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Very low levels of education and cognitive reserve

A clinicopathologic study

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ABSTRACT

Objective: We conducted a clinicopathologic study in a large population with very low levels of education to determine whether very few years of education could contribute to cognitive reserve and modify the relation of neuropathologic indices to dementia.

Methods: In this cross-sectional study, we included 675 individuals 50 years of age or older from the Brazilian Aging Brain Study Group. Cognitive abilities were evaluated through a structured interview with an informant at the time of autopsy, including the Clinical Dementia Rating (CDR) scale. Neuropathologic examinations were performed using immunohistochemistry and following internationally accepted criteria. Multivariate linear regression models were conducted to determine whether the association between cognitive abilities (measured by CDR sum of boxes) and years of education was independent of sociodemographic variables and neuropathologic indices, including neuritic plaques, neurofibrillary tangles, lacunar infarctions, small-vessel disease, and Lewy bodies. In addition, interaction models were used to examine whether education modified the relation between neuropathologic indices and cognition.

Results: Mean education was 3.9 ± 3.5 years. Formal education was associated with a lower CDR sum of boxes ($\beta = -0.197$; 95% confidence interval −0.343, −0.052; $p = 0.008$), after adjustment for sociodemographic variables and neuropathologic indices. Furthermore, education modified the relationship of lacunar infarcts with cognitive abilities ($p = 0.04$).

Conclusions: Even a few years of formal education contributes to cognitive reserve. *Neurology*® 2013;81:650–657

GLOSSARY

AD = Alzheimer disease; **BABSG** = Brazilian Aging Brain Study Group; **CDR** = Clinical Dementia Rating; **H&E** = hematoxylin & eosin.

The cognitive reserve theory is increasingly used to explain the clinicopathologic dissociation observed in Alzheimer disease (AD).[1] Approximately 30% of cognitively normal subjects have intermediate- to high-likelihood AD pathology at autopsy.[2–7] According to this theory, subjects with greater cognitive reserve require a more severe neuropathologic burden to reach the threshold for clinical dementia.[8]

Previous clinicopathologic studies suggest that although education is not directly related to the development of neuropathologic lesions, it appears to reduce the impact of such lesions on the development of dementia, thereby increasing cognitive reserve. However, the studies supporting this hypothesis have investigated populations with relatively high levels of educational attainment, with mean formal education ranging from 9 to 18 years.[8–12] Little information is available regarding the effect of very few years of education on cognitive reserve. Low educational attainment is the reality for a high proportion of the elderly worldwide. According to a report from the United Nations Education, Scientific and Cultural Organization, nearly 800 million adults remained illiterate in 2009, representing about 16% of the global population.[13] Most of

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Table 1 Demographic, clinical, and neuropathologic data of subjects with and without any formal education (n = 675)

	No formal education	Formal education ≥1 y	p
Age, y, mean (SD)[a]	78.95 (10.84)	72.79 (11.55)	<0.0001
Males, n (%)[b]	38 (29.23)	284 (52.11)	<0.0001
Race, n (%)[b,c]			0.002
White	75 (58.14)	393 (74.01)	
Black	21 (16.28)	54 (10.17)	
Admixed	33 (25.58)	84 (15.82)	
Socioeconomic class, n (%)[b,d]			<0.0001
High	15 (11.54)	179 (32.84)	
Middle	61 (46.92)	252 (46.24)	
Low	54 (41.54)	114 (20.92)	
Contact with the informant, n (%)[b]			0.77
Daily	100 (81.97)	421 (80.81)	
Weekly	22 (18.03)	100 (19.19)	
CDR, n (%)[b]			0.001
0	46 (35.38)	289 (53.03)	
0.5	18 (13.85)	86 (15.78)	
1	20 (15.38)	57 (10.46)	
2	15 (11.54)	39 (7.16)	
3	31 (23.85)	74 (13.58)	
CDR sum of boxes, mean (SD)[a]	6.58 (6.93)	4.27 (6.31)	0.0003
Braak and Braak (NFT), n (%)[b]			0.06
0	24 (18.46)	142 (26.06)	
I	16 (12.31)	97 (17.80)	
II	35 (26.92)	132 (24.22)	
III	19 (14.62)	75 (13.76)	
IV	16 (12.31)	40 (7.34)	
V	13 (10.00)	28 (5.14)	
VI	7 (5.38)	31 (5.69)	
CERAD (NP), n (%)[b]			0.24
0	77 (59.23)	354 (64.95)	
A	14 (10.77)	66 (12.11)	
B	19 (14.62)	73 (13.39)	
C	20 (15.38)	52 (9.54)	
Lacunar infarction, n (%)[b]			0.44
0	82 (63.08)	383 (70.28)	
1	18 (13.85)	58 (10.64)	
2	6 (4.62)	18 (3.30)	
≥3	24 (18.46)	86 (15.78)	
Small-vessel disease, n (%)[b]			0.003
Absent	56 (45.53)	314 (60.15)	
Mild	30 (24.39)	116 (22.22)	
Moderate and severe	37 (30.08)	92 (17.62)	

