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Education and cognitive resilience: the role of schooling characteristics in shaping an ability to maintain high levels of cognitive functioning after the onset of disease

Author
Eng, Chloe

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Education and cognitive resilience: the role of schooling characteristics in shaping an ability to maintain high levels of cognitive functioning after the onset of disease

by
Chloe Eng

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Approved:

DocuSigned by:
M. Maria Glymour
7EEF9BD435A141C...
M. Maria Glymour
Chair

DocuSigned by:
John Kornak
John Kornak

DocuSigned by:
B88FE81929CB431...
Rachel Whitmer

Committee Members

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Education and cognitive resilience: the role of schooling characteristics in shaping an ability to maintain high levels of cognitive functioning after the onset of disease

Chloe W. Eng

ABSTRACT

This dissertation explores the role of educational characteristics as a marker of cognitive resilience. Incident stroke is often accompanied by acute deficits and declines in cognitive ability as well as long-term acceleration of cognitive decline. These resulting impairments and dementia drastically affect quality of life, and patients with dementia after stroke are at increased risk of death and disability. Education has been consistently identified as a predictor of cognition after stroke, but mechanisms behind this relationship are not fully understood. One hypothesis considers cognitive resilience, suggesting that education provides individuals with cognitive tools to maintain cognitive functioning amidst a clinically meaningful amount of neurodegeneration or injury. However, studies of this relationship are hindered by a lack of universally accepted definitions of cognitive resilience. Furthermore, some studies suggest that the commonly used measure of attained education may not capture variation in cognition as well as alternative measures such as educational quality and literacy.

The relationship between stroke and dementia has the potential to be used to study cognitive resilience and reserve, a critical issue in cognitive aging research. By using stroke as a well-defined and clearly diagnosed disease with a known time of event onset, studies can be conducted to assess for differences between educational subgroups and to differentiate between normal-age related decline and disease-related pathological processes. Therefore, this proposal aims to investigate the influence of educational characteristics on cognitive resilience after stroke.

Chapter 1 examines memory trajectories before, at the time, and after stroke in a nationally representative sample to assess where along the development of stroke education may benefit cognition. More years of attained education was associated with a small decrease in memory

decrement at the time of stroke and a slight slowing of memory decline after stroke onset. However the benefits of education lie primarily in pre-existing cognitive reserve prior to stroke, with individuals of higher attained education declining only slightly slower than individuals with lower education. Chapter 2 estimates the extent to which educational characteristics modify the effect of history of stroke on dementia risk, finding that state-level administrative school quality is a predictor of late-life dementia incidence, independently of own educational attainment. Chapter 3 investigates whether education influences individuals' cognitive responses to markers of disease pathology in the brain, finding that contrary to previous studies, the relationship between white matter hyperintensities and cognition does not differ by level of education. Together, these studies address the gap in understanding of mechanisms behind cognitive resilience by investigating whether increases in education allow people to maintain cognitive functioning following the onset of disease, and assessing where education is most beneficial along the development of disease.

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INTRODUCTION

Education is a well-established predictor of dementia risk, with higher education consistently predicting higher late-life cognitive functioning and decreased dementia risk in the United States (1–5). As a lifecourse exposure, education has appeal as an easily reportable exposure that is thought to remain relatively stable across the lifecourse in comparison to other socioeconomic characteristics, such as income or occupation. It exists upstream from other lifecourse exposures, making it an attractive target for health-benefitting interventions. Furthermore, increased schooling has been shown to increase resources such as earnings while also shaping health-benefitting behaviors and decision-making in adulthood (6,7). However, the specific mechanisms driving the relationship between education and late-life cognitive health remain not fully understood.

Cognitive reserve and resilience

The concepts of cognitive reserve and resilience have been suggested as potential explanations for the mechanisms for the relationship between education and post-stroke cognition. Educational attainment has been widely attributed to increases in cognitive reserve and resilience. However, these terms are poorly defined, and sometimes used interchangeably. It has been suggested that this is due to reserve being conceptualized in two different ways: as brain reserve, referring to differences in the brain itself that increase tolerance of pathology, and cognitive reserve, which refers to individual differences in how some people perform tasks to be more resilient than others. The idea of cognitive reserve hypothesizes that the brain uses pre-existing cognitive processing approaches or finds new ways to compensate in coping with brain damage, and has been suggested as an explanation for individual differences in susceptibility to age-related brain changes. Others have framed cognitive resilience, or the ability of the brain to buffer against disease and recover from trauma, as having the similar effect. In 2017, the NIA hosted the Cognitive Aging Summit III to

highlight the need for operational definitions of cognitive reserve, resilience, and related concepts, and to address the barrier in progress from this lack of clear and universally accepted nomenclature.

Post-stroke dementia

In order to assess cognitive resilience and individual ability to maintain cognitive functioning in the face of disease, this project explores educational differences in late-life cognition in response to stroke onset. Acute stroke is characterized as a clearly defined and well-diagnosed disease with a known time of onset, and a strong influence on cognition - individuals with a history of stroke are more than twice as likely to develop dementia compared to stroke-free individuals (8,9). Therefore, we consider cognition and dementia incidence following the onset of stroke, with the aim of determining whether education allows individuals to better maintain cognitive functioning or buffer against the cognitively detrimental event of a stroke.

Challenges in conceptualizing education

Further complicating the relationship between education and cognitive resilience are inconsistencies in educational characteristics across subgroups. Individuals are more likely to follow educational trajectories similar to that of their parents, and an individual attending a four-year university as a first-generation college student may differ in individual characteristics from an individual from a highly educated family (10). Many older adults in the US today entered formal schooling at a time in history when states had legal racial segregation, meaning that the quality of education differed between White and Black Americans. Even after mandated desegregation, a year of schooling may have different worth due to de facto racial residential segregation or differences in downstream economic opportunities from persisting systemic racism (11–19). Education is also often self-reported and is therefore subject to recall bias. However, studies report higher misclassification at lower levels of education, meaning that any bias would likely be closer to the null

leading to an underestimation of the true effect of education (20,21). In order to address these limitations, this dissertation investigates potential differential returns to education across racial/ethnic groups. Historical state-level administrative school quality is also considered to assess whether the broader school environment and state-level investment into education influences later-life health, independent of own self-reported degree attainment.

Dissertation objectives

Therefore the objective of this dissertation is to assess the contribution of educational characteristics, considered as both years attained and administrative state-level quality measures, to cognitive resilience, conceptualized as cognition after stroke. This dissertation uses three data sources to characterize cognitive reserve and resilience in three distinct settings across different cognitive outcomes: (1) the Health and Retirement Study (HRS), a large, nationally representative study with continuous monitoring of longitudinal episodic memory; (2) members of Kaiser Permanente Northern California, comprising a racially/ethnically diverse cohort of older adults with approximately equal access to healthcare and electronic medical record diagnoses of dementia; and (3) the Kaiser Healthy Aging and Diverse Life Experiences (KHANDLE) study and the Study of Healthy Aging in African Americans (STAR), two pooled studies of Northern California older adults with comprehensive cognitive functioning and brain imaging measures.

Chapter 1 builds upon previous findings that stroke-related differences in memory trajectories arise prior to the onset of stroke with an immediate drop at the time of stroke by examining whether stroke-related memory trajectories differ by education in HRS (22–24). More years of attained education was associated with a small decrease in memory decrement at the time of stroke and a slight slowing of memory decline after stroke onset. However the benefits of education lie primarily in pre-existing cognitive reserve prior to stroke, with individuals of higher attained education declining only slightly slower than individuals with lower education. Chapter 2

aims to further disentangle the established relationship between education and post-stroke cognition by considering state-level administrative school quality as part of the educational experience not captured by years of attained education alone. This work finds that improvements in state-level administrative school quality are associated with decreased incidence of dementia independently of education, and school quality may buffer against the harmful cognitive effects of stroke. Finally, chapter 3 considers whether the relationship between education and post-stroke dementia extends to white matter hyperintensities, as a well-established imaging marker of brain pathology that precedes stroke and is known to influence dementia risk. Contrary to other studies, we find no evidence that education helps individuals maintain cognitive functioning in the face of vascular brain pathology in a racially/ethnically diverse sample of older adults.

Together, these studies address the gap in understanding of mechanisms behind cognitive resilience by investigating where education is most beneficial along the development of disease. By identifying the influence of an individual's educational experience on cognitive resilience after stroke, this research will start to disentangle the differences between natural processes of age-related cognitive decline and cognitive reserve and resilience in the context of physical disease.

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CHAPTER 1

Differential benefits of education for stroke-related cognitive trajectories among Black and White US older adults

Chloe W. Eng[a], Rachel A. Whitmer[b], John Kornak[a], M. Maria Glymour[a]

Affiliations: (a) Department of Epidemiology and Biostatistics, University of California San Francisco, (b) Department of Public Health Sciences, University of California Davis

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Abstract

Introduction: Higher education is associated with lower risk of post-stroke dementia; it remains unclear whether this relationship is attributable to pre-stroke cognitive reserve or arises as a differential response to the effects of stroke. We compare whether memory trajectories before, at the time of, and during stroke differ by education, and assess whether this relationship contributes to Black/White disparities in stroke-related memory.

Methods: Stroke-free Health and Retirement Study participants aged ≥50 years in 1998 (n = 16,238) were interviewed biennially over up to 20 years for first self- or proxy-reported stroke (n = 2,019). Annual rates of episodic memory change before and after stroke and decrements at the time of stroke were compared using segmented linear regression models. Models assessed for whether memory differed across years of attained education, and secondary analyses investigated whether the influence of education differed between Black and White participants.

Results: Each year increase in education was associated with higher average memory across all participants (β: 0.061; 95% CI: 0.058, 0.065) and lessened the effect of stroke on memory prior to stroke (β per year before stroke x education: 0.005; 95% CI: 0.004, 0.007), at the time of stroke (β for discontinuity at stroke onset x education: 0.018; 95% CI: 0.004, 0.031), and following stroke in survivors (β per year since stroke x education: 0.003; 95% CI: 0.001, 0.005). Black participants saw smaller returns to memory with increased education prior to stroke, but memory scores declined slower each year post-stroke with each year of increased education (β: 0.005; 95% CI: 0.000, 0.011) compared to white participants.

Conclusion: Differences in stroke-related memory trajectories across levels of education were driven primarily by higher average memory scores prior to the onset of stroke with small effects seen on trajectories of decline. Effects of education differed by race as well, but did not make up for pre-existing memory disparities by race.

INTRODUCTION

Education has been identified as a consistent predictor of long-term cognition after stroke. Studies suggest that higher levels of educational attainment are associated with less extreme cognitive deficits in stroke survivors and with a decreased risk of post-stroke dementia.[1–3] However, the mechanisms through which education influences post-stroke cognition after the cognitively debilitating event of a stroke remain unclear. Some posit that increases in structural capacity in the brain, or "hardware", from increased education are present prior to the onset of disease. This theory of brain reserve suggests that physical increase in neurons or synapses allows individuals to tolerate more disease injury before cognitive function is impaired. A related but distinct theory is that of cognitive reserve, which hypothesizes that individuals with higher education can use their brain's "software" to adapt to disease-related changes and damage, such as the use of alternate brain networks to maintain cognitive functioning. Alternatively, increased education leads to downstream health-benefitting resources that could lead to individuals with higher education simply experiencing less severe strokes, and having access to better care at the time of and following stroke.[4–7] Most prior research also examines cognitive outcomes only after stroke which may incorrectly attribute pre-stroke differences to differences arising as a consequence of stroke.[3,8]

Building on previous work examining memory decline before, during, and after stroke in this sample, we evaluated the relationship between educational attainment and stroke-related memory trajectories among Black and White participants in the nationally representative Health and Retirement Study (HRS).[9–11] We tested the influence of attained education on stroke-related memory trajectories, in hopes of further disentangling the mechanisms behind the relationship of education and stroke-related cognition. The relationship between education and late-life cognition has been previously shown to differ across Black and White Americans, likely due at least in part to differential access to education, racial differences in the quality of education received, and

downstream opportunities following degree attainment,[12,13] and it has been well established that Black Americans are at higher risk of stroke and dementia (regardless of stroke status) than any other racial ethnic group in the US.[14–17] Therefore, we also investigate whether the benefit of education for stroke-related cognitive trajectories differs between Black and White US older adults, based on previous research that a year of education does not lead to equivalent cognitive returns between White and Black older adults.[12,13]

METHODS

Study Population

HRS is a study of community-dwelling middle-aged and older adults in the US, initiated in 1992. Enrollment was modified in 1998 to achieve a nationally representative sample of US adults over age 50, and has fielded additional enrollment waves every six years to represent subsequent generational birth cohorts. Study recruitment and design have been published elsewhere.[18–20] Biennial interviews are ongoing and typically conducted via telephone, with the present study including data from 1998 through the 2018 interview wave. Proxies complete "exit interviews" after death of a participant to provide information on major health events preceding the participant's death (such as a fatal stroke). HRS is sponsored by the National Institute on Aging, National Institutes of Health and conducted by the University of Michigan, Ann Arbor. All study participants gave informed consent and HRS was approved by the institutional review board at the University of Michigan. The current study, as a secondary analysis of deidentified publicly available HRS data, was certified as exempt from review by the University of California, San Francisco Institutional Review Board. All data and materials have been made publicly available through the Institute for Social Research at the University of Michigan, Ann Arbor and can be accessed at https://hrsdata.isr.umich.edu/data-products/public-survey-data.

From the 19,111 HRS participants age 50+ in 1998, participants were excluded if reporting prevalent stroke at baseline or missing information on date of stroke (n=1,058) or missing all cognitive tests across study follow-up (n=1,432) or if missing state of birth (n=10). Further exclusions included those who were missing race/ethnicity or did not report white or black race (n=361) and those missing education (n=1) or any covariates (n=21) for a final analytic sample of 16,238 individuals.

Educational Attainment

Participants self-reported highest grade of school or year of college completed at baseline. Education was analyzed in continuous years with 0 representing no formal education, 1-11 representing primary and secondary grades, 12 representing high school completion, 13-15 representing some college, 16 representing college graduate, and 17 representing post-graduate education of any kind.

Stroke

Stroke status was determined using self-reported doctor's diagnosis of stroke answering the question, "Has a doctor ever told you that you had a stroke?" If patients were deceased or otherwise unavailable for direct interview, patients' stroke status was reported by proxy informants. Prior analyses of stroke in HRS and other studies of older adults have found that self-reported stroke incidence does not differ greatly from physician-verified strokes.[21] All memory reports after date of first stroke were considered post-stroke cognition; information was not collected on subsequent strokes or stroke subtypes, and transient ischemic attacks were not measured.

Consistent with previous investigations in this sample,[9–11] participants were classified into three categories for the entirety of the follow-up period: (1) stroke survivors: participants

experiencing stroke at any point who survived to participate in a subsequent interview; (2) stroke decedents: participants experiencing stroke at any point who did not survive to participate in subsequent interviews (i.e. who died from any cause including but not restricted to stroke); and (3) stroke-free participants: those reporting no stroke throughout the follow-up period. Trajectories for stroke survivors and stroke decedents were calculated using months prior to stroke or months since stroke for each memory measurement ascertainment. For stroke-free participants, trajectories of memory were calculated for age-related memory decline.

Memory

Immediate and delayed (5-minute) recall tests of a verbally-presented 10-word list of common nouns were used to assess memory, which have been previously suggested to be relevant predictors of impairment after incident stroke.[22] If individuals were too impaired to participate in assessments, proxy informants such as spouses rated participant's memory on a 5-point Likert scale and completed the Jorm Informant Questionnaire for Cognitive Decline,[23,24] for which validity and reliability as a comparable alternative to in-person assessments have been documented elsewhere.[25,26] A previously created composite score combining proxy and direct memory measurements for HRS was used as the measure of memory at each data collection wave.[20,27] Memory scores were z-standardized using the population-weighted mean and standard deviation of the full 1998 sample. The final standardized measures ranged from -6.02 to 3.14, with each unit change corresponding to a one standard deviation change in the 1998 population.

