0.07), and father's death (β =-0.11; 95% CI: -0.20 to -0.01) were associated with worse cognition.

Conclusion: Adverse childhood exposures overall were not associated with worse cognition in older adults in a diverse sample, although three ACEs were associated with worse cognitive outcomes.

Strengths and limitations of this study

- Evidence on the effect of ACEs on late-life cognitive performance and decline is mixed, with very little research conducted in populations with substantial racial/ethnic diversity.
- In the Kaiser Healthy Aging and Diverse Life Experiences cohort, comprising participants aged 65 years and older identifying as Black, Asian-American, Latino, or White, exposure to Adverse Childhood Experiences (ACE) was not associated with worse late-life cognition in any racial/ethnic group, and associations did not differ by age of ACE exposure
- Only parental remarriage and parental death were consistently associated with worse cognitive outcomes in late life.
- Primary limitations of the present study include reliance on a cross-sectional sample and self-reported ACEs.

Introduction

Adverse childhood experiences (ACEs), such as abuse, violence, and household dysfunction have lasting harmful impacts on adult physical and mental health,[1–3] but evidence on the effect of ACEs on late-life cognitive performance and decline is mixed.[4–6] 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] Prior studies indicate heterogeneities in the association of ACEs and cognitive outcomes by age of exposure, type of ACE, race/ethnicity, and sources of resilience. For example, Ravona-Springer (2012) found that death of a parent during childhood was associated with substantially higher risk of dementia when the experience occurred between the ages of 0 and 6, but the excess dementia risk attenuated the older the age of ACE exposure. Additional findings suggest that while some ACEs appear to adversely affect late-life cognitive functioning, other ACEs predict better cognitive outcomes.[6,10]

Both exposure to and consequences of ACEs may differ by race/ethnicity. Significant racial and ethnic differences in the prevalence of ACEs as well as between types of adversities have been documented.[11] To date, there has been only one multi-racial study evaluating ACEs and cognition: Barnes et al found no association between early-life adverse events and cognitive decline in Whites, while early-life food deprivation was associated with better cognitive outcomes for African Americans.[4] No other studies have directly compared effects across racial/ethnic groups.

We investigated the association of ACEs with later-life cognitive performance in the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) cohort. We hypothesized that ACE exposure would predict worse late-life cognition for all racial/ethnic groups, with the largest effects associated with experiences when aged 0-6 years.

Methods:

Study participants and data collection

We used baseline data from the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) cohort, which comprises community-dwelling older adults residing in the San Francisco Bay and Sacramento areas of California. KHANDLE aims to evaluate how race/ethnicity and life course health and sociocultural factors influence late-life brain health and cognitive decline. Individuals eligible for KHANDLE: were long-term members of Kaiser Permanente Northern California, an integrated healthcare delivery system; were age 65 years or older on January 1, 2017; spoke English or Spanish; and had previously participated in Kaiser Permanente multiphasic health checkup exams between 1964-1985. Stratified random sampling by race/ethnicity and educational attainment was used with the goal of recruiting approximately equal proportions of Asian, Black, Latino, and White participants and achieving diversity in educational attainment. Exclusion criteria included: electronic medical record diagnosis of dementia or other neurodegenerative disease (frontotemporal dementia, Lewy body disease, Pick's disease, Parkinson's disease with dementia, Huntington's disease); and presence of health conditions that would impede participation in study interviews, defined by hospice activity in the past 12 months, history of severe chronic obstructive pulmonary disease in the past 6 months,

congestive heart failure hospitalizations in the past 6 months, and history of end stage renal disease or dialysis in the past 12 months. At baseline, 1,712 individuals were enrolled. Individuals who self-identified as Native Americans (n=3) or refused to self-identify race/ethnicity (n=1) were dropped from the sample used in this analysis. After excluding 13 individuals who were missing all cognitive measures used in this analysis and 34 individuals missing all ACEs, the final analytic sample size was 1,661. All respondents provided informed consent and completed an interview in English or Spanish either in-home or at a Kaiser Permanente Facility (approximately 40% of baseline interviews were conducted at a facility and 60% in-home).

Kaiser Permanente Northern California (KPNC) is a large, integrated healthcare delivery system that provides comprehensive medical care to over 4 million members.[12] Prior work indicated the member population was generally representative of the overall regional population, though individuals at extreme tails of the income distribution were underrepresented.[13–15] The KPNC older adult population (aged 65+) are generally similar to the population of seniors residing in Northern California with respect to medical history of chronic conditions, including diabetes, hypertension, heart disease, and asthma, and lifestyle factors, including smoking, obesity, and sedentary lifestyle.[15]

Measures

Our cognitive outcomes are standardized scores from the following three cognitive domains: verbal episodic memory, semantic memory, and executive functioning. These scores were obtained from the Spanish and English Neuropsychological Assessment Scales (SENAS), which was given to all participants in their preferred language (English or Spanish).[16] The SENAS is a battery of cognitive tests that has previously undergone extensive development for valid comparisons of cognition across racial/ethnic and linguistically diverse groups. Verbal episodic memory composite scores were derived from a multiracial word-list-learning test. Semantic memory composite scores were derived from verbal (object-naming) and nonverbal (picture association) tests. Executive function composite scores were obtained using component tasks of category fluency, phonemic (letter) fluency, and working memory (digit-span backward, visual-span backward, list sorting). Details of the administration procedures, development, and psychometric characteristics have been extensively described in previous publications.[16] Analyses used cognitive data for everyone who had cognitive measures for at least one of the three cognitive domains.

