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Cognitive reserve in midlife is not associated with amyloid- β deposition in late-life

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Abstract

We examined associations between cognitive reserve and late-life amyloid- β deposition using florbetapir positron emission tomography (PET). We used data from the Atherosclerosis Risk in Communities (ARIC) and ARIC-PET Study. 330 dementia-free participants underwent PET scans. Mean global cortical standardized uptake value ratio (SUVR) > 1.2 was defined as elevated. Midlife cognition was significantly associated with late-life cognition, but not with late-life elevated SUVR; education was not associated with late-life SUVR, but was strongly associated with late-life cognition. Cognitive reserve may reduce dementia risk by mitigating the impact of Alzheimer's Disease pathology on the clinical expression of dementia, rather than by altering its pathogenesis.

Keywords

PET imaging; amyloid; education; epidemiology; cohort study; human

INTRODUCTION

Higher education and cognitive abilities in early adulthood have consistently been associated with lower incidence of dementia [1]. These associations have been interpreted as manifestations of cognitive reserve. However, there is interest in determining whether this is due to structural differences, including those detectable by brain imaging, or through the

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cognitive strategies and compensatory mechanisms associated with higher education and greater intellectual activity[2]. A study by Plassman et al[3] found moderate correlations between education and intelligence in early adult life with cognitive status 50 years later. Other studies have also found correlations between early- and late-life cognitive ability[4]. The evidence regarding the association between education and amyloid deposition has been more limited. A recent study using data from the Alzheimer's Disease Neuroimaging Initiative found that education duration was not correlated with amyloid deposition[5]. Additionally, findings from the Epidemiological Clinicopathological Studies in Europe (ECLIPSE)[6] showed education was associated with lower likelihood of dementia at death and greater brain volume, but not associated to neurodegeneration or vascular pathologies.

Participants in the Atherosclerosis Risk in Communities (ARIC) study had their cognitive performance assessed in midlife. More than 300 participants of ARIC subsequently underwent florbetapir positron emission tomography (PET) in late-life, approximately 20 years after assessment of vascular risk factors, cognition, and education. This allowed us to pursue the following aims: to 1) examine the associations of midlife cognitive function and education level with late-life amyloid- β deposition, and 2) determine whether the association of education with late-life cognitive function is independent of amyloid- β deposition and markers of small vessel disease. We hypothesized that midlife cognitive ability and education level would be associated with late-life cognitive ability but not with brain amyloid- β deposition.

METHODS

Study participants

The ARIC study is an on-going, prospective cohort of adults from 4 U.S. communities that began in 1987–1989. The ARIC cohort underwent cognitive testing including at the second (1990–1992) and fifth (2011–2013) visits. A subset of participants without dementia at the fifth visit underwent MRI and subsequent florbetapir PET imaging as part of the ARIC-PET ancillary study[7]. Of the 346 ARIC-PET participants, we excluded persons who did not self identify as black or white (n=2), one person who ultimately received an adjudicated diagnosis of dementia, persons missing APOE genotype (n=4), or other covariates (n=9) for an analytic sample of 331.

Standardized uptake value ratio (SUVR)

The standardized uptake value ratio (SUVR) is a measure of relative amyloid- β presence, calculated as the standardized uptake value of florbetapir in a specific region of interest (ROI) divided by the standardized uptake value in the cerebellum. For the present analysis we used global cortical SUVR, a weighted average (based on ROI size) of the precuneus, orbitofrontal cortex, prefrontal cortex, superior frontal cortex, lateral temporal lobe, parietal lobe, occipital lobe, anterior cingulate, and posterior cingulate. Because of the skewed distribution of SUVR, we dichotomized SUVR at the median value of 1.2, with values >1.2 classified as “elevated” as has been previously done[7].

Cognitive factor scores

At visit 5, cognitive assessment was done using a battery consisting of 10 tests, including assessments of memory, language, and executive function. Three of these tests were also administered at visit 2. Latent variable methods were used to summarize these tests into a factor score representing general cognitive performance[8]. Scores were standardized such that a factor score of 1 represents general cognition that is 1 standard deviation above the mean.

Education

Education level was assessed at baseline and categorized into three groups as 1) less than high school (HS), 2) high school, high school equivalency, or vocational school, and 3) any college, graduate, or professional school.

Statistical analysis

We used logistic regression to examine the association of cognitive function at visits 2 and 5, separately, and education level with elevated SUVR. Models were adjusted for age, sex, and APOE. For cognitive function, we also adjusted for education. To examine the association between late-life cognitive factor scores and education, we used linear regression. To determine whether the difference in cognitive factors scores by education could be explained by amyloid- β deposition and small vessel disease, we also fit a model that included adjustment for smoking status, drinking status, hypertension, diabetes, total cholesterol, body mass index, global SUVR, brain-volume percentage of white matter hyperintensities, and the presence of lacunar infarcts smaller than 20mm. Lastly, we also used linear regression to examine the association between midlife cognitive scores and late-life cognitive scores.

All analyses were stratified by race and used Stata/SE 14.2 (College Station, TX).

RESULTS

At visit 5, the mean age of participants was 76 years (25th-75th percentiles: 71–80; range: 67–88), 57% were female, and 43% were black. Mean SUVR was 1.29 (25th-75th percentiles: 1.12, 1.41; range: 0.95, 2.31). Cognitive factor scores in midlife were not associated with late-life elevated SUVR in either white (OR=1.03, 95% CI: 0.63–1.68) or black participants (OR=0.88, 95% CI: 0.49–1.58). However, higher late-life cognitive factor scores were significantly associated with reduced odds of late-life elevated SUVR in white participants (OR=0.61, 95% CI: 0.38–0.97), though not significantly in black participants (OR=0.71, 95% CI: 0.39, 1.27). Education was not significantly associated with SUVR in either group (Table 1).

