Received: 3 June 2021 | Revised: 13 October 2021 | Accepted: 25 October 2021

DOI: 10.1002/alz.12542

Alzheimer's & Dementia®
THE JOURNAL OF THE ALZHEIMER'S ASSOCIATION

FEATURED ARTICLE

# Education, but not occupation, is associated with cognitive impairment: The role of cognitive reserve in a sample from a low-to-middle-income country

Claudia K. Suemoto[1] | Laiss Bertola[1] | Lea T. Grinberg[2,3] | Renata E. P. Leite[2] | Roberta D. Rodriguez[4] | Pedro H. Santana[1] | Carlos A. Pasqualucci[2] | Wilson Jacob-Filho[1] | Ricardo Nitrini[4]

[1] Division of Geriatrics, University of São Paulo Medical School, Sao Paulo, Brazil

[2] Department of Pathology, University of São Paulo Medical School, Sao Paulo, Brazil

[3] Memory and Aging Center, University of California San Francisco, San Francisco, California, USA

[4] Department of Neurology, University of São Paulo Medical School, Sao Paulo, Brazil

**Correspondence**
Claudia K. Suemoto, University of São Paulo Medical School, 455 Doutor Arnaldo Avenue, room 1355, São Paulo, SP, Brazil.
E-mail: cksuemoto@usp.br; csuemoto@gmail.com

**Funding information**
the Sao Paulo Research Foundation, Grant/Award Numbers: 06/55318-1, 09/09134-4, 16/24326-0; Alzheimer's Association Research Fellowship, Grant/Award Number: 18-566005; NIH, Grant/Award Number: K24053435

## Abstract

**Introduction:** Education, and less frequently occupation, has been associated with lower dementia risk in studies from high-income countries. We aimed to investigate the association of cognitive impairment with education and occupation in a low-middle-income country sample.

**Methods:** In this cross-sectional study, cognitive function was assessed by the Clinical Dementia Rating sum of boxes (CDR-SOB). We investigated the association of occupation complexity and education with CDR-SOB using adjusted linear regression models for age, sex, and neuropathological lesions.

**Results:** In 1023 participants, 77% had < 5 years of education, and 56% unskilled occupations. Compared to the group without education, those with formal education had lower CDR-SOB (1–4 years: $\beta$ = -0.99, 95% confidence interval [CI] = −1.85; −0.14, $P$ = .02; ≥5 years: $\beta$ = −1.42, 95% CI = −2.47; −0.38, $P$ = .008). Occupation complexity and demands were unrelated to cognition.

**Discussion:** Education, but not occupation, was related to better cognitive abilities independent of the presence of neuropathological insults.

KEYWORDS
cognitive impairment, developing countries, education, occupation

## 1 | BACKGROUND

Cognitive reserve (CR) refers to the flexibility and adaptability of cognitive networks to successfully cope with age-related brain pathology.[1] The cognitive abilities that are acquired during the life course mitigate the loss of function related to neuropathology in a dynamic process between CR and underlying brain reserve.[2] CR has been rarely measured directly due to its theoretical nature. However, several studies suggest that it is possible to measure the CR by integrating three components: (1) a socio-behavioral or functional measure of CR, (2) a cognitive function measure, and (3) an objective measure of age-related neuropathological changes.[1] Socio-behavioral proxies, often neglecting the neuropathological component, are the most frequent approach to study CR. They include formative factors believed to contribute to boosting CR, like educational attainment, occupation complexity, intelligence quotient, and physical activity.[1] Confluent evidence suggests that these proxies combined were associated with a 46% lower risk for incident dementia.[3]

Because different exposures across the lifespan can determine the CR, each proxy factor may contribute uniquely to building the reserve. Prior work by this group showed that even a few years of education contributed to CR with evidence of an interaction between low education and lacunar infarction on cognitive function.[4] Similarly, low education and smaller hippocampal volumes showed a multiplicative effect

  

on memory function in a sample with a median of only 4 years of formal education.[5] Education, one of the most explored CR proxies,[6] is an early-life contributor to CR, while occupation reflects a more downstream exposure during adulthood.[7] A recent systematic review, which included studies with dementia-related neuropathology measures, showed a consistent protective effect of education against cognitive impairment. In contrast, the association with occupation showed inconsistent results.[8] A well-characterized cohort with a wide variety of occupations and educational attainment is well posed to clarify this question. Most cohorts from high-income countries (HIC) are enriched for individuals with high educational attainment (12+ years) and relatively complex occupations.[9,10] Cohorts from low-/middle-income countries (LMIC) with more representation of low-complexity occupation and education suggest that both CR proxies were associated with lower dementia risk, but they lack neuropathological evaluation.[11,12] Here we used a well-characterized clinicopathological cohort of 1023 individuals with a wide range of occupational complexity and educational attainment to investigate the impact of education and occupation as proxies of CR on cognitive impairment. We also interrogated whether education and occupation protect against cognitive impairment associated with neurodegenerative and cerebrovascular lesions.