KHANDLE fielded a modified version of the assessment of ACEs used in the Reasons for Geographic and Racial Disparities in Stroke (REGARDS) cohort.[17] Participants were asked aloud by the interviewer if they had experienced each of 9 ACEs when they were age 16 or younger: parents were divorced or separated; parents remarried; witnessed domestic violence; substance abuse by a family member; loss of a job by a parent; parent had to go to jail; serious illness of a family member; death of mother; and death of father. If any ACE was experienced, respondents were asked the youngest age at which they experienced the event. A composite ACE score was constructed as a count of the number ever experienced, with the scores ranging from 0 if no ACE had been experienced to 9 if every ACE had been experienced. For individuals missing one or more ACE item, we imputed the values to the average of the total observed ACEs

for that individual (i.e., if the individual responded to 6 ACE items and endorsed 3 of them, the values of the missing 3 items were imputed to 0.5). Since few people reported more than 4 ACEs (n=161), the count of ACEs was top coded at 4 for our analyses. Age-specific ACEs were constructed as the count of the number of experiences reported as first occurring in specific age categories (0-6, 7-12, and 13-16).

Because ACEs are experienced in early life, there are few plausible confounders that might influence both ACEs and late-life cognitive outcomes. All models were either adjusted for or stratified by race/ethnicity (classified as Black, White, Latino, or Asian). All models were also adjusted for linear and quadratic terms for year of age over 65 at cognitive assessment, sex, and parental education. Parental educational attainment was reported by the respondent as highest level of education completed. Maternal and paternal education for primary and secondary education was coded as number of years of primary or secondary education, ranging from 0 to 12. We additionally adjusted for parental higher education as a continuous predictor: 0=no higher education; 1=some college but no degree or associates degree; 2=bachelor's degree, master's degree or other higher education. If values for parental education were missing (n=276 and n=417 missing for maternal and paternal, respectively) they were coded as 0 (lowest category), and we additionally adjusted for an indicator variable for missingness.

Statistical Analysis:

Baseline variables gender, race/ethnicity, and parental education were tabulated by ACE composite score. The prevalence of each ACE was estimated for the entire sample and stratified by race/ethnicity.

If the effect of ACEs were the same for all three domains of cognition, it would be most efficient to estimate a single mixed model including each individual's three outcome assessments (verbal memory, semantic memory, and executive function) and derive a single effect estimate applicable to all domains. This added efficiency is especially important when estimating race/ethnicity specific effects where sample sizes are smaller. Before estimating such a model, we first had to assess whether it was appropriate to estimate a single effect of ACE exposure on all three cognitive domains within each racial/ethnic group.

In initial models, we therefore tested for domain-specific effects of composite ACE score on cognition for each racial/ethnic group. To do this, we used a mixed-effects linear regression model with the three standardized cognitive domains as outcomes with random intercepts to account for within-person correlation between cognitive domains. All models were controlled for indicators of cognitive domain (e.g., verbal memory or semantic memory, with executive function treated as the reference outcome), allowing for the possibility that average score differs between domains. We also included interactions between race/ethnicity and domain (allowing for the possibility that domain differences vary by race/ethnicity) and interactions between each person's composite ACE score and each race/ethnicity-domain combination (allowing for the possibility that the effect of ACE exposure differs for any combination of race/ethnicity and cognitive domain). An F-test for the null hypothesis that the race/ethnicity-specific ACE associations with cognition varied significantly across domains indicated evidence of

heterogeneity (P=0.09). When we evaluated individual comparisons, we found one significant domain-specific difference: the association between ACE score and semantic memory among Asian American respondents. For both other domains in Asian Americans and for all domains in the other three racial/ethnic groups, the statistical tests indicated estimation of a single parameter for estimated effects of ACEs on cognition was appropriate. In all subsequent models, interactions between Asian American, semantic memory, and the ACE measure were included to estimate the association of ACEs with semantic memory among Asian Americans separately from all other associations. In these models, the coefficient for the ACE measure can be interpreted as the association of ACEs with cognition, averaged across domains (results are very similar to what would be obtained if the different domains were averaged in advance and treated as a single outcome) except excluding the effect of ACEs on semantic memory among Asian Americans. Associations between ACE exposure and semantic memory among Asian American respondents are reported in Appendix tables 1-4.

We then used covariate-adjusted linear mixed models to estimate the association of composite ACE score with cognition in pooled analyses and in models stratified by race-ethnicity. To evaluate whether differences in coefficients between racial/ethnic groups were statistically significant, we incorporated race/ethnicity by ACE score interactions and used an F-test. Because of limited prior evidence on racial/ethnic specific associations, we present these even when the F-test indicated no evidence of statistically significant heterogeneity.

Covariate adjusted mixed-effects linear regression models were also estimated to evaluate the association between composite ACE scores at specific age categories (0-6, 7-12, and 13-16) and cognition for the full sample and in models stratified by race/ethnicity.

Finally, we evaluated the association of each of the 9 individual ACEs and standardized cognitive score and whether these associations differed by race/ethnicity or by age ranges of exposure (0-6; 7-12; 13-16). Results for age-specific associations with individual ACE exposures are given in the Appendix table 5.

Analyses were conducted using STATA SE 15 (STATA Corporation, College Station, TX, 2003).

Results

Among the 1,661 participants enrolled in the KHANDLE baseline, 69% reported experiencing at least one ACE prior to age 16: 448 individuals (27%) reported experiencing 1 ACE; 336 (20%) reported 2 ACEs; 203 (12%) reported 3 ACEs, and 161 (10%) reported 4+ ACEs (Table 1). Among the 9 individual ACEs, illness in the family had the highest overall prevalence at 36%, followed by domestic violence (23%), and parental divorce (22%) (Figure 1). Both the distribution of total ACE score and the prevalence of each specific ACE varied by race/ethnicity.

In covariate-adjusted mixed-effects linear regression models, there was no association between the composite ACE score and standardized cognition when considering all racial/ethnic groups in a pooled analysis (β =0.01; 95% CI, -0.01 to 0.03) (Table 2). Age-specific ACE exposures were not significantly associated with cognition (ACE scores ages 0-6, β =0.01; 95% CI, -0.03 to 0.05;

ACE scores ages 7-12, β = -0.03; 95% CI, -0.07 to 0.01; or ACE score ages 13-16, β = 0.01; 95% CI, -0.05 to 0.06) (Table 2). When evaluating the association between total ACE score and cognition for each racial/ethnic group, the only apparent association was for Asian Americans, among whom each unit increase in the composite ACE was associated with better cognitive scores (estimated association based on verbal memory and executive function, β =0.07; 95% CI, 0.01 to 0.14). Although this individual race-specific association was statistically significant, the overall test for differences in the association of ACE composite score and cognition across racial/ethnic groups was not significant (p=0.13) after excluding the single Asian-semantic memory comparison.

