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Education differentially contributes to cognitive reserve across racial/ethnic groups

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Abstract

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CONFLICTS OF INTEREST

The authors listed certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Introduction: We examined whether educational attainment differentially contributes to cognitive reserve (CR) across race/ethnicity.

Methods: A total of 1553 non-Hispanic Whites (Whites), non-Hispanic Blacks (Blacks), and Hispanics in the Washington Heights-Inwood Columbia Aging Project (WHICAP) completed structural magnetic resonance imaging. Mixture growth curve modeling was used to examine whether the effect of brain integrity indicators (hippocampal volume, cortical thickness, and white matter hyperintensity [WMH] volumes) on memory and language trajectories was modified by education across racial/ethnic groups.

Results: Higher educational attainment attenuated the negative impact of WMH burden on memory ($\beta = -0.03$; 99% CI: −0.071, −0.002) and language decline ($\beta = -0.024$; 99% CI:− 0.044, −0.004), as well as the impact of cortical thinning on level of language performance for Whites, but not for Blacks or Hispanics.

Discussion: Educational attainment does not contribute to CR similarly across racial/ethnic groups.

Keywords

cognitive aging; cognitive reserve; education; racial/ethnic differences

1 | BACKGROUND

Studies of neurodegeneration and biomarkers among patients with Alzheimer's disease (AD) have revealed substantial heterogeneity in the association between levels of cognitive function for a given level of neurodegeneration.[1,2] The theory of cognitive reserve (CR) has been proposed as a way to explain these clinicopathologic discrepancies.[3-6] CR refers to intraindividual characteristics that preserve cognitive function in the presence of diminished brain integrity associated with diseases of aging.[7] Studies suggest that life-course experiences, such as education, contribute to the development of CR.[8] For instance, more years of education is associated with lower dementia risk and delayed age of dementia onset.[9] However, the majority of CR studies have been focused largely on non-Hispanic White (White) samples. Given the historical differences in access and quality of education across racial/ethnic groups, it is unclear whether education contributes to CR comparably across racial/ethnic groups.[10] Accurate characterization and quantification of CR across racially/ethnically diverse older adults may lead to identification of modifiable life-course factors that could increase CR and delay the onset and progression of AD.

Evaluation of CR involves examining whether a proxy measure of CR (ie, years of education) modifies the relationship between an indicator of brain integrity (ie, neuroimaging markers of hippocampal volume, cortical thickness, or degree of white matter hyperintensity [WMH] burden) and a cognitive or clinical outcome.[8] However, there is some evidence that the relationship between brain integrity and cognition differs by racial/ethnic group,[11] suggesting racial/ethnic differences in the neurobiological substrates that underlie cognitive impairment. As a result, there may be racial/ethnic variation in moderation of the relationship of cognitive outcomes to specific brain integrity indicators.

The purpose of this study was to examine whether education contributes to CR, by moderating the relationship between indicators of brain integrity and cognitive trajectories similarly across racial/ethnic groups. As illustrated in Figure 1, we hypothesized that indicators of brain integrity (hippocampal volume, cortical thickness, and WMH burden), would differentially relate to level and change in cognition across Black, Hispanic, and White older adults ("a" path). Given historical racial/ethnic inequalities in quality of education, the contribution of years of education to CR is likely reduced for racial/ethnic minorities ("b" path).[12] Thus, we hypothesized that among Whites, education would contribute to CR by providing a buffer against the effects of reduced brain integrity on level and change in cognition ("c" path). We focus only on years of education in this study because it is the most frequently used proxy of CR[13] in the literature. It was not the goal of this study to provide comprehensive examination of other potential life-course contributors to CR.

2 | METHODS

2.1 | Participants

The 1553 participants in this sample were community-living Medicare recipients 65 years and older recruited from northern Manhattan to participate in the Washington Heights-Inwood Columbia Aging Project (WHICAP) (See Tang et al., 2001 for study procedures and a detailed description of the larger WHICAP sample.) Recruitment occurred in three waves: 1992 (N = 2126), 1999 (N = 2180), and 2009 (N = 2128). Participants completed a baseline cognitive assessment, in English or Spanish (based on language preference), and were followed up at 18- to 24-month intervals for up to 25 years. This study was approved by institutional review boards at Columbia University Medical Center. Written informed consent was obtained.

A subset of 761 participants from the 1992/1999 cohorts and 879 participants from the 2009 cohort, who were free of dementia at their prior visit, underwent structural magnetic resonance imaging (MRI). Participants were excluded from the current analyses if they (1) self-reported a primary race/ethnicity other than White, Black, or Hispanic (N = 32); or (2) were missing data on education, the brain integrity variables of interest, or all cognitive test performance data (N = 55). When the subset of 1553 participants included in the current sample was compared to the entire WHICAP sample, participants in the current study were younger at their initial enrollment (73.7 vs 77.4), had higher average education (11.39 vs 9.33), higher baseline memory (0.47 vs 0.03 on a standardized composite score) and higher language scores (0.58 vs 0.02), and were less likely to be a woman (63.7% vs 69.0%), and more likely to remain cognitively unimpaired throughout the study (87.1% vs 74.0%). (A detailed description of sampling procedures is provided in Figure 2.)

2.2 | Measures

2.2.1 | Predictors: measures of brain integrity—All magnetic resonance images were obtained from scanners at Columbia University Medical Center. Imaging from the 1992/1999 cohorts was obtained from 2005 to 2007 on a 1.5 Tesla (T) Philips Intera scanner,

while a 3.0T Philips Achieva scanner was used from 2011 to 2014 to collect data from the 2009 cohort.

Total intracranial volume (ICV) and total hippocampal volume (across hemispheres) were derived from T1-weighted images (repetition time = 20 ms, echo time = 2.1 ms, field of view 240 cm, 256 × 160 matrix, 1.3 mm slice thickness). Raw total hippocampal volume was standardized and corrected for ICV via regression path in the latent variable model described below.

