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RESEARCH ARTICLE

Higher literacy is associated with better white matter integrity and cognition in middle age

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Abstract

Introduction: Literacy can be a better measure of quality of education. Its association with brain health in midlife has not been thoroughly investigated.

Methods: We studied, cross-sectionally, 616 middle-aged adults (mean age of 55.1 ± 3.6 years, 53% female and 38% Black) from the Coronary Artery Risk Development in Young Adults (CARDIA) study. We correlated literacy with cognitive tests, gray matter volumes, and fractional anisotropy (FA) values (indirect measures of white matter integrity) using linear regression.

Results: The higher-literacy group ($n = 499$) performed better than the low-literacy group ($n = 117$) on all cognitive tests. There was no association between literacy and gray matter volumes. The higher-literacy group had greater total-brain FA and higher temporal, parietal, and occipital FA values after multivariable adjustments.

Discussion: Higher literacy is associated with higher white matter integrity as well as with better cognitive performance in middle-aged adults. These results highlight the importance of focusing on midlife interventions to improve literacy skills.

KEYWORDS

CARDIA study, cognitive reserve, literacy, white matter integrity

1 | INTRODUCTION

Dementia affects 50 million people worldwide¹ and with demographic shifts, this number is projected to increase 4-fold in the next 30 years.² Growing evidence suggests that modifiable risk factors account for up to one third of dementia cases.^{3–6} Low education level is one of those risk factors with many studies reporting that higher education is associated with a lower risk of developing dementia in older adults.^{7–11}

Cognitive reserve is the theory used to explain why higher educational level seems to be protective against the development of

dementia symptoms.¹² Although years of education has been extensively used as a proxy of cognitive reserve, other proxies such as literacy, measured using reading abilities, has been underexplored. Literacy may be a better proxy than years of education, because it can reflect the quality of formal education received interacted with innate characteristics such as genetics. Many studies have explored the underlying mechanism by which greater cognitive reserve measured by years of formal education may protect against dementia symptoms.^{13–19} However, the associations between literacy, measured through a reading ability test, and brain health outcomes have not been

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RESEARCH IN CONTEXT

- 1. Systematic Review:** The authors reviewed the literature using traditional (e.g., PubMed) sources. Education, occupation, and cognitively stimulating leisure activities have been positively associated with brain structure, cognitive function, and lower risk of dementia in older adults. These relevant studies are appropriately cited. Literacy, a better measure of quality of education, has not been thoroughly investigated regarding brain health outcomes, especially in midlife.
- 2. Interpretation:** Our findings call attention to another potential measurement of cognitive reserve beyond years of formal education. Literacy measured by reading abilities was associated with better cognitive function and higher white matter integrity in midlife. Midlife may be an important window of opportunity for dementia-preventive interventions based on literacy learning.
- 3. Future Directions:** Our research was cross-sectional and could not rule out reverse causality. Therefore, longitudinal studies are needed to confirm the hypothesis that higher literacy levels might protect against the development of dementia symptoms.

thoroughly investigated. Furthermore, whether those mechanisms are present as early as in midlife is unknown. It is important to understand the literacy-related protective mechanisms and when they occur in the life course to develop tailored dementia-preventive strategies to increase the chances of success.

In the present study, we aimed to determine whether literacy is associated with cognitive function and brain structure in midlife. We hypothesized that higher literacy would be associated with better scores on cognitive tests and larger gray matter volumes, as well as with greater white matter integrity.

2 | METHODS

2.1 | Participants

We studied participants from the Coronary Artery Risk Development in Young Adults (CARDIA) study, a multisite, community-based prospective cohort study of 5115 Black and White adults, initially aged 18–30 years old and healthy at baseline (1985–1986). Participants were recruited from four US cities (Birmingham, Alabama; Oakland, California, Chicago, Illinois; and Minneapolis, Minnesota) by random-digit dialing from total communities or specific census tracts, except for Oakland, where participants were randomly selected from a health-care plan. Although there were no specific eligibility criteria, the participant composition at each site was approximately balanced at each site by age, race, sex, and education.^{20,21} CARDIA participants have been followed prospectively every 2 to 5 years.