Interactions between race/ethnicity and age-specific ACE exposures were also non-significant. There was no evidence of associations between age-specific ACE exposures and cognition overall, although Asian Americans exposed to ACEs age 13-16 averaged worse cognition β =-0.12; 95% CI, -0.24 to 0.00) (Table 2).

Pooling across all race/ethnicities, three types of ACE exposures were associated with worse cognition: parent remarried; death of mother; and death of a father (Table 3). Although there were some differences in the associations of individual ACEs with standardized cognition between racial/ethnic groups, differences were consistent with chance (i.e., the tests of heterogeneity in the ACE associations with cognition across racial/ethnic groups were not statistically significant). Patterns were generally similar when evaluating cognition based on indicator variables for age of first exposure overall and race/ethnicity (Appendix Table 1).

Discussion

Retrospectively reported exposure to childhood ACEs was prevalent in a sample of long-term elderly Kaiser Permanente Northern California (KPNC) members, but ACEs were not associated with cognition in later-life among White, Black, or Latino respondents. Results were similar for total ACE count and ACE exposures during age groups categorized as 0-6, 7-12, and 13-16. Among Asian American respondents, higher ACE count was associated with slightly better overall cognition, albeit a difference too small to be of notable clinical significance. Among the individual ACEs, three experiences were associated with significantly worse cognition when pooling across all racial/ethnic groups, but when examining each racial/ethnic group separately, point estimates indicated adverse associations only for parents remarried and death of a mother (albeit with wide confidence intervals in racial/ethnic group specific estimates). For other ACEs, associations were inconsistent and, in several instances, positive. All racial/ethnic differences in ACE by cognition associations were consistent with chance.

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.[1,18] Early life stress predicts both hippocampus and amygdala development in children as well as children's cognitive and affective functioning.[19–21] 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.[22] However, prior findings in early work on ACEs and cognition has been mixed and has been conducted in predominantly White samples. Very few prior studies include multi-racial samples or assessments with both age-specific ACE exposure and late-life cognitive outcomes. This is

important to evaluate because race/ethnicity is strongly associated with economic, social, political, and environmental factors that influence cognitive aging. These factors may modify the consequences of ACEs for cognition in late life or may create selection processes such that only especially resilient individuals survive to late life. For example, increased exposure to extreme adversity across the lifecourse may blunt the special relevance of childhood adversity among racial/ethnic minorities in the United States.

Our findings do suggest that parental remarriage and parental death are associated with worse cognitive outcomes in late life. The exposures were common, especially for racial/ethnic minorities. The importance of these experiences over other adversities may imply the special relevance of a child being separated from the parent.

Prior studies have documented significant racial and ethnic differences in the prevalence of total ACEs as well as between types of adversity, such as incarceration of a family member versus domestic violence, in the U.S.[11] ACEs are strongly patterned by socioeconomic status and neighborhood context.[23] Barnes et al reported that in a cohort of 6,105 older African Americans and Whites followed for up to 16 years, there was no association between early life adverse events and rate of cognitive decline in Whites, while food deprivation and being thinner than average in early life were associated with better cognitive outcomes for African Americans.[4] Food deprivation is not commonly used in ACE surveys and was not included in the KHANDLE baseline survey.

Although point estimates for the effects of ACEs among Whites were generally more adverse than for other racial/ethnic groups, only for Asian American did we find evidence of a statistically significant difference. Among Asian Americans, higher ACE count was associated with better overall cognition. It is difficult to theorize how ACEs might enhance later life cognition. The positive association observed among older Asian Americans may be due to chance, selective survival, or differential recall. Especially among Asian Americans in the KHANDLE sample, many of whom were born outside the US, individuals who have migrated, survived to late life, and enrolled in the study may be an extraordinarily resilient group. This type of selection could lead to inverse associations if both ACE exposure and other determinants of late life cognition influence the process that leads to study enrollment. Chance is also a plausible explanation, as indicated by the non-significant F-test for heterogeneity between racial/ethnic groups.

The limitations of the present study include reliance on a cross-sectional sample and self-reporting ACEs. This precludes evaluating within-person cognitive decline and increases vulnerability to confounding. However, confounding seems unlikely to account for the largely null results reported here. Several different ACE assessment instruments, reflecting different levels of trauma, are currently in use across the field. 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. Finally, sample size is an important limitation, although for the overall and race-specific estimates of composite ACE score and cognition associations, confidence intervals were fairly narrow and inconsistent with especially large

benefits or harms. KHANDLE is, to our knowledge, the only available community-based study with information on the four largest racial/ethnic groups represented in the US and rigorous cognitive assessments in older adults. We have reported finely grained results to facilitate future meta-analyses. This study did not directly address dementia because the participants were screened at baseline to be free of dementia. Differences in cognitive performance in late life are relevant for anticipating dementia risk, however, because of the established importance of cognitive reserve.[24,25] 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] Our findings, therefore, if taken at face value, suggest these ACEs may not have major relevance for subsequent dementia risk.

Our results suggest that previously reported findings linking ACEs to cognitive outcomes in late life may be over-estimated or may not hold in many communities. These findings should be interpreted cautiously until replicated in additional multi-ethnic samples. Given the robust evidence of early life experiences overall for cognitive reserve and dementia risk, these results would suggest a focus on other aspects of childhood, such as material deprivation or educational experiences.

Figure 1 caption: Grey vertical line segments indicate exact binomial confidence intervals

Competing interests: authors declare no competing interests.

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Patient and public involvement: Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research**.**

Patient consent for publication: Not required.

Ethics Approval: Ethical approval was granted by the Kaiser Permanente Northern California Institutional Review Board (IRB Number: CN-16-2786).

Data availability statement: De-identified data are available to qualified investigators from the KHANDLE Leadership Committee upon approval for the purposes of replicating procedures and results.