A cortical thickness composite was created using FreeSurfer (version 5.1 for the 1992/1999 cohorts and version 6.0 for the 2009 cohort) T1-weighted images. The composite included the following nine "AD signature" regions, averaged across hemisphere[15]: rostral medial temporal lobe, angular gyrus, inferior frontal lobe, inferior temporal lobe, temporal pole, precuneus, supramarginal gyrus, superior parietal lobe, and superior frontal lobe. Cortical thickness was averaged across regions and standardized.

Total WMH volumes were acquired from T2-weighted fluid-attenuated inversion recovery (FLAIR) images using previously described procedures (repetition time = 11,000 ms, echo time 144.0 ms, inversion time 2800, field of view 25 cm, 2 nex (number of excitations), 256 × 192 matrix with 3 mm slice thickness).[16] To facilitate interpretation of effects in a single model, indicators of brain integrity were either standardized to be on the same scale or reverse coded (ie, larger values indicate more brain integrity). Values for WMH volumes were reversed, with higher values reflecting lower WMH burden/more brain integrity and then log-transformed to normalize their distribution.

2.2.2 | Outcomes: neuropsychological measures—Memory and language composites were derived from a previously published confirmatory factor analysis (CFA) that determined that memory and language were the two cognitive domains captured by the WHICAP neuropsychological battery.[17] These composite scores are invariant across racial/ethnic groups[18] and across English and Spanish speakers.[17] Memory was assessed by the immediate, delayed, and recognition trials from the Selective Reminding Test (SRT).[19] Language was assessed via confrontation naming, letter and category fluency, verbal abstract reasoning, repetition, and comprehension. Each cognitive variable was converted to standardized scores using means and standard deviations from the entire WHICAP sample at baseline. Composite scores were computed by averaging the standardized scores within each of the cognitive domains on each occasion.

2.2.3 | Moderators: race/ethnicity and years of education—Self-reported race/ethnicity was classified based on the 1990 U.S. Census guidelines. The highest self-reported completed grade of school was used as an indicator of years of educational attainment.

2.2.4 | Covariates—Although participants were asked whether they are male or female, we will use the term "sex/gender" because it is unknown whether participants actually reported their sex or their gender.[20] A binary variable was created to indicate participation in either imaging sample (0 = 2005, 1 = 2011).

2.3 | Statistical analyses

2.3.1 | General modeling approach—Cognitive trajectories for the two domains (memory, language) were characterized by estimating two separate known-class mixture models, with race/ethnicity as the known-class grouping variable. This known grouping variable is incorporated into these models as a moderator variable, allowing model parameters to vary as a function of membership in the identified groups. Time scores were created and centered at the study visit at which the neuroimaging data were collected, indicating the amount of time (in years from the scan) that each respondent participated in sessions before and after their scan. Thus, intercepts indicate cognitive performance at the time of scan, and slopes indicate the average rate of decline throughout the study. We then used joint modeling, which combines a latent growth model with a survival model, to account for the influence of differential attrition due to death on cognitive trajectories. The hazard function from the survival model was regressed on growth trajectories, predictors, moderators, and interaction terms and allowed to vary across racial/ethnic groups. For all analyses, missing data were handled using full information maximum likelihood. Both *P*-values and confidence intervals were used to determine statistical significance.[21] To decrease the likelihood of type I error due to multiple comparisons we used a *P*-value of .001 (or 99% confidence interval).

2.3.2 | Estimated models—First, we estimated unconditional known-class joint mixture models (ie, included no covariates), and racial/ethnic differences in intercept and slope were examined using the "Model Constraint" option in Mplus.

Next, two separate conditional known-class joint mixture models (one model per cognitive domain), which included covariates, were estimated. We used a single indicator latent variable to adjust hippocampal volume for head size (ICV) and identify the effect of hippocampal volume on cognitive outcomes independent of any confounding effect of ICV on those outcomes. WMH burden and cortical thickness were not adjusted for ICV or modeled through a latent variable. Years of education was included in these models and centered at 11 years. Sex/gender and imaging cohort indicators were also included and centered at 0.5 for intercept and slope. Age was not included in these models because its effects on cognition were entirely mediated by the brain variables. Similar findings have been reported.[22] Brain integrity variables, education, and covariates were regressed on the intercept (current performance) and slope (rate of decline) for memory and language trajectory models and allowed to vary across racial/ethnic groups.

Finally, we re-estimated the two conditional models to include interaction terms for each education by brain integrity variable combination on each growth factor (eg, education x WMH burden on current performance, education x WMH burden on rate of decline, etc.). A total of six interaction terms were specified for each of the two conditional models and effects were allowed to vary across racial/ethnic groups.

2.3.3 | Sensitivity analyses—A series of sensitivity analyses were conducted to determine whether racial/ethnic differences in the distribution of educational attainment influenced our findings. For example, it is possible that differences in the protective effects

of education may be due to an over-representation of higher levels of educational attainment in Whites. The two previously described conditional mixture models were estimated in: (1) a subgroup of participants with <16 years of education; (2) a subgroup of Whites and Blacks matched for years of education (White and Hispanic participants were not matched due to the small number of White participants at the lower end of the education distribution); and (3) a subgroup of Whites and Blacks with >12 years of education. To further clarify our findings, we conducted additional analyses to determine if moderation by years of education differs across levels of education, by replacing the continuous education variable with two linear splines to capture change from 0 through 11 years of education, as well as from 12 through 20 years of education. Finally, because we combined two imaging subsamples that were examined at different stages in our longitudinal study, we examined whether patterns of association differed across the 2005 and 2011 imaging samples. The original conditional mixture models were refit to include education x imaging sample, imaging sample x brain integrity, education x brain integrity interaction terms, as well as a three-way education x brain integrity x imaging sample interaction term.