Continued

these individuals live in developing countries, which already are home to approximately 60% of the subjects who have dementia.[14]

In this study, we examined the cognitive reserve theory in a population with a high prevalence of extremely low levels of formal education. Furthermore, we tested the hypothesis that even a few years of formal education would reduce the deleterious effects of neuropathologic indices (i.e., AD pathologic changes, lacunar infarctions, small-vessel disease, and Lewy body pathology) on the likelihood of having cognitive impairment.

METHODS

Participants. Subjects were participants in the Brazilian Aging Brain Study Group (BABSG) from the University of São Paulo. Inclusion and exclusion criteria for the BABSG were previously described.[15] From February 2004 to February 2009, a total of 1,980 persons aged 50 years or older were included in the BABSG. Of these, the first consecutive 675 persons underwent a complete clinical and neuropathologic diagnosis and were included in this study.

Standard protocol approvals, registrations, and patient consents. The study was approved by the local ethical committee, and a voluntarily signed informed consent was obtained by the next-of-kin who provided autopsy and brain donation consent and permission to obtain necessary clinical and functional information.

Clinical data. Upon arrival at the autopsy service, a knowledgeable informant was identified to provide information using a validated semistructured interview. Requirement for being an informant included having close weekly contact with the deceased subject during the last 6 months. Informants were the son or daughter in 69.9%, the spouse in 7.8%, a grandchild in 7.3%, and a sibling in 6.2% of the cases. The remaining 8.8% were other family members. Contact with the informant was categorized as daily or weekly. The interview protocol included demographic data collection of age, sex, ethnicity, and educational attainment. Educational attainment was obtained by inquiring about the number of years in which the deceased attended school. A series of semistructured scales, including the Clinical Dementia Rating (CDR) scale and the Informant Questionnaire of the Cognitive Decline in the Elderly, determined cognitive and functional status.[16,17] CDR sum of boxes was obtained for all subjects. The interview was conducted by a skilled team of gerontologists. The final diagnosis was reached by consensus among an experienced gerontologist and a behavioral neurologist.

In a previous study, we prospectively compared the sensitivity and specificity of our protocol when applied to informants of living patients, with the diagnosis established in our memory clinic where the same patients were submitted to a full cognitive assessment, neurologic examination, and neuroimaging. Sensitivity was 86.6% and specificity was 84.4% for the diagnosis of dementia.[18]

Socioeconomic status was determined through a Brazilian scale that classifies subjects in 5 strata. Stratum A is the highest income and stratum E the lowest. For analysis and inclusion in the multivariate model, individuals were grouped into 3 categories: low socioeconomic status (strata D and E), middle status (stratum C), and high status (strata A and B).[19]

Neuropathologic assessment. Autopsy was performed within 20 hours of death. Upon brain procurement, the left hemisphere

