Dialogues in Health 5 (2024) 100183

Contents lists available at ScienceDirect

Dialogues in Health

journal homepage: www.elsevier.com/locate/dialog

The impact of education level and socioeconomic status on the association between depressive symptoms and memory in an older population in Latin America: An exploratory analysis from the Brazilian Longitudinal Study of Aging (ELSI-BRAZIL)

Karla Loss [a,1], Wilson Fandino [b,1], Bassel Almarie [c], Blanca Bazan-Perkins [d,e], Julia Minetto [f], Nadine Aranis [g], Thiago Monaco [h], Aisha Aladab [i], Kevin Pacheco-Barrios [c,j,2,**], Felipe Fregni [c,2,*]

[a] Pediatrics Department. Federal University of Espirito Santo, Brazil
[b] Anaesthetics Department, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom
[c] Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA
[d] Laboratory of Immunopharmacology, Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas, Mexico City, Mexico
[e] Tecnológico de Monterrey, Escuela de Medicina y Ciencias de la Salud, Mexico City, Mexico
[f] Liver Transplantation Department, Garrahan Pediatric Hospital, Buenos Aires, Argentina
[g] Servicio de Medicina Física y Rehabilitación, Clínica Alemana Universidad del Desarrollo, Santiago, Chile
[h] Eurofarma Laboratorios, Sao Paulo (SP), Brazil
[i] Pulmonary Division, Hamad General Hospital, Qatar
[j] Universidad San Ignacio de Loyola, Vicerrectorado de Investigación, Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Lima, Peru

ARTICLE INFO

Keywords:
Memory
Cognitive impairment
Depressive symptoms
Aging
Socioeconomic status
Educational level

ABSTRACT

Purpose: The globally increasing older population raises concerns about age-related conditions, including cognitive impairment and depressive symptoms. In Latin America, nearly one-third of the population is affected by either of these conditions. However, data investigating the association between cognitive impairment and depressive symptoms, particularly in Brazil, are limited to small-scale studies that have not carefully examined the critical effects of variables such as education level and socioeconomic status on this relationship. We aimed at exploring this association in a representative population-based cohort.

Methods: We used the Brazilian Longitudinal Study of Aging (ELSI-BRAZIL) database to examine the relationship between depressive symptoms and cognitive impairment in Brazilian older adults, adjusted for potential confounders. Direct acyclic graphs and multivariable linear regression were used to build our model. Depressive symptoms were measured using a short version of the Center for Epidemiologic Studies Scale (CES D-8), and combined memory recall test as a surrogate of cognitive impairment.

Results: The study included 8280 participants. Only education level was identified as a confounder for the relationship between memory loss and depressive symptoms. After adjusting for age, sex, and education level, there was strong evidence for a negative association between depressive symptoms and memory performance. For every 5-unit increase in the CES D-8 score, there was a reduction in memory capacity, translating to a loss of

Abbreviations: ELSI-BRAZIL, Brazilian Longitudinal Study of Aging; CES D-8, Center for Epidemiologic Studies Depression Scale (eight-item version); SES, Socioeconomic Status; IRB, Institutional Review Board; CWRT, Combined Words Recall Test; DAGs, Direct Acyclic Graphs; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; CIE, Change in Estimates.

* Correspondence to: F. Fregni, Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, 96 13th Street, Charlestown, Boston, MA, USA.

** Correspondence to: K. Pacheco-Barrios Universidad San Ignacio de Loyola, Vicerrectorado de Investigación, Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, 550 La Fontana Avenue, 15023 Lima, Peru.

E-mail addresses: kpachecobarrios@mgh.harvard.edu (K. Pacheco-Barrios), felipe.fregni@mgh.harvard.edu (F. Fregni).