3 | RESULTS

3.1 | Participant characteristics

Participant characteristics are presented in Table 1. Hispanic participants were older when neuroimaging data were collected and completed fewer years of education compared with White and Black participants. Diagnostic status upon neuroimaging data collection also varied across racial/ethnic groups, with Whites more likely to be classified as cognitively normal ($X^2 = 8.56$, $P = 0.01$).

Average time in the study from baseline assessment was 6.64 years and average time from baseline to when neuroimaging data were collected was 3.86 years. Study attrition due to death or non-death dropout is presented in Figure S1.

3.2 | Associations between education, brain integrity, and memory/language trajectories

Results from the conditional models are presented in Table S1. Larger hippocampal volume was associated with higher current performance and less decline across all groups and cognitive domains. However, the relationship between hippocampal volume and language decline was stronger for Whites compared with Blacks ($\beta = 0.068$; 99% CI: 0.007, 0.141). Higher WMH burden was associated with lower current memory and language performance for Blacks, but not Hispanics or Whites. Cortical thickness was positively associated with current memory and language performance for Whites and Hispanics, but not for Blacks.

We examined whether parameter estimates differed between the current sample and the larger WHICAP sample by conducting multiple-group conditional models that did not include the brain integrity variables, within each racial/ethnic group (Table S2). The relationship between education and memory and language growth parameters was similar across the current and larger samples within each racial/ethnic group.

3.3 | Interactions between education and brain integrity measures on cognitive trajectories

As shown in Figure 3 and Table 2, the relationship between WMH burden and memory and language decline was weaker for Whites with higher education than in Whites with lower education (education x WMH burden interaction for decline in memory, $\beta = -0.032$; 99% CI: −0.071, −0.002, and language, $\beta = -0.024$; 99% CI:−0.044, −0.004), but this was not seen among Blacks or Hispanics.

Similarly, higher education buffered the negative impact of cortical thinning on current language performance for Whites (Figure 4; education x cortical thickness interaction for level of language performance, $\beta = -0.020$; 99%CI:−0.039, −0.002). No reliable interactions between education and brain integrity measures were noted for Blacks or Hispanics. Results did not change when individuals with mild cognitive impairment (MCI) and incident dementia were excluded from the analyses.

Results did not change when we performed sensitivity analyses in individuals with <16 years of education, >12 years of education, and the education-matched subsample. Interactions with linear splines did not reach statistical significance in either model, suggesting that the cognitive benefit provided by an additional year of education is similar across education levels (ie, for Whites going from 9 to 10 years of education provides approximately the same benefit as going from 15 to 16 years).

Sensitivity analyses comparing the two non-overlapping imaging sub-samples found no reliable imaging group x brain integrity or imaging group x education interactions, suggesting that the relationships between education, brain integrity, and cognitive trajectories do not differ across imaging samples. In addition, no reliable three-way interactions were observed, suggesting that observed education x brain integrity interactions are equivalent across imaging samples.

4 | DISCUSSION

We hypothesized that among Whites, but not Blacks or Hispanics, educational attainment would contribute to CR by providing a buffer against the effects of depleted brain integrity on cognitive trajectories. This was supported: more years of education buffered the negative impact of higher WMH burden on memory and language decline and cortical thinning on current language performance for Whites but not for Blacks or Hispanics. We also found that the relationship of brain integrity indicators to cognitive function differed across race/ethnicity, replicating and expanding on prior work in this cohort.[11] Specifically, WMH burden was more strongly associated with memory and language performance for Blacks than for other racial/ethnic groups; cortical thickness was a stronger predictor of language performance for Whites and Hispanics than for Blacks; and the relationship between hippocampal volume and language decline was stronger for Whites compared with Blacks.

Prior research suggests that educational attainment may contribute to CR by changing dendritic and synaptic complexity or overall brain plasticity.[23,24] Several studies have demonstrated the contribution of education to CR[7,25-28] in predominantly White samples,

or in diverse samples where race/ethnicity is treated as a confounding variable. These studies did not consider racial/ethnic patterns in school quality.[12] Most Black older adults in the United States were born and raised in the South,[29] where Jim Crow laws enforced segregation and limited opportunities such as education, health care, housing, and the labor market.[30] Across all U.S. States, before and after Brown *v.* Board, racist policies and residential segregation forced Black children to attend underfunded schools that had large student/teacher ratios, shorter term length, lower teacher salaries, and inadequate budgets for supplies and school buildings.[31] As a result of these structural inequalities in school opportunities, returns to education, such as literacy skills, are lower on average among African Americans than among Whites.[32,33] Older Caribbean-born Hispanics who grew up outside of the United States, also had fewer opportunities to attend school and/or receive a poor quality of education.[34-38]

Education is differentially associated with entry into various adult opportunities that might contribute to CR across racial/ethnic groups. Racism in the labor market has served to counteract the benefits of schooling for Black Americans. For example, Black men continue to have lower employment rates than White men across education levels,[39] suggesting that, for Blacks, years of education is a poorer indicator of experiences related to CR during adulthood. It is also possible that the modifying effect of education on brain integrity is altered by psychosocial factors associated with poorer cognitive test performance, including stress associated with institutional racism and discrimination.[40]

Our results are not attributable to higher average education among Whites. Sensitivity analyses demonstrated that education provides CR for Whites, but not for Blacks, when (1) evaluating a subgroup of Whites and Blacks matched for years of education, (2) restricting both groups to have <16 years of education, and (3) restricting analyses to those with >12 years of education. Furthermore, there was no evidence that the moderation provided by an additional year of education among Whites differed across levels of education.