Covariates

Models were adjusted for stroke-free participants' interview age or age at stroke for those experiencing stroke, centered at 75 years. The following demographics were collected at HRS entry: race, gender, birthplace region (Census-defined Northeast, Midwest, South, West, or outside US),

mother's education (<8 years, 8+ years, unknown),[28,29] and height[30,31] as a proxy for advantageous early life environments whose benefits may persist into old age. Analyses additionally included an indicator for the wave of individuals' first cognitive assessment to adjust for practice effects of repeated memory testing.[32]

Statistical Analysis

Longitudinal trajectories of memory scores were estimated using segmented linear mixed models with individual-level random intercepts, consistent with previous studies conducted in this sample.[9–11,33] Models contained all stroke-survivors, stroke decedents, and stroke-free participants with corresponding indicators for stroke-status during follow-up as well as the following predictors specific to stroke status: time until stroke for stroke survivors and decedents; time since stroke for stroke survivors; age at stroke or stroke-free age at study visit; and all covariates. A regression discontinuity indicator for immediate decrement in memory performance at the time of first stroke was included for participants who survived stroke, representing acute decreases in memory at stroke onset. Changes in memory were thus estimated as a function of time until stroke for participants who experienced stroke and additionally as time following stroke for stroke-survivors, estimating separate pre- and post-stroke slopes, and as age-related memory decline for stroke-free participants. Predicted memory scores were calculated for all stroke categories, with the intercept representing an epoch-specific stroke-free 75-year-old individual.

We first estimated trajectories of memory change, testing for effect modification by educational attainment for memory trajectories in all stroke groups. After testing for further effect modification by race, we then estimated trajectories of memory change in race-stratified models to assess whether the effects of education on memory trajectories differed between White and Black participants. All analyses were weighted according to the 1998 sample weights to be representative

of the 1998 community-dwelling US population age 50 or more at baseline. Analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Over up to a possible 20 years of follow-up, a total of 2,019 individuals experienced incident stroke: 1,346 nonfatal and 673 fatal. Overall, there were 2,411 Black individuals (14.9%) and 13,827 (85.2%) individuals. Education was statistically significantly different across stroke groups (p<.0001), with stroke-free participants having the highest average education of 12.4 ± 3.0 years, followed by stroke survivors (12.1 ± 3.0 years) and stroke decedents (11.6 ± 3.1). Full sample characteristics are presented in Table 1.

Table 1.1: Baseline characteristics of participants by stroke status in the unweighted analytic sample

	Stroke-free N = 14,219		Stroke Survivors N = 1,346		Stroke Decedents N = 673		P-value
	N/Mean	SD / %	N/Mean	SD / %	N/Mean	SD / %	
Age at initial visit	65.73	10.01	67.19	9.35	73.02	9.20	<.0001
Gender							0.0524
Male	6,177	43.44	561	41.68	264	39.23	
Female	8,042	56.56	785	58.32	409	60.77	
Race							<.0001
White	12,192	85.74	1,101	81.8	534	79.35	
Black	2,027	14.26	245	18.2	139	20.65	
Years of Education	12.39	2.96	12.11	3.03	11.58	3.13	<.0001
Mother's Education							0.0013
< 8 years	5,127	36.06	513	38.11	277	41.16	
8+ years	7,673	53.96	693	51.49	312	46.36	
Missing/unknown	1,419	9.98	140	10.4	84	12.48	
Height (meters)	1.69	0.10	1.68	0.10	1.68	0.09	<.0001
Southern birthplace	2,351	16.53	271	20.13	138	20.51	0.0002
Memory Score*	1.02	0.55	0.97	0.52	0.72	0.64	<.0001

SD: standard deviation. IQR: interquartile range. P-value for differences across epoch calculated using chi-square statistic for categorical covariates and analysis of variance (ANOVA) for continuous covariates.
* Memory scores z-standardized to 1998 sample mean and SD; 1-unit change represents 1 standard deviation.

Age-adjusted stroke incidence rates using 2000 census estimates as the referent age distribution are shown in Table 2. Overall stroke incidence was 6.64 per 1,000 person-years. Nonfatal strokes were more common, with an incidence rate of 4.76 per 1,000 person-years compared to 1.89 fatal strokes per 1,000 person years. Incidence rates for all strokes were higher in Black participants compared to White, with Black participants experiencing 9.73 strokes per 1,000 person-years and White participants experiencing 6.41 strokes per 1,000 person years.

Table 1.2: Age-Standardized* Stroke Incidence Rates† (weighted to be representative for US community-residing individuals aged 50 and older at the start of each epoch)

	All participants		Black Participants only		White Participants only	
	Events	Incidence Rate	Events	Incidence Rate	Events	Incidence Rate
All strokes	6,515,467	6.64 (6.64, 6.65)	845,434	9.73 (9.71, 9.76)	5,670,033	6.41 (6.41, 6.42)
Survivors only	4,395,154	4.76 (4.75, 4.76)	544,691	6.90 (6.88, 6.93)	3,850,463	4.58 (4.58, 4.59)
Decedents only	2,120,313	1.89 (1.88, 1.89)	300,743	2.83 (2.82, 2.84)	1,819,570	1.83 (1.83, 1.83)

* Standardized to the US population according to 2000 US census estimates.
† Presented as incidence per 1,000 person-years.

Stroke-free participants

Among stroke-free participants (Table 3), higher education was associated with an increase in memory score of 0.061 (95% CI: 0.058, 0.065) SD per additional year of attained education. Each one-year increase in age was associated with a decrease of -0.102 (95% CI: -0.103, -0.101) SD in average memory scores; each year increase in education was associated a decline that was 0.003 (95% CI: 0.003, 0.004) SD slower per year increase in age, or the equivalent of 0.013 standard deviations per year difference between an individual with a high school degree and a 4-year college degree.

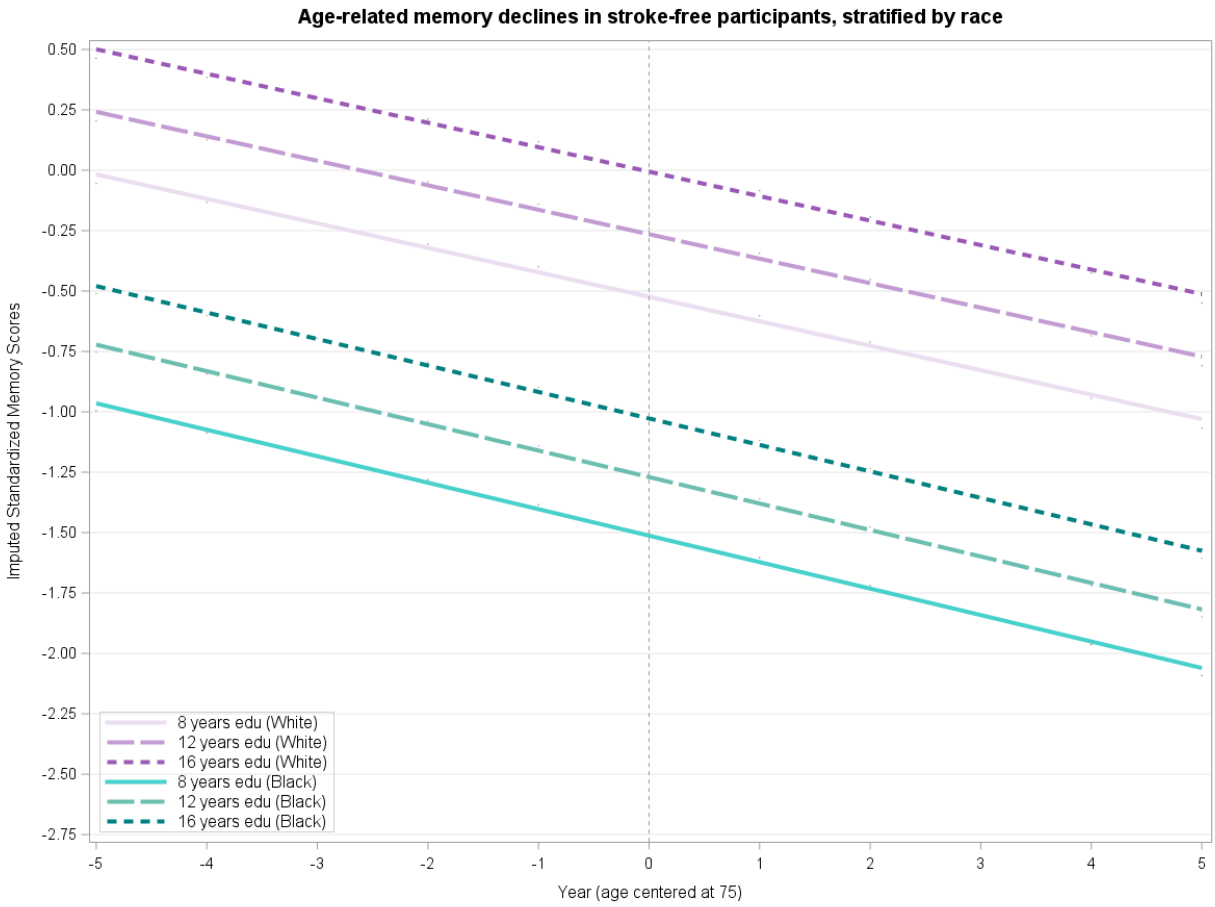
Table 1.3: Covariate-adjusted associations between stroke-status and memory scores in population-weighted mixed linear regression models (weighted to be representative for US community-residing individuals aged 50 and older at the start of each epoch)

	Beta	95% CI		P-value
		Lower	Upper	
Intercept†	-0.2487	-0.2707	-0.2267	<.0001
Education	0.0613	0.0575	0.0650	<.0001
Stroke-Free Participants				
Age (years)	-0.1021	-0.1028	-0.1013	<.0001
Age (years) x education	0.0032	0.0030	0.0035	<.0001
Stroke Survivors				
Indicator‡	-0.2637	-0.3127	-0.2148	<.0001
Indicator x education	0.0078	-0.0064	0.0220	0.2827
Stroke age (years)	-0.0945	-0.0979	-0.0911	<.0001
Stroke age (years) x education	0.0022	0.0011	0.0033	<.0001
Time until stroke (years)	-0.1454	-0.1571	-0.1337	<.0001
Time until stroke (years) x education	0.0054	0.0042	0.0067	<.0001
Discontinuity at time of stroke§	-0.4197	-0.4744	-0.3650	<.0001
Discontinuity at time of stroke x education	0.0175	0.0037	0.0312	0.0129
Time since stroke (years)	-0.0611	-0.0765	-0.0457	<.0001
Time since stroke (years) x education	0.0033	0.0013	0.0054	0.0017
Stroke Decedents				
Indicator‡	-0.7808	-0.8600	-0.7015	<.0001
Indicator x education	-0.0288	-0.0525	-0.0050	0.0177
Age of stroke (years)	-0.0881	-0.0936	-0.0827	<.0001
Age of stroke (years) x education	0.0027	0.0010	0.0045	0.0021
Time until stroke (years)	-0.2336	-0.2509	-0.2163	<.0001
Time until stroke (years) x education	-0.0011	-0.0030	0.0009	0.2944

Figure 1 and Supplemental Table 2 show differences in stroke-free memory decline across education in race-stratified models. Black stroke-free participants had average memory scores that were, on average, -0.920 (95% CI: -0.955, -0.886) lower than White stroke-free participants. Black stroke-free participants also benefitted less from each year of education, with a benefit that was -0.012 (95% CI: -0.021, -0.003) SD lower than White participants per increased year of education. Decline was also faster by -0.013 (95% CI: -0.015, -0.011) SD per year among Black participants, which was slightly steeper by -0.002 (95% CI: -0.002, -0.001) SD for each additional year of education. Therefore Black participants with a high school degree had a decline that was 12.7%

faster than White participants with equivalent education; Black participants with a 4-year college degree had a decline that was 21.6% faster than White participants with equivalent education.

Figure 1.1



Stroke Survivors

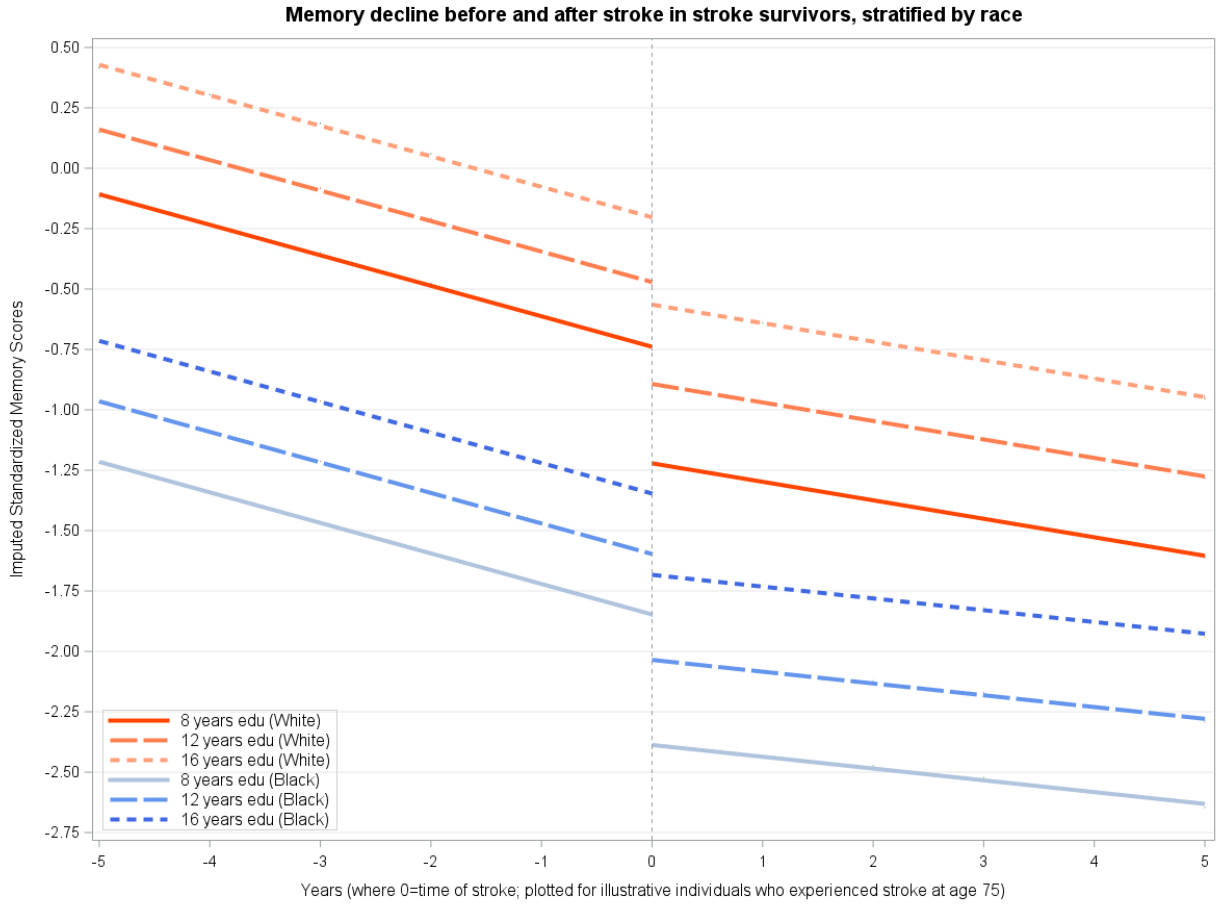
Stroke survivors (Table 3) had average memory scores that were -0.26 (95% CI: -0.31, -0.22) SD lower than stroke-free participants; the difference between stroke-free and stroke survivors was smaller by 0.008 (95% CI: -0.006, 0.022) SD per year of education, though this difference did not reach statistical significance. Each additional year of age at the time of stroke was associated with a -0.095 (95% CI: -0.098, -0.091) SD lower average memory score, with small differences across educational attainment (β: 0.002; 95% CI: 0.001, 0.003; p=<.0001). Each year change until stroke onset was associated with a -0.145 (95% CI: -0.157, -0.134) SD decrease in

memory, though pre-stroke annual decline was slower by 0.005 (95% CI: 0.004, 0.007) SD for each year of attained education. There was an immediate decrement at the time of stroke of –0.420 (95% CI: -0.474, -0.365) SD; this decrement was smaller by 0.018 (95% CI: 0.004, 0.031) per additional year of attained education, or a 0.070 SD smaller decrement for individuals with a 4-year college degree compared to individuals with a high school degree. Following stroke, memory scores decreased by -0.061 (95% CI: -0.077, -0.046) SD per year, with statistically significant but small differences across levels of attained education (β: 0.003; 95% CI: 0.001, 0.005; p=0.0017).