At baseline, participants mean age was 24.8 (\pm 3.7) years and 48.4% were White. At the year 30 visit, a total of 3358 participants remained in the CARDIA study. Attrition was more common among men, Black participants, and those with a lower level of education (Table S1 in supporting information).²² A subset of individuals ($n = 663$) participated in the CARDIA Brain MRI Substudy, which was conducted at three of the sites (Birmingham, Oakland, and Minneapolis).²³ We restricted our analytic cohort to participants who completed neuroimaging and excluded 24 individuals because of magnetic resonance imaging (MRI) artifacts for a total of 639. Twenty-three more individuals were excluded because of missing data on the cognitive and literacy assessments for a total of 616 individuals.

Compared to the other CARDIA participants, those in the MRI study were similar in age, years of education, and on literacy level. However, they were more likely to be White and male and less likely to have comorbidities (Table S2 in supporting information).

2.2 | Standard protocol approvals, registrations, and patient consents

The CARDIA study was approved by institutional review boards at study sites and at the CARDIA coordinating center and was conducted per the Declaration of Helsinki principles. Participants provided written informed consent at each CARDIA visit, and CARDIA Brain MRI participants provided written informed consent separately from the main study.

2.3 | Demographic and clinical characteristics

At the first CARDIA visit, age, sex, race, and years of education were self-reported. Throughout the other visits, the following variables were measured: hypertension, diabetes, and hypercholesterolemia were determined via a combination of self-report, clinic assessments, laboratory data, and medication use; obesity was defined as a body mass index equal or greater than 30 kg/m². Physical activity was measured with a scale based upon self-report of weekly activities with higher scores indicating more intense physical exercise in exercise units, where 300 exercise units is equivalent to national guidelines recommending 30 minutes of moderate physical activity for 5 days per week.²⁴ Current cigarette smoking was based on self-reported definition of smoking at least five cigarettes per week almost every week. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale (score 16 or greater suggesting dysthymia during the past week in general populations).²⁵ For our analysis, we used these measures assessed at year 30. Apolipoprotein E (APOE) genotype was determined using standard methods and coded as $\epsilon 4$ yes or no.^{26,27}

2.4 | Literacy assessment

The Rapid Estimate of Adult Literacy in Medicine–Short Form (REALM-SF) was used to measure literacy at year 30. The test consists of asking

the participant to read aloud seven words related to health: “behavior,” “exercise,” “menopause,” “rectal,” “antibiotics,” “anemia,” and “jaundice.” The score ranges from 0 to 7, based on the participant’s ability to read the word correctly. This test has been validated as a literacy measurement²⁸ and has good correlation with the test’s longer 66-word version.²⁹ According to the norms previously published, the cut-off score of 7 defines high literacy.²⁹ Previous work also showed a correspondence between high literacy defined by the score of 7 and health outcomes such as fewer visits to emergency departments³⁰ and better reproductive health.³¹

2.5 | Cognitive evaluation

At year 30, participants completed six cognitive tests. Global cognition was assessed with the Montreal Cognitive Assessment (MoCA).³² Episodic memory was assessed with the delayed recall task of the Rey Auditory Verbal Learning Test (RAVLT),³³ a word list task. Executive functioning was assessed with the Digit Symbol Substitution Test (DSST),³⁴ a measure of processing speed and the Stroop test,³⁵ a measure of interference and the letter fluency, which assesses lexical retrieving ability.³⁶ Language was evaluated with the categorical and phonemic verbal fluency, which assess the ability to generate words within a specific semantic and phonemic category, respectively.^{37,38} Raw scores for each measure were converted into z-scores with higher z-scores reflecting better performance.