Although no reliable brain by education interactions were demonstrated for the Hispanic group, there was a trend toward significance for the education x cortical thickness interaction on language decline. Rather than buffer the negative impact of cortical thinning, higher education worsened the effect of cortical thinning on language decline. Similar patterns have been reported in recent literature.[7,27] One possible interpretation is that education is protective at higher levels of brain integrity, but when brain integrity is depleted, more education is detrimental.[7] Other socio-cultural factors, such as degree of bilingualism, might also affect the relationship between cortical thickness and cognitive outcomes.[41]

Although educational attainment represents an important early life experience, its effect on late-life cognitive trajectories is likely mediated by a host of protective factors. Perhaps other early life experiences[42] (eg, literacy, childhood socioeconomic status, neighborhood factors) better promote these protective mediators among Blacks and Hispanics. CR is challenging to study because there are no direct measures; it is a hypothetical construct.[43] Future research needs not only identify the multiple life-course factors that underlie this construct but also ensure that proxies for CR are relevant across racial/ethnic groups.

The sample was recruited from northern Manhattan residents, which is a limitation for national generalizability. Selective participation in imaging data collection may also limit generalizability. Whites in the 2005 imaging sample had higher rates of incident dementia and MCI than White WHICAP participants who did not receive imaging. This might explain why racial/ethnic differences in rate of decline were inconsistent with previous work in the larger WHICAP sample, showing steeper rates of memory and language decline in Hispanics compared with Whites.[44] However, the relationship between growth parameters and educational attainment was similar for the current sample and larger WHICAPsample within each racial/ethnic group. We did not include age as a covariate because it was entirely mediated by the brain variables; therefore the associations with the brain measures might also be understood as associations with age.

There are also several differences between the 2005 and 2011 imaging samples, including the 2005 sample being less educated, older, and more likely to be cognitively impaired. The use of two different MRI scanners (1.5T in the 2005 sample and 3.0T in the 2011 sample) and FreeSurfer versions (5.1 for the 2005 sample and 6.0 for the 2011 sample) may have led to increased variability in derived brain integrity estimates, particularly for hippocampal volume.[45,46] However, relationships between education, brain integrity, and cognitive trajectories were not reliably different between the two imaging samples. A recent cross-sectional study in this WHICAP sample[26] demonstrated differences between the imaging samples in the moderating effects of education. Conflicting results may be due to the current study accounting for differential attrition due to death. Not accounting for such selection processes can lead to inflated estimates of the relationship between cognitive trajectories and education.[47]

Our main finding was that years of education contributed to CR only among Whites, but not among Blacks and Hispanics. Previous studies have controlled for race/ethnicity rather than examined differences between groups. As our findings suggest, such an approach ignores racial/ethnic variability in factors thought to influence CR and likely overestimates the contribution of education to reserve for racial/ethnic minorities. Explicit examination of racial/ethnic differences provides a more accurate understanding of the life-course factors that contribute to CR and may lead to identification of factors that may narrow racial/ethnic inequalities in onset and progression of AD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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REFERENCES

1. Knopman DS, Parisi JE, Salviati A, Floriach-Robert M, Boeve BF, Ivnik RJ. Neuropathology of cognitively normal elderly. J Neuropathol Exp Neurol. 2003;62:1087–1095. [PubMed: 14656067]
2. Yaffe K, Weston A, Graff-Radford NR. Association of plasma beta-amyloid level and cognitive reserve with subsequent cognitive decline. JAMA. 2011;305:261–266. [PubMed: 21245181]
3. Stern YWhat is cognitive reserve? Theory and research application of the reserve concept. J Intl Neupsychol Soc. 2002;8:448–460.
4. Stern YCognitive reserve. Neuropsychologia. 2009;47:2015–2028. [PubMed: 19467352]
5. Stern YCognitive reserve in ageing and Alzheimer's disease. Lancet Neurol. 2012;11:1006–1012. [PubMed: 23079557]
6. Satz PBrain reserve capacity on symptom onset after brain injury: a formulation and review of evidence for threshold theory. Neuropsychology. 1993;7:273–278.
7. Mungas D, Gavett B, Fletcher E, Tomaszewski Farias S, DeCarli C, Reed BR. Education amplifies brain atrophy effect on cognitive decline: implications for cognitive reserve. Neurobiol Aging. 2018;68: 142–150. [PubMed: 29798764]
8. Stern Y, Arenaza-Urquijo EM, Bartres-Faz D, et al.Whitepaper: defining and investigating cognitive reserve, brain reserve, and brain maintenance. Alzheimer's Dement. 2018:1–7.
9. Amieva H, Mokri H, Le Goff M, et al.Compensatory mechanisms in higher-educated subjects with Alzheimer's disease: a study of 20 years of cognitive decline. Brain. 2014;137:1167–1175. [PubMed: 24578544]
10. Glymour MM, Manly JJ. Lifecourse social conditions and racial and ethnic patterns of cognitive aging. Neuropsychol Rev. 2008;18:223–254. [PubMed: 18815889]
11. Zahodne LB, Manly JJ, Narkhede A, et al.Structural MRI predictors of late-life cognition differ across African Americans, Hispanics, and Whites. Curr Alzheimer Res. 2015;12:632–639. [PubMed: 26027808]
12. Manly JJ, Byrd D, Touradji P, Sanchez D, Stern Y. Literacy and cognitive change among ethnically diverse elders. Int J Psychol. 2004;39: 47–60.
13. Malek-Ahmadi M, Lu S, Chan Y, Perez SE, Chen K, Mufson E. Static and dynamic cognitive reserve proxy measures: interactions with Alzheimer's disease neuropathology and cognition. J Alzheimer's Dis Parkinsonism. 2017;7:1–16.
14. Tang MX, Cross P, Andrews H,et al.Incidence of Alzheimer's disease in African-Americans, Caribbean Hisapnics and Caucasians in northern Manhattan. Neurology. 2001;56:49–56. [PubMed: 11148235]
15. Dickerson BC, Bakkour A, Salat DH, et al.The cortical signature of Alzheimer's disease: regionally specific cortical thinning relates to symptom severity in very mild to mild AD dementia and is detectable in asymptomatic amyloid-positive individuals. Cerebral Cortex. 2009;19:497–510. [PubMed: 18632739]
16. Brickman AM, Schupf N, Manly JJ, et al.Brain morphology in older African Americans, Caribbean Hispanics, and Whites from Northern Manhattan. Arch Neurol. 2008;65:1053–1061. [PubMed: 18695055]
17. Siedlecki KL, Manly J, Brickman AM, Schupf N, Tang M, Stern Y. Do neuropsychological tests have the same meaning in spanish speakers as they do in english speakers. Neuropsychology. 2010;24: 402–411. [PubMed: 20438217]
18. Avila JF, Arce Renteria M, Witkiewitz K, Verney SP, Vonk JMJ, Manly JJ. Measurement invariance of neuropsychological measures of cognitive aging across race/ethnicity by sex/gender groups. Neuropsychology. 2019;25(9):901–909.
19. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. Neurology. 1974;24:1019–1025. [PubMed: 4473151]
20. Tannenbaum C, Greaves L, Graham ID. Why sex and gender matter in implementation research. BMC Med Res Methodol. 2016;16: 145–157. [PubMed: 27788671]
21. du Prel JB, Hommel G, Rohrig B, Blettner M. Confidence Interval or P-Value?. Dtsch Arztebl Int. 2009;106:335–339. [PubMed: 19547734]