Table 1 Continued

	No formal education	Formal education ≥1 y	p
Braak and Braak (Lewy bodies), n (%)[e,f]			0.21
0	122 (94.57)	480 (89.89)	
I–III	1 (0.78)	19 (3.56)	
IV	1 (0.78)	14 (2.62)	
V–VI	5 (3.88)	21 (3.93)	
Total, n (%)	130 (19.26)	545 (80.74)	

Abbreviations: CDR = Clinical Dementia Rating; CERAD = Consortium to Establish a Registry for Alzheimer's Disease; NFT = neurofibrillary tangles; NP = neuritic plaques.
[a] Unpaired t test. [b] χ^2 test. [c] Missing data (n = 660). [d] Missing data (n = 667). [e] Missing data (n = 663). [f] Fisher exact test.

was fixed in 10% buffered paraformaldehyde for 14 to 21 days, sectioned in 1-cm-thick slabs, and inspected macroscopically. Thirteen samples (middle frontal gyrus, middle and anterior temporal gyri, angular gyrus, superior frontal gyrus and anterior cingulate gyrus, visual cortex, hippocampus and parahippocampal gyrus at the level of lateral geniculate body, amygdala at the level of mammillary bodies including the ambiens gyrus, basal ganglia at the level of the anterior commissure, thalamus, midbrain, pons, medulla oblongata, and cerebellum) were blocked in paraffin for microscopic examination. All extra macroscopic lesions were also sampled for microscopic evaluation.

All sampled regions were stained with hematoxylin & eosin (H&E). Selected sections were immunostained with antibodies against β-amyloid (4G8, dilution 1:10.000; Signet Pathology Systems, Dedham, MA), against phospho-tau (PHF-1, dilution 1:2.000; gift of Prof. Peter Davies, NY), and against α-synuclein (EQV-1, 1:10.000; gift of Kenji Ueda, Tokyo, Japan), as described previously.[15] All sections were submitted to antigenic retrieval using a steamer. The reactions were detected using the Vectastain Elite ABC Kit (Vector Laboratories, Burlingame, CA). Whenever necessary for accurate diagnosis, other regions were immunostained and/or additional antibodies including TDP-43 were used. Neuropathologic diagnoses were conducted by 2 experienced neuropathologists blinded to all clinical data.

AD neuropathologic lesions. The criteria of the Consortium to Establish a Registry for Alzheimer's Disease were used to classify the neuritic plaques into 4 possible groups: absent, sparse, moderate, or frequent.[20] The neurofibrillary tangles were staged according to the Braak classification in stages 0 to VI.[21]

Cerebrovascular assessment. Vascular changes were analyzed semiquantitatively using H&E staining in all 13 routinely sampled areas plus additional areas with suspected vascular lesions detected at the macroscopic examination.[22] Additional staining such as periodic acid-Schiff, Perls, and Klüver-Barrera was used at pathologist discretion. The presence of diffuse small-vessel disease, lacunae, and large infarcts was registered by topography, size, and number. Cerebral amyloid angiopathy was identified using immunohistochemistry for β-amyloid.

Small-vessel disease was assessed in all 13 areas using a 4-point scale (0–3) based on severity. The average of cortical area stages was used. The number and size of lacunar and microinfarcts were recorded in all 14 regions, using H&E-stained sections. The number of lacunar infarcts found in strategic areas to cognition (thalamus, frontocingular cortex, basal forebrain, caudate nucleus, inferotemporal gyri, hippocampus, and angular gyrus) was used for classifying lacunar infarcts on a 6-point scale (0 = none; 1 = up to 2 lacunae; 2 = up to 4 lacunae; 3 = up to 6 lacunae; 4 = up to 8 lacunae; and 5 = more than 8 lacunae).