**RESEARCH IN CONTEXT**

1. **Systematic review**: We reviewed the literature using PubMed. Education and occupation have been associated with lower risk of dementia in several studies; however, the interaction of these protective factors with brain pathology on the dementia risk was less investigated with most studies from high-income countries. These relevant citations are appropriately cited.
2. **Interpretation**: Few years of education was associated with lower risk of cognitive impairment and interacted with lacunar infarcts. Otherwise, occupation complexity and demands were not related to cognitive abilities or interacted with neuropathologic lesions.
3. **Future directions**: Our study highlights the importance of even few years of education as a proxy for cognitive reserve in low-income settings. Future studies should expand our findings for education and occupation by including the longitudinal follow-up of participants followed by neuropathologic evaluation.

## 2 | METHODS

### 2.1 | Participants

A full-body autopsy is mandatory in the city of Sao Paulo for non-traumatic deaths, whose causes are not defined by health-care professionals before death. The Sao Paulo Autopsy Service from the University of Sao Paulo (SPAS-USP) performs ≈14,000 autopsies per year and accounts for ≈20% of death certifications in Sao Paulo.[13] The Biobank for Aging Studies (BAS) has collected brain donations in the SPAS-USP from 2004 to the present date (n = 1212). Inclusion criteria were age at death of 30 years or older and the presence of a knowledgeable informant to provide clinical information, who had at least weekly contact with the deceased in the 6 months prior to death. Exclusion criteria were brain tissue incompatible with neuropathological analyses (e.g., cerebrospinal fluid pH < 6.5 or major acute brain lesions including hemorrhages) or inconsistent data provided by the next of kin. The interviewers are trained to identify when information on one questionnaire contradicts the other, and we exclude cases in which any sign of inconsistency in the interview is detected.[14] For this study, we excluded participants with incomplete data for education (n = 52) and occupation (n = 137). While the next of kin wait for the autopsy procedures, they received information about the study and were invited to donate the deceased's brain after signing informed consent. The local ethics committee approved this study.

### 2.2 | Clinical and cognitive evaluation

The next of kin answered a semi-structured questionnaire that assessed clinical and functional information. The interview was conducted by trained gerontologists and lasted ≈40 minutes. Sociodemographic information included age at death, sex, race, education, and occupation. Race was reported by the next of kin according to the categories from the Brazilian census: White, Black, Brown, and other races (Asian and Native Brazilian).

Cognitive function was assessed using the Clinical Dementia Rating.[15] Due to the cross-sectional design, only the informant section of the CDR was applied. This approach was previously validated and showed good evidence of validity for detecting cognitive impairment by an informant in *post mortem* settings.[16] The CDR is a structured interview that assesses six cognitive and functional domains: memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Participants were rated on a 5-point scale for each domain according to the severity of the cognitive symptoms: 0, no impairment; 0.5, questionable impairment; 1, mild impairment; 2, moderate impairment; and 3, severe impairment. The CDR sum of boxes (CDR-SOB) is calculated by summing the score in each domain, and it ranges from 0 to 18 points.[17] Cognitive impairment was defined by an overall CDR classification of 0.5 or greater.

### 2.3 | Education and occupation

Education was reported by the next of kin as the number of years that the deceased attended school. Education had a skewed distribution in our sample; therefore, participants were categorized as having no formal education, 1 to 4 years of formal education, and 5 years or more of education.

Occupation was defined as the job that participants performed most of the time during their life. It was categorized as skilled (e.g., doctor, engineer, lawyer, teacher, manager), semiskilled (e.g., shop keeper, driver, mechanic, hairdresser, security guard), and unskilled (e.g., agricultural worker, housekeeper, bricklayer, gardener, and cook). Housework was classified as an unskilled occupation.