Figure 2 and Supplemental Table 2 show differences in memory decline across education in race-stratified models for stroke-survivors. Black participants experiencing and surviving stroke benefitted less than white participants for each year increase in attained education. Black participants had memory scores that were -0.213 (95% CI: -0.333, -0.093) SD lower on average than White participants with the same number of years of education; this difference was larger by -0.022 (95% CI: -0.058, 0.014) SD for each additional year of attained education, though did not reach statistically significance. Black participants also had lower average memory scores compared to White participants for each additional year of age at the time of stroke by -0.010 (95% CI: -0.019, -0.000). Decline prior to the onset of stroke was faster for Black participants, with a decrease for each year prior to stroke that was -0.022 (95% CI: -0.033, -0.010) SD faster than White participants. At the time of stroke, Black participants had an immediate decrement that was less severe than White participants by 0.097 (95% CI: -0.027, 0.222) SD, though not statistically significantly. The effects of education on memory decline prior to stroke onset and on decrements in memory at the time of stroke did not differ between Black and White participants. There were however small differences by race and education for decline after stroke; Black participants had decline that was 0.011 (95% CI: -0.006, 0.028) SD slower than white participants with an additional benefit of 0.005 (95% CI: 0.000, 0.011) SD per year for each additional year of attained education, or an

approximate decline that was 0.021 SD slower per year for Black individuals with a college degree compared to Black individuals with a high school degree.

Figure 1.2



Stroke Decedents

Stroke decedents had average memory scores that were -0.781 (95% CI: -0.860, -0.702) SD lower than stroke-free participants (Table 3). Each additional year of attained education was associated with a memory score that was an additional -0.029 (95% CI: -0.053, -0.005) SD lower. Each year increase in age at stroke was associated with a -0.088 (95% CI: -0.094, -0.083) SD lower average memory score, with a small but statistically significant interactive effect of age at stroke and education on memory scores (β: 0.003; 95% CI: 0.001, 0.005; p=0.0021). Decedents had a

decline of -0.234 (95% CI: -0.251, -0.216) SD per year prior to stroke, which did not appear to significantly differ across levels of education.

Figure 1.3

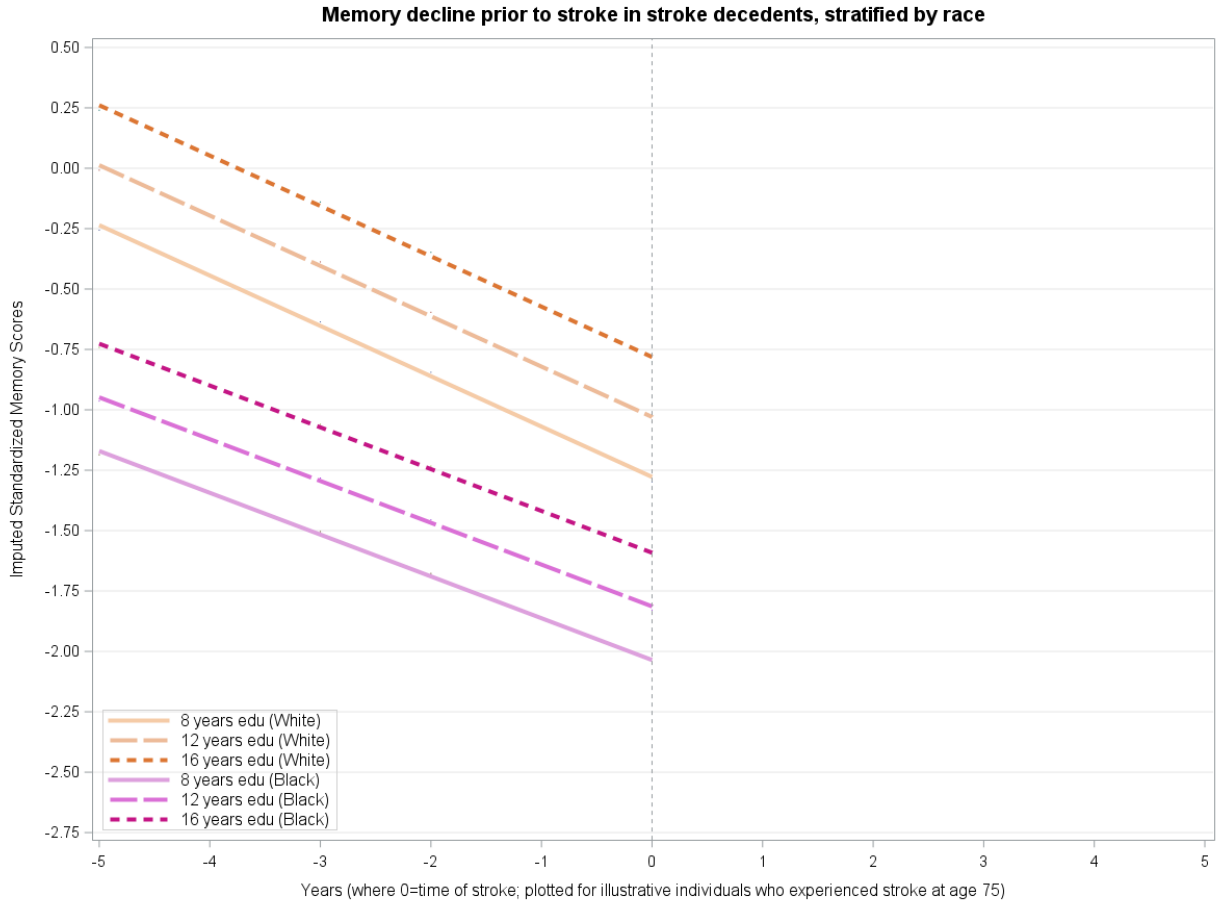


Figure 3 and Supplemental Table 2 show differences in memory decline across education in race-stratified models for stroke-decedents. Black stroke decedents had memory scores that were on average 0.138 (95% CI: -0.047, 0.323) SD higher than White stroke decedents, which did not appear to differ by education (β: -0.003; 95% CI: -0.057, 0.051). The effects of education on stroke age did not differ by race as well (β: 0.000; 95% CI: -0.004, 0.004). Black stroke decedents had a slower memory decline prior to stroke than white stroke decedents by 0.018 (95% CI: 0.001, 0.035)

SD per year, though decline was steeper at higher levels of education with Black four-year college graduates having decline that was steeper by -0.016 per year compared to Black high school graduates.

DISCUSSION

Among this nationally representative sample of older US adults, we found small but significant differences in memory trajectories by education, with higher levels of education associated with slower decline in stroke survivors both prior to the onset of stroke and following the occurrence of stroke. We additionally observed decreased decrements at the time of stroke onset with increases in attained education. However, decline prior to stroke did not differ by level of education among decedents, and differences in memory were driven primarily by pre-existing differences in memory by educational attainment. The effects of education on stroke-related memory differed across the continuum of stroke, but disparities were driven mostly by pre-existing racial differences in memory scores.

This study contributes significantly to our understanding of the relationship between education and cognition. Previous work has examined the relationship between educational attainment and post-stroke dementia, but few studies have examined how education influences trajectories of cognitive functioning before and at the time of incident stroke.[2,3,34,35] We found that resilience to the cognitively detrimental effects of stroke arose primarily from differences in pre-morbid cognitive ability that persisted across the disease progression, rather than as improved responses to disease advancement with increased educational attainment. These results provide further evidence for the passive theory of cognitive reserve, which posits that individuals with higher education maintain higher levels of cognitive functioning compared to individuals with less education, but decline at a similar rate.[36–38] Though we found evidence for decreased decline with higher education, effect sizes were small. The difference in average memory score between a high

school graduate and a college graduate was 0.245 SD. In contrast, the benefit for college graduate compared to a high school graduate was only a 0.022 SD slower annual memory decline prior to stroke (from an annual decline of -0.145 SD among high school graduates), a 0.070 SD lower decrement at the time of stroke (from a decrement of -0.420 SD among high school graduates), and a 0.013 SD slower annual memory decline following stroke (from an annual decline of -0.061 SD among high school graduates).

Our findings that the benefits of education were often lower for Black participants compared to White participants are consistent with previous research finding differential benefits of education across racial/ethnic groups.[12,13] It is important to note that participants in the 1998 wave of the Health and Retirement Study were born prior to 1949 and entered schooling during a time when almost all people raised in the US South attended segregated schools.[39] As a result, a year of education is likely not equivalent across Black and White participants due to systemic discrimination affecting educational quality, access to higher education, and downstream economic opportunities.[39,40] The exception to the decreased returns benefits occurred in decline after stroke which was slower for Black participants compared to White participants. However it is possible that this was a result of selective survival among Black participants who were more likely to experience fatal strokes and had lower memory test scores at baseline as a result of systemic oppression experienced across the lifecourse.

There were several limitations to this study. Our model specification assumed a monotonic linear increase in memory with each increasing year of education; in previous studies, we found that this represented the relationship between education and cognition in the HRS sample reasonably well.[41] Another limitation of this study includes the use of self or proxy-reported strokes that are subject to recall bias and do not differentiate between stroke sub-types or consider transient ischemic attacks. However, previous studies have found similar rates of incident stroke in HRS self-reports and in medical-record verification of stroke outcomes.[21] Though imperfect, with

investigations suggesting that misreporting of strokes in HRS is nonsystematic with a sensitivity of 74% and specificity of 93% to detect strokes recorded through Centers for Medicare and Medicaid Services, self-reported strokes in HRS allowed us to estimate trends across the US in the absence of a national infrastructure for systematic stroke reporting.[42] Furthermore, approximately 87% of strokes in the US are ischemic, making it a reasonable assumption that our results reflect a weighted average effect of all stroke types more heavily weighted to represent ischemic strokes.[43,44] We also required participants to have at least one memory score, which limits the ability to assess individuals who were too impaired to complete cognitive testing. To address this, we used a composite memory score as our outcome that allowed us to estimate memory using previously validated proxy reports in participants that were too impaired to complete cognitive testing or that were otherwise unable to participate in that wave.[27] Despite limitations, this study has strength as a source of continuous monitoring for continuous memory change in a large representative sample of community-dwelling individuals over up to 20 years of follow-up. As a result, we had sufficient sample size to estimate changes in memory prior to and at the time of stroke in addition to post-stroke trajectories, and to examine the potentially moderating roles of education and race.

In this study, we found that education primarily benefits stroke-related cognition through existing cognitive functioning rather than in improved responses to the onset of disease. Education was associated with differences in trajectories of memory decline, but effects were small and did not contribute significantly to a narrowing of educational disparities in cognition at the time of stroke. Future studies may further investigate whether observed pathways arise as a biologic response to disease or through increased access to health-benefitting resources such as acute care, as well as consider potential interventions to narrow pre-existing disparities by education and race.

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Table 1.S1: Baseline characteristics of participants by stroke status in the weighted analytic sample

	Stroke-free N = 49,898,936		**Stroke Survivors** N = 4,395,154		**Stroke Decedents** N = 2,120,313	
	N/Mean	SE / %	N/Mean	SE / %	N/Mean	SE / %
Age at initial visit	64.16	0.10	66.37	0.32	72.82	0.41
Gender						
Male	22,465,678	45.02	1,901,841	43.27	808,175	38.12
Female	27,433,258	54.98	2,493,313	56.73	1,312,138	61.88
Race						
White	45,378,436	90.94	3,850,463	87.61	1,819,570	85.82
Black	4,520,500	9.06	544,691	12.39	300,743	14.18
Years of Education	12.64	0.03	12.28	0.09	11.74	0.12
Mother's Education						
< 8 years	16,530,258	33.13	1,536,352	34.96	848,068	40.00
8+ years	28,689,384	57.50	2,410,609	54.85	1,012,368	47.75
Missing/unknown	4,679,294	9.38	448,193	10.20	259,877	12.26
Height (meters)	1.70	0.00	1.69	0.00	1.68	0.00
Southern birthplace	7,139,809	14.31	778,553	17.71	366,926	17.31
Memory Score*	1.09	0.00	1.03	0.01	0.77	0.03

SD: standard deviation. IQR: interquartile range. P-value for differences across epoch calculated using chi-square statistic for categorical covariates and analysis of variance (ANOVA) for continuous covariates.

* Memory scores z-standardized to 1998 sample mean and SD; 1-unit change represents 1 standard deviation.

Table 1.S2: Covariate-adjusted associations between stroke-status and memory scores in population-weighted mixed linear regression models, assessing for differences across race/ethnicity

	Beta	95% CI		P-value
		Lower	Upper	
Intercept†	-0.247	-0.269	-0.225	<.0001
Education	0.062	0.058	0.066	<.0001
Black Race	-0.920	-0.955	-0.886	<.0001
Education x black race	-0.012	-0.021	-0.003	0.0113
Stroke-Free Participants				
Age (years)	-0.101	-0.102	-0.100	<.0001
Age (years) x education	0.003	0.003	0.003	<.0001
Age (years) x black race	-0.013	-0.015	-0.011	<.0001
Age (years) x education x black race	-0.002	-0.002	-0.001	<.0001
Stroke Survivors				
Indicator‡	-0.234	-0.287	-0.182	<.0001
Indicator x education	0.009	-0.008	0.025	0.3027
Indicator x black race	-0.213	-0.333	-0.093	0.0005
Indicator x education x black race	-0.022	-0.058	0.014	0.2302
Stroke age (years)	-0.094	-0.097	-0.090	<.0001
Stroke age (years) x education	0.002	0.001	0.004	0.0003
Stroke age (years) x black race	-0.010	-0.019	0.000	0.0406
Stroke age (years) x education x black race	-0.001	-0.004	0.002	0.4495
Time until stroke (years)	-0.143	-0.155	-0.131	<.0001
Time until stroke (years) x education	0.005	0.004	0.007	<.0001
Time until stroke (years) x black race	-0.022	-0.033	-0.010	0.0003
Time until stroke (years) x education x black race	-0.002	-0.006	0.002	0.3194
Discontinuity at time of stroke§	-0.431	-0.488	-0.374	<.0001
Discontinuity x education	0.018	0.003	0.033	0.0206
Discontinuity x black race	0.097	-0.027	0.222	0.1242
Discontinuity x education x black race	0.007	-0.031	0.045	0.7041
Time since stroke (years)	-0.062	-0.077	-0.046	<.0001
Time since stroke (years) x education	0.002	0.000	0.005	0.0449
Time since stroke (years) x black race	0.011	-0.006	0.028	0.2134
Time since stroke (years) x education x black race	0.005	0.000	0.011	0.0519
Stroke Decedents				
Indicator‡	-0.799	-0.888	-0.711	<.0001
Indicator x education	-0.023	-0.053	0.007	0.1397
Indicator x black race	0.138	-0.047	0.323	0.1440
Indicator x education x black race	-0.003	-0.057	0.051	0.9132
Age of stroke (years)	-0.087	-0.093	-0.080	<.0001
Age of stroke (years) x education	0.002	0.000	0.005	0.0340
Age of stroke (years) x black race	-0.009	-0.025	0.006	0.2455
Age of stroke (years) x education x black race	0.000	-0.004	0.004	0.8563
Time until stroke (years)	-0.236	-0.253	-0.219	<.0001
Time until stroke (years) x education	0.001	-0.002	0.003	0.6383
Time until stroke (years) x black race	0.018	0.001	0.035	0.0404
Time until stroke (years) x education x black race	-0.004	-0.009	0.001	0.1240