Lewy body pathology. The presence of Lewy bodies was classified using the Braak staging for Parkinson disease ranging from stages 0 to VI.[23]

Statistical analysis. The main dependent variable was cognitive ability assessed with the CDR sum of boxes (continuous outcome). We initially conducted univariate analysis to examine whether the groups with and without any formal education, and those with and without cognitive impairment were different regarding demographics and neuropathologic features. We used χ^2 tests or Fisher exact test when appropriate for categorical variables and unpaired *t* tests for continuous variables. Multivariate linear regression analysis was conducted to determine whether the association between cognitive ability and education was not confounded by sociodemographic data and neuropathologic features. Education was the main independent variable and was modeled as a continuous measure. The initial model examined the association between education and cognitive ability adjusting for the effects of demographic factors including age at death, sex, socioeconomic status, race, and contact with the informant. Race and socioeconomic status were coded as dummy variables. Further multivariate linear regression models were performed to adjust the association of cognitive ability and education for the presence of neuropathologic indices, measured as ordinal variables.

We conducted additional multivariate linear regression analyses with the addition of interaction terms in order to test the hypothesis that education modifies the relationship of neuropathologic indices and cognitive ability. The *p* values for interaction and other terms in the model were calculated using likelihood ratio tests.

The level of significance of all tests was set at 5% in 2-tailed tests. The statistical analyses were performed using Stata statistical software version 11.0 (Stata Corp., College Station, TX).

RESULTS A total of 675 individuals were included in the study; 47.7% were male. The mean age was 74.0 ± 11.7 years and mean educational level was 3.9 ± 3.5 years, 19.3% of the sample had never been to school, and 60.7% had between 1 and 4 years of formal education. Cognitive impairment was present in 50.4% of the subjects divided as CDR 0.5 (30.6%), CDR 1 (22.6%), CDR 2 (15.9%), and CDR 3 (30.9%). Braak stage ≥IV was found in 33.9%, and moderate to severe neuritic plaques were found in 24.3%. Lacunar infarcts and small-vessel disease were present in 31.1% and 42.6% of the subjects, respectively. We found a Braak stage ≥IV (neocortical involvement) for Lewy body pathology in 9.8% of our sample. Univariate analysis was next performed to evaluate the association of the main demographics and neuropathologic variables to groups with and without any formal education (table 1). Those without formal education were older, more likely to be female, had lower socioeconomic status, and had higher frequency of small-vessel disease. We next compared those with and without cognitive impairment (table 2). The group with cognitive impairment was older, more likely to be female, had lower educational attainment, and had a higher frequency of AD-related and vascular pathology.

Table 2 Demographic, clinical, and neuropathologic data from participants with and without cognitive impairment (n = 675)

	Normal cognition	Cognitive impairment	p
Education, y, mean (SD)[a]	4.55 (3.69)	3.22 (3.16)	<0.0001
Age, y, mean (SD)[a]	70.75 (11.84)	77.15 (10.58)	<0.0001
Males, n (%)[b]	180 (53.73)	142 (41.76)	0.002
Race, n (%)[b,c]			0.49
White	233 (71.91)	235 (69.94)	
Black	32 (9.88)	43 (12.80)	
Admixed	59 (18.21)	58 (17.26)	
Socioeconomic class, n (%)[b,d]			0.36
Low	94 (28.06)	100 (29.41)	
Middle	164 (48.96)	149 (43.82)	
High	77 (22.99)	91 (26.75)	
Contact with the informant[b]			0.008
Daily	255 (77.04)	266 (85.26)	
Weekly	76 (22.96)	46 (14.74)	
Braak and Braak (NFT), n (%)[e]			<0.0001
0	117 (34.93)	49 (14.41)	
I	66 (19.70)	47 (13.82)	
II	89 (26.57)	78 (22.94)	
III	34 (10.15)	60 (17.65)	
IV	21 (6.27)	35 (10.29)	
V	5 (1.49)	36 (10.59)	
VI	3 (0.90)	35 (10.29)	
CERAD (NP), n (%)[b]			<0.0001
0	250 (74.63)	181 (53.24)	
A	38 (11.34)	42 (12.35)	
B	34 (10.15)	58 (17.06)	
C	13 (3.88)	59 (17.35)	
Lacunar infarction, n (%)[b]			<0.0001
0	266 (79.40)	199 (58.53)	
1	28 (8.36)	48 (14.12)	
2	7 (2.09)	17 (5.00)	
≥3	34 (10.15)	76 (22.35)	
Small-vessel disease, n (%)[b]			<0.0001
Absent	211 (66.14)	159 (48.77)	
Mild	69 (21.63)	77 (23.62)	
Moderate and severe	39 (12.23)	90 (27.61)	
Braak and Braak (Lewy bodies), n (%)[e,f]			0.06
0	306 (93.01)	296 (88.62)	
I–III	11 (3.34)	9 (2.69)	
IV	5 (1.52)	10 (2.99)	
V–VI	7 (2.13)	19 (5.69)	
Total, n (%)	335 (49.63)	340 (50.37)	