[1] First authors

[2] Equally contributing senior authors.

https://doi.org/10.1016/j.dialog.2024.100183
Received 17 April 2024; Received in revised form 2 May 2024; Accepted 27 May 2024
Available online 6 June 2024

approximately one word in the combined words recall test (mean − 0.18, 95% CI -0.22; −0.15, $P < 0.001$). In addition, we found strong evidence for an interaction between socioeconomic status and depressive symptoms. Subjects belonging to medium socioeconomic status (SES) showed more pronounced memory decline, when compared to those with lower SES (mean − 0.28, 95% CI -0.42 to −0.14, $P < 0.001$).
Conclusions: In adults aged over 50, after adjusting for sex, age, and educational level, a 5-unit increase in CES D-8 score is associated with loss of one point in the combined memory recall test. This association seems to be confounded by educational level and significantly modified by socioeconomic status.

1. Introduction

The association between depression and cognitive impairment in the older population has been well-established over the years. Depression and cognitive impairment share common risk factors, such as cardiovascular and cerebrovascular comorbidities, alongside underlying pathophysiological mechanisms, including plaque deposition and alterations in brain microRNA patterns. (1,2) Early studies suggested that depressive symptoms can serve as the initial manifestation of cognitive impairment, develop as a psychological effect of perceiving cognitive impairment, (3,4) or be a consequence of cumulative less meaningful cognitive engagement over the years because of depression-related behavioral modifications. (5) Additionally, severe or prolonged depression has been linked to a higher risk of dementia. (6) On the other hand, the causality could be in the other direction: cognitive impairment leading to depression. (1)

Even though the relationship between depression and cognitive impairment seems to be well established, there are important factors that might confound this relationship, including educational level and socioeconomic status (SES). Since these factors are substantially more important in Latin America, given the high rates of low educational level and SES, it is important to re-examine the relationship between depression and cognitive impairment in populations in Latin America. (7)

In recent years, there has been a demographic shift marked by an increase in the older population. As individuals age, cognitive decline becomes more evident. (8) In Latin America alone, the prevalence of cognitive impairment reaches up to 34%, possibly due to the increased presence of modifiable risk factors when compared to high-income countries. (9) Concurrently, mental health conditions, including depression and depressive symptoms, have emerged as highly prevalent conditions within this demographic population, and are associated with an increase in age. (10) Moreover, the average prevalence of depression is approximately 32%, surging even higher in developing nations to around 40%. (11,12) In Brazil, the prevalence of depressive symptoms in individuals >65 years is estimated to be 37.2%, which is higher than the reported in developed countries. (13)

This demographic shift together with the complex relationship between depression and cognitive decline in the older population underscores the necessity of further exploring this association. The majority of studies investigating the link between depressive symptoms and cognition, specifically in Brazil, are limited to small-scale studies using convenience sampling methods. (14,15) Moreover, studies of larger sample sizes overlooked the evaluation of this association. For instance, in a study investigating the risk factors associated with subjective cognitive decline, depressive symptoms were excluded from the analysis. (16) Therefore, we aimed to investigate the relationship between depressive symptoms and cognitive impairment, measured by memory test in a large population–based sample, the Brazilian Longitudinal Study of Aging (ELSI-Brazil) wave 1. The main objective was to study depressive symptoms as the exposure factor for individuals interviewed in the ELSI-Brazil study and assessing memory loss as the main marker of cognitive impairment. In addition, we investigated the potential confounders and effect modifiers in this relationship.

2. Materials and methods

2.1. Materials

All variables were extracted from the open-access ELSI-Brazil questionnaire. (17) This questionnaire was designed to explore factors associated with aging in adults aged 50 years or older across five geographic regions in Brazil (north, north-east, center-west, south, and south-east), spanning 70 municipalities. The sampling method used a design with selection stages, combining stratification of municipalities, census tracts, and households to ensure a representative cohort of urban and rural areas including small, medium, and large cities. Participants provided a informed consent approved by the IRB of the original study. (17)

The original dataset comprised 1083 variables, including potential outcomes and independent variables. These variables were distributed in the following sections: Section E (sociodemographic characteristics), Section F (neighborhood), Section G (discrimination), Section H (life and health history), Section I (work and retirement), Section K (family members support), Section L (health behaviors), Section M (women's health), Section N (general health and diseases), Section O (oral health), Section P (disability), Section Q (cognition), Section P (depressive symptoms), Section S (psychosocial), Section T (use of medications), Section U (use of health services) and physical measurements. A comprehensive description of the original dataset can be found in the individual and household interview questionnaires, which are readily available on the internet [https://elsi.cpqrr.fiocruz.br/en/home-english/questionnaires/].