To better investigate the cognitive demands associated with each occupation, we used the 2010 Standard Occupational Classification of the O*Net database.[18] The O*Net database was created by the United States Department of Labor, Employment and Training Administration and contains specific descriptors of the abilities used in each occupation. First, we extracted the O*Net abilities list.[19] Then, three independent judges (a neuropsychologist [L.B.], a geriatrician [C.K.S.], and a neurologist [R.D.R.]) rated which one of the 52 items from the O*Net abilities list was associated with higher cognitive complexity. Only 24 items had full accordance among the three raters and were selected for dimension reduction analysis. A principal component analysis (PCA) was conducted on the 24 items and generated four components: (1) language (oral comprehension and expression, speech clarity, and recognition), (2) cognitive flexibility (visualization, originality, fluency of ideas and category flexibility), (3) reasoning (deductive and inductive reasoning, and speed of closure), and (4) perceptual-spatial orientation (auditory attention, response orientation, and spatial orientation) (Supplementary Methods and Figure S1 in supporting information). We also extracted a single component including all 24 items to represent a global measure of cognitive demand.

## 2.4 | Neuropathological evaluation

Brain tissue was obtained within 24 hours of death. The full description of the BAS neuropathology protocol has been published elsewhere[14 and a] detailed description is provided in the Supplementary Methods. Neuropathologic diagnoses were made blinded to the clinical status.

AD-related pathology was scored using the Braak and Braak staging for neurofibrillary pathology and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) criteria for neuritic plaques.[20,21] The Braak neurofibrillary tangle (NFT) score was categorized in Braak and Braak 0–II (absence to low burden of neurofibrillary tangles), III–IV (moderate burden), and V–VI (severe burden), and the CERAD score was categorized in 0-A (absence or sparse neuritic plaques), B (moderate amount of neuritic plaques), and C (frequent amount of neuritic plaques). Moreover, cerebral amyloid angiopathy (CAA) was analyzed using amyloid beta (A$\beta$) immunostaining. The localization of CAA (meningeal, gray matter, and/or white matter), as well as the severity and presence of capillary amyloid deposition, were examined.[22] CAA was considered present if widespread parenchymal pathology was observed in at least three different cortical areas (binary variable).

Assessment of cerebrovascular lesions was done macroscopically and microscopically. Histological evaluation using hematoxylin and eosin-stained slides was performed in all sampled areas. The presence of small vessel disease (SVD) was evaluated according to the degree of vessel changes, localization, and extension of disease. The SVD changes included small-vessel arteriolosclerosis/atherosclerosis and lipohyalinosis.[23] SVD was considered a binary variable with the presence of SVD requiring at least moderate or severe microvascular changes in three or more cortical regions.[23] Additionally, lacunar infarcts were registered by topography, stage, size, and number. Infarcts were also considered a binary variable and considered present when the participants had one large chronic infarct (> 1 cm) or at least three lacunae (< 1 cm) in any of the following strategic areas: thalamus, frontocingular cortex, basal forebrain and caudate, medial temporal area, or angular gyrus.[2] Lewy-type pathology was classified according to Braak et al.,[24] and the Braak Lewy body disease (LBD) score was categorized as 0 (absence of LBD), I–III (LBD limited to the brainstem), IV–VI (LBD in the cortex).

## 2.5 | Statistical analysis

We compared sociodemographic and clinical variables according to the presence of cognitive impairment (CDR≥0.5), using chi-square tests for categorical variables and unpaired t-test for interval ones. Moreover, we investigated the associations of education and occupation with study variables, using Chi-square tests and one-way analysis of variance according to variable type. We examined the association of education and occupation (independent variables) with neuropathology (dependent variable) using logistic regression models adjusted for age at death (discrete variable) and sex (binary variable). The associations of education and occupation with the CDR-SOB were investigated using linear regression models in two adjusted models. Education (no formal education, 1–4 years, and ≥5 years) and occupation (unskilled, semiskilled, and skilled) were the independent variables, and the CDR-SOB (discrete variable) was the dependent variable. The first model was adjusted for sociodemographic variables (age, sex, and race [White and Black]). The second model included the sociodemographic variables and the neuropathological lesions: (1) Braak NFT score categorized in Braak and Braak 0–II, III–IV, and V–VI; (2) CERAD score categorized in 0-A, B, and C; (3) infarcts (binary variable), (4) SVD (binary variable), (5) CAA (binary variable), and (6) Braak LBD score categorized in 0, I–III, IV–VI. To investigate whether the association between each neuropathological lesion and CDR-SOB differed by the educational level, we considered interaction terms between each brain lesion and education (categorized in 0–4 years and > 4 years) in linear regression models adjusted for age, sex, race, and other neuropathological lesions not included in the interaction term. We performed similar analyses to investigate the association between occupation and CDR-SOB, including the interaction between occupation categories (unskilled and semi-skilled plus skilled jobs) and each neuropathologic lesion. Education and occupation were used as binary variables to facilitate the interpretation of the interaction models.