2.6 | Brain structure measurements

At year 30, brain MRI was obtained including structural MRI and diffusion tensor imaging (DTI), in 3T MR scanners (Philips 3T Achieva/2.6.3.6 platform in Birmingham; Siemens 3T Tim Trio/VB 15 platform in Minneapolis; Siemens 3T Tim Trio/VB 15 platform in Oakland) using standardized protocols. Acquisition parameters have been described in detail elsewhere.^{23,39–41} White matter hyperintensities were estimated from the sagittal 3D fluid-attenuated inversion recovery (FLAIR), T1, and T2 sequences using a supervised learning-based multi-modal lesion segmentation technique, which was trained on manually delineated ground-truth segmentation labels (see Launer et al.²³ for a detailed description). Volumetric measurements for normal and abnormal (with white matter hyperintensities) tissues were calculated within each region of interest (ROI), as well as in larger anatomical regions obtained by grouping single ROIs within a hierarchical representation.^{42,43} DTI images were used to calculate maps of fractional anisotropy (FA) using standard methods.⁴⁴ We examined total gray matter volume; gray matter volume within inferior frontal, temporal, and occipital lobes; and hippocampal gray matter volume, each corrected for intracranial volume (ICV; consisting of total brain volume plus cerebrospinal fluid) to account for variation in head size. We examined mean white matter FA values across the brain (total FA) as well as white matter FA by lobe, with mean white matter FA values within a particular lobe averaged across the left and right hemispheres. All the

FA measures were extracted from the white matter only, not from gray matter nor whole brain. All brain structure outcomes were converted to z-scores (using means and standard deviations from all participants who had these data), with higher z-scores reflecting larger gray matter volumes and higher FA.

2.7 | Statistical analysis

We first compared the higher literacy group to the low literacy group on demographics and clinical characteristics using Mann–Whitney for continuous variables and chi square for categorical variables. To examine the associations between literacy and brain structure and cognition, we conducted unadjusted and adjusted linear regression models with outcomes of z-scores for brain structure (gray matter and FA values) and cognitive values. Adjusted models included demographics (age, sex, and race) and health factors found to be associated with lower literacy: smoking, depressive symptoms, physical activity, diabetes, and hypertension. We also included scanner site in the models. In a sensitivity analysis, we added years of education in the model to account for the possible confounding effect of years of education.

2.8 | Data availability

Anonymized data are available from the CARDIA Coordinating Center (cardia.dopm.uab.edu/contact-cardia). A description of the National Heart, Lung, and Blood Institute policies governing the data and describing access to the data can be found online (cardia.dopm.uab.edu/study-information/nhlbi-data-repository-data).

3 | RESULTS

The median age of participants was 56 years old, (interquartile range [IQR] 53, 58), median education of 16 years (IQR 13, 16), 53.2% were female ($n = 337$) and 38.5% ($n = 237$) were Black (Table 1). The higher-literacy group ($n = 499$) had more years of education and had a higher proportion of women and lower proportion of Black individuals (Table 1). They also had a higher level of physical activity; less smoking, depressive symptoms, and hypertension; and lower obesity (Table 1). Age, high cholesterol, diabetes, and the presence of APOE $\epsilon 4$ were similar between the high- and low-literacy groups (Table 1).

In unadjusted models, the higher-literacy group performed better on all cognitive tests, including the MoCA (Beta = 1.3, 95% confidence interval [CI] = 1.1, 1.5, $P < 0.001$), the DSST (Beta = 0.8, 95% CI = 0.6, 1.0, $P < 0.001$), the RAVLT delayed recall (Beta = 0.8, 95% CI = 0.6, 0.9, $P < 0.001$), the Stroop test (Beta = -0.8 , 95% CI = -1.0 , -0.6 , $P < 0.001$), the Letter fluency test (Beta = 1.1, 95% CI = 0.9, 1.3, $P < 0.001$), and Categorical fluency test (Beta = 0.7, 95% CI = 0.5, 0.9, $P < 0.001$). After multivariable adjustments for demographics (age, sex, and race) and health factors (smoking, depressive symptoms, exercise, diabetes, and hypertension) the associations remained significant. The

TABLE 1 Characteristics of the 616 CARDIA participants by literacy

Characteristic Median and [IQR] or N (%)	Overall n = 616	Low literacy n = 117	High literacy n = 499	P-value
Age, y	56 [53, 58]	56 [53, 58]	56 [52.5, 58]	0.819
Education, y	16 [13, 16]	13 [12, 15]	16 [14, 17]	<0.001
Female, n (%)	337 (53.2)	47 (40.2)	280 (56.1)	0.003
Black, n (%)	237 (38.5)	77 (65.9)	170 (34.1)	<0.001
Physical activity	288 [144, 504]	216 [84, 446]	302 [152.2, 513]	0.021
Current smoking, n (%)	73 (11.8)	27 (23.3)	46 (9.3)	<0.001
Obesity, n (%)	217 (34.3)	49 (42.2)	165 (33.1)	0.078
Depressive symptoms, n (%)	86 (13.8)	24 (20.9)	57 (11.6)	0.013
Hypertension, n (%)	210 (33.1)	54 (46.2)	149 (29.9)	0.001
Hypercholesterolemia, n (%)	64 (10.7)	10 (9.3)	53 (11.2)	0.704
Diabetes, n (%)	64 (10.2)	13 (11.2)	49 (9.9)	0.798
APOE ϵ 4, n (%)	182 (28.8)	43 (36.9)	135 (29.0)	0.147

Abbreviations: APOE, apolipoprotein E; IQR: interquartile range.