2.2. Data cleaning

Each variable within the ELSI questionnaire was individually assessed to determine association with cognition from both clinical and biological perspectives. Those variables found unrelated were subsequently removed. Categorical variables were recoded when deemed appropriate, and category levels with few observations were merged with the adjacent category, provided that the recoding was pertinent from a clinical standpoint. The variables included in this study after the data-cleaning process are listed in Supplementary Material 1.

2.3. Main outcome

We defined memory loss as a surrogate outcome for cognitive impairment. Memory loss was measured by recording the number of words recalled by the interviewee after the interviewer presented a deliberately lengthy list of 10 words. Following the reading, the interviewee was asked to promptly repeat the words, and a score from 0 to 10 was recorded (immediate recall test). Subsequently, the interviewee engaged in two tasks: listing as many recalled names of animals as possible within one minute and writing the initials of their name on a piece of paper. After completing these tasks, the interviewee was asked to list again the initial 10 words, and a score from 0 to 10 was also recorded (delayed recall test). The time elapsed between the immediate and delayed recall test was approximately 5 min. Finally, a combined score ranging from 0 to 20 was generated by summing the scores obtained from immediate recall and delayed recall tests. We used this

combined score as a surrogate outcome for cognitive impairment based on previous literature that pointed to both immediate and delayed word recall tests as predictors of cognitive decline. (18) This variable, hereafter referred to as combined words recall test (CWRT), was treated as continuous for analysis purposes.

2.4. Main exposure

In our study, we used the eight-item version of the Center for Epidemiological Studies Depression Scale (CES D-8) as a validated tool for assessing depressive symptoms experienced by participants in the last week. The scale included eight questions related to general feelings experienced during the week, including feelings of depression, feelings that things were more difficult than they used to be, sleep issues, happiness, loneliness, enjoyment of life, sadness, and feeling unable to carry out tasks. (19) These items were included in the ELSI questionnaire with four possible answers: yes, no, does not apply, or did not know/did not answer. After excluding participants for whom these questions did not apply, and participants who did not answer the questions, we generated a score from 0 to 8, based on the number of positive answers obtained. The variable CES D-8 was treated as continuous for the main analysis.

2.5. Covariates

Sociodemographic covariates included age, self-reported sex, race, educational level, and SES. Household income per capita was used to stratify participants into their SES, utilizing as reference the year of 2014. (20) Clinical covariates included self-reported previous diagnoses of hypertension, stroke, and diabetes. Obesity was defined by a body mass index exceeding 30 kg per square meter, calculated using weight and height measured during the study interview. Lifestyle variables encompassed smoking, current alcohol consumption, and physical activity level. Social connectivity factors, such as meeting with relatives and talking with children. Sensorial factors comprising self-reported vision and hearing impairments were also incorporated.

3. Methods

The present study was reported according to the STROBE guidelines. (21) In order to investigate the available evidence, we conducted a Medline search for population-based epidemiological studies, using the search terms: ("cognition disorders, memory, cognitive dysfunction"[Mesh] OR) AND ("depressive symptoms, mood disorder" [Mesh] OR) AND ("aged, adult" [MESH] OR) AND ("Brazil"), without language or publication date restrictions. All analyses were conducted with Stata® 18.0 (StataCorp. 2023, College Station, TX).

3.1. Descriptive analysis

For descriptive purposes, all available observations were included, following a complete-case analysis approach. All descriptive data were summarized with mean and standard deviation, with prior confirmation of the normal distribution of outcomes. Additionally, categorical variables were described in frequency and proportions.