We combined the categories of education and occupation into four groups: low education and low occupation, high education and low occupation, low education and high occupation, and high education and high occupation. To simplify the number of categories for the combined

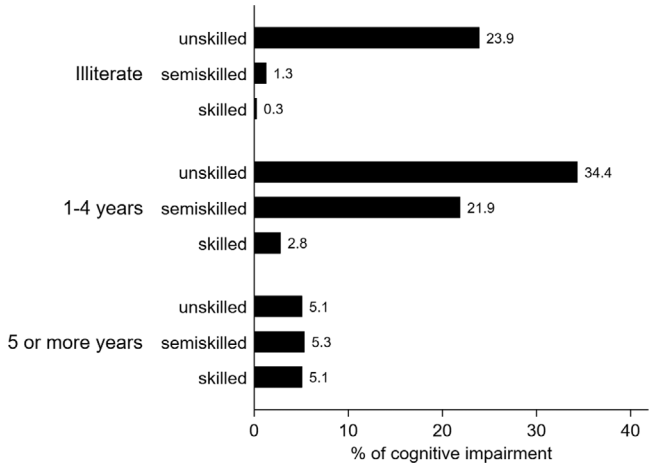


**FIGURE 1** Relative frequency (%) of cognitive impairment (Clinical Dementia Rating > 0), according to categories of education and occupation (n = 1023)

variable, low education was defined as four or fewer years of education, and low occupation was defined as an unskilled occupation. The association between CDR-SOB and the combined variable for education and occupation was investigated using linear regression models adjusted for sociodemographic and neuropathologic variables.

Finally, we investigated the relationship between occupation demands (reasoning, orientation, flexibility, and language) and CDR-SOB using adjusted linear models. The occupation demand variables were categorized in tertiles because a large proportion of our sample were housekeepers (n = 73) or housewives (n = 254) and had the same values for the demand variables. The associations between tertiles of occupation demands and CDR-SOB were investigated using linear regression models adjusted for age, sex, race, and other neuropathological lesions. The alpha level was set at 0.05 in two-tailed tests. We used Stata 15 for statistical analyses (StataCorp 2017).

## 3 | RESULTS

The mean age of the 1023 participants was 74.0±11.8 years, 51% were women, and 70% were White. The mean education of the sample was 4.1±3.7 years, and 56%, 36%, and 8% had unskilled, semi-skilled, and skilled occupations, respectively. Cognitive impairment was present in 393 (38%) participants with 11% of the sample with CDR = 0.5 and 27% with CDR ≥ 1. Participants with cognitive impairment were older, more women, had fewer years of formal education, and had higher frequency of unskilled occupation (Table 1). About 81% of participants with cognitive impairment had 4 years or less education and unskilled or semi-skilled jobs (Figure 1). Lower education was associated with older age, female sex, unskilled occupation, a higher frequency for NFTs, and SVD (Table S1 in supporting information). Unskilled occupations were related to older age, female sex, and higher Braak scores for NFTs (Table S2 in supporting information). Education was not associated with any neuropathologic lesion, while semi-skilled and skilled occupations were related to higher odds of moderate to frequent deposition of neuritic plaques in adjusted analyses for age at death and sex (Table 2).

Compared to the group with no formal education, participants with some degree of formal education had on average lower CDR-SOB scores after adjustments for age, sex, race, and neuropathologic lesions (1–4 years of education: $\beta = -0.99$, 95% confidence interval [CI] = −1.85; −0.14, $P = .02$; ≥ 5 years: $\beta = -1.42$, 95% CI = −2.47; −0.38, $P = .008$; Table 3). When we investigated the interaction between education and neuropathology, we found a nonsignificant borderline interaction between education and infarcts ($P = .07$), suggesting worse cognitive function in participants with both low education and infarcts (Figure 2).

On the other hand, cognitive abilities were not related to occupation complexity (Table 3) nor occupation demands (Table 4). Moreover, the interactions between occupation and neuropathology were not significant ($P > .05$ for all interactions; Figure S2 in supporting information). In addition, we did not find associations of CDR-SOB with the combined categories of education and occupation (Table S3 in supporting information).

## 4 | DISCUSSION

In a large sample of individuals with mainly low education and unskilled occupations, we found that even a few years of education was associated with better cognitive function. On the other hand, occupation complexity and work-related cognitive demands were not associated with CDR-SOB scores. Moreover, the combination of education and occupation categories was not related to cognitive abilities.