Abbreviations: CERAD = Consortium to Establish a Registry for Alzheimer's Disease; NFT = neurofibrillary tangles; NP = neuritic plaques.
[a] Unpaired *t* test. [b] χ^2 test. [c] Missing data (n = 660). [d] Missing data (n = 667). [e] Fisher exact test. [f] Missing data (n = 663).

Multivariate linear regression analyses were performed to examine the association between cognitive abilities and education, adjusting for sociodemographics and presence of neuropathologic lesions (table 3). In the full model, each year of education on average was associated with a −0.197 unit lower CDR sum of boxes (β = −0.197; 95% confidence interval −0.343, −0.052; $p = 0.008$). Therefore, education was associated with better cognitive abilities independent of sociodemographics and neurodegenerative and cerebrovascular lesions.

Finally, we performed additional linear regression models with CDR sum of boxes as the dependent variable, including terms for interaction between education and each of the neuropathologic lesions, and controlling for sociodemographic characteristics and other lesions. Education modified the relation between lacunar infarcts and cognitive ability ($p = 0.04$). Significant interactions were not observed between education and AD neuropathologic features, Lewy body pathology, or small-vessel disease (table 4 and the figure).

DISCUSSION Our findings show that very few years of formal education was associated with less cognitive impairment when compared with no formal education and that this relationship does not depend on demographic and socioeconomic characteristics and neuropathologic features related to AD, cerebrovascular lesions, and Lewy body pathology. There was a dose effect of education such that higher levels of schooling were associated with the lowest frequency of cognitive impairment.

Furthermore, our findings agree with previous neuropathologic studies showing that higher education is associated with lower prevalence of dementia through increasing cognitive reserve.[8–11] However, other studies included mostly persons with secondary school or more years of education and cannot necessarily be generalized to populations with very low levels of education. The effect of only a few years of education on cognitive reserve has not yet been well established. Thus, the major contribution of this study is to demonstrate that even a few years of education is sufficient to contribute to cognitive reserve and through this mechanism reduce the frequency of cognitive impairment, independent of the neuropathologic burden.

Very high levels of education, as seen in previous studies, may at least partly reflect the intellectual abilities of a person, and it is therefore less clear whether the education itself adds to the cognitive reserve or whether persons who receive more education have more cognitive reserve to begin with.[24] Access to only a few years of education will depend less on the intellectual abilities of a child, as opposed to postsecondary education. Therefore, the current study provides additional evidence that education itself actually contributes to the cognitive reserve.

It has been hypothesized that higher prevalence of dementia in low educated individuals with low socioeconomic level is related to increased risk of cerebrovascular lesions, because this population has low access to diagnosis and effective control of hypertension, diabetes, and dyslipidemia.[11] Poor control of vascular risk factors may result in cerebrovascular damage, which, in turn, is frequently found in association with AD neuropathologic lesions.[25] In fact, in a collaborative neuropathologic study, low education was not associated with increased vascular neuropathology, but it should be noted that in this study the median years of education was 9 years, much higher than the 4 years of our study.[10] Our findings supporting the relationship between education and lower frequency of cognitive impairment were also shown and extended to be independent of cerebrovascular lesions, in line with other samples of more educated individuals.