Cognitive factor scores in midlife were associated with cognitive factor scores in late-life (Table 2). Education was strongly associated with late-life cognitive factor scores in both black and white participants, with those with a college, graduate, or professional schooling having cognitive scores approximately 1 standard deviation higher than participants with a less than high school education (Table 2, Model1). This association remained after

additional adjustment for risk factors, for markers of small vessel disease, and for SUVR (Table 2, Model 2).

DISCUSSION

We found that cognitive scores in midlife and education were not associated with late-life SUVR, suggesting that education and cognitive function in midlife do not affect long-term brain amyloid accumulation. We also found that the strong association between education and late-life cognitive function persisted after adjustment for SUVR and markers of small vessel disease. Together these imply that cognitive reserve works by means independent of detectable cerebrovascular disease or brain amyloid. We found similar associations in black and white participants.

Studies have documented associations between early-life cognitive ability and education with late-life dementia risk[1,6,9]; however, few have been able to use brain imaging to correlate education and midlife cognitive function with any measure of Alzheimer's Disease (AD) pathology, in order to clarify the mechanisms of these associations. Our results build on evidence from other studies that found lifestyle factors were not associated with AD biomarkers, but were associated with cognitive performance[10], that intellectual enrichment does not predict markers of AD[11], and that education is associated with lower likelihood of dementia at death and greater brain volume, but is not associated with neurodegeneration or vascular pathologies[6]. Lastly, results from a prospective analysis in BIOCARD showed that the association between cognitive reserve and long-term cognitive trajectories differed by baseline cognitive status (i.e. cognitive normal, mild cognitive impairment). This suggests that the observed benefit of cognitive reserve on dementia progression occurs through a delay in onset of clinical symptoms[12].

The strengths of our study include the community-based sample of black and white adults, information on cognitive function in midlife and late-life, and the availability of structural MRI and PET imaging. A limitation is that it was restricted to persons free of dementia and those who were able to tolerate PET and MRI scans; however, our current model of the pathogenesis of Alzheimer's disease suggests amyloid deposition begins up to 20 years before clinical symptoms become apparent[13,14]. Additionally, we were unable to explore certain aspects of education, such as the incremental benefit of each additional year of education or educational quality.

Our results add to the growing body of literature that midlife cognitive ability and higher education reduce dementia risk by mitigating the impact of AD pathology on the clinical expression of dementia, rather than altering its fundamental pathogenesis.

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Table 1.

Adjusted odds ratio (95% CI) for global cortex SUVR >1.2 (median) with cognition, change in cognition, and education, by race

	<u>White (n=188)</u>	<u>Black (n=143)</u>
	Model 1[†]	Model 1[†]
<u>Cognitive factor score[‡]</u>		
Visit 2 (1990–1992)	1.03 (0.63, 1.68)	0.88 (0.49, 1.58)
Visit 5 (2011–2013)	0.61 (0.38, 0.97) [*]	0.71 (0.39, 1.27)
<u>Education level</u>		
< High school	1 (ref)	1 (ref)
High school, GED, or vocational school	0.82 (0.31, 2.15)	0.94 (0.34, 2.59)
College, graduate, or professional school	0.85 (0.31, 2.30)	1.05 (0.38, 2.89)

[†]Model 1 was adjusted for age, sex, APOE, education. The likelihood ratio test to the fully adjusted model was not statistically significant

[‡]Higher cognitive factor scores indicate better performance. Scores are standardized per standard deviation. The estimates for Visit 2 and Visit 5 cognitive factor scores are from separate models.

^{*}p-value<0.05

^{**}p-value<0.01

Table 2.

Beta coefficients (95% CI) for the association of mid-life cognitive factor scores (1990–1992) and education with late-life (2011–2013) cognitive factor scores, by race

Outcome=late-life cognitive factor scores	White (n=188)		Black (n=143)	
	Model 1	Model 2	Model 1	Model 2
Mid-life cognitive factor score [†]	0.62 (0.48, 0.75) **	0.63 (0.49, 0.76) **	0.52 (0.37, 0.66) **	0.50 (0.34, 0.66) **
Education level				
< High school	0 (ref)	0 (ref)	0 (ref)	0 (ref)
High school, GED, or vocational school	0.58 (0.26, 0.90) **	0.43 (0.09, 0.77) *	0.72 (0.41, 1.02) **	0.65 (0.33, 0.97) **
College, graduate, or professional school	1.04 (0.71, 1.37) **	0.77 (0.40, 1.13) **	1.17 (0.87, 1.48) **	1.13 (0.81, 1.45) **

Model 1: adjusted for age, sex, APOE, education

Model 2: adjusted for the variables in Model 1 plus cigarette smoking status (current; former; never), drinking status (current; former; never), hypertension (yes;no based on systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90, or use of blood pressure lowering medication), diabetes (self-reported diagnosis or medication use), total cholesterol, body mass index, global SUVR, brain-volume percentage of white matter hyperintensities, and presence of lacunar infarcts smaller than 20mm

* p-value<0.05

** p-value<0.01

[†] Higher cognitive factor scores indicate better performance. Scores are standardized per standard deviation