Similar to our previous smaller study on the association between education and cognition (n = 675),[4] education predicted better cognitive abilities even when we included several brain pathologies in the multiple regression models (n = 1023). Unfortunately, low education is common in LMIC with a prevalence of 76%.[25] The burden of low education on dementia risk in LMIC was the highest among nine modifiable risk factors with 11% of dementia cases being attributable to low education.[25] In Brazil, where the average education among older adults was only 5 years,[26] illiteracy doubled the incidence rate of dementia compared to having 8 years or more of education.[27] Education is considered an early contributor of the CR that was shown previously to be protective against cognitive decline independent of the neuropathologic burden.[28,29] Moreover, education modified the association between neurodegenerative and cerebrovascular lesions in previous studies.[4,30] A recent study with 752 participants for the Religious Orders Study and Memory Aging Project (ROSMAP) found that education was only related to the baseline level of cognitive function. However, it was not related to the slower rate of cognitive decline, later onset of decline near dementia onset or death, or residual cognitive decline not attributable to the neuropathologic burden, contradicting most of the CR theory.[9] Moreover, Wilson et al. found that the interaction between higher education and neurodegenerative markers was related to the earlier onset of accelerated cognitive decline.[9] Further-

**TABLE 1** Characteristics of the sample according to the presence of cognitive impairment (n = 1023)

| | All | Cognitive impairment | | |
|---|---|---|---|---|
| | (n = 1023) | No (n = 630) | Yes (n = 393) | *P* |
| Age (years), mean (SD)* | 74.0 (11.8) | 71.5 (11.9) | 77.9 (10.6) | <.001 |
| Male, %† | 48.5 | 52.4 | 42.2 | .002 |
| Education (years), mean (SD)* | 4.1 (3.7) | 4.6 (3.8) | 3.4 (3.3) | <.001 |
| Occupation, %† | | | | <.001 |
| Unskilled | 55.8 | 51.1 | 63.4 | |
| Semi-skilled | 35.9 | 40.5 | 28.5 | |
| Skilled | 8.3 | 8.4 | 8.1 | |
| BB, %† | | | | |
| *0–II* | 64.5 | 75.2% | 47.3% | <.001 |
| *III–IV* | 24.3 | 21.4% | 28.8% | |
| *V–VI* | 11.2 | 3.3% | 23.9% | |
| CERAD, %† | | | | |
| *Absent or scarce* | 61.2 | 69.4% | 48.1% | <.001 |
| *Moderate* | 13.6 | 13.7% | 13.5% | |
| *Frequent* | 25.2 | 17.0% | 38.4% | |
| BB LBD, %† | | | | |
| *0* | 90.3 | 92.4% | 87.0% | <.001 |
| *I–III* | 4.4 | 4.8% | 3.8% | |
| *IV–VI* | 5.3 | 2.9% | 9.2% | |
| Infarcts, %† | 12.1 | 5.2% | 23.2% | <.001 |
| Small vessel disease, %† | 14.2 | 8.7% | 22.9% | <.001 |

Abbreviations: BB LBD, Braak & Braak score for Lewy body disease; BB, Braak & Braak score for neurofibrillary tangles; CERAD, Consortium to Establish a Registry for Alzheimer's Disease score for neuritic plaques; SD, standard deviation.
*Unpaired t-test.
†Chi-square test.

**TABLE 2** Association of neuropathology with education and occupation (n = 1023)

| | Education* | | Occupation† | |
|---|---|---|---|---|
| | OR (95% CI) | *P* | OR (95% CI) | *P* |
| BB NFT ≥ IV | 1.16 (0.75–1.78) | .50 | 1.06 (0.74–1.53) | .74 |
| CERAD ≥ Moderate | 1.14 (0.76–1.70) | .53 | 1.53 (1.08–2.18) | .02 |
| BB LBD ≥ IV | 1.31 (0.66–2.61) | .43 | 1.05 (0.57–1.95) | .88 |
| Infarcts | 0.97 (0.59–1.58) | .90 | 0.94 (0.61–1.44) | .77 |
| Small vessel disease | 0.75 (0.46–1.23) | .25 | 0.90 (0.60–1.37) | .63 |

Abbreviations: BB LBD, Braak & Braak score for Lewy body disease; BB NFT, Braak & Braak score for neurofibrillary tangles; CERAD, Consortium to Establish a Registry for Alzheimer's Disease score for neuritic plaques; CI, confidence interval; OR, odds ratio.
*5 or more years of education compared to 0-4 years.
†Semi-skilled and skilled occupation compared to unskilled occupation.
Notes: Logistic regression models adjusted for age and sex. Neuropathology was the dependent variable and was used as binary variable.

more, a prior study showed higher education was related to lower frequency of cerebral infarcts,[9] while we did not find any associations of education with neurodegenerative and cerebrovascular lesions.