22. Mungas D, Reed BR, Farias ST, DeCarli C. Age and education effects on relationships of cognitive test scores with brain structure in demographically diverse older persons. Psychol Aging. 2009;24: 116–128. [PubMed: 19290743]
23. Lesuis SL, Hoeijmakers L, Korosi A, et al.Vulnerability and resilience to Alzheimer's disease: early life conditions modulate neuropathology and determine cognitive reserve. Alzheimers Res Ther. 2018;10: 95–115. [PubMed: 30227888]
24. Malek-Ahmadi M, Lu S, Chan Y, Perez SE, Chen K, Mufson EJ. Dynamic cognitive reserve proxy measures: interactions with Alzheimer's disease neuropathology and cognition. J Alzheimers Dis Parkinsonism. 2017;7:390. [PubMed: 29423338]
25. Stern Y, Albert S, Tang M, Tsai W. Rate of memory decline in AD is related to education and occupation: congitive reserve?. Neurology. 1999;53:1942–1947. [PubMed: 10599762]
26. Zahodne LB, Mayeda ER, Hohman TJ, et al.The role of education in a vascular pathway to episodic memory: brain maintenance or cognitive reserve?. Neurobiol Aging. 2019;84:109–118. [PubMed: 31539647]
27. O'Shea DM, Langer K, Woods AJ, et al.Educational attainment moderates the association between hippocampal volumes and memory performances in healthy older adults. Front Aging Neurosci. 2018;10:1–9. [PubMed: 29403371]
28. Pettigrew C, Soldan A. Definint cognitive reserve and implications for cognitive aging. Curr Neurol Neuroscie Rep. 2019;19(1):1.
29. Ruggles S, Sobek M, Alexander T, Integrated Public Use Microdata Series: Version 3.0. Minneapolis, MN: Minnesota Population Center; 2004.
30. Barnes LL, Bennett DA. Alzheimer's disease in African Americans: risk factors and challenges for the future. Health Aff. 2014;33:580–586.
31. Hedges IV, Laine RD, Greenwald R. Does money matter? A meta-analysis of studies of the effects of differential school inputs on student outcomes. Educational Researcher. 1994;23:5–14.
32. Manly JJ, Jacobs DM, Touradji P, Small SA, Stern Y. Reading level attenuates differences in neuropsychological test performance between African American and White elders. Je IntNeupsychol Soc. 2002;8:341–348.
33. Cohen DJ, White S, Cohen SB. Mind the gap: the black-white literacy gap in the National assessment of adult literacy and its implications. J Literacy Res. 2012;44:123–148.
34. Duncan B, Trejo SJ. Assessing the socioeconomic mobility and integration of U.S. immigrants and their descendants. ANNALS Am Acad Pol Soc Sci. 2015;657:108–135.
35. Latin American Economic Outlook 2017. Santiago, Chile: CEPAL; 2016.
36. Card D, Krueger AB. School resources and student outcomes: an overview of the literature and new evidence from North and South Carolina. J Econ Perspect. 1996;10:31–50.
37. Sisco S, Gross AL, Shih RA, et al.The role of early-life educational quality and literacy in explaining racial disparities in cognition in late life. J Gerontol B: Psychol Sci Soc Sci. 2013;70:557–567.
38. Manly JJ, Jacobs DM, Sano M, Bell K, Merchant CA, Small SA, et al.Effect of literacy on neuropsychological test performance in nondemented, education-matched elders. Je Int Neupsychol Soc. 1999;5:191–202.
39. McDaniel A, DiPrete TA, Buchmann C, Shwed U. The black gender gap in educational attainment: historical trends and racial comparisons. Demography. 2011;48:889–914. [PubMed: 21638226]
40. Barnes LL, Lewis TT, Begeny CT, Bennett DA, Wilson RS. Perceived discrimination and cognition in older African Americans. J Int Neupsycholl Soc. 2012;18:856–865.
41. Bialystok E, Anderson JAE, Grundy JG. Interpreting cognitive decline in the face of cognitive reserve: does bilingualism affect cognitive aging?. Linguistic Approaches Bilingualism. 2018:1–20.
42. Xu H, Yang R, Qi X. Association of lifespan cognitive reserve indicator with dementia risk in the presence of brain pathologies. JAMA Neurol. 2019;76:1184–1191. [PubMed: 31302677]
43. Jones RN, Manly JJ, Glymour MM, Rentz DM, Jefferson AL, Stern Y. Conceptual and measurement challenges in research on cognitive reserve. J Int Neupsychol Soc. 2011;17:593–601.