Furthermore, unlike previous studies, we found that the relationship between lacunar infarcts and cognitive ability is modified according to the level of education such that the odds of cognitive impairment associated with infarctions were lower among those with more years of education. These data provide evidence that education not only provides a cognitive advantage such that persons with more education may require a higher degree of cerebrovascular pathology in order to develop cognitive impairment but that education is also associated with mechanisms that reduce the impact of lacunar infarcts on cognition.

We did not find an interaction between education and AD neuropathologic features, as described in other

Table 3 Multivariate linear regression models showing the β coefficient, SE, 95% CI, and *p* value for the outcome of Clinical Dementia Rating sum of boxes (n = 675)

	β	SE	95% CI	*p*
Model 1				
Education	−0.235	0.082	−0.396 to −0.074	0.004
Age	0.163	0.023	0.119 to 0.207	<0.0001
Sex	−0.979	0.506	−1.973 to 0.014	0.05
Race[a]				
Black	0.910	0.784	−0.630 to 2.450	0.25
Admixed	−0.504	0.672	−1.823 to 0.815	0.45
SES[b]				
Middle	−0.699	0.049	−1.940 to 0.815	0.45
High	−1.145	0.057	−2.613 to 0.323	0.13
Proximity to the informant	−0.604	0.048	−1.826 to 0.618	0.33
Model 2				
Education	−0.197	0.074	−0.343 to −0.052	0.008
Age	0.011	0.024	−0.037 to 0.059	0.65
Sex	−0.151	0.465	−1.065 to 0.763	0.75
Race[a]				
Black	0.916	0.708	−0.475 to 2.307	0.20
Admixed	0.575	0.610	−1.772 to 0.623	0.35
SES[b]				
Middle	−0.026	0.583	−1.171 to 1.119	0.96
High	−0.286	0.688	−1.637 to 1.065	0.68
Contact with the informant	−0.460	0.566	−1.571 to −0.651	0.42
NFT	0.900	0.226	0.455 to 1.344	<0.0001
NP	1.146	0.340	0.477 to 1.815	0.001
Lacunar infarction	1.046	0.233	0.588 to 1.504	<0.0001
Small-vessel disease	0.842	0.308	0.237 to 1.446	0.006
Lewy body pathology	1.071	0.340	−0.405 to 1.737	0.002

Abbreviations: CI = confidence interval; NFT = neurofibrillary tangles; NP = neuritic plaques; SE = standard error; SES = socioeconomic status.
[a] Reference, white. [b] Reference, low SES.

Table 4 Multivariate linear regression analysis showing β coefficients (SE), 95% CI, and *p* values for the outcome of cognitive impairment considering the interaction of education and presence of neuropathologic lesions adjusted for age, sex, race, socioeconomic class, and other neuropathologic lesions (n = 675)

Variable	β (SE)	95% CI	*p*
Education	−0.195 (0.102)	−0.395 to −0.006	0.06
NFT	0.905 (0.262)	0.390 to 1.420	0.001
NFT × education	−0.001 (0.034)	−0.069 to 0.066	0.97
Education	−0.182 (0.086)	−0.350 to −0.014	0.03
NP	1.217 (0.394)	0.444 to 1.990	0.002
NP × education	−0.021 (0.059)	−0.137 to 0.095	0.72
Education	−0.120 (0.082)	−0.282 to 0.041	0.14
Lacunar infarction	1.480 (0.310)	0.871 to 2.088	<0.0001
Lacunar infarction × education	−0.133 (0.063)	−0.257 to −0.010	0.04
Education	−0.174 (0.089)	−0.348 to 0.001	0.05
Small-vessel disease	0.977 (0.418)	0.155 to 1.799	<0.0001
Small-vessel disease × education	−0.039 (0.081)	−0.199 to 0.121	0.63
Education	−0.181 (0.075)	−0.329 to −0.033	0.02
Lewy body pathology	0.816 (0.309)	0.210 to 1.422	0.008
Lewy body pathology × education	−0.143 (0.122)	−0.383 to 0.097	0.24

Abbreviations: CI = confidence interval; NFT = neurofibrillary tangles; NP = neuritic plaques; SE = standard error.