We did not find any association between occupation complexity and cognitive abilities. Likewise, occupation did not modify the association between neuropathology and cognitive function in our study. Indeed, the association of occupation and cognitive function has been mixed. While some studies found that occupation complexity was protective against dementia,[31–33] others found no association.[8,34,35] Occupation complexity is considered a more downstream proxy of CR that

**TABLE 3** Association of Clinical Dementia Rating sum of boxes with education and occupation (n = 1023)

| | Univariate | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|
| | *β* (95% CI) | *P* | *β* (95% CI) | *P* | *β* (95% CI) | *P* |
| Education (years)* | | | | | | |
| 1–4 | −1.77 (−2.79; −0.76) | .001 | −0.96 (−1.95; 0.03) | .06 | −0.99 (−1.85; −0.14) | .02 |
| 5 or more | −3.05 (−4.24; −0.76) | <.001 | −1.16 (−2.37; 0.03) | .06 | −1.42 (−2.47; −0.38) | .008 |
| Occupation† | | | | | | |
| Semiskilled | −1.53 (−2.36; −0.70) | <.001 | −0.42 (−1.29; 0.45) | .34 | −0.37 (−1.12; 0.39) | .34 |
| Skilled | −0.53 (−1.96; 0.90) | .47 | 0.73 (−0.7; 2.16) | .32 | −0.16 (−1.40; 1.08) | .80 |

*Reference: no formal education.
†Reference: unskilled.
Notes: Model 1: linear regression model adjusted for age, sex, and race.
Model 2: linear regression model adjusted for age, sex, race, neurofibrillary tangles (Braak & Braak score), neuritic plaques (CERAD score), Lewy body disease (Braak LBD score), infarcts, small vessel disease, and cerebral amyloid angiopathy.
Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; LBD, Lewy body disease.