44. Avila JF, Vonk JMJ, Verney SP, et al.Sex/gender differences in cognitive trajectories vary as a function of race/ethnicity. Alzheimer's Dement. 2019;15(12):1516–1523. [PubMed: 31606366]

45. Stankiewiez JM, Glanz BI, Healy BC, Arora A, Neema M. Brain MRI lesion load at 1.5T and 3T versus clinical status in Multiple Sclerosis. J Neuroimaging. 2011;21:50–56.

46. Chepkoech JL, Walhovd KB, Grydeland H, Fjell AM. Effects of change in FreeSurfer version on classification accuracy of patients with alzheimer's disease and mild cognitive impairment. Human Brain Mapping. 2016;37:1831–1841. [PubMed: 27018380]

47. Weuve J, Proust-Lima C, Power MC, et al.Guidelines for reporting methodological challenges and evaluating potential bias in dementia research. Alzheimers Dement. 2015;11:1098–1109. [PubMed: 26397878]

RESEARCH IN CONTEXT

1. Systematic review: Literature was reviewed using traditional sources (eg, PsycINFO, PubMed). Because few known studies have examined the contribution of education to cognitive reserve (CR)CR across racial/ethnic groups, research describing educational and socio-cultural differences between racial/ethnic groups, as well as a review of the literature on CR, was used to inform hypotheses in the current study.
2. Interpretation: Our findings suggest that the contribution of education to CR is not commensurate across racial/ethnic groups.
3. Future directions: This study takes an important first step in understanding the life-course factors that contribute to CR. Additional studies are warranted to further understand the drivers of racial inequalities in dementia. Examples include: (a) accurately identifying the multiple life-course factors that underlie CR; (b) racial/ethnic differences in the relationship between contributors to CR and longitudinal changes in brain integrity across diagnostic categories; and (c) investigating the potential for racial/ethnic-specific factors that increase CR to delay the onset and progression of dementia.