Table 1: Descriptive Statistics, KHANDLE Cohort

Variable	Level	Composite ACE Score				
		0	1	2	3	4+
N	1,661	513 (100%)	448 (100%)	336 (100%)	203 (100%)	161 (100%)
Age (years), mean (SD)	76.0 (6.8)	75.7 (6.6)	76.6 (6.9)	76.1 (6.9)	76.0 (6.7)	74.6 (6.4)
Gender	Female	223 (43.5%)	182 (40.6%)	133 (39.6%)	74 (36.5%)	63 (39.1%)
	Male	290 (56.5%)	266 (59.4%)	203 (60.4%)	129 (63.5%)	98 (60.9%)
Race/Ethnicity	Asian	181 (35.3%)	111 (24.8%)	68 (20.2%)	29 (14.3%)	14 (8.7%)
	Black	105 (20.5%)	116 (25.9%)	92 (27.4%)	66 (32.5%)	48 (29.8%)
	Latino	71 (13.8%)	82 (18.3%)	85 (25.3%)	51 (25.1%)	49 (30.4%)
	White	156 (30.4%)	139 (31.0%)	91 (27.1%)	57 (28.1%)	50 (31.1%)
Maternal education	Mean years of education among those with <=12 years, (SD)	8.46 (4.73)	7.76 (4.87)	7.78 (4.74)	7.98 (5.00)	7.83 (4.76)
	Some college but no degree/ associates degree	59 (11.5%)	51 (11.4%)	38 (11.3%)	25 (12.3%)	14 (8.7%)
	Bachelor's or more	63 (12.3%)	34 (7.6%)	32 (9.5%)	18 (8.9%)	10 (6.2%)
Paternal education	Mean years of education among those with <=12 years, (SD)	8.51 (4.75)	7.29 (5.16)	6.82 (5.36)	6.19 (5.21)	6.53 (5.45)
	Some college but no degree/ associates degree	60 (11.7%)	43 (9.6%)	32 (9.5%)	21 (10.3%)	12 (7.5%)
	Bachelor's or more	110 (21.4%)	70 (15.6%)	46 (13.7%)	14 (6.9%)	15 (9.3%)

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Table 2. Mixed-effects linear regression coefficients (95% confidence intervals) for the difference in cognitive scores associated with total childhood or age-specific count of ACEs (0 to 4+), overall and stratified by race/ethnicity.

	Total childhood ACEs β (95% CI)	Early childhood (0-6 years) ACEs β (CI)	Middle childhood (7-12 years) ACEs β (CI)	Adolescent (13-16 years) ACEs β (CI)
Full sample	0.01 (-0.01, 0.03)	0.01 (-0.03, 0.05)	-0.03 (-0.07, 0.01)	0.01 (-0.05, 0.06)
White	0.00 (-0.04, 0.05)	0.01 (-0.05, 0.08)	-0.03 (-0.09, 0.03)	0.07 (-0.03, 0.17)
Black	0.01 (-0.03, 0.05)	0.04 (-0.02, 0.10)	-0.03 (-0.09, 0.03)	-0.01 (-0.09, 0.08)
Asian-American	0.07 (0.01, 0.14)	0.06 (-0.05, 0.17)	0.00 (-0.11, 0.10)	-0.12 (-0.24, 0.00)
Latino	-0.01(-0.06, 0.04)	-0.04(-0.10, 0.03)	-0.01 (-0.08, 0.05)	0.03 (-0.06, 0.13)
P-value from an F-test for interaction between ACE composite score and race/ethnicity	0.13	0.17	0.26	0.80

*** All models adjusted for age (linear and quadratic), sex, parental education and race/ethnicity (unless stratified by race/ethnicity).**

**** All models provide a single coefficient for associations with verbal episodic memory, semantic memory, and executive function, with the exception of the coefficients for ACE association with semantic memory among Asian Americans, which are estimated separately and presented in the supplement.**

Table 3. Mixed effects linear regression coefficients (95% confidence intervals) for the difference in memory scores associated with each ACE, overall and stratified by race/ethnicity.

ACEs	Overall β (95% CI)	White β (95% CI)	Black β (95% CI)	Asian β (95% CI)	Latino β (95% CI)	P-value for interaction with race/ethnicity**
Parents divorced	-0.03 (-0.11, 0.04)	-0.10 (-0.24, 0.04)	-0.03 (-0.15, 0.09)	0.09 (-0.16, 0.35)	-0.00 (-0.14, 0.14)	0.20
Parents remarried	-0.11 (-0.20, -0.03)	-0.10 (-0.26, 0.07)	-0.04 (-0.18, 0.09)	-0.08 (-0.34, 0.19)	-0.18 (-0.34, -0.03)	0.74
Domestic violence	0.01 (-0.06, 0.08)	0.07 (-0.07, 0.21)	-0.00 (-0.12, 0.12)	0.19 (0.00, 0.38)	-0.07 (-0.21, 0.06)	0.11
Witnessed substance abuse	-0.06 (-0.14, 0.01)	-0.08 (-0.21, 0.06)	0.02 (-0.11, 0.15)	0.18 (-0.10, 0.46)	-0.16 (-0.29, -0.02)	0.05
Parent job loss	0.04 (-0.04, 0.11)	0.10 (-0.04, 0.23)	-0.04 (-0.19, 0.10)	0.16 (-0.04, 0.37)	-0.04 (-0.19, 0.12)	0.26
Parent in jail	-0.10 (-0.21, 0.01)	-0.16 (-0.43, 0.10)	-0.09 (-0.27, 0.08)	0.17 (-0.11, 0.45)	-0.13 (-0.32, 0.05)	0.29
Family member illness	0.02 (-0.04, 0.08)	0.06 (-0.06, 0.17)	-0.05 (-0.17, 0.06)	0.11 (-0.04, 0.26)	0.00 (-0.12, 0.13)	0.29
Death of mother	-0.18 (-0.30, -0.07)	-0.10 (-0.34, 0.14)	-0.15 (-0.36, 0.06)	-0.19 (-0.48, 0.10)	-0.29 (-0.49, -0.09)	0.67
Death of father	-0.11 (-0.20, -0.01)	0.05 (-0.15, 0.25)	-0.14 (-0.31, 0.03)	-0.10 (-0.33, 0.12)	-0.21 (-0.39, -0.02)	0.55