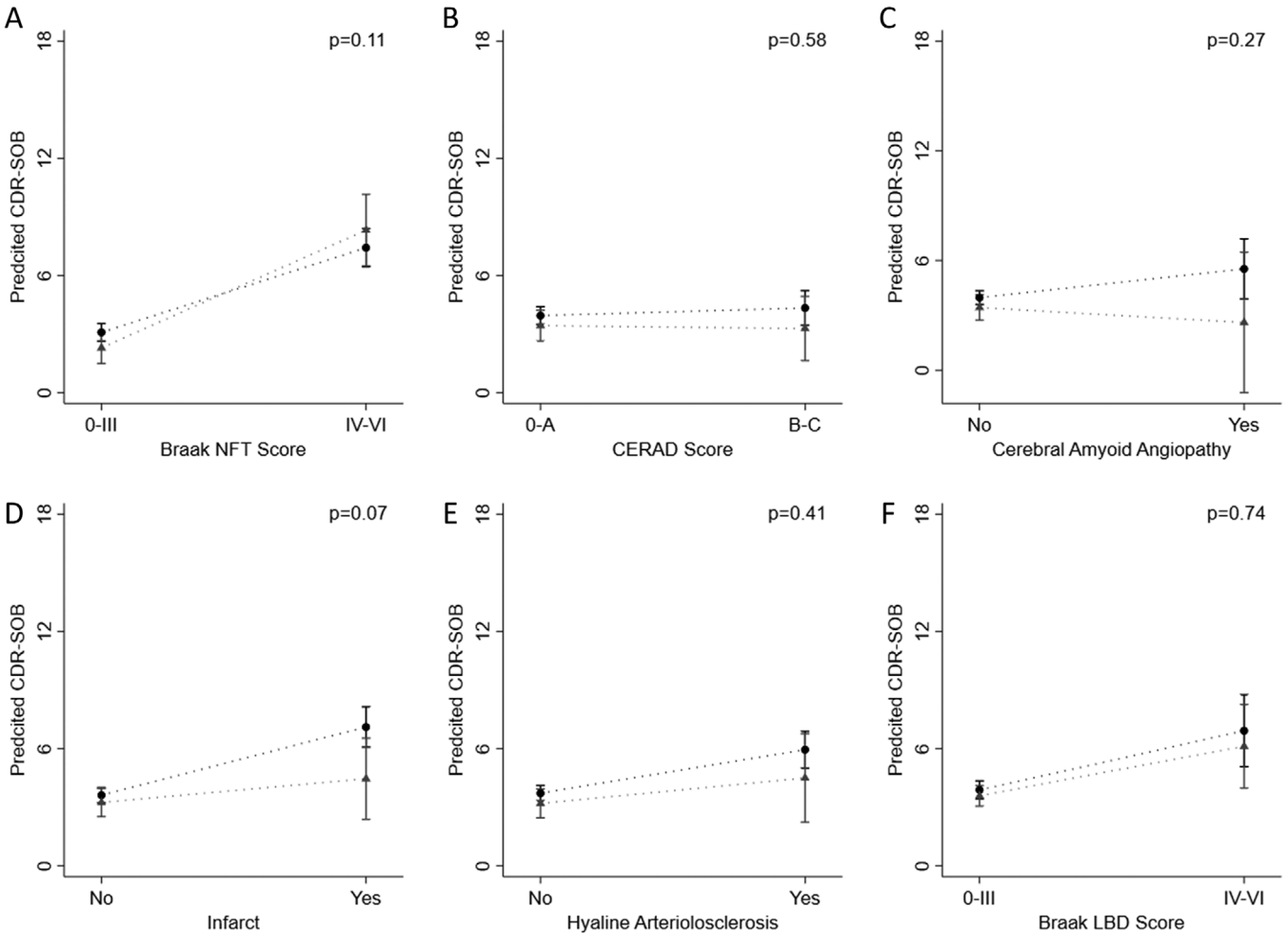


**FIGURE 2** Predicted Clinical Dementia Rating sum of boxes (CDR-SOB; y-axis) considering an interaction term of education (black circle: 0–4 years of education, and gray triangle: ≥ 5 years of education) with (A) neurofibrillary tangles (NFT; Braak NFT score); (B) neuritic plaques (Consortium to Establish a Registry for Alzheimer's Disease [CERAD] score); (C) cerebral amyloid angiopathy; (D) lacunar infarcts; (E) small vessel disease; and (F) Lewy body disease (LBD; Braak LBD score). *P*-values for the interaction between education and each neuropathological lesion

**TABLE 4** Association between Clinical Dementia Rating sum of boxes and occupation demands (n = 1002)*

| Demand | Univariate | Model 1 | Model 2 | Model 3 |
|---|---|---|---|---|
| Reasoning | | | | |
| 2nd tertile | −0.78 (−1.76; 0.20) | 0.58 (−0.50; 1.65) | 0.19 (−0.74; 1.11) | 0.27 (−0.66; 1.20) |
| 3rd tertile | −1.10 (−2.02; −0.18)* | −0.10 (−1.12; 0.93) | −0.31 (−1.20; 0.58) | −0.12 (−1.04; 0.81) |
| Orientation | | | | |
| 2nd tertile | 0.77 (−0.51; 2.05) | −0.12 (−1.37; 1.13) | −0.48 (−1.55; 0.60) | −0.53 (−1.60; 0.54) |
| 3rd tertile | −1.39 (−2.24; −0.53)* | −0.46 (−1.48; 0.56) | −0.14 (−1.03; 0.74) | −0.28 (−1.17; 0.62) |
| Flexibility | | | | |
| 2nd tertile | −1.89 (−2.81; −0.97)* | −0.12 (−1.37; 1.13) | −0.48 (−1.55; 0.60) | −0.53 (−1.60; 0.54) |
| 3rd tertile | −0.96 (−1.93; 0.01) | −0.46 (−1.48; 0.56) | −0.14 (−1.03; 0.74) | −0.28 (−1.17; 0.62) |
| Language | | | | |
| 2nd tertile | −2.06 (−3.03; −1.09)* | −0.48 (−1.61; 0.65) | −0.25 (−1.23; 0.72) | −0.20 (−1.17; 0.78) |
| 3rd tertile | −0.81 (−1.71; 0.11) | 0.38 (−0.67; 1.43) | 0.16 (−0.75; 1.06) | 0.40 (−0.54; 1.33) |
| Global | | | | |
| 2nd tertile | −1.44 (−2.39; −0.49) | −0.26 (−1.36; 0.84) | −0.02 (−0.97; 0.92) | 0.03 (−0.92; 0.98) |
| 3rd tertile | −1.34 (−2.28; −0.40) | −0.17 (−1.27; 0.94) | −0.38 (−1.33; 0.57) | −0.20 (−1.18; 0.79) |

Notes: Reference: 1st tertile (lower occupation demand score).
Model 1: linear regression model adjusted for age, sex, and race.
Model 2: linear regression model adjusted for age, sex, race, neurofibrillary tangles (Braak & Braak score), neuritic plaques (CERAD score), Lewy body disease (Braak LBD score), infarcts, small vessel disease, and cerebral amyloid angiopathy.
Model 3: Linear regression model adjusted for age, sex, race, neuropathological lesions described in Model 2, and education.
*$P < .05$.
Abbreviations: CERAD, Consortium to Establish a Registry for Alzheimer's Disease; CI, confidence interval; LBD, Lewy body disease.