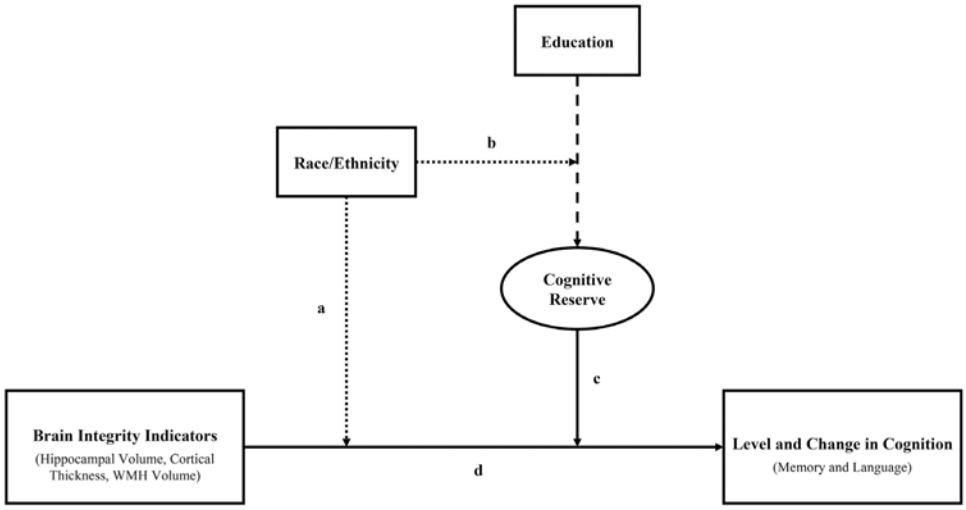

FIGURE 1.
Schematic representation of conceptual framework

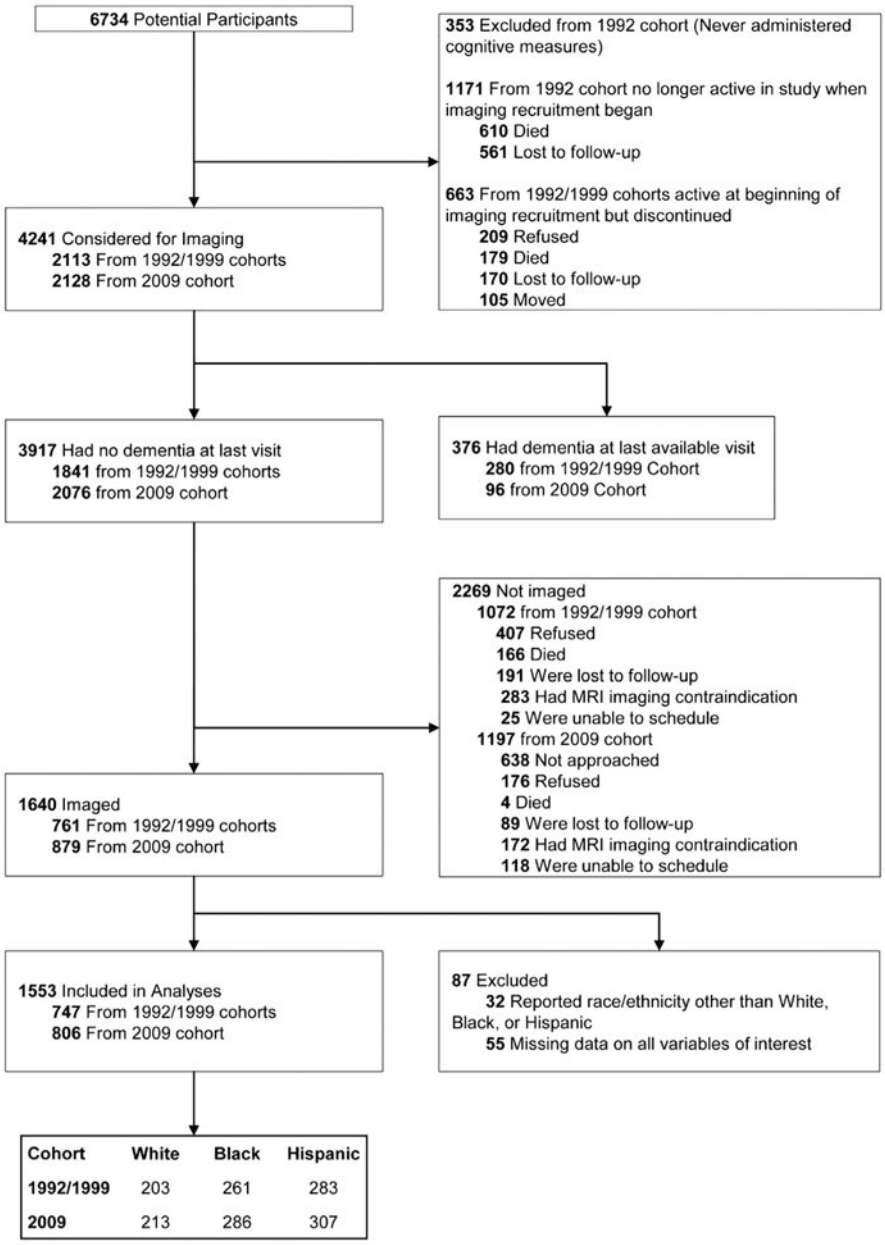

FIGURE 2.
Schematic representation of derived imaging sample

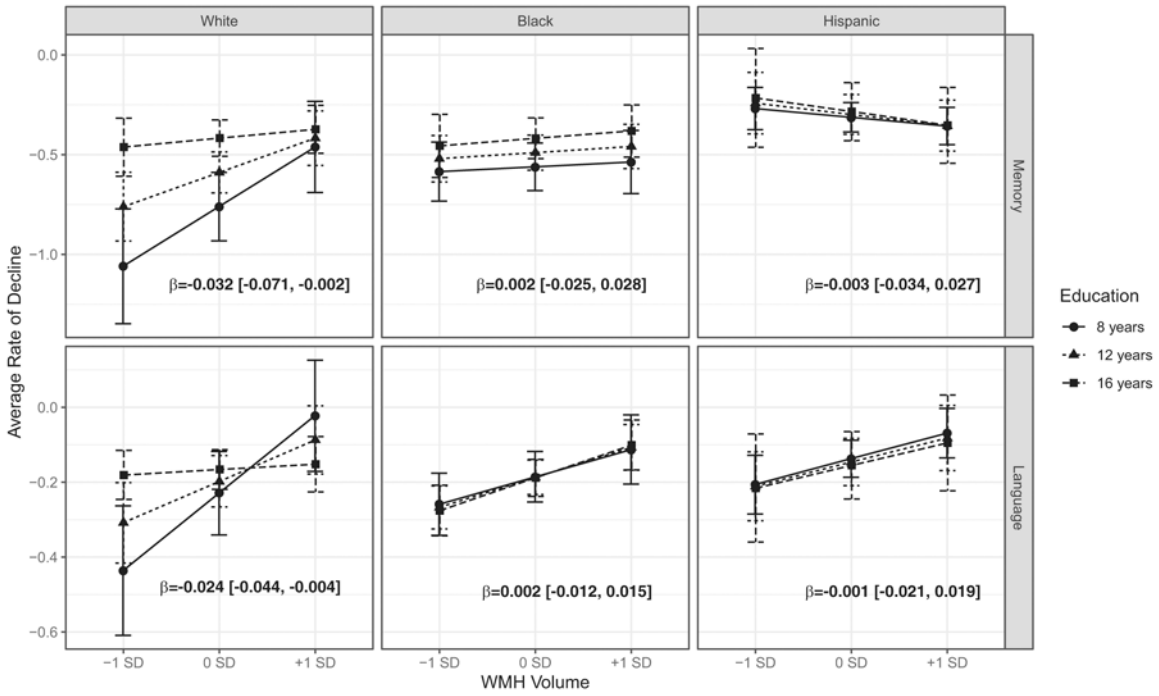

FIGURE 3.

Education x white matter hyperintensity (WMH) volume interactions on decline in memory and language performance across racial/ethnic groups. The panel on the left shows that for Whites, the relationship between WMH burden and memory and language decline was weaker among those with higher education (16 years) than among those with lower education (8 years and 12 years). For Blacks and Hispanics (middle and right panels), the relationship between WMH burden and memory and language decline was similar across education levels