3.2. Data analysis

In accordance with the proposed objectives of this study, we sought to develop an exploratory explanatory model. The following variables were identified as potential theoretical confounders for the relationship between depressive symptoms and cognitive function: age, sex, alcohol, smoking, physical activity, hearing impairment, vision impairment, education level, SES, conversation with relatives, conversation with children, race, diabetes, hypertension, stroke, and obesity.

Direct acyclic graphs (DAGs) were sketched to explore the association between cognitive function and depressive symptoms, and all potential confounders listed above (Supplementary material 2). The DAGs were created using DAGitty 3.0 software. (22)

The study involved constructing DAGs to identify potential confounders, colliders, and mediators. An unadjusted model was developed, including the CES D-8 score as exposure and the CWRT as outcome. Age and sex were included a priori due to their clinical and biological importance. Thus, a baseline linear regression model was constructed with CWRT as a continuous outcome, and CES D-8, age, and sex as explanatory variables. Potential confounders were added sequentially to the baseline model using a forwards selection strategy. Variables with a change in estimates (CIE) exceeding 10% were considered confounders for the relationship between cognitive function and depressive symptoms. A multivariable linear regression model adjusted for surveys was developed, including the main exposure, age, sex, and confounders identified as variables with CIE $>$ 10%.

We also explored potential interactions in the adjusted model. In particular, we hypothesized that sex, race, physical activity and SES could modify the relationship between CES D-8 and CWRT.

In evaluating the assumptions for linear regression, histograms, and qnorm plots were obtained for CWRT and CES D-8 to determine normality, scatterplots representing CWRT and CES D-8 were generated to evaluate linearity, and residuals were plotted against CES-D8 values to assess homoscedasticity.

In a sensitivity analysis, a saturated model was constructed including all variables identified as potential confounders in the DAGs. This saturated model, along with a baseline model including only age and sex as predictor variables, was compared with our proposed model, in order to check the robustness of the results. In addition, we compared the results when including CES D-8 as a continuous or binary variable. To this end, the variable CES D-8 was categorized according to the presence of non-severe (CES D-8 from 0 to 3) or severe (CES D-8 from 4 to 8) depressive symptoms. (19) We also included interaction terms in the adjusted model between CES D-8 score and sex, race, physical activity and SES as potential effect modifiers in the relationship between depressive symptoms and memory in our population. Finally, the *E*-value was calculated to assess the robustness against unmeasured confounding. (23) The code used in STATA to perform all analyses are presented in Supplementary material 4.

4. Results

4.1. Study population

A total of 9412 participants were included in the ELSI wave 1 cohort. Among these, 1132 were excluded for not being the primary respondent for the survey or having missing data concerning depressive symptoms (Fig. 1). Consequently, the final sample comprised 8280 participants, with a mean age of 62.7 +/− 9.5 years. Of these participants, approximately half were female (56.2%), self-identified as belonging to the brown racial category (47.6%), and had an educational background of $<$4 years (53.1%). Moreover, the majority of participants were classified within the SES strata of D/E (90%). The analysis revealed a mean CES D-8 score of 4 $\pm$ 1.8, with 53.3% of participants exhibiting severe depressive symptoms. The baseline characteristics including demographics, motor, sensorial, and the presence of comorbidities were described based on the presence or absence of severe depressive symptoms (Table 1).

4.2. Association between depressive symptoms and memory

Four models were constructed to explore the relationship between depressive symptoms and memory. The unadjusted model demonstrated a negative association between memory and CES D-8 score, yielding a coefficient of −0.23 (95% CI -0.28; −0.18, $P < 0.001$). The baseline model, adjusted for sex and age, revealed an amplified influence of CES