Figure 1.S1

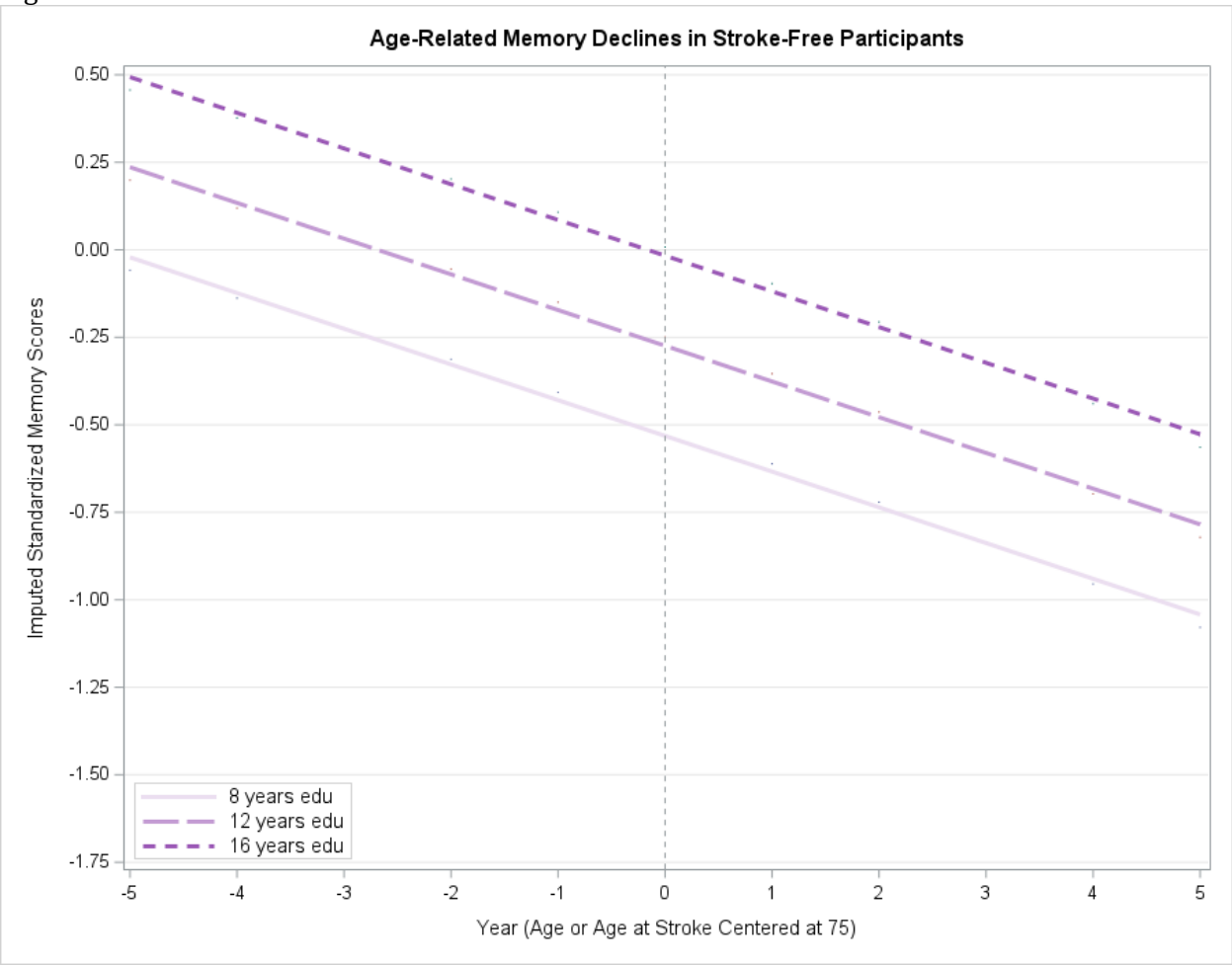

Age-Related Memory Declines in Stroke-Free Participants
Imputed Standardized Memory Scores
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-1.25
-1.50
-1.75
8 years edu
12 years edu
16 years edu
-5
-4
-3
-2
-1
0
1
2
3
4
5
Year (Age or Age at Stroke Centered at 75)

Figure 1.S2

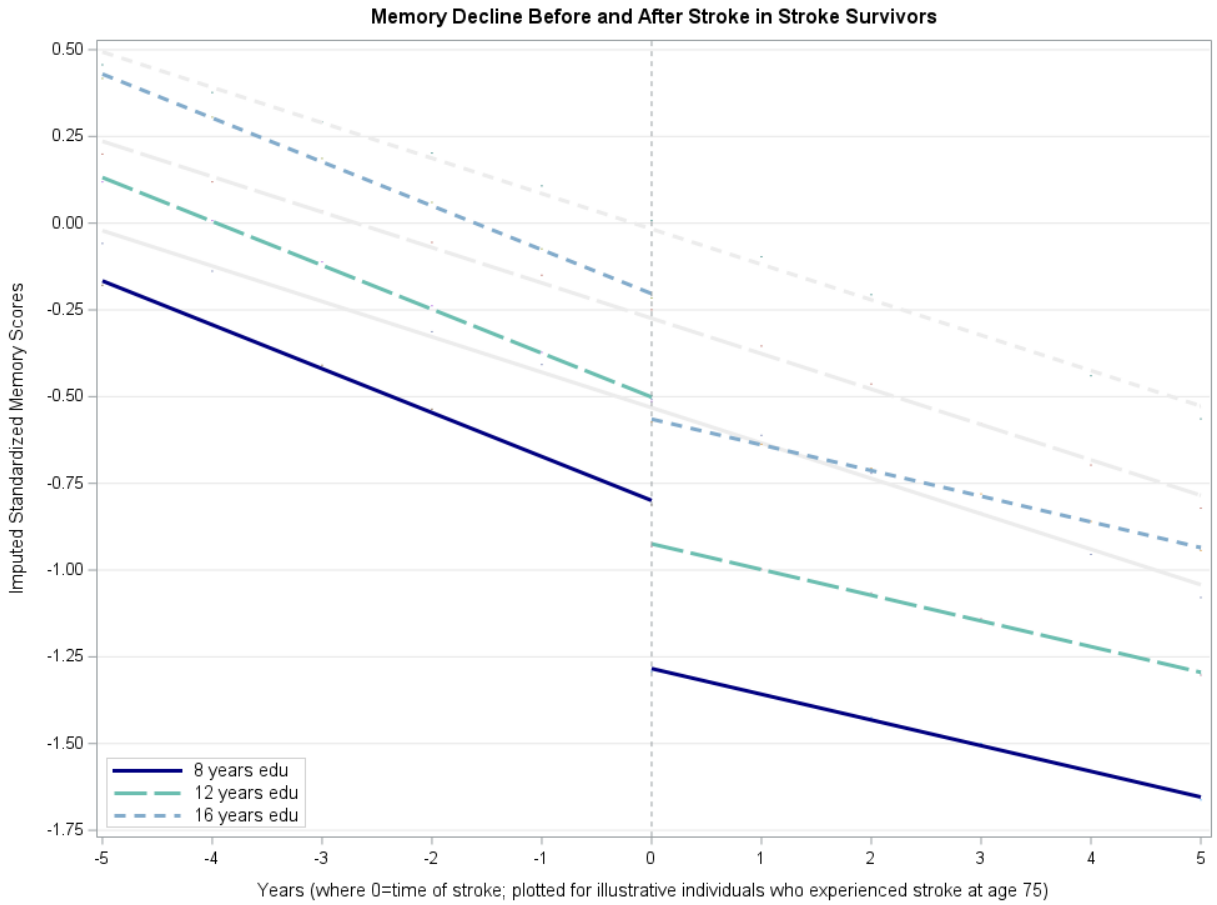
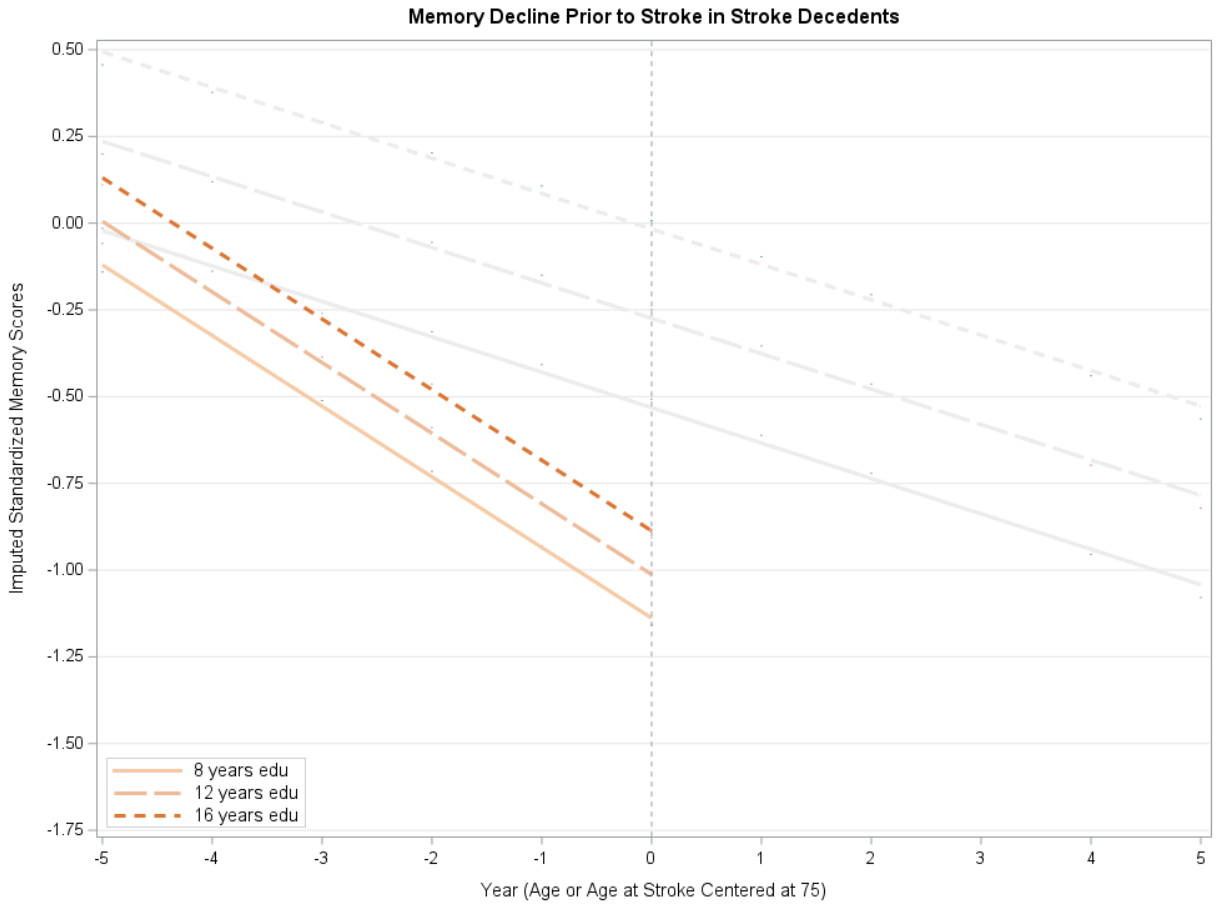

Memory Decline Before and After Stroke in Stroke Survivors
Imputed Standardized Memory Scores
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-1.25
-1.50
-1.75
8 years edu
12 years edu
16 years edu
-5
-4
-3
-2
-1
0
1
2
3
4
5
Years (where 0=time of stroke; plotted for illustrative individuals who experienced stroke at age 75)

Figure 1.S3


Memory Decline Prior to Stroke in Stroke Decedents
Imputed Standardized Memory Scores
0.50
0.25
0.00
-0.25
-0.50
-0.75
-1.00
-1.25
-1.50
-1.75
8 years edu
12 years edu
16 years edu
-5
-4
-3
-2
-1
0
1
2
3
4
5
Year (Age or Age at Stroke Centered at 75)

CHAPTER 2

Education and cognitive resilience: the influence of educational quality on dementia incidence in normal aging and after onset of stroke

Chloe W. Eng[a], Maria Glymour[a], John Kornak[a], Rachel Whitmer[b], Paola Gilsanz[c]

Affiliations: (a) Department of Epidemiology and Biostatistics, University of California San Francisco, (b) Department of Public Health Sciences, University of California Davis, (c) Division of Research, Kaiser Permanente Northern California

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ABSTRACT

Introduction: Higher education is associated with lower dementia risk in the general population and following the neurologically debilitating event of a stroke, possibly attributable to resilience towards neurodegenerative pathology. Whether quality of education is a contributing factor to this pathway is unclear.

Methods: We analyzed current Kaiser Permanente Northern California members born 1946 or earlier who participated in the Multiphasic Health Checkups (MHC) (n=216,430). Stroke and dementia diagnoses were obtained from medical records from January 1, 1996-September 30, 2017. Year-, state-, and race-specific educational quality measures of student-teacher ratio, term length, and attendance ratio were obtained from the Digest of Education Statistics and analyzed as a component mixture. Cox proportional hazards models were used to estimate whether education predicted dementia after stroke onset. Stroke was treated as a time-varying exposure with age as the time scale.

Results: Each tertile increase in educational quality was associated with a 25% lower hazard of incident dementia (HR: 0.75; 95% CI: 0.65, 0.86). For stroke-stratified models, a tertile increase in educational quality was associated with a 13% lower hazard of incident dementia among stroke-free individuals, but a 24% lower hazard of incident dementia after stroke.

Conclusion: Increased educational quality was associated with lower incidence of dementia regardless of stroke status, and may allow individuals to maintain some cognitive function after the onset of stroke. Further research is needed to consider the potential for selective survival by education among those with lower education.

INTRODUCTION

Education has been established as a strong predictor of late-life cognitive function and dementia risk, but causal pathways behind this association remain poorly understood (1,2). Several mechanisms have been hypothesized, including (1) socioeconomic benefits such as labor market benefits from increased credentials, access to more advantaged social networks, and increased resources for health-benefitting behaviors, as well as (2) biologic characteristics such as increased cognitive engagement through prolonged schooling and more cognitively complex occupations. However, most studies examine only years of attained education, an easily collected measure in research but one that ignores that a year of education may not be equal in value across subgroups of individuals.

One reason that a year of education may differ across individuals is differences in experienced educational quality. Educational quality has long been studied as a predictor of downstream economic outcomes, but is an underutilized measure to address hypothesized mechanisms behind the education and late-life cognition relationship (3–7). Several studies have investigated literacy as a measure of educational quality and its link to late-life cognitive health, and it could be theorized higher quality schooling that leads to improvements in literacy and other classroom skills make each year of schooling more valuable (8,9). Higher quality education may also lead children to remain in school longer, contributing to the well-established link between educational attainment and dementia risk, though it is also possible that selection into higher quality schools is a downstream result of other early-life socioeconomic advantages (10,11).

Operationalization of educational quality remains a major challenge in studying its effects on late-life health. Educational quality is highly patterned by race, geographic region, and year, making it difficult to disentangle downstream effects of structural racism or period effects. Previous studies on the relationship between administrative educational quality and late-life health have looked only at term length or at predicted years of education based on the quality and average attainment of the

state in that year (4,12). However these approaches either disregard possibly independent markers of educational quality other than term length or the potential for joint additive effects across multiple measures, or are unable to account for differential contributions of educational quality measures to the outcome of interest.