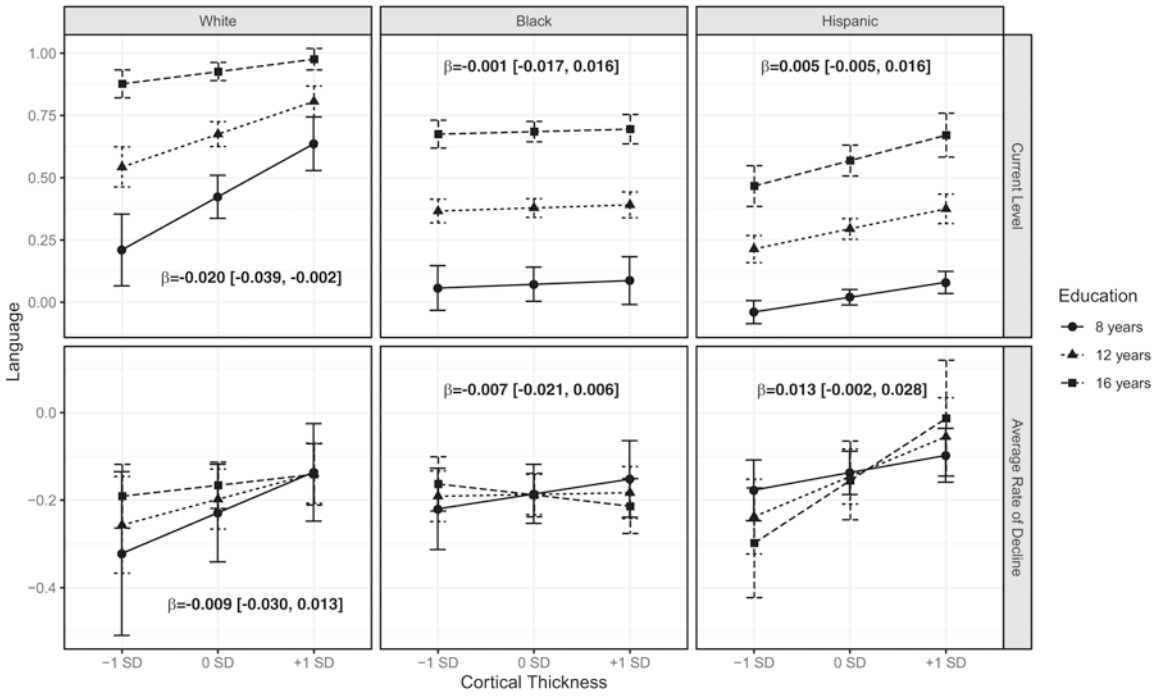

FIGURE 4.

Education x cortical thickness interactions on level and decline in language performance across racial/ethnic groups. The panel on the left shows that for Whites, the relationship between cortical thickness and current level of language functioning was weaker among those with higher education (16 years) than among those with lower education (8 years and 12 years). For Blacks and Hispanics (middle and right panels), the relationship between cortical thickness and language level and decline was similar across education levels

TABLE 1

Characteristics of study participants

Characteristics	White (N = 416)	Black (N = 547)	Hispanic (N = 590)	Group differences[c]
Age at baseline, mean (SD)	73.88 (5.6)	73.66 (5.7)	73.74 (5.2)	W = B = H
Age at scan, mean (SD)	77.15 (6.5)	77.06 (6.7)	78.43 (6.3)	W = B < H
Years of education, mean (SD)	14.72 (3.4)	12.86 (3.5)	7.70 (4.4)	W > B > H
Women, N (%)	232 (56)	361 (66)	397 (67)	W < B = H
2005 Scan sample, N (%)[a]	203 (49)	261 (48)	283 (48)	W = B = H
Years in study, mean (SD)	7.08 (4.6)	7.04 (4.9)	7.89 (5.7)	W = B = H
Diagnosis at baseline, N (%)				
Normal	350 (84)	432 (79)	436 (74)	W > B > H
Mild cognitive impairment (MCI)	66 (16)	115 (21)	154 (35)	
Diagnosis at scan, N (%)				
Normal	338 (81)	408 (74)	435 (74)	W > B = H
Mild cognitive impairment (MCI)	75 (18)	119 (22)	110 (19)	
Dementia	3 (1)	20 (4)	45 (7)	
Brain indicators, mean (SD)				
Adjusted Hippocampal volume	0.169 (0.99)	−0.095 (1.02)	−0.031 (0.96)	W > B = H
Cortical thickness	2.59 (.12)	2.55 (0.13)	2.58 (0.12)	W = H > B
WMH burden[b]	0.118 (0.82)	−0.123 (1.02)	0.030 (1.09)	W = H < B

Abbreviations: W, White; B, Black; H, Hispanic; WMH, White Matter Hyperintensities; SD, standard deviation; No, number.

[a]Imaging data was obtained from the 2005 imaging sample on a 1.5T scanner and from the 2011 imaging sample on a 3.0T scanner.

[b]WMH Volume values are reversed, with smaller values indicating less brain integrity (more WMH burden).

[c]$P < .05$ as determined by Tukey's HSD multiple-comparisons between racial/ethnic groups.

TABLE 2

Interaction Effects (99% confidence intervals) of education and brain integrity on level and rate of decline for memory and language by race/ethnicity

	Memory model			Language model		
	White	**Black**	**Hispanic**	**White**	**Black**	**Hispanic**
Level on						
Education x Hippocampal Volume	−0.012 (−0.049, 0.024)	−0.019 (−0.058, 0.019)	−0.006 (−0.027, 0.015)	−0.016 (−0.038, 0.007)	−0.006 (−0.035, 0.023)	0.000 (−0.014, 0.014)
Education x Cortical Thickness	−0.005 (−0.030, 0.020)	0.004 (−0.021, .024)	0.003 (−0.009, 0.016)	−0.020 (−0.039, −0.002)[a]	−0.001 (−0.017, 0.016)	0.005 (−0.005, 0.016)
Education x WMH Burden	−0.005 (−0.033, 0.023)	−0.003 (−0.024, 0.018)	0.000 (−0.018, 0.018)	0.006 (−0.012, −0.023)	−0.006 (−0.024, 0.011)	−0.001 (−0.012, 0.011)
Rate of Decline on						
Education x Hippocampal Volume	0.010 (−0.043, 0.064)	0.005 (−0.035, 0.045)	−0.004 (−0.042, 0.034)	0.012 (−0.029, 0.054)	0.003 (−0.014, 0.019)	0.002 (−0.019, 0.022)
Education x Cortical Thickness	−0.006 (−0.046, 0.034)	−0.008 (−0.031, 0.015)	0.015 (−0.016, 0.045)	−0.009 (−0.030, 0.013)	−0.007 (−0.021, 0.006)	0.013 (−0.002, 0.028)
Education x WMH Burden	−0.032 (−0.07, −0.002)[a]	0.002 (−0.025,0.028)	−0.003 (−0.034, 0.027)	−0.024 (−0.044, −0.004)[a]	0.002 (−0.012, 0.015)	−0.001 (−0.021, 0.019)

Abbreviations: WMH, white matter hyperintensity.

[a] $P < .001$.