*** All models adjusted for age (linear and quadratic), sex, parental education, and race/ethnicity (unless stratified by race/ethnicity).**

****P values reflect the F-test of the interaction between individual ACEs and race/ethnicity**

***** All models provide a single coefficient for associations with verbal episodic memory, semantic memory, and executive function, with the exception that coefficients for ACE association with semantic memory among Asian Americans are estimated separately and presented in the supplement**

References

1. Felitti VJ, Anda RF, Nordenberg D, Williamson DF, Spitz AM, Edwards V, et al. Relationship of Childhood Abuse and Household Dysfunction to Many of the Leading Causes of Death in Adults. Am J Prev Med. 1998 May;14(4):245–58.

2. Anda RF, Felitti VJ, Bremner JD, Walker JD, Whitfield Ch, Perry BD, et al. The enduring effects of abuse and related adverse experiences in childhood: A convergence of evidence from neurobiology and epidemiology. Eur Arch Psychiatry Clin Neurosci. 2006 Apr;256(3):174–86.

3. Baglivio M, Swartz, Kimberly, Huq, Mona Sayedul, Sheer, Amy, Hardt, Nancy. The Prevalence of Adverse Childhood Experiences (ACE) in the Lives of Juvenile Offenders. 2014;

4. Barnes LL, Wilson RS, Everson-Rose SA, Hayward MD, Evans DA, Mendes de Leon CF. Effects of early-life adversity on cognitive decline in older African Americans and whites. Neurology. 2012 Dec 11;79(24):2321–7.

5. Korten NCM, Penninx BWJH, Pot AM, Deeg DJH, Comijs HC. Adverse Childhood and Recent Negative Life Events: Contrasting Associations With Cognitive Decline in Older Persons. J Geriatr Psychiatry Neurol. 2014 Jun;27(2):128–38.

6. Ritchie K, Jaussent I, Stewart R, Dupuy A-M, Courtet P, Malafosse A, et al. Adverse childhood environment and late-life cognitive functioning: Childhood adversity and late-life cognition. Int J Geriatr Psychiatry. 2011 May;26(5):503–10.

7. Villarejo A, Bermejo-Pareja F, Trincado R, Olazarán J, Benito-León J, Rodríguez C, et al. Memory impairment in a simple recall task increases mortality at 10 years in non-demented elderly. Int J Geriatr Psychiatry. 2011 Feb;26(2):182–7.

8. Luppa M, Luck T, Weyerer S, Konig H-H, Brahler E, Riedel-Heller SG. Prediction of institutionalization in the elderly. A systematic review. Age Ageing. 2010 Jan 1;39(1):31–8.

9. Wagner DC, Short JL. Longitudinal predictors of self-rated health and mortality in older adults. Prev Chronic Dis. 2014 Jun 5;11:E93.

10. Ravona-Springer R, Beeri MS, Goldbourt U. Younger Age at Crisis Following Parental Death in Male Children and Adolescents Is Associated With Higher Risk for Dementia at Old Age: Alzheimer Dis Assoc Disord. 2012;26(1):68–73.

11. Mersky JP, Janczewski CE. Racial and ethnic differences in the prevalence of adverse childhood experiences: Findings from a low-income sample of U.S. women. Child Abuse Negl. 2018 Feb;76:480–7.

12. Klein NP, Fireman B, Goddard K, Zerbo O, Asher J, Zhou J, et al. Vaccine effectiveness of cell-culture relative to egg-based inactivated influenza vaccine during the 2017-18 influenza season. Huber VC, editor. PLOS ONE. 2020 Feb 26;15(2):e0229279.

13. Gordon NP, Kaplan GA. Some evidence refuting the HMO "favorable selection" hypothesis: the case of Kaiser Permanente. Adv Health Econ Health Serv Res. 1991;12:19–39.

14. Krieger N. Overcoming the absence of socioeconomic data in medical records: validation and application of a census-based methodology. Am J Public Health. 1992 May;82(5):703–10.

15. Gordon NP. Similarity of the Kaiser Permanente Senior Member Population in Northern California to the Non-Kaiser Permanente Covered and General Population of Seniors in Northern California: Statistics from the 2009 California Health Interview Survey. Kaiser Permanente Northern California Division of Research; 2012.

16. Mungas D, Reed BR, Crane PK, Haan MN, González H. Spanish and English Neuropsychological Assessment Scales (SENAS): Further Development and Psychometric Characteristics. Psychol Assess. 2004 Dec;16(4):347–59.

17. Howard VJ, McClure LA, Glymour MM, Cunningham SA, Kleindorfer DO, Crowe M, et al. Effect of duration and age at exposure to the Stroke Belt on incident stroke in adulthood. Neurology. 2013 Apr 30;80(18):1655–61.

18. Anda RF, Dong M, Brown DW, Felitti VJ, Giles WH, Perry GS, et al. The relationship of adverse childhood experiences to a history of premature death of family members. BMC Public Health. 2009 Dec;9(1):106.

19. Pechtel P, Pizzagalli DA. Effects of early life stress on cognitive and affective function: an integrated review of human literature. Psychopharmacology (Berl). 2011 Mar;214(1):55–70.

20. Ivy AS, Rex CS, Chen Y, Dube C, Maras PM, Grigoriadis DE, et al. Hippocampal Dysfunction and Cognitive Impairments Provoked by Chronic Early-Life Stress Involve Excessive Activation of CRH Receptors. J Neurosci. 2010 Sep 29;30(39):13005–15.

21. Oh DL, Jerman P, Silvério Marques S, Koita K, Purewal Boparai SK, Burke Harris N, et al. Systematic review of pediatric health outcomes associated with childhood adversity. BMC Pediatr. 2018 Dec;18(1):83.