This issue of how to assess multiple correlated exposures is not unique to education, and methodologies from fields such as environmental or nutritional epidemiology have been developed to address this gap. Many of these approaches look at chemical mixtures, which tend to cluster or co-occur but may have independent effects on health (13–16). This study extends the concept of a mixture effect to combine multiple administrative educational quality measures, investigating educational quality as a policy-modifiable characteristic of the schooling experience and its association with late-life dementia risk. We assess this both in the general population and after incidence of stroke, considering dementia risk after stroke onset as a marker of cognitive resilience in response to the cognitively debilitating event of a stroke. Based on a priori assumptions of unmeasured characteristics affecting quality between segregated and non-segregated schools and racial differences in the value of education for downstream socioeconomic opportunities, we also examine associations of educational quality with late-life dementia risk across racial ethnic groups.

METHODS

Study Population

Kaiser Permanente Northern California (KPNC) is a large, integrated healthcare delivery system providing comprehensive medical care to over 4.6 million members (approximately 30% of the geographic region). The member population is generally representative of the overall regional population, but underrepresents individuals at extreme tails of the income distribution (17–19). Seniors (age ≥65) covered by KPNC are similar to the general population of seniors residing in Northern California with respect to history of chronic conditions, including diabetes, hypertension, heart disease, and asthma, and lifestyle factors, including smoking, obesity, and sedentary lifestyle

(18). The present study includes KPNC members who were enrolled and age ≥60 years as of 1/1/1996 (the year KPNC implemented electronic medical records). Eligible members were still alive, current KPNC members, and had no stroke or dementia diagnosis as of 1/1/1996. Cohort members were followed for incident dementia until end of health plan membership (defined as a gap in membership of ≥3 months), death, or 12/31/2017 (end of study period).

From a total of 532,222 individuals with KPNC medical records, we excluded those who had stroke or dementia diagnoses or died prior to 1/1/1996 (n=74,472), participants under the age of 60 years on 1/1/1996 (n=287,573), individuals who were not active KPNC members at the start of the study period (n=79,697), if missing a multiphasic health checkup (MHC) visit during which they would have reported demographic information including state of birth (n=9,082), individuals who reported a stroke during an MHC visit (n=323), missing sex (n=3), missing race/ethnicity (n=101), missing education (n=8,197), missing state of birth (n=26,642), or for years with missing compulsory schooling laws (n=2,374) for a final analytic sample of 43,758 participants.

Educational quality

Average state-level educational quality data was extracted from the Biennial Survey of Education in the United States (Office of Education, various years) and the Federal Digest of Educational Statistics (20). Year- and state-specific measures of (1) term length (TL) days in the academic school year, (2) attendance ratio (ATTr) as the fraction of enrolled children who attended on an average day, and (3) student-teacher ratio (STr) as the ratio of students to employed instructional staff were obtained covering the years of 1908 to 1962 as measures of quality consistently reported by most states for most of the 20th century. STr was reverse coded with lower values representing more students per teacher for consistency with the other educational quality measures. Separate race-, state-, and year-specific quality measures were obtained for years in which states observed de jure school segregation for Black students prior to the Brown v. Board of Education (1954) ruling established racial segregation in schools as unconstitutional. As students in

segregated states were not directly exposed to the schooling characteristics of their Black/White counterparts, a state-/year-specific measure of inequality was also calculated for all three measures as the ratio of Black to White values with lower values representing more inequality. Non-segregated states were assigned a value of 1 to represent no inequality.

Additionally, compulsory schooling laws (CSLs) from 1908 to 1962 were previously compiled using federal education reports that were usually available biennially (21–23). State-specific data were collected on the following three measures: 1) mandatory age at school enrollment, 2) youngest age to legally drop out of school, and 3) youngest age when individuals could receive a work permit.

Each individual was linked to the nine state-level educational quality measures for their state of birth in the year that they were six years of age under the assumption that interstate moves were uncommon prior to this age (24). Age six was chosen since it was the average age of entry into formal schooling; less than 40% of five-year-old children attended formal kindergarten in the time when MHC participants were entering schooling (25). White participants in segregated states were assigned the average state values of TL, ATTr, and STr for White schools and Black participants in segregated states were assigned the average state values of TL, ATTr, and STr for Black schools. As data was not available for de jure and de facto segregation of other racial/ethnic groups, Latino, Asian, and Native American participants in segregated states were also assigned TL, ATTr, and STr for Black schools based on historical exclusion from White schools (26–28).

Stroke

Incident stroke diagnoses were obtained from electronic medical records of inpatient and outpatient encounters between 1/1/1996 and 12/31/2013 based on International Classification of Diseases, Ninth Revision (ICD-9) diagnostic codes for ischemic stroke or transient ischemic attack (433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.00, 434.01, 434.10, 434.11, 434.90, 434.91, 435.0, 435.1, 435.3, 435.8, 435.9). Stroke was considered a time-varying confounder for which

participants contributed stroke-free person-time prior to the onset of stroke, and poststroke person-time following an incident stroke.

Dementia

Incident dementia diagnoses were ascertained from electronic medical records of inpatient and outpatient encounters between 1/1/1996 and 12/31/2013 based on ICD-9 diagnostic codes for Alzheimer's disease (331.0), vascular dementia (290.4x), and nonspecific dementia (290.0, 290.1x, 290.2x, 290.3, 294.2x, 294.8). A similar set of ICD-9 codes has been previously shown to have a sensitivity of 77% and a specificity of 95% compared with a consensus diagnosis of dementia using the combination of medical records review, physical examination, structured interviews and a neuropsychiatric battery (29).

Covariates

Demographic characteristics of age, sex, and race/ethnicity (Asian, Black, Hispanic/Latino, White and other racial/ethnic group or missing) were obtained from KPNC medical records. Categories of educational attainment was self-reported in the MHC questionnaires as 0–6 years, 7–9 years, 10–11 years, 12 years, technical/business degree, partial college attendance, college graduate, or postgraduate education. Models also adjusted for state level characteristics of birth states that may be associated with educational quality measures such as the percentage of considered to be urban, the percentage that self-reported as Black, and the census region (Northeast, Midwest, South, West). A fixed indicator of whether the state in which a participant entered school had legal racial segregation in that year was also included.

Statistical Analysis

In order to address the issue of correlated state-level educational quality measures, we use quantile g-computation (QGCOMP) to analyze state-level educational quality characteristics as a mixture of distinct exposures that arise from state-level investment into education across states and years. (30). QGCOMP was initially developed to address the tendency for clustering and correlation among exposures to metals or chemicals in environmental by combining correlated measures into a weighted index based on conditional contributions to an outcome of interest. The use of weighted indices like QGCOMP has been proposed as an alternative to traditional regression analyses that do not account for strong correlation structures of the exposures, and to shrinkage/regularization methods (lasso, elastic net) and factor analysis which identify groupings of exposures independent of their potential relationships with the outcome of interest (16,30–32). Full details on the method development are published elsewhere (16,30,32).

Briefly, QGCOMP starts by quantizing all exposures X_j to X_j^q, in this case the nine state-level educational quality measures. The "Q-model" is estimated as a traditional regression of the outcome on all quantized exposure parameters (treating the exposure parameters as continuous measures), and includes confounders and nuisance effect modifiers. The Q-model parameters are used to predict counterfactual outcomes Y_a of every potential outcome under each exposure regimen for each observation by regressing the entire set of counterfactuals on the treatment. We next calculate psi (ψ) as the weighted sum of all β_j (representing the effect size for exposure *j*), which is interpreted as the effect of increasing all X_j by one quantile at the same time – in this study, by one tertile. To calculate ψ, weights for the relative contribution of each exposure component are also created separately for positive and for negative effects, calculated as the proportion of the negative or positive proportional effect of each specific exposure component. When all effect estimates in the counterfactual g-computation model are in the same direction, the denominator to calculate weights is equal to ψ. For a continuous outcome in a linear model, the final model is therefore $Y_i = \beta_0 + \psi S_i +$

ε_i, where ψ represents the causal dose-response parameter of the entire summed exposure mixture (with a 1-unit change representing the effect estimate of increasing every mixture component by 1 quantile simultaneously) and S_i is the observed exposure index for each individual (the sum of the product of each weight and the quantized version of the *j*th exposure for the *i*th individual).

We used QGCOMP with time-varying Cox proportional hazards models to estimate the association between educational quality and dementia risk using age as the timescale, adjusting for sociodemographic characteristics and state-level covariates sequentially (33). Because the majority of Black school values were clustered at the lower end of the distribution and model fit using the AIC and BIC was best with a lower number of quantiles, analytic models used tertiles to categorize educational quality. In analyses considering stroke as an effect modifier, participants contributed stroke-free person-time until the diagnosis of a stroke, after which they contributed post-stroke person-time following stroke onset. Analyses were run in the overall pooled sample as well as stratified by stroke status and by racial/ethnic group. Analyses were performed using SAS version 9.4 (SAS Institute Inc.) and the QGCOMP package in R version 3.6.0.

RESULTS

The mean age of participants at start of follow up in 1996 was 75.0 years of age (SD=6.5 years) (**Table 1**). A total of 8,005 participants experienced incident stroke during the follow-up period. The majority of participants identified as White (n=21,050; 72.6%) followed by those who identify as Black (4,912; 16.9%).

Table 2.1: Baseline demographic characteristics by stroke status

	Overall sample N = 28,996		**Stroke-free through follow-up** n =20,991		**Experienced incident stroke in follow-up** n = 8,005		P-value
	N/Mean	SD / %	N/Mean	SD / %	N/Mean	SD / %	
Average follow-up (years)	8.42	6.74	9.3	7.05	6.14	5.19	<.0001
Demographic Characteristics							
Baseline age	75.02	6.49	75.01	6.6	75.08	6.22	0.4050
Gender							0.1641
Male	12,430	42.87%	8,946	42.62%	3,484	43.52%	
Female	16,566	57.13%	12,045	57.38%	4,521	56.48%	
Race/Ethnicity							0.0004
*AI/AN/PI**	69	0.00%	52	0.00%	2	0.00%	
Asian	1,142	3.94%	881	4.20%	261	3.26%	
Black	4,912	16.94%	3,520	16.77%	1,392	17.39%	
Latino	953	3.29%	681	3.24%	272	3.40%	
Mixed	870	3.00%	589	2.81%	281	3.51%	
White	21,050	72.60%	15,268	72.74%	5,782	72.23%	
Education							0.0896
0-9 years	2,577	8.89%	1,886	8.98%	691	8.63%	
10-12 years	9,609	33.14%	6,914	32.94%	2,695	33.67%	
Trade/business	2,477	8.54%	1,782	8.49%	695	8.68%	
Partial college	5,354	18.46%	3,863	18.40%	1,491	18.63%	
College graduate	3,534	12.19%	2,628	12.52%	906	11.32%	
Postgraduate edu	5,445	18.78%	3,918	18.67%	1,527	19.08%	
Birth state region							0.0582
Midwest	5,778	19.93%	4,207	20.04%	1,571	19.63%	
Northeast	2,975	10.26%	2,167	10.32%	808	10.09%	
South	6,567	22.65%	4,667	22.23%	1,900	23.74%	
West	13,676	47.17%	9,950	47.40%	3,726	46.55%	
State-level covariates							
Attended de jure segregated school	7,186	24.78%	5,115	24.37%	2,071	25.87%	0.0080
% Black	0.07	0.11	0.07	0.11	0.07	0.12	0.0081
% Urban	0.59	0.19	0.57	0.19	0.56	0.19	0.0375

SD: standard deviation. P-value for differences across epoch calculated using chi-square statistic for categorical covariates and analysis of variance (ANOVA) for continuous covariates.
* AI/AN/PI includes American Indian, Alaska Native, and Pacific Islander, and was analyzed with mixed race individuals as a singular category due to small sample sizes and based on the complexity of historical educational experiences for both groups.

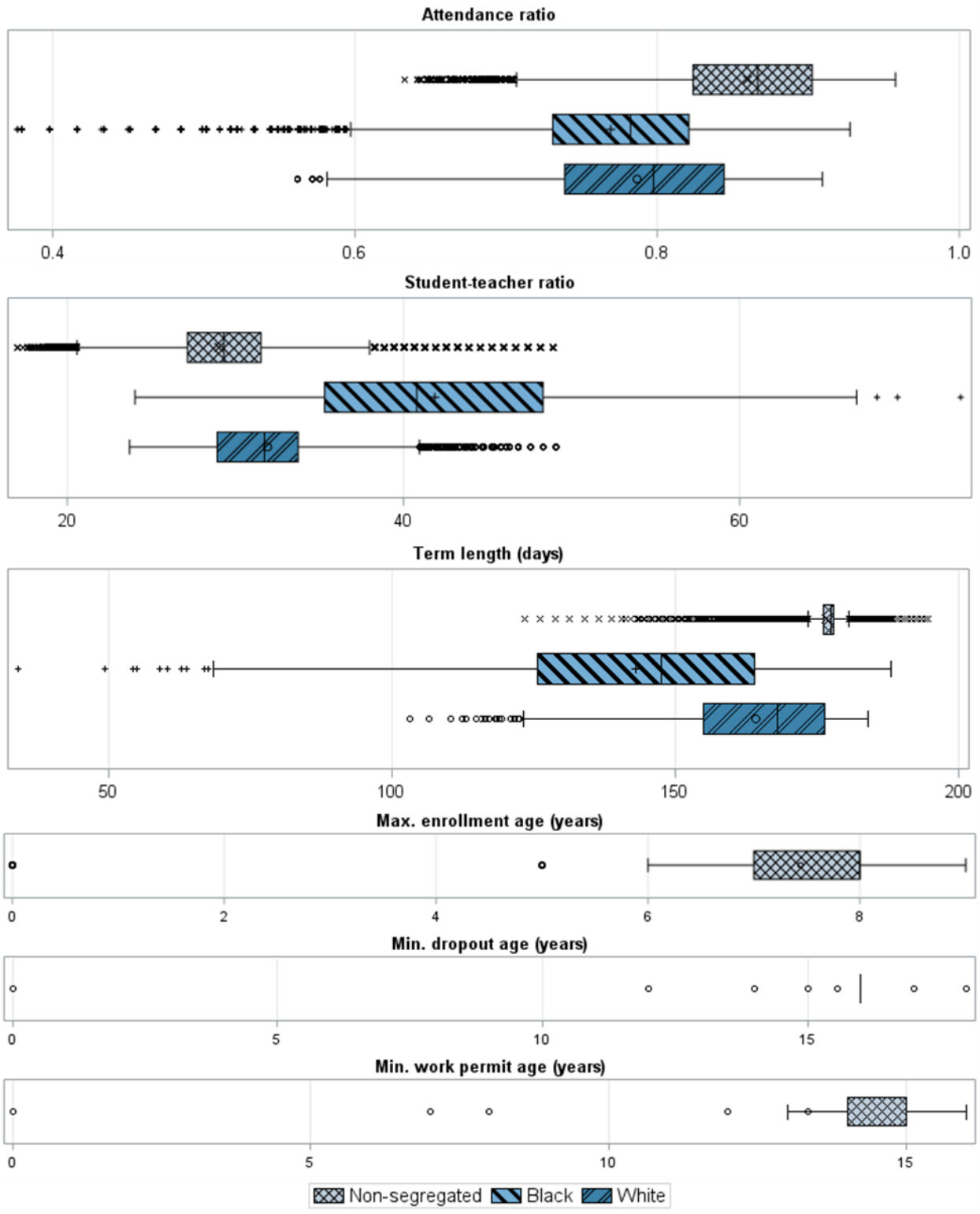

Figure 2.1: Distribution of educational quality measures. Non-segregated includes all non-segregated states, and formerly segregated states after legal integration. Black values represent Black only schools in segregated states during de jure segregation. White values represent White only schools in segregated states during de jure segregation.