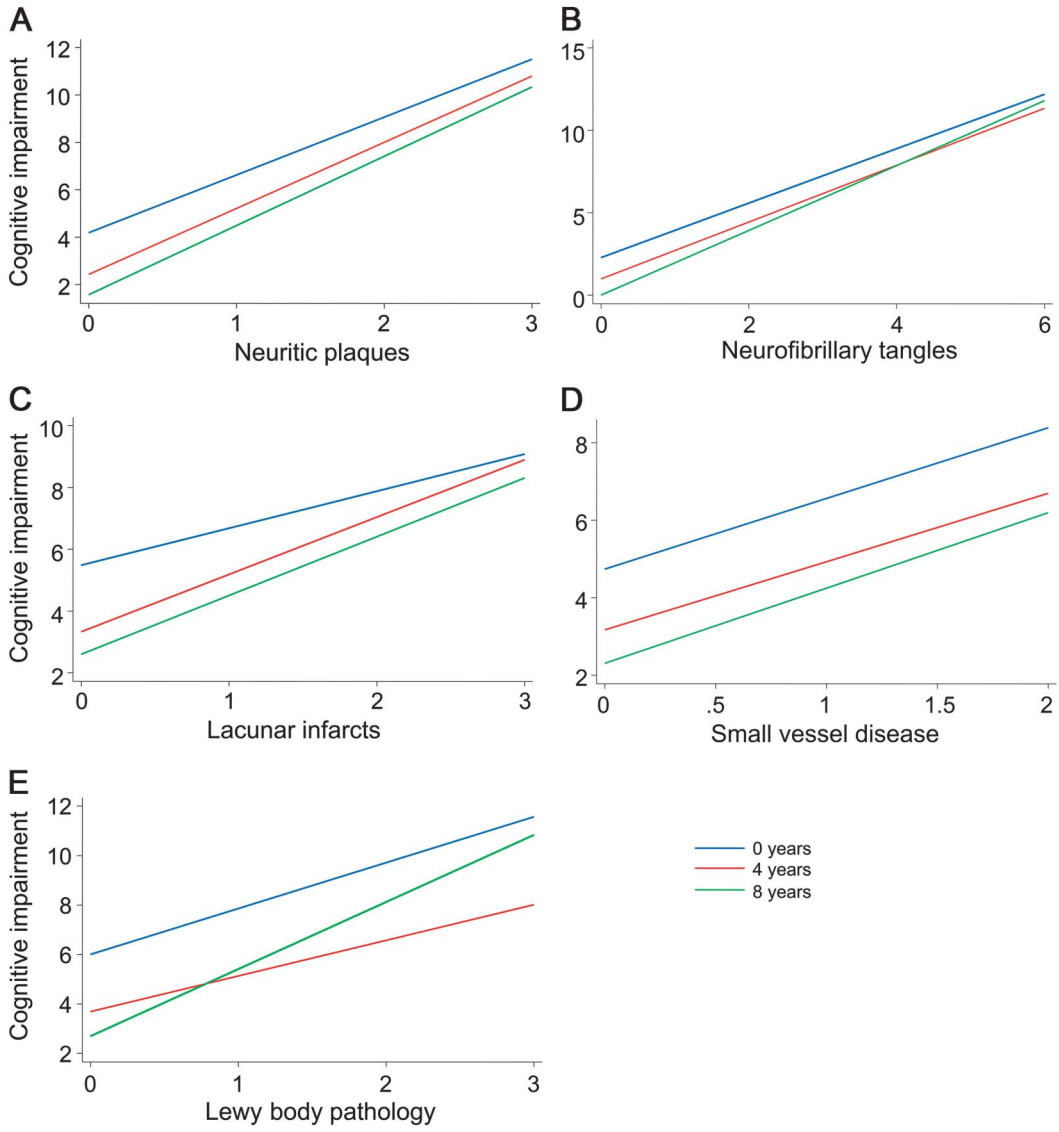
studies.[8,9] However, given the truncated range of education, we may not have been able to detect this association in our sample because of limited power. Studies including larger samples and with diverse profiles of education may help to further investigate this hypothesis.