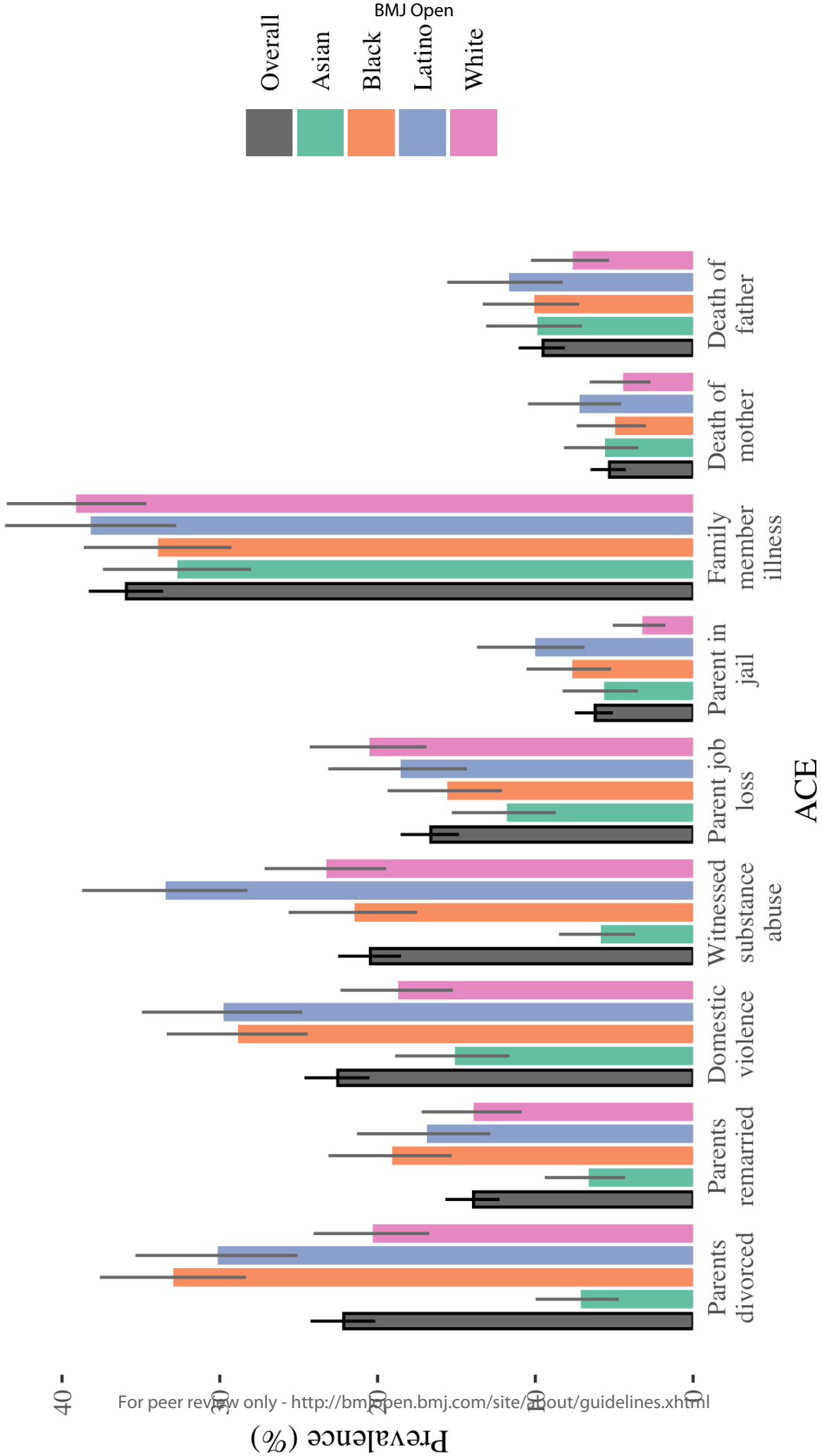
22. Howell KH, Miller-Graff LE. Protective factors associated with resilient functioning in young adulthood after childhood exposure to violence. Child Abuse Negl. 2014 Dec;38(12):1985–94.

23. Walsh D, McCartney G, Smith M, Armour G. Relationship between childhood socioeconomic position and adverse childhood experiences (ACEs): a systematic review. J Epidemiol Community Health. 2019 Dec;73(12):1087–93.

24. Scarmeas N, Stern Y. Cognitive reserve: Implications for diagnosis and prevention of Alzheimer's disease. Curr Neurol Neurosci Rep. 2004 Oct;4(5):374–80.

25. Scarmeas N, Stern Y. Cognitive Reserve and Lifestyle. J Clin Exp Neuropsychol. 2003 Aug;25(5):625–33.

26. Barnes DE, Covinsky KE, Whitmer RA, Kuller LH, Lopez OL, Yaffe K. Predicting risk of dementia in older adults: The late-life dementia risk index. Neurology. 2009 Jul 21;73(3):173–9.



Results from Asian and semantic memory omnibus testing

Appendix Table 1. Regression estimates for the interaction of composite ACE score, race/ethnicity, and the domain of the cognitive measure.

Variable	Beta Coef.	Confidence intervals	P-value
Composite ACE score*	0.01	(-0.06, 0.08)	0.81
Asian executive	ref	ref	
Asian semantic by ACE score	0.13	(0.04 , 0.21)	0.00
Asian verbal by ACE score	0.00	(-0.08 , 0.08)	0.99
Black executive by ACE score	0.02	(-0.08 , 0.11)	0.71
Black semantic by ACE score	-0.01	(-0.10 , 0.09)	0.92
Black verbal by ACE score	-0.002	(-0.10 , 0.09)	0.97
Latino executive by ACE score	-0.03	(-0.12 , 0.07)	0.61
Latino semantic by ACE score	-0.00	(-0.10 , 0.10)	0.99
Latino verbal by ACE score	-0.01	(-0.11 , 0.09)	0.90
White executive by ACE score	-0.04	(-0.13 , 0.05)	0.40
White semantic by ACE score	-0.02	(-0.11 , 0.07)	0.67
White verbal by ACE score	-0.01	(-0.10 , 0.08)	0.87
F-test	**0.10**		

* The main effect of for Composite ACE score refers to the estimate for executive function among Asian American respondents. All other terms refer to the deviation from that effect for the specified racial/ethnic group in the specified cognitive domain. The P-value tests whether that deviation is consistent with the null.