is directly influenced by educational attainment during childhood and early adulthood. The decreased dementia risk related to occupation may be related to exposure to stressful work-related events, rather than related only to the effect of cognitively stimulating activities on brain reserve.[36] Considering that occupation complexity could not capture the cognitive demands related to participants' work, we calculated these demands based on a previous study that found a lower dementia risk among participants with occupations with demands involving information processing and pattern detection.[19] The absence of association with work demands may be related to the low diversity of demands in our sample, where more than 30% of the sample were housewives or housekeepers, a reality that was very different from the German cohort.[19] The concept of CR was originated to describe non-pathologic contributors to cognitive ability;[1] therefore, our findings of no association of education with any neuropathology is expected.

Our findings of cognitive abilities being associated with education, but not with occupation, is in line with a study from the 10/66 Dementia Research Group with data from Cuba, the Dominican Republic, Venezuela, Peru, Mexico, and China. In this study, education was protective against dementia incidence (hazard ratio [HR] = 0.89, 95% CI = 0.81–0.97), while occupation was not associated with dementia risk (HR = 1.04, 95% CI = 0.95–1.13).[11] In contrast, low occupational complexity was responsible for 38% of dementia cases, with an increase in population-attributable fraction to 45% when both low education and occupation were considered in another cross-sectional Brazilian study.[12] It is important to note that these studies did not have neuropathological evaluation. We are unaware of other studies investigating both education and occupation in the same sample with clinicopathologic information.

This study adds important evidence on the role of education as a proxy of the CR as we analyzed data from more than one thousand participants with complete neuropathologic evaluation from an LMIC. Nineteen percent of the sample had no education and 58% had 1 to 4 years of formal education. Similarly, 56% had unskilled jobs and only 8% had skilled jobs that required a university degree. This lower socioeconomic profile is very different from previous studies on CR performed in HIC.[8] Another important strength is the investigation of interactions of several neuropathologic lesions with education and occupation. The investigation of these interactions is considered a more accurate measure of CR than the simple evaluation of the associations between CR proxies and cognitive function.[1]

On the other hand, the study limitations need also to be highlighted. This is a cross-sectional study, and participants were not followed before death. However, it is important to highlight we acquired education and occupation data from the lifespan, bringing some longitudinal perspective to the association between the cognitive reserve proxies and cognitive abilities in this study. The informant provided socioeconomic and clinical information on the deceased. To overcome this important limitation, we only included informants with at least weekly contact with the deceased and excluded cases with inconsistent information based on the presence of conflicting information in different cognitive and functional questionnaires. Although the CDR-SOB was

not validated for *post mortem* settings, the interviewers were exhaustively trained in the CDR application, and the overall CDR classification showed good validation in *post mortem* studies.[16] Despite all these precautions regarding the quality of clinical information provided by the informant, recall bias could still be present. Although selection bias is another threat to study validity, we had previously shown that demographic data in our sample are similar to data from individuals who die in the city of Sao Paulo and are not submitted to an autopsy, which suggests that our sample is representative of local deaths.[14] Moreover, residual confounding could still be present even after model adjustments for sociodemographic variables. Another limitation is the possibility of type 1 error due to multiple testing performed in this study. Finally, the interaction between infarcts and education did not reach statistical significance, which suggests that a larger sample size would be required to confirm our findings.

In conclusion, in 1023 participants with mostly low education and unskilled occupations, even a few years of education was associated with better cognitive function. On the other hand, occupation was not associated with cognitive function and it did not show interactions with neuropathological lesions. Future longitudinal studies from LMIC with more precise measures of lifestyle and social-behavioral activities prior to death are important to confirm the role of cognitive reserve in preventing dementia later in life.

## ACKNOWLEDGMENTS

This work was supported by the Sao Paulo Research Foundation (grant numbers 06/55318-1, 09/09134-4, 16/24326-0); Alzheimer's Association Research Fellowship (grant number 18-566005). LTS is funded by NIH K24053435.

## CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

## ORCID

*Claudia K. Suemoto* https://orcid.org/0000-0002-5942-4778

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## SUPPORTING INFORMATION

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**How to cite this article:** Suemoto CK, Bertola L, Grinberg LT, et al. Education, but not occupation, is associated with cognitive impairment: The role of cognitive reserve in a sample from a low-to-middle-income country. *Alzheimer's Dement*. 2021;1-8. https://doi.org/10.1002/alz.12542