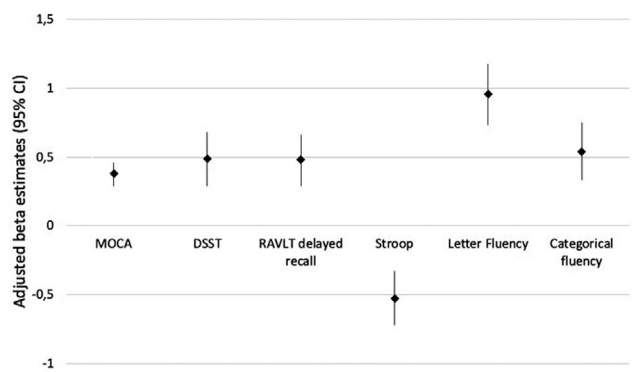


FIGURE 1 Adjusted beta estimates and 95% confidence intervals (CI) of the association between literacy (high vs. low) and cognitive scores. The beta estimates are adjusted for demographics, smoking, depressive symptoms, physical activity, and hypertension. Cognitive z-scores per literacy group. DSST, Digit Symbol Substitution Test; MoCA, Montreal Cognitive Assessment; RAVLT, Rey Auditory Verbal Learning Test

high-literacy group had approximately 0.5 greater z-score (or less in the case of Stroop test) than the low-literacy group in all cognitive tests. The results did not change after adjusting for years of education in the sensitivity analysis. Figure 1 depicts the beta estimates and CIs of each association after multivariable adjustments.

The higher-literacy group did not have larger total or regional gray matter volumes in unadjusted models, nor after multivariable adjustments.

In terms of white matter integrity, in unadjusted models the high-literacy group had higher total FA values (Beta = 0.4, 95% CI = 0.1, 0.6, P = 0.003), temporal FA values (Beta = 0.4, 95% CI = 0.1, 0.6, P = 0.002), parietal FA (Beta = 0.4, 95% CI = 0.1, 0.6, P = 0.002), and occipital FA (Beta = 0.4, 95% CI = 0.1, 0.6, P = 0.002). Those associations remained significant after adjustments for demographics (age, sex, race; Table 2). The total and regional FA values of the high-literacy group were around 0.3 z-scores higher than the low-literacy

group after adjusting for demographics plus health factors (smoking, depressive symptoms, exercise, diabetes, and hypertension; Table 2). The results did not appreciably change after adjusting for years of education in the sensitivity analysis.

4 | DISCUSSION

In this cohort of middle-aged individuals from different regions of the United States, a higher literacy level was associated with better cognitive function and higher white matter integrity in most brain regions. We did not find an association between literacy and gray matter volumes.

Although previous studies have shown similar associations in older adults using years of education as a cognitive reserve proxy, our research unveils that they are present as early as in midlife, which has not been demonstrated before in a large racially and sexually balanced sample. Midlife may be an important window of opportunity for dementia-preventive interventions based on literacy learning in individuals who may not have been able to increase their literacy abilities when they were school-age.