Appendix Table 2. Final regression model results estimating one effect of composite ACE score on semantic memory among Asian American respondents and another effect for all other racial/ethnic group and cognitive domain combinations.

Variables	Beta Coef.	Confidence intervals	P-value
Composite score main effect	0.01	(-0.01 , 0.03)	0.42
Composite score by indicator for Asian respondents predicting semantic memory domain	-0.03	(-0.10 , 0.03)	0.34
Asian semantic	-0.11	(-0.21 , -0.02)	0.02
Asian verbal	0.34	(0.23 , 0.46)	<0.00
Black executive	-0.31	(-0.43 , -0.19)	<0.00
Black semantic	-0.56	(-0.68 , -0.44)	<0.00
Black verbal	-0.20	(-0.32 , -0.08)	<0.00
Latino executive	-0.06	(-0.18 , 0.06)	0.32
Latino semantic	0.23	(0.10 , 0.35)	0.00
Latino verbal	0.01	(-0.11 , 0.13)	0.89
White executive	0.51	(0.40 , 0.62)	<0.01
White semantic	0.61	(0.50 , 0.72)	<0.01
White verbal	0.09	(-0.02 , 0.20)	0.11

Appendix Table 3. Mixed effects linear regression coefficients (95% confidence intervals) for the difference in cognitive scores associated with total childhood or age-specific count of ACEs (0 to 4+), overall and stratified by race/ethnicity. [with Asian Semantic Memory]

	Total childhood ACEs Beta (95% CI)	Early childhood (0-6 years) ACEs Beta (CI)	Middle childhood (7-12 years) ACEs Beta (CI)	Adolescent (13-16 years) ACEs Beta (CI)
Full sample	0.01 (-0.01, 0.03)	0.01 (-0.03, 0.05)	-0.03 (-0.07, 0.01)	0.01 (-0.05, 0.06)
White	0.00 (-0.04, 0.05)	0.01 (-0.05, 0.08)	-0.03 (-0.09, 0.03)	0.07 (-0.03, 0.17)
Black	0.01 (-0.03, 0.05)	0.04 (-0.02, 0.10)	-0.03 (-0.09, 0.03)	-0.01 (-0.09, 0.08)
Asian-American	0.07 (0.01, 0.14)	0.06 (-0.05, 0.17)	0.00 (-0.11, .10)	-0.12 (-0.24, 0.00)
Asian American, Semantic memory	0.01(-0.06, 0.08)	0.05 (-0.06, 0.15)	0.01 (-.09, 0.11)	-0.08 (-0.21, 0.04)
Latino	-0.01(-0.06, 0.04)	-0.04(-0.10, 0.03)	-0.01 (-0.08, 0.05)	0.03 (-0.06, 0.13)

*** All models adjusted for age (linear and quadratic), sex, parental education and race/ethnicity (unless stratified by race/ethnicity).**

**** This table matches Table 2 in the manuscript, with the addition of the coefficients for ACE association with semantic memory among Asian American**

Table 4. Mixed effects linear regression coefficients (95% confidence intervals) for the difference in memory scores associated with each ACE, overall and stratified by race/ethnicity.

ACEs	Overall	White	Black	Asian	Asian, semantic	Latino
Parents divorced	-0.03 (-0.11,0.04)	-0.10 (-0.24,0.04)	-0.03 (-0.15,0.09)	0.09 (-0.16,0.35)	0.20 (-0.11, 0.52)	-0.00 (-0.14,0.14)
Parents remarried	-0.11 (-0.20,-0.03)	-0.10 (-0.26,0.07)	-0.04 (-0.18,0.09)	-0.08 (-0.34,0.19)	-0.24 (-0.57, 0.08)	-0.18 (-0.34,-0.03)
Domestic violence	0.01 (-0.06,0.08)	0.07 (-0.07,0.21)	-0.00 (-0.12,0.12)	0.19 (0.00,0.38)	-0.02 (-0.25, 0.21)	-0.07 (-0.21,0.06)
Witnessed substance abuse	-0.06 (-0.14,0.01)	-0.08 (-0.21,0.06)	0.02 (-0.11,0.15)	0.18 (-0.10,0.46)	-0.04 (-0.39, 0.30)	-0.16 (-0.29,-0.02)
Parent job loss	0.04 (-0.04,0.11)	0.10 (-0.04,0.23)	-0.04 (-0.19,0.10)	0.16 (-0.04,0.37)	0.08 (-0.17, 0.34)	-0.04 (-0.19,0.12)
Parent in jail	-0.10 (-0.21,0.01)	-0.16 (-0.43,0.10)	-0.09 (-0.27,0.08)	0.17 (-0.11,0.45)	-0.16 (-0.51, 0.19)	-0.13 (-0.32,0.05)
Family member illness	0.02 (-0.04,0.08)	0.06 (-0.06,0.17)	-0.05 (-0.17,0.06)	0.11 (-0.04,0.26)	0.04 (-0.14, 0.22)	0.00 (-0.12,0.13)
Death of mother	-0.18 (-0.30,-0.07)	-0.10 (-0.34,0.14)	-0.15 (-0.36,0.06)	-0.19 (-0.48,0.10)	-0.54 (-0.89,,-0.18)	-0.29 (-0.49,-0.09)
Death of father	-0.11 (-0.20,-0.01)	0.05 (-0.15,0.25)	-0.14 (-0.31,0.03)	-0.10 (-0.33,0.12)	-0.08 (-0.36, 0.20)	-0.21 (-0.39,-0.02)

All models adjusted for age (linear and quadratic), sex, parental education, and race/ethnicity (unless stratified by race/ethnicity). ** This table matches Table 3 in the manuscript, with the addition of the coefficients for ACE association with semantic memory among Asian American