The present study is a postmortem cross-sectional study and therefore has some limitations. We observed a difference of age between the groups with and without formal education. This result is probably related to the secular trend of education in Brazil. Epidemiologic studies demonstrate that older individuals have lower levels of education compared with younger subjects. Older subjects living in urban centers were frequently born and raised in rural areas and had limited access to school.[26] However, the cross-sectional nature of our study does not permit excluding the possibility of survival bias. For this reason, all multivariate models were adjusted for age.

The effect attributable to education could be confounded by other variables such as complex mental activities and specific behavior or lifestyle that were not included in our multivariate model. Nevertheless, in a recent study, education was described as the most effective component of cognitive reserve, associated with better performance in diverse cognitive domains, and its effect was independent of reading capacity, socioeconomic status, and cognitive activity throughout life.[27] Furthermore, recent evidence demonstrates that literacy and the first few years of education are associated with remarkable changes in cortical network organization and function.[28] The advances provided by previous studies together with the results of our study are evidence supporting the hypothesis that elementary education is a simple and powerful strategy to reduce the prevalence of dementia in illiterate populations. Such intervention would have a strong health policy implication because two-thirds of people with dementia live in developing countries where the prevalence of illiteracy is still high.[13,14]

Additional limitations are acknowledged. The clinical information was obtained through an informant and thus our measurement of cognitive ability may have been less accurate than a direct assessment. Although this is a potential limitation, we used 2 tests validated for informant-based assessment to increase the reliability of this evaluation, as recommended by the literature.[29] In addition, high levels of correspondence for the diagnosis of both dementia and normal cognition were obtained between the interviewing protocol used in this study and a gold standard interview performed with the patient and informant, as described previously.[18] Furthermore, an immediate postmortem interview may be helpful because the interval of time between the clinical and neuropathologic examination is minimal. This study investigated a convenience population submitted to mandatory autopsy examination due to unknown cause of death. This sample may not represent other subjects not submitted to autopsy. Compared with Brazilian community-dwelling studies, the prevalence of cognitive impairment was higher and the prevalence of illiteracy was slightly lower in this study.[30] Further investigations with a broader sample including individuals with known cause of death are required to extend the validity of our results.

Figure Predicted values of cognitive impairment considering formal education and neuropathologic lesions



Predicted values of cognitive impairment (Clinical Dementia Rating sum of boxes) considering different neuropathologic lesions (A: neuritic plaques; B: neurofibrillary tangles; C: lacunar infarcts; D: small-vessel disease; and E: Lewy body pathology) for participants with 0 years of education (10th percentile: blue line), 4 years of education (50th percentile: red line), and 8 years of education (90th percentile: green line). Predicted values of cognitive function obtained by multivariate linear models adjusted for age, sex, race, socioeconomic status, closeness of the informant, and all other neuropathologic lesions.

AUTHOR CONTRIBUTIONS

Dr. Farfel, Dr. Nitrini, Dr. Suemoto, Dr. Grinberg, and Dr. Jacob Filho were responsible for study design. Dr. Farfel, Dr. Nitrini, Dr. Suemoto, Dr. Grinberg, Dr. Bennett, Dr. Fregni, Dr. Pasqualucci, and Dr. Jacob Filho contributed to manuscript writing. Dr. Farfel, Dr. Nitrini, Dr. Suemoto, Dr. Grinberg, Dr. Ferretti, Dr. Leite, E. Tampellini, L. Lima, D.S. Farias, R.C. Neves, Dr. Rodriguez, Dr. Menezes, and Dr. Jacob Filho were responsible for data analysis or interpretation. Dr. Grinberg and Dr. Rodriguez were responsible for neuropathologic readings. All authors reviewed the manuscript.

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DISCLOSURE

The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

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