Distributions of state-level educational quality measures are shown in **Figure 1**, representing the state-level average values in place at the time when participants were assumed to have entered formal schooling at age 6. Across the analytic sample, students attending Black schools had an average attendance ratio was 80.34% (SD: 6.31) of enrolled students, student-teacher ratio was 33.93 (SD: 8.27) students per teacher, and term length was 165.39 (SD: 20.11) days. Mean White or non-segregated school attendance ratio was 81.66% (SD: 4.78) of enrolled students, mean student-teacher ratio was 30.56 (SD: 3.99) students per teacher, and mean term length was 171.08 (SD: 10.57) days. Statistically significant differences between White and Black schools were observed for attendance ratio, student-teacher ratio, and term-length (all p<.0001), with white students having 1.87% higher mean attendance, 7.33% fewer mean students per teacher, and 4.57% longer mean term lengths than black students of the same year and state. State maximum mandatory age at enrollment into schooling was 7.5 years (IQR: 7.0-8.0, range: 6.0 to 9.0), minimum dropout age was 16 years (IQR:, range: 12-18), and minimum age to obtain a work permit was 14.2 years (IQR: 14-15, range: 9-16).

Table 2.2: Age-adjusted stroke and dementia incidences

	Events	Person-years	Crude Incidence Rate (per 1,000 PY)
Incident stroke*	8,005	170,353	46.99
Incident dementia (all)	10,092	282,086	35.78
Stroke-free person-time only	*7,167*	*244,285*	*29.34*
Post-stroke person-time only	*2,925*	*37,801*	*77.38*

*Excludes strokes occurring following diagnosis of dementia as individuals were censored upon experiencing the study outcome of interest.

Table 2 shows crude incidence rates for stroke and dementia during follow-up. A total of 8,005 individuals experienced a stroke during follow-up, or a crude incidence rate of 46.99 per 1,000 person years. The crude incidence rate for dementia during follow-up was 35.78 per 1,000 person years. Among stroke-free person-time only, 7,167 individuals contributed 244,285 person-years for a crude dementia incidence rate of 29.34 per 1,000 person years. Crude dementia incidence was

much higher among participants who had previously experienced a stroke, with an incidence rate of 77.38 per 1,000 person-years.

Table 3 shows the mixture effect of educational quality measures on dementia incidence. In the overall sample adjusting for individual characteristics, increasing all exposure components by 1 tertile was associated with a 20% decrease in hazard of dementia (HR: 0.80; 95% CI: 0.71, 0.91). After further adjusting for state characteristics (geographic region, percent of state considered urban, percent of state identifying as black), a 1-tertile increase in all exposure components was associated with a 25% decrease in dementia incidence (HR: 0.75; 95% CI: 0.65, 0.86). In models considering stroke-free follow-up time only, a 1-tertile increase in all exposure components was associated with a 13% decrease in hazard of dementia (HR: 0.87; 95% CI: 0.73, 1.03) though this did not reach statistical significance. The effect of educational quality was estimated to be larger in follow-up among participants who had experienced a stroke, with a 1-tertile increase in all exposure components being associated with a 24% decrease in hazard of dementia (HR: 0.76; 95% CI: 0.59, 0.97). Variable loadings representing association strength of each mixture component conditional on all other mixture components also differed across strata of stroke status (Figure 2), with higher racial inequalities in student-teacher ratio being the strongest contributor to the overall mixture effect among stroke-free participants but not among those experiencing incident stroke, and a lower mandatory age at enrollment more strongly driving an association with dementia risk in participants experiencing stroke than in stroke-free participants.

Table 3. Mixture effect hazard ratio for a 1 standard deviation change in all state-level administrative school quality measures simultaneously

	Overall				Stroke-Free follow-up				After incident stroke			
	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value
		Lower	Upper			Lower	Upper			Lower	Upper	
Model 1	0.80	0.71	0.91	0.0009	0.91	0.78	1.07	0.2610	0.79	0.63	1.00	0.0479
Model 2	0.75	0.65	0.86	0.0191	0.87	0.73	1.03	0.1036	0.76	0.59	0.97	0.0287

Model 1 adjusts for baseline age, participant own education, sex, race/ethnicity, and whether attended segregated school prior to 1954. Model 2 additionally adjusts for census region of birth (Midwest, Northeast, South, West), percent of state considered urban, and percent of state population identifying as Black. All pooled (Overall) models adjust for stroke status.

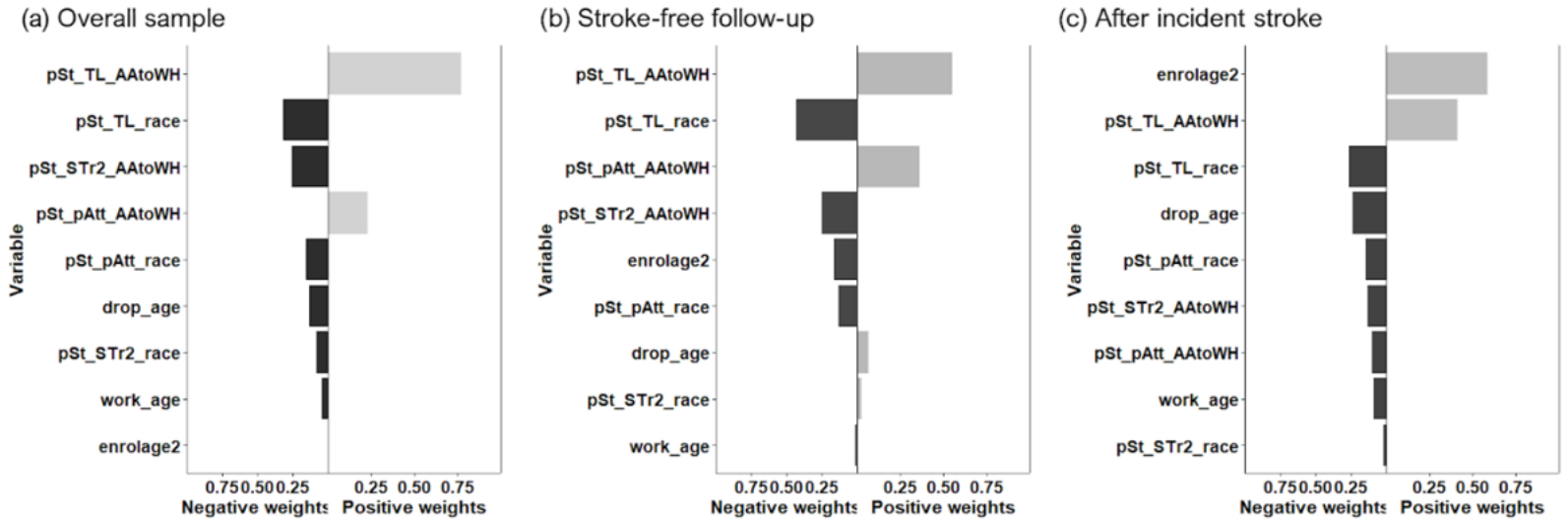

Figure 2. Component loadings for overall mixture effects in (a) the overall sample, (b) during stroke-free follow-up, and (c) among post-stroke follow-up time.

Race-stratified models suggested possible differences across racial ethnic groups, but results were limited by small sample sizes (Table 4). For White participants, each 1-tertile increase in educational quality was associated with a 18% decrease in hazard of dementia (HR: 0.82; 95% CI: 0.70, 0.96). Educational quality appeared to have a larger effect in other racial/ethnic groups compared to White participants, but estimates did not reach statistical significance and interpretation of results may have been hindered by a clustering of educational quality exposure values in the lowest tertile for non-white racial/ethnic groups. When examining stroke-specific subgroups, both Black and White participants showed similar patterns of educational quality having a larger effect during follow-up after incident stroke compared to stroke-free follow-up. Sample sizes of participants experiencing a stroke were too small among Asian, Latino, and AI/AN/PI/mixed-race participants to estimate race-stratified effects.

Table 4. Mixture effect log hazard ratio (representing the change in the expected conditional hazard) and confidence intervals for 1 standard deviation change in all state-level administrative school quality measures simultaneously and dementia risk overall and stratified by stroke status, by racial/ethnic groups

	Overall				Stroke-Free through follow-up				Experienced incident stroke			
	HR	95% CI		P-value	HR	95% CI		P-value	HR	95% CI		P-value
		Lower	Upper			Lower	Upper			Lower	Upper	
Asian	0.68	0.12	3.88	0.6652								
Black	0.71	0.45	1.12	0.1415	0.94	0.54	1.65	0.8283	0.81	0.35	1.89	0.6263
Latino	0.72	0.16	3.18	0.6682	0.92	0.15	5.49	0.9256				
Other	0.53	0.24	1.18	0.1203	0.63	0.22	1.76	0.3770				
White	0.82	0.70	0.96	0.0148	0.91	0.75	1.11	0.3596	0.81	0.62	1.08	0.1516

All models adjust for baseline age, participant own education, sex, race/ethnicity, whether attended segregated school prior to 1954, census region of birth (Midwest, Northeast, South, West), percent of state considered urban, and percent of state population identifying as Black. Models including only participants who experienced a stroke did not converge for Asian, Latino, and other (American Indian, Alaska Native, Pacific Islander, other mixed race) participants due to inadequate sample size.

DISCUSSION

In this sample of older adults, increases in a composite measure of state-level administrative educational quality records were associated with a lower risk of dementia incidence independently of own attained education. For each increase in tertile across all educational quality characteristics, hazard of dementia incidence decreased by 25%. Favorable educational characteristics were more beneficial for late-life dementia risk among those who experienced a stroke compared to the stroke-free population, and potentially among non-White racial/ethnic groups compared to White participants, though subgroup analyses across racial/ethnic classifications were hindered by a lack of adequate sample size.

Our results support the small but growing literature linking improved educational quality measures to late-life health outcomes (4,12,34–37). However, operationalizing the concept of educational quality and other highly correlated but distinct measures remains a major challenge in research. Previous studies have examined educational quality in relation to health as individual measures of administrative educational quality (12), as averages of educational quality measures (34), or as a composite measure of policy-predicted years of education, representing the years of attained education expected for the individual given their race, sex, state, year of birth, and state-/year-specific variations in school quality (4). This paper instead applies QGCOMP, a novel causal inference method to combine this complex area-level historical data as an example of a potential application for social epidemiology and aging research. GQCOMP allowed us to estimate a mixture effect that reflected the relative contributions of each educational quality characteristic to late-life dementia and the correlation structure of these highly related but distinct measures, rather than treating each characteristic as equally contributing to dementia incidence (30).

It is impossible to examine education in current older adults while ignoring the inextricable link between race and US schooling as a result of historical school segregation, with Black schools having less favorable educational quality characteristics in segregated states compared to White-only

schools (3,4). In the United States, years of education have been shown to have differential effects across racial/ethnic groups for a number of late-life health outcomes (38–40). Most US adults in current studies of aging grew up prior to mandatory desegregation of schooling and, regardless of their current state of residence, the majority of current Black adults were born and raised in the southern US, where Jim Crow laws led to significantly lower quality education for Black students (41). In order to recognize the effects of segregation, we also include measures of inequality between Black-only and White-only schools, under the assumption that states that were less equal for our administrative educational quality measures were likely less equal for other aspects of schooling or for downstream economic opportunities of schooling such as earnings (7,42). In our composite measure of educational quality, state-level inequality measures defined as the ratio of Black-only segregated schools to White-only schools contributed to individual dementia risk conditional on other educational quality components. This is especially pertinent as the issue of racial inequalities in schooling persists today through de facto segregation, and the current unequal distribution of resources and funding to schools may have lasting effects on present students later in life (43).

Also notable was the finding that educational quality was more beneficial among individuals having already experienced stroke, with a 24% reduction in dementia hazard compared to 13% in stroke-free individuals. Dementia risk was also higher among individuals who experienced a stroke with an incidence rate of 77.38 per 1,000 person-years, compared to an incidence rate of 29.34 per 1,000 person-years among stroke-free individuals. One potential explanation for this finding is the concept of cognitive reserve. Cognitive reserve posits that the brain can better actively cope with brain damage by using pre-existing cognitive processes or enlisting compensatory processes resulting from experiences throughout the lifecourse, such as education. Cognitive reserve can be further classified as either neural reserve or neural compensation, with the first being observed in the healthy brain and the latter referring to alterations in normal cognitive processing that arise in response to brain pathology, such as the effects of stroke (44–46). The finding that educational

quality was more beneficial among those who had experienced stroke would suggest a neural compensation pathway, with the increased benefit arising in response to the detrimental pathology associated with a stroke. Conversely, it is possible that similarly to higher educational attainment, higher educational quality leads to financial or social resources that allow individuals to seek better treatment at the time of stroke and leads to improved long-term health outcomes following stroke (47,48). However, unlike most large studies examining the relationship between stroke and dementia, all members of our sample had approximately equal access to and coverage for healthcare (17).

A major strength of this study was the use of Kaiser Permanente Northern California members. Eligibility for this study required participation in a multiphasic health checkup in the mid-20th century, meaning that all participants were located in California by mid-life and were Kaiser members throughout at least part of mid-life and all of late life. This means that members were residents of Northern California and had similar healthcare through the majority of their adult life, despite just over half of participants attending formal schooling in the other US Census geographic regions of the Midwest (20%), Northeast (10%), and South (23%), taking away any other geographic variation in adult life that may have further influenced dementia risk. This analysis also included a long follow-up period of up to twenty-one years with ascertainment of disease status for stroke and dementia from electronic health records, which are less subject to recall and reporting bias than self-report measures (49).

Our study had several limitations. There is significant variation in quality within states that was not captured in our quality measures, and state-level educational quality may not translate to actual experienced schooling. Local public schools are often largely funded by property taxes that disproportionately benefit schools with more affluent catchment areas, and the available administrative measures do not capture other aspects of the classroom environment, such as teacher training and expenditures. For this reason, results should be interpreted as a marker of state-level

investment into education rather than a measurement of participant's experienced classroom environment. However, we consider state-level administrative school characteristics to be a reasonable marker of educational quality, as the majority of school policies during the time period when current older adult KPNC members entered schooling were determined at the state-level (50). Another limitation was the measurement of only White and Black schooling experiences. We addressed this by assigning Latino, Asian, and Native American participants to the TL, ATTr, and STr for Black schools. While we recognize that each Latino, Asian, and Native American students of this time period had distinct schooling experiences from each other and depending on geographic location, we made this assignment based on historical exclusion from White schools such as: the US Supreme Court decision in Gong Lum v. Rice (1927) that upheld states' rights to segregate Chinese Americans as non-White, compulsory national attendance for Native American children missionary boarding schools into the early 20th century, and exclusion of Mexican American students that led to the federal appeals court decision to desegregate California public schools for Latino, Asian, and Native American students in Westminster School Dist. V. Mendez (1947) (26–28).

This study highlights the role of state-level schooling characteristics on late-life dementia risk, independent of own attained education, suggesting that educational attainment alone may not capture the full schooling experience. Furthermore, school quality may contribute to cognitive resilience as seen in our finding that benefits of educational quality were larger following onset of stroke compared to in stroke-free participants, and future studies are needed to further disentangle this potential pathway between the educational experience and late-life cognitive health. These findings provide further evidence for the importance of early-life education for late-life cognitive health and add to the growing literature linking educational quality to late life health, as well as having major implications for policies related to school quality and distribution of resources.

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CHAPTER 3

Education, white matter hyperintensities, and cognition in a diverse sample of older adults

Chloe W. Eng[a], Paola Gilsanz[b], John Kornak[a], Maria Glymour[a], Rachel Whitmer[c]

Affiliations: (a) Department of Epidemiology and Biostatistics, University of California San Francisco, (b) Division of Research, Kaiser Permanente Northern California, (c) Department of Public Health Sciences, University of California Davis

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ABSTRACT

Introduction: Higher education predicts better late-life cognition among older adults, but mechanisms are poorly understood. We examined whether education modified the pathway between vascular injury and late-life cognition.

Methods: Analyses pooled imaging data from the multiethnic Kaiser Healthy Aging and Diverse Life Experience Study (KHANDLE; n=327) and the Study of Healthy Aging in African Americans (STAR; n=226), two parallel studies of older adult long-term Kaiser Permanente members, with up to 3 waves of cognitive measures. Self-reported education was considered as continuous years of completed education. White matter hyperintensities (WMH) were obtained through 3T MRI. Cerebral WMH volume was log-transformed and regressed on total cerebral volume. Cognitive domains of verbal episodic memory (VRMEM) and executive function (EF) were measured using the Spanish and English Neuropsychological Assessment Scales (SENAS) and z-standardized. Domain-stratified regression models examined (1) independent effect of WMH adjusting for education, and (2) effect modification by education on the relationship between WMH and cognition. All models were adjusted for age, race/ethnicity, gender, and study.