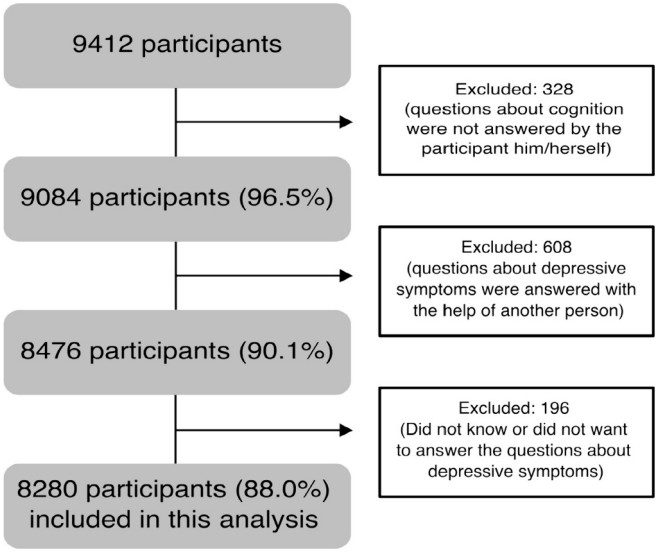

Fig. 1. Flowchart of patients included in the analysis.

D-8 score on memory, with a coefficient of −0.27 (95% CI -0.31; −0.23, $P < 0.001$). In the multiple linear regression adjusted model, only educational level was identified as a confounder and independent predictor in the relationship between depressive symptoms and memory, with a coefficient of −0.18 (95% CI -0.22; −0.15, P < 0.001) (Table 2). Lastly, in the saturated model including all variables, the model revealed a negative effect for every unit increase in the CES D-8 score (coefficient − 0.15, 95% CI -0.19; −0.11, *P*-value<0.001). (Supplemental material 3).

4.3. Effect modification

We identified SES as an effect modifier for the relationship between depressive symptoms and memory (Fig. 2). Participants categorized in the SES stratum C presented a more pronounced decrease on the CWRT for each unit increase on the CES D-8 scale when compared with participants categorized in the strata D/E. Accordingly, individuals in the SES stratum C showed an average reduction of 0.43 words for every unit increase in depression symptoms. On the other hand, among those in SES strata D/E, there was an average reduction of 0.15 words for every unit increase in depressive symptoms. Sex, race, and physical activity presented no effect modification in the relationship between depressive symptoms and memory loss.

4.4. Sensitivity analysis

Sensitivity analyses showed a negative association between the CES D-8 category and words combined scores, indicating that the group with severe depressive symptoms is associated with lower scores (coefficient − 0.63, 95% CI -0.77; −0.49, *P*-value<0.001). Similarly, negative associations were demonstrated in various age categories, suggesting a decline in scores with advancing age. Men showed lower scores compared to women. In contrast, higher education levels (1–4, 5–8, >8) were positively associated with words combined scores. All reported coefficients were statistically significant ($p < 0.001$). The model's R-squared value was 0.26, indicating 26% of the variance in words combined scores was explained by the predictors.

The *E*-value for the model including CES D-8 as categorical variable as exposure and adjusted for sex, age and educational level was 1.68, with a lower bound of the 95% confidence interval 1.56. Thus, with the

Table 1
Baseline characteristics of the study sample, according to the presence of non-severe vs. severe depressive symptoms.