The cognitive reserve theory provides the rationale for why low education level is a risk factor for dementia. Cognitive reserve is the term used to describe the adaptability of cognitive processes that explain why some persons are less susceptible to brain aging and neurodegenerative diseases.^{12,45} Some lifetime exposures such as education, occupational complexity, and social engagement and the interaction of those factors with genetic or other innate characteristics are believed to build cognitive reserve. Among the proposed cognitive reserve mechanisms are greater resilience to brain pathology such as vascular lesions,⁴⁶ hippocampal atrophy,¹⁴ and Alzheimer's disease pathology;^{15,16} the development of compensatory strategies; and greater brain structure including gray matter volume^{17,18} and white matter connectivity.^{19,47} The positive associations we found between high literacy, cognition, and white matter integrity contributes to the

TABLE 2 Association between literacy and brain MRI measures

	Bivariate (adjusted for ICV)		Adjusted for demographics		Adjusted for demographics, depressive symptoms, physical activity, smoking, diabetes, and hypertension	
	Estimate [95% CI]	P	Estimate [95% CI]	P	Estimate [95% CI]	P
FA, z-value						
Total FA	0.37 [0.13, 0.61]	0.002	0.32 [0.07, 0.57]	0.011	0.32 [0.05, 0.58]	0.018
Frontal FA	0.23 [−0.02, 0.59]	0.066	0.21 [−0.05, 0.48]	0.113	0.20 [−0.00, 0.49]	0.170
Temporal FA	0.40 [0.15, 0.65]	0.002	0.45 [0.18, 0.72]	0.001	0.42 [0.15, 0.70]	0.003
Parietal FA	0.39 [0.14, 0.64]	0.002	0.35 [0.01, 0.62]	0.009	0.33 [0.06, 0.61]	0.018
Occipital FA	0.40 [0.15, 0.65]	0.002	0.38 [0.11, 0.64]	0.005	0.40 [0.13, 0.68]	0.004

Abbreviation: CI, confidence Interval; FA, fractional anisotropy; MRI, magnetic resonance imaging; ICV, intracranial volume.

cognitive reserve literature supporting literacy as a measurement of reserve, going beyond the classical use of years of education. Although cross-sectional and not designed to establish causality, our study may suggest that acquiring literacy can be an important strategy for building cognitive reserve, both by improving cognitive abilities and possibly by increasing brain structural connectivity measured by white matter FA. While we cannot determine the directionality of the association, our finding sheds light on a possible mechanism underlying the role of illiteracy as a risk factor for dementia,^{48,49} although the possibility of reverse causality cannot be ruled out based on the results.

Aligned with our findings, previous work has found associations between literacy skills and cognitive functioning.^{50,51} Literacy skills seem to be more strongly associated with cognitive abilities compared to years of education. This might explain why some cognitive tests are better predictors of cognitive impairment when they are adjusted for literacy abilities rather than years of education.⁵² Among the cognitive abilities evaluated, the executive and language functions assessed by the Letter Fluency test were the most associated with high literacy. The increase in almost 1.0 z-score point in the high-literacy group can be explained by the fact that acquiring literacy skills is a strongly language-related process.

MRI techniques can inform about measurements of brain structure. The FA values are thought to indirectly reflect axon integrity and white matter structural connectivity.^{44,53} The higher the FA, the stronger the connection between two brain regions. Although previous work found an association between late-life literacy acquisition and larger gray matter volumes in persons who learned to read as adults,⁵⁴ we did not find an association between literacy skills and gray matter volumes. Nevertheless, the association between literacy and white matter integrity seems to be more consistent and was previously described in smaller studies.^{55–57} Similarly, occupational complexity, another proxy of cognitive reserve, was found to be associated with FA values, but not gray matter,⁵⁸ suggesting that white matter integrity may be more sensitive to environmental stimuli. Recently, a large Chinese study with young adults also did not find an association between cognitive function and gray matter volume but did find an association with measurements of white matter integrity.⁵⁹

The present study analyzed a large sample with balanced representativity of White and Black individuals, and men and women. However, because the MRI sample had more White individuals and men, selection bias may have occurred, similar to previous neuroimaging studies. Furthermore, the sample has a higher level of education than persons living in low- and middle-income countries, which prevents the generalizability of the results in these settings. Limitations include cross-sectional design, which does not rule out reverse causality, and possible limited power for detecting gray matter differences. Moreover, the REALM-SF cut-off score of 7 may not reflect those attained using the standard 66-word REALM version.

Our findings support the importance of building cognitive reserve through literacy possibly by improving cognitive abilities and increasing white matter integrity. Low literacy is associated with poor health outcomes⁶⁰ and further longitudinal studies might clarify whether improving literacy can improve cognition and white matter integrity, as a way to increase cognitive reserve and prevent dementia.

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CONFLICTS OF INTEREST

The authors declare they have no competing interests related to the present research. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

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

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