Results: Participants were on average 75.2 years of age and had 14.7 years of education, with 60.4% of the sample identifying as female and 52.8% of the sample identifying as Black. WMH volume was associated with late-life cognition (β: -0.064; 95% CI: -0.097, -0.031; p=<.01) and cognitive decline (β for 1 year increase in age and 1 unit increase in WMH: -0.004, 95% CI: -0.008, -0.001; p=0.02). The association between WMH and cognition (interaction p=0.97) or cognitive decline (interaction p=0.92) did not appear to differ meaningfully by education.

Conclusion: Cognitive reserve did not appear to be beneficial for the effects of brain pathology on late-life cognition in a diverse sample of community dwelling older adults.

INTRODUCTION

Higher educational attainment is consistently associated with improved late-life cognitive functioning and a lower risk of dementia (1–3). Fewer studies have investigated the mechanisms through which education may influence cognition, and the extent to which protective effects arise from increased socioeconomic resources versus biologic pathways remains unclear.

One proposed biologic pathway for the protective effect of education on late-life cognition is the concept of cognitive reserve (4,5). Cognitive reserve theory hypothesizes that the brain uses cognitive processing adaptations accumulated throughout the lifecourse to compensate for brain damage, allowing an individual with higher education to maintain cognitive performance despite accumulation of detrimental brain pathology (4,6–8). These coping mechanisms arguably lead to individual differences in susceptibility to age-related brain changes, with education attenuating the effects of brain pathology on cognition. A number of studies have recently found support for this hypothesis, demonstrating that brain pathology in the form of white matter hyperintensities has a weaker effect on cognition among individuals with higher levels of education (9–17). However these studies were conducted in selected samples, and may not be generalizable to other geographic locations or racial/ethnic groups.

The purpose of the current study was therefore to build upon previous findings of a cognitive reserve pathway in a racially/ethnically diverse sample of older adults from Northern California. We aimed to (1) quantify the contribution of brain vascular injury, measured as WMH, to late-life cognition in a racially/ethnically diverse sample of older adults, and (2) assess whether education plays a role in the relationship between WMH and late-life cognition. We hypothesized that the relationship between WMH and cognition would be weaker among those with higher levels of education, as a result of higher educated individuals having higher levels of cognitive reserve.

METHODS

Study Population

The study sample consisted of two pooled studies consisting of long-term members of an integrated health care delivery system in Northern California: the Kaiser Health Aging and Diverse Life Experiences Study (KHANDLE) and the Study of Healthy Aging in African Americans (STAR). KHANDLE and STAR are related studies of aging in older adults, with KHANDLE aiming to investigate lifecourse influences on racial/ethnic differences in cognitive aging and STAR expanding on KHANDLE surveys to further characterize the distinct lifecourse experience of current older Black Americans. To be eligible for both studies, participants were free of dementia diagnosis at baseline and participated in the Kaiser Permanente Multiphasic Health Checkup (MHC) exams between 1964 and 1985). KHANDLE participants were recruited from current Kaiser Permanente Northern California (KPNC) members over the age of 65 on January 1, 2017, through stratified random sampling to recruit approximately equal proportions of participants across major racial/ethnic groups (Asian, Black, Latino, White) and levels of education, for a baseline sample of 1,712 individuals. STAR participants were recruited from current KPNC members who self-identified as Black and were over the age of 50 on January 1, 2018, through stratified random sampling to recruit approximately equal proportions of participants across levels of education, for a baseline sample of 764 individuals. KHANDLE and STAR participants were followed annually with up to three waves of data included in the present study. A random subset of KHANDLE and STAR participants were selected to undergo brain imaging at the University of California Davis (completed KHANDLE n=331, STAR n=230). Participants were further excluded if missing education (n=0), WMH measures (KHANDLE n=2, STAR n=1), any study covariates (STAR n=1), or all cognitive assessments (KHANDLE n=2, STAR=2) for a final analytic sample of 553 individuals with brain imaging (KHANDLE n=327, STAR n=226).

Education

Education was self-reported at baseline as years attained if less than a high school degree was obtained, and as highest level of degree attainment if the participant completed schooling past the completion of high school (some college, associate degree, bachelor's degree, master's degree, or doctoral degree). Completion of the general education diploma (GED; n=46) or high school diploma and/or certifications were also obtained. For sensitivity analyses, education was further dichotomized with low defined as high school degree attainment or less versus high including any post-secondary schooling. Years of attained education was also examined, and was calculated based on the average number of years to complete each degree, with some college or an associate degree assigned a value of 14 years, a bachelor's degree assigned a value of 16 years, and any graduate education assigned a value of 18 years. Individuals completing formal training lasting greater than six months and resulting in a certificate were given an extra additional year of education.

Magnetic Resonance Imaging (MRI)

Magnetic resonance images were obtained in a 3T Siemens Tim Trio in the Imaging Research Center (IRC) at the UC Davis Medical Center in Sacramento, CA. The following established sequences for neuronal injury were gathered with a 32-channel phased-array head coil: (1) fluid attenuated inverse recovery (FLAIR) T2-weighted images (TR=8,000 ms, TE=98 ms, TI=2,200 ms, 320x320 pixels per slice, 48 slices, voxel size: 0.8Ã~0.8 Ã~2.0 mm); (2) high-angular-resolution diffusion spectrum MRI (DSI) images (TR=7,600 ms, TE=88 ms, B value = 1,000, 128x128 voxels per slice, 60 slices, 64 gradient directions, voxel size: 2.0Ã~2.0 Ã~2.0mm); and (3) magnetization-prepared rapid acquisition gradient echo (MPRAGE) T1-weighted images (TR=2,000 ms, TE=2.88 ms, TI=1,100 ms, 256x256 pixels per slice, 208 slices, voxel size: 1.0Ã~1.0 Ã~1.0 mm). Total cerebrum and WMH volumes were derived through procedures that have previously been published in detail elsewhere (18,19). WMH volumes were heavily right-skewed and were log-transformed. Log-transformed

WMH was subsequently regressed on total cerebral volume, and the residual was used as a measure of WMH adjusted for total cerebral volume.

SENAS Cognition

Cognitive domains of verbal episodic memory and executive functioning were obtained using the Spanish and English Neuropsychological Assessment Scales (SENAS), which was given to all participants at each visit in their preferred language (English or Spanish). The SENAS is a battery of cognitive tests that has previously undergone extensive development for valid comparisons of cognitive change across racial/ethnic and linguistically diverse groups. Eighteen Verbal episodic memory composite scores were derived from a multitrial 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 (20,21). All cognitive measurements were z-standardized using the domain-specific full sample mean and standard deviation at baseline. Because semantic memory was not collected in follow-up waves conducted as telephone visits instead of in-person due to COVID-19, semantic memory scores were not considered in analyses. Study cohort-specific practice effects were imposed as offsets in statistical analyses.

Covariates

Age was ascertained as the time between each visit date and participant DOB from electronic medical records. Participants self-reported race/ethnicity, sex/gender, place of birth, and parental education in baseline surveys. For race/ethnicity, participants self-reported any of 24 racial/ethnic identities with the additional option of an open field write-in category. Participants reporting multiple racial/ethnic identities across multiple major classifications (Asian, Black, Latino, Native

American, White) were additionally classified as multiracial. Sex/gender was considered as a binary variable. Place of birth was reported as US state or foreign country, and was subsequently categorized as US census geographic region (Midwest, Northeast, South, West) or foreign born. Parental education was reported separately as mother's and father's education using the same reporting format as participant education and was considered as >8th grade versus 8th grade or less. Based on previous investigations into this measure in this population that found consistently good model fit with the inclusion of missing values in the low education category, unknown or missing parental education was included in the 8th grade or less category (22).

Statistical Analysis

Linear mixed-effects regression models were used to estimate the effects of WMH on cognition and cognitive decline. Models first regressed WMH on education to explore the possibility of a mediating pathway through WMH for education and cognition. The initial model then evaluated whether WMH and education had independent effects on cognition with subsequent models adding interaction terms between WMH and education to test the hypothesis that education may modify the relationship between WMH and cognition, defined as the presence of multiplicative interaction.

Cognition was considered in separate models as (A) overall cognition over all study follow-up waves, and as (B) cognitive decline through the inclusion of separate interaction terms between WMH, education, and WMH by education with visit age. Primary models examined cognition as composite cognition, treating each z-scored cognitive domain (verbal episodic memory, executive functioning) as a clustered but distinct outcome for a possibility of up to six outcome measures for each participant (two domains per wave in up to three waves). Models included categorical, unordered indicators for cognitive domain type. We also quantified whether there were significant differences for the relationship between education, WMH, and cognition across cognitive domains, and present secondary results stratified by domain. All models were fully adjusted for covariates.

Models also included random intercepts to account for within-person correlation between cognitive domains in primary models examining composite cognition and across study visits for cognitive decline models. Sensitivity analyses were additionally conducted to obtain effect estimates for WMH on cognition in participants with low education and with high education in stratified models. Analyses were conducted in SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Table 3.1 summarizes characteristics of KHANDLE and STAR participants included in analyses. The average age at baseline was 75.2 ± 6.1 years with an average of 1.5 visits (± 0.5). The majority of the sample was female (60.4%) and approximately half of the sample reported Black race/ethnicity (52.8%). Participants had on average 14.8 ± 2.6 years of education, with almost half (47.2%) having at least a bachelor's degree. The most common place of birth was the US West region (51.0%), followed by the US South (24.4%) and birth in a country outside of the US (13.4%). STAR participants were on average older, more likely to be female, were less likely to have at least a bachelor's degree, and less likely to be born outside of the US. Baseline cognitive scores and white matter hyperintensity volume also differed significantly across studies. Associations between levels of education and WMH were small and not clinically significant compared to the referent group of HS or less (some college β=0.002, 95% CI: -0.385, 0.390, p=0.99; associate's β=-0.015, 95% CI: -0.478, 0.447, p=0.95; bachelor's β=0.017, 95% CI: -0.379, 0.412, p=0.93; graduate school β=-0.017, 95% CI: -0.428, 0.395, p=0.94; overall F-test for interaction p=0.99) and therefore mediation of the relationship between education and cognition through WMH was not considered as a potential pathway.

Table 3.1: Baseline demographic characteristics of STAR and KHANDLE participants

	Overall		KHANDLE		STAR		P-value*
	N=553		n=327		n=226		
	N/ Mean	%/ SD	N/ Mean	%/ SD	N/ Mean	%/ SD	
Baseline age (years)	72.00	8.03	75.15	6.06	67.43	8.35	<.01
Average visits (#)	1.98	0.82	1.98	0.82	1.97	0.82	0.77
Sex/Gender (n/%)							<.01
Female	334	60.4	179	54.74	155	68.58	
Male	219	39.6	148	45.26	71	31.42	
Race/Ethnicity (n/%)							<.01
Asian	77	13.92	77	23.55	0	0	
Black	292	52.8	66	20.18	226	100	
Latino	91	16.46	91	27.83	0	0	
White	93	16.82	93	28.44	0	0	
Multi-race/ethnicity (n/%)	32	5.79	25	7.65	7	3.1	<.01
Education (years)							<.01
HS or less	90	16.27	58	17.74	32	14.16	
Some college	137	24.77	68	20.80	69	30.53	
Associate degree	65	11.75	35	10.70	30	13.27	
Bachelor's degree	142	25.68	92	28.13	50	22.12	
Graduate degree	119	21.52	74	22.63	45	19.91	
High maternal education (n/%)	186	33.63	130	39.76	56	24.78	<.01
High paternal education (n/%)	218	39.42	132	40.37	86	38.05	0.34
Birth region (n/%)							<.01
Midwest	40	7.23	22	6.73	18	7.96	
Northeast	22	3.98	15	4.59	7	3.10	
South	135	24.41	54	16.51	81	35.84	
West	282	50.99	166	50.76	116	51.33	
Non-US born	74	13.38	70	21.41	4	1.77	
WMH (unadjusted)	0.01	1.41	0.01	1.85	0.01	1.60	<.01
Baseline cognition scores							
Verbal episodic memory	0.23	0.85	0.43	0.87	0.32	0.86	<.01
Executive function	0.35	0.72	0.42	0.63	0.38	0.68	<.01

Continuous variables are presented as mean and SD; categorical variables are presented as count and percent. P-values indicate comparisons between KHANDLE study participants and STAR study participants.

Table 3.2 shows associations between education and WMH with composite cognition. WMH and education were independently associated with cognitive performance. Each unit increase in WMH was associated with a decrease in cognitive performance of -0.064 (95% CI: -0.097, -0.031) SD, independent of education. Considering a HS degree or less as the referent group, those attending some college had higher cognitive performance scores of 0.208 (95% CI: 0.055, 0.361) SD, those with an associate's degree had higher scores of 0.245 (95% CI: 0.061, 0.429) SD, those with a bachelor's degree had higher scores of 0.394 (95% CI: 0.238, 0.551) SD, and those with any graduate degree had higher scores of 0.595 (95% CI: 0.432, 0.758) SD. In models considering cognitive decline, WMH was also associated with cognitive decline independently of education, with each increase in WMH being associated with a cognitive decline of -0.004 (95% CI: -0.007, -0.001) SD per additional year of age. Education was not associated with cognitive decline, therefore models for cognitive decline presented exclude the interaction between education and white matter hyperintensities. The association between WMH and cognition (interaction p=0.97) or cognitive decline (interaction p=0.92) did not appear to differ meaningfully by education.

Table 3.2: Associations between WMH and education with composite cognition in models for (A) cognitive performance and (B) cognitive decline.

	Est	CI		P-value	Est	CI		P-value
		Lower	Upper			Lower	Upper	
Models for cognitive performance and cognitive decline estimating independent effects of WMH and education								
	A. Cognitive performance model				***B. Cognitive decline model***			
WMH	-0.064	-0.097	-0.031	0.01	0.228	-0.012	0.468	0.06
Education				<.01*				<.01*
Some college	0.208	0.055	0.361	0.01	0.217	0.063	0.370	0.01
Associate's	0.245	0.061	0.429	0.01	0.257	0.073	0.441	0.01
Bachelor's	0.394	0.238	0.551	<.01	0.397	0.241	0.553	<.01
Graduate school	0.595	0.432	0.758	<.01	0.601	0.438	0.764	<.01
Age	-0.034	-0.041	-0.026	<.01	-0.032	-0.040	-0.025	<.01
WMH x AGE	-	-	-	-	-0.004	-0.008	-0.001	0.02
Models for cognitive performance and cognitive decline testing for multiplicative interaction between WMH and education*								
	A. Cognitive performance model				***B. Cognitive decline model***			
WMH	-0.087	-0.166	-0.008	0.03	0.105	-0.556	0.766	0.75
Education				<.01*				<.01*
Some college	0.199	0.043	0.355	0.01	-1.680	-3.135	-0.225	0.02
Associate's	0.236	0.050	0.423	0.01	-0.861	-2.659	0.937	0.35
Bachelor's	0.385	0.226	0.544	<.01	-0.563	-2.000	0.875	0.44
Graduate school	0.586	0.420	0.752	<.01	0.539	-0.999	2.076	0.49
WMH x EDU				0.97*				0.92*
Some college	0.033	-0.063	0.130	0.50	0.061	-0.740	0.862	0.88
Associate's	0.034	-0.090	0.159	0.59	0.361	-0.631	1.353	0.48
Bachelor's	0.021	-0.074	0.116	0.66	0.232	-0.586	1.051	0.58
Graduate school	0.026	-0.075	0.128	0.61	0.025	-0.824	0.874	0.95
Age	-0.034	-0.041	-0.026	<.01	-0.044	-0.059	-0.028	<.01
WMH x AGE	-	-	-	-	-0.002	-0.011	0.006	0.59
Age x EDU								0.04*
Some college	-	-	-	-	0.026	0.006	0.045	0.01
Associate's	-	-	-	-	0.015	-0.009	0.040	0.22
Bachelor's	-	-	-	-	0.013	-0.006	0.032	0.19
Graduate school	-	-	-	-	0.000	-0.020	0.021	0.98
Age x WMH x EDU								0.91*
Some college	-	-	-	-	-0.001	-0.012	0.009	0.81
Associate's	-	-	-	-	-0.005	-0.019	0.008	0.46
Bachelor's	-	-	-	-	-0.003	-0.014	0.008	0.54
Graduate school	-	-	-	-	0.000	-0.012	0.011	0.99

*Starred P-values represent the overall F-test for the relationship between categorical variables and cognition.