Appendix Table 5. Association of ACEs based on interaction terms between race/ethnicity and ages ACE experienced

	Parents divorced	Parents remarried	Domestic violence	Witnessed substance abuse	Parent job loss	Parent in jail	Family member illness	Death of mother	Death of father
	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)
Black, 0-6	0.23 (-0.00, 0.46)	-0.02 (-0.42, 0.37)	0.12 (-0.18, 0.42)	0.07 (-0.27, 0.41)	-0.15 (-0.59, 0.29)	-0.31 (-1.17, 0.54)	0.04 (-0.26, 0.33)	-0.05 (-0.90, 0.80)	0.35 (-0.17, 0.87)
Black, 7-12	-0.13 (-0.45, 0.20)	0.43 (0.11, 0.76)	-0.15 (-0.40, 0.11)	0.09 (-0.19, 0.37)	0.10 (-0.19, 0.40)	0.43 (-0.14, 0.99)	0.00 (-0.22, 0.22)	-0.00 (-0.73, 0.73)	-0.49 (-1.07, 0.08)
Black, 13-16	-0.03 (-0.53, 0.47)	0.04 (-0.41, 0.49)	-0.12 (-0.62, 0.37)	0.30 (-0.08, 0.69)	-0.35* (-0.74, 0.03)	0.43 (-0.52, 1.39)	-0.08 (-0.38, 0.22)	-0.40 (-0.97, 0.18)	-0.17 (-0.59, 0.26)
Latino, 0-6	0.28 (0.02, 0.53)	-0.08 (-0.48, 0.32)	-0.03 (-0.33, 0.26)	-0.10 (-0.40, 0.21)	-0.56 (-0.95, -0.17)	-0.05 (-0.98, 0.87)	-0.17 (-0.47, 0.12)	0.15 (-0.53, 0.82)	0.29 (-0.26, 0.84)
Latino, 7-12	0.14 (-0.21, 0.48)	0.43 (0.07, 0.80)	-0.17 (-0.45, 0.10)	-0.07 (-0.33, 0.20)	0.22 (-0.09, 0.53)	0.18 (-0.38, 0.74)	0.02 (-0.20, 0.24)	0.02 (-0.76, 0.80)	-0.25 (-0.75, 0.26)
Latino, 13-16	-0.04 (-0.55, 0.47)	-0.02 (-0.49, 0.44)	-0.31 (-0.91, 0.28)	-0.11 (-0.50, 0.29)	0.00 (-0.46, 0.46)	0.36 (-0.58, 1.29)	0.19 (-0.13, 0.52)	-0.10 (-0.70, 0.49)	-0.24 (-0.75, 0.28)
Asian, 0-6	0.34 (-0.03, 0.71)	-0.10 (-0.68, 0.48)	0.29 (-0.06, 0.64)	0.31 (-0.15, 0.78)	-0.03 (-0.50, 0.44)	0.09 (-0.70, 0.88)	0.06 (-0.23, 0.34)	-0.09 (-0.74, 0.57)	0.25 (-0.25, 0.75)
Asian, 7-12	-0.05 (-0.53, 0.43)	0.28 (-0.16, 0.72)	0.05 (-0.26, 0.35)	0.34 (-0.19, 0.86)	0.31 (-0.02, 0.64)	0.40 (-0.25, 1.06)	0.08 (-0.14, 0.30)	-0.10 (-1.15, 0.95)	-0.45 (-1.05, 0.14)
Asian, 13-16	0.17 (-0.63, 0.97)	-0.37 (-0.95, 0.22)	-0.59 (-1.18, -0.00)	-0.13 (-0.66, 0.40)	-0.25 (-0.72, 0.21)	-0.18 (-1.22, 0.87)	0.15 (-0.17, 0.48)	-0.10 (-0.51, 0.30)	-0.16 (-0.61, 0.29)

White, 0-6	-0.15 (-0.32, 0.02)	-0.02 (-0.31, 0.28)	0.02 (-0.19, 0.24)	0.02 (-0.22, 0.25)	0.26 (0.02, 0.50)	0.26 (-0.44, 0.95)	0.06 (-0.12, 0.23)	-0.29 (-0.79, 0.20)	-0.36 (-0.73, 0.01)
White, 7-12	-0.01 0.95	-0.41 (-0.65, -0.17)	0.07 (-0.12, 0.27)	-0.09 (-0.27, 0.09)	-0.02 (-0.22, 0.17)	-0.37 (-0.83, 0.09)	0.02 (-0.12, 0.16)	0.15 (-0.46, 0.76)	0.27 (-0.13, 0.68)
White, 13-16	0.15 (-0.23, 0.54)	0.04 (-0.28, 0.36)	0.03 (-0.33, 0.40)	-0.12 (-0.38, 0.15)	0.27 (0.01, 0.53)	-0.27 (-1.12, 0.59)	-0.02 (-0.25, 0.20)	-0.32 (-0.91, 0.27)	0.10 (-0.22, 0.42)

*** All models adjusted for age (linear and quadratic), sex, parental education and race/ethnicity (unless stratified by race/ethnicity).**

**** All models provide a single coefficient for associations with verbal episodic memory, semantic memory, and executive function, with the exception that coefficients for ACE association with semantic memory among Asian Americans are estimated separately and presented in the supplement.**

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3
Methods			
Study design	4	Present key elements of study design early in the paper	3
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	3-4
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	3-4
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	4-5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*4-5*
Bias	9	Describe any efforts to address potential sources of bias	4-5
Study size	10	Explain how the study size was arrived at	4
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	4
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	5
		(*b*) Describe any methods used to examine subgroups and interactions	5
		(*c*) Explain how missing data were addressed	5
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	
		(*e*) Describe any sensitivity analyses	
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	6
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	6
		(b) Indicate number of participants with missing data for each variable of interest	
Outcome data	15*	Report numbers of outcome events or summary measures	6-7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	6-7

		(*b*) Report category boundaries when continuous variables were categorized	
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	7
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	7-8
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	7-9
Generalisability	21	Discuss the generalisability (external validity) of the study results	8-9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	9

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.