The effects of WMH differed across cognitive domains in primary models (p<.01 for both cognitive performance and cognitive decline), and models showing cognitive domain-stratified analyses for the relationship between education and WMH with cognition are shown in Table 3.3 for verbal episodic memory and Table 3.4 for executive functioning. In domain-specific analyses, WMH and education were independently associated with cognitive performance across both cognitive domains. The effects of WMH were similar across cognitive domains, with each unit increase in WMH being associated with a 0.109 (95% CI: -0.154, -0.064, p=<.01) SD lower average verbal episodic memory compared a lower average executive functioning by 0.092 (95% CI: -0.130, -0.053, p=0.01) SD,, independently of education. Education was also associated with both verbal episodic memory (p=<.01) and executive functioning (p<0.01), independently of WMH. However unlike in models pooled across cognitive domains, WMH did not appear to have an association with decline for verbal episodic memory (0.000, 95% CI: -0.001, 0.001, p=0.69) or executive functioning (0.000, 95% CI: -0.001, 0.001, p=0.59).

In models assessing for cognitive performance, education did not appear to significantly modify the relationship between WMH and verbal episodic memory (some college β=-0.023, 95% CI: -0.168, 0.123, p=0.76; associate's β=0.009, 95% CI: -0.178, 0.196, p=0.93; bachelor's β=-0.009, 95% CI: -0.152, 0.135, p=0.91 graduate school β=-0.035, 95% CI: -0.187, 0.118, p=0.66; overall F-test for interaction p=0.98) or the relationship between WMH and executive functioning (some college β=0.058, 95% CI: -0.066, 0.182, p=0.36; associate's β=0.067, 95% CI: -0.092, 0.226, p=0.41; bachelor's β=0.073, 95% CI: -0.049, 0.195, p=0.24 graduate school β=0.046, 95% CI: -0.085, 0.176, p=0.49; overall F-test for interaction p=0.83). In models assessing for cognitive decline, education also did not appear to significantly modify the relationship of WMH and age on verbal episodic memory (Table 3.3) or executive function (Table 3.4).

Table 3.3: Associations between WMH and education with verbal episodic memory in models for (A) cognitive performance and (B) cognitive decline.

	Est	CI		P-value	Est	CI		P-value
		Lower	Upper			Lower	Upper	
Models for cognitive performance and cognitive decline estimating independent effects of WMH and education								
	A. Cognitive performance model				***B. Cognitive decline model***			
WMH	-0.109	-0.154	-0.064	<.01	-0.098	-0.168	-0.027	0.01
Education								
Some college	0.321	0.089	0.553	0.01	0.321	0.090	0.553	0.01
Associate's	0.316	0.039	0.593	0.03	0.317	0.040	0.594	0.03
Bachelor's	0.418	0.182	0.653	<.01	0.418	0.182	0.653	<.01
Graduate school	0.545	0.299	0.792	<.01	0.546	0.299	0.792	<.01
Age	-0.020	-0.022	-0.019	<.01	-0.020	-0.022	-0.019	<.01
WMH x AGE	-	-	-	-	0.000	-0.001	0.001	0.68
Models for cognitive performance and cognitive decline testing for multiplicative interaction between WMH and education*								
	A. Cognitive performance model				***B. Cognitive decline model***			
WMH	-0.094	-0.212	0.024	0.12	-0.229	-0.425	-0.032	0.02
Education								
Some college	0.326	0.090	0.562	0.01	-0.088	-0.460	0.284	0.64
Associate's	0.323	0.043	0.604	0.02	0.030	-0.425	0.486	0.90
Bachelor's	0.423	0.184	0.663	0.00	0.267	-0.101	0.636	0.15
Graduate school	0.551	0.301	0.801	<.01	0.393	0.008	0.778	0.05
WMH x EDU				0.98				0.40
Some college	-0.023	-0.168	0.123	0.76	0.133	-0.106	0.373	0.28
Associate's	0.009	-0.178	0.196	0.93	0.320	-0.001	0.641	0.05
Bachelor's	-0.009	-0.152	0.135	0.91	0.108	-0.123	0.339	0.36
Graduate school	-0.035	-0.187	0.118	0.66	0.175	-0.074	0.425	0.17
Age	-0.020	-0.022	-0.019	<.01	-0.023	-0.026	-0.020	<.01
WMH x AGE	-	-	-	-	0.002	0.000	0.004	0.09
Age x EDU								0.04
Some college	-	-	-	-	0.006	0.002	0.010	0.00
Associate's	-	-	-	-	0.004	-0.001	0.009	0.09
Bachelor's	-	-	-	-	0.002	-0.002	0.006	0.28
Graduate school	-	-	-	-	0.002	-0.002	0.006	0.28
Age x WMH x EDU								0.11
Some college	-	-	-	-	-0.002	-0.005	0.000	0.09
Associate's	-	-	-	-	-0.004	-0.008	-0.001	0.02
Bachelor's	-	-	-	-	-0.002	-0.004	0.001	0.22
Graduate school	-	-	-	-	-0.003	-0.006	0.000	0.04

*Starred P-values represent the overall F-test for the relationship between categorical variables and cognition.

Table 3.4: Associations between WMH and education with executive functioning in models for (A) cognitive performance and (B) cognitive decline.

	Est	CI		P-value	Est	CI		P-value
		Lower	Upper			Lower	Upper	
Models for cognitive performance and cognitive decline estimating independent effects of WMH and education								
	A. Cognitive performance model				***B. Cognitive decline model***			
WMH	-0.092	-0.130	-0.053	<.01	-0.077	-0.143	-0.011	0.02
Education				<.01*				<.01*
Some college	0.232	0.034	0.430	0.02	0.232	0.034	0.430	0.02
Associate's	0.226	-0.011	0.462	0.06	0.226	-0.010	0.463	0.06
Bachelor's	0.539	0.338	0.741	<.01	0.539	0.338	0.740	<.01
Graduate school	0.823	0.613	1.033	<.00	0.823	0.613	1.033	<.01
Age	-0.020	-0.022	-0.019	<.01	-0.020	-0.022	-0.019	<.01
WMH x AGE	-0.092	-0.130	-0.053	<.01	0.000	-0.001	0.001	0.59
Models for cognitive performance and cognitive decline testing for multiplicative interaction between WMH and education*								
	A. Cognitive performance model				***B. Cognitive decline model***			
WMH	-0.144	-0.245	-0.044	0.01	-0.247	-0.433	-0.061	0.01
Education				<.01*				<.01*
Some college	0.213	0.012	0.414	0.04	-0.189	-0.540	0.161	0.29
Associate's	0.208	-0.031	0.447	0.09	-0.055	-0.486	0.375	0.80
Bachelor's	0.523	0.319	0.727	<.01	0.393	0.046	0.739	0.03
Graduate school	0.805	0.591	1.018	<.01	0.676	0.314	1.038	0.00
WMH x EDU				0.83*				0.35*
Some college	0.058	-0.066	0.182	0.36	0.186	-0.041	0.413	0.11
Associate's	0.067	-0.092	0.226	0.41	0.337	0.032	0.642	0.03
Bachelor's	0.073	-0.049	0.195	0.24	0.158	-0.060	0.376	0.15
Graduate school	0.046	-0.085	0.176	0.49	0.215	-0.021	0.450	0.07
Age	-0.020	-0.022	-0.019	<.01	-0.023	-0.026	-0.020	<.01
WMH x AGE	-	-	-	-	0.001	-0.001	0.003	0.19
Age x EDU								0.04*
Some college	-	-	-	-	0.006	0.002	0.009	0.01
Associate's	-	-	-	-	0.004	-0.001	0.009	0.13
Bachelor's	-	-	-	-	0.002	-0.002	0.005	0.37
Graduate school	-	-	-	-	0.002	-0.002	0.006	0.38
Age x WMH x EDU								0.21*
Some college	-	-	-	-	-0.002	-0.004	0.001	0.16
Associate's	-	-	-	-	-0.004	-0.007	0.000	0.04
Bachelor's	-	-	-	-	-0.001	-0.004	0.001	0.37
Graduate school	-	-	-	-	-0.002	-0.005	0.000	0.09

*Starred P-values represent the overall F-test for the relationship between categorical variables and cognition.

Sensitivity analyses estimating the relationship between WMH and cognition in education-stratified models are presented in Table S3.1, treating education as a binary measure of a high school degree or less versus any formal education past a high school degree. Among both strata of education, each unit increase in WMH was similarly associated with approximately a 0.07 SD lower average cognition (low education β=-0.070, 95% CI: -0.16, 0.02, p=0.11; high education β=-0.065, 95% CI: -0.10, -0.03, p=<.01). In models assessing decline among those with low education, there was no meaningful association between WMH and cognitive decline (β=-0.001; 95% CI: -0.010, 0.007, p=0.74). The relationship was slightly larger among those with high education, with each increase in WMH associated with a decline of -0.004 (95% CI: -0.009, -0.001, p=0.02) SD per year, or a decline of approximately -0.04 SD per decade of decline.

DISCUSSION

This study examined whether education had a modifying effect on the relationship between white matter hyperintensities and late-life cognition in a racially/ethnically diverse sample of adults from Northern California. As hypothesized, white matter hyperintensities and education were consistently associated with late-life cognition and cognitive decline for both verbal episodic memory and executive functioning, independent of one another. However, we did not detect any statistically significant multiplicative interaction between education and WMH in relation to cognition, suggesting that any educational differences on the relationship between WMH and cognition in our sample were likely not meaningful indicators of reserve.

The concept of reserve in relation to the aging brain can be classified as two forms: brain (passive) reserve and cognitive (active) reserve. Brain reserve posits that benefits come from the physical structure of the brain, and that having more of this "hardware" allows the brain to sustain higher levels of damage until clinical expressions of symptoms emerge. This model assumes that there is some distinct threshold of brain damage below which clinical impairment is inevitable, and

is hypothesized to arise from early-life developmental environments (11). In contrast, cognitive reserve models posit that the brain actively adapts to physical damage by relying on pre-existing processes or enlisting compensatory processes, similar to updating of software. Cognitive reserve suggests that two individuals may have the same level of brain damage from disease, but the individual with higher cognitive reserve may be able to sustain more damage before the presentation of clinical impairment compared to the individual with lower cognitive reserve. As a result, there is no assumption of a fixed cutoff or threshold at which functional impairment occurs, and between-person differences are instead the result of individual ability to maintain function for longer amidst the presence of damage (4,5,8). For this study, we examined cognitive reserve due to its strong theorized relationship to education and subsequent cognitively stimulating environments, though it is important to note that definitions of reserve differ across prior studies and education is sometimes considered a predictor of brain reserve as well (23). Additionally, we used a measure of white matter hyperintensities adjusted for cerebral volume to account for some of the interpersonal difference in physical brain reserve, though this was inadequate in fully controlling for the effects of brain reserve.

There are several analytic approaches used to study cognitive reserve. One proposed method is the use of a residualized measure of cognitive reserve, in which cognitive reserve is analyzed as a reserve index. Using the residualization method, cognitive reserve is considered as the residual variance in cognition remaining after adjusting for one or more factors of brain pathology and demographic characteristics, or the difference between observed cognitive function and expected cognitive function based on physical brain and demographic variables. This method has been suggested as a promising approach to decomposing variance in cognitive test scores across pathological and demographic characteristics (24–26). However, this approach may also be influenced by regression to the mean, especially in small samples that may not fully approximate the true relationship. Furthermore, simulations show that this reserve index is likely to be highly collinear with the dependent cognition variable, and may reflect the relationship between the

physical brain characteristic and cognition rather than underlying resilience (27). More commonly used is an effect modification model, which includes an interaction term between the cognitive reserve measure (often education) and third measure, in this case WMH as a measure of vascular brain injury (28). This interaction approach retains the main effects of the resilience factor and brain characteristics unlike with the residualization approach, though as with the residualization approach, interpretation of results is limited to group-level interpretations that may not be translatable to use in clinical settings (27).

A number of previous studies have found evidence for the cognitive reserve hypothesis using the interaction method (29), with WMH having a larger association with cognition among individuals of lower educational attainment compared to individuals of higher educational attainment (9–14,16). Our results finding no evidence supporting the cognitive reserve hypothesis were consistent with one recent study. However it is important to note that this study looked at a composite cognitive reserve score that included other factors in addition to education across multiple countries, and included younger participants with an age range of 35-81 years (15), whereas the present study included adults over the age of 50 from a small regional area of Northern California and looked only at education as a predictor of resilience.

One potential reason for inconsistencies in findings between the present investigation and other studies could be differences in cognitive testing. KHANDLE and STAR both use the SENAS, which has been extensively developed and validated for use across languages, ages, and education (20,21,30). Several of the previously conducted studies used MMSE as their outcome of interest (9,12,16), which has been previously shown to have ceiling effects for cognitively normal individuals or at higher levels of education (31,32). As a result, further research is needed to determine whether the lower association between WMH and cognition at higher levels of cognition may arise from a lack of variance in cognition captured within this group. However this alone does not explain our contradictory findings as several other studies used a full neuropsychological battery comparable to

the SENAS (10,11), and one study finding evidence for the cognitive reserve hypothesis considered incident cognitive impairment and dementia as their outcome of interest (13).

This study had several limitations and strengths. Due to inadequate sample sizes, many of our results were largely imprecise and caution should be taken in their interpretation; across strata of education and covariates, we were unable to compare racial/ethnic differences in the present study. However, the community-based racial/ethnic representation in this sample remains a major strength, as many studies of US older adults include primarily White participants and are often highly selected samples from medical settings. KHANDLE and STAR participants were also recruited from long-term members of Kaiser Permanente Northern California, and our findings may not be generalizable to other geographic groups. Conversely, this long-term managed care organization membership is a strength for internal validity of our findings, as it can be assumed that all individuals in our study had approximately equal access to healthcare for a large portion of their adult lives.

In conclusion, we found that although both education and WMH were independently associated with late-life cognition, any differences by education on the association between WMH and cognition were not clinically significant indicators of cognitive reserve benefits in this sample of racially/ethnically diverse older adults with representation at all levels of education. Further research is needed to explore whether these findings are generalizable to other populations and possible explanations for the contradiction of our findings to previous studies, as well as further investigations into the possible role of brain reserve and structure for cognitive health in older adults.

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Table S3.1. Associations between WMH and cognition, stratified by low vs. high education (defined as a high school degree or less versus any education past high school)

	Est	CI		P-value	Est	CI		P-value
		Lower	Upper			Lower	Upper	
Low education (HS degree or less)								
	A. Cognitive performance				**B. Cognitive decline**			
WMH	-0.070	-0.156	0.017	0.11	0.043	-0.624	0.710	0.90
Age	-0.044	-0.061	-0.027	<.01	-0.044	-0.061	-0.027	<.01
WMH x AGE					-0.001	-0.010	0.007	0.74
High education (any > HS)								
	A. Cognitive performance				**B. Cognitive decline**			
WMH	-0.065	-0.102	-0.029	<.01	0.265	-0.009	0.539	0.06
Age	-0.032	-0.040	-0.024	<.01	-0.030	-0.038	-0.022	<.01
WMH x AGE					-0.005	-0.009	-0.001	0.02

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