Variable	CES D-8* (0–3) (*N* = 3871, 46.7%)	CES D-8* (4–8) (*N* = 4409, 53.3%)
Age (years)		
50–54	902 (23.5)	1146 (26.1)
55–59	744 (19.3)	742 (20.7)
60–64	695 (18.1)	588 (16.9)
65–69	574 (14.9)	425 (13.4)
70–74	439 (11.4)	425 (9.7)
75–79	285 (7.4)	336 (7.7)
80–84	137 (3.6)	179 (4.1)
≥85	71 (1.9)	66 (1.5)
Sex		
Female	1868 (48.3)	2788 (63.2)
Male	2003 (51.7)	1621 (36.8)
Race		
White	1614 (43.2)	1495 (35.3)
Black	350 (9.4)	445 (10.5)
Brown	1665 (44.6)	2132 (50.3)
Yellow	38 (1.0)	41 (1.0)
Indigenous	67 (1.8)	126 (3.0)
Education (years)		
None	495 (12.9)	708 (16.2)
1–4	1400 (36.3)	1773 (40.4)
5–8	750 (19.5)	949 (21.7)
≥8	1208 (31.3)	954 (21.8)
SES †		
E (0 - R$ 1254)	2689 (69.5)	3521 (79.9)
D (R$ 1255 - R$ 2004)	653 (16.9)	562 (12.7)
C (R$ 2005 - R$ 8640)	486 (12.5)	311 (7.1)
B (R$ 8641 - R$ 11,261)	19 (0.5)	10 (0.2)
A (> R$ 11,262)	24 (0.6)	5 (0.1)
Physical activity §		
None	1238 (32.4)	1637 (37.6)
Mild	1232 (32.3)	1246 (28.6)
Moderate	1050 (27.5)	1147 (26.3)
Vigorous	301 (7.9)	326 (7.5)
Alcohol consumption		
Never	2623 (67.8)	3339 (75.7)
Less than once a month	251 (6.5)	248 (5.6)
Once a month or more	995 (25.7)	822 (18.6)
Smoking		
Never	1736 (44.9)	1991 (45.2)
Current or past smoker	2135 (55.1)	2418 (54.8)
Diabetes	575 (14.9)	735 (16.8)
Hypertension	1871 (48.4)	2477 (56.3)
Obesity (BMI > 30 kg/m2) ‡	1052 (27.9)	1309 (30.6)
Stroke	120 (3.1)	267 (6.1)
Hearing Self-assessment		
Good or very good	2880 (74.4)	2939 (66.7)
Regular, bad or very bad	991 (25.6)	1470 (33.3)
Vision Self-assessment (far and near)		
Good or very good	2134 (55.1)	1659 (37.6)
Regular, bad or very bad	1737 (44.9)	2750 (62.4)
Conversation with children		
Never or less than once a year	364 (12.2)	426 (12.2)
Less than monthly	141 (4.8)	181 (5.2)
Monthly	302 (10.2)	355 (10.2)
Weekly	2163 (72.8)	2525 (72.4)
Meet with relatives		
Never or less than once a year	560 (15.0)	792 (18.7)
Less than monthly	1066 (28.7)	1262 (29.8)
Monthly	690 (18.6)	846 (20.0)
Weekly	1402 (37.7)	1332 (31.5)

*Short version of Center for Epidemiologic Studies Depression Scale, (reference). † Monthly per-capita income, in Brazilian reals. ‡ Body mass index. § None: ≤3 times a week of 10-min walk; mild: >3 times a week of 10-min walk; moderate: >3 times a week of moderate exercise; vigorous: >3 times a week of vigorous exercise. SES: Socioeconomic status.

Table 2
Two multivariable linear models exploring the association between depressive symptoms (measured with a short version of Center for Epidemiologic Studies Depression Scale, CED—D8), and memory (measured with mean combined words recall test, MCWR). The unadjusted model yielded a MCWR of −0.23 (95% CI -0.28 to −0.18, *p*-value <0.001). The results of a saturated model, including all potential confounders, is provided in Supplementary Material 3.

Variable	Baseline Model ($R^2 = 0.14$)			Adjusted Model ($R^2 = 0.26$)		
	MCWR	**95% CI**	***P*-value**	**MCWR**	**95% CI**	**P-value**
CES D-8	−0.27	−0.32 to −0.23	<0.001	−0.18	−0.22 to −0.15	<0.001
Age (years)						
50–54	0.00	–	–	0.00	–	–
55–59	−0.52	−0.75 to 0.30	<0.001	−0.28	−0.48 to −0.09	0.005
60–64	−0.94	−1.22 to −0.66	<0.001	−0.58	−0.82 to −0.34	<0.001
65–69	−1.47	−1.80 to −1.15	<0.001	−0.87	−1.13 to −0.61	<0.001
70–74	−2.18	−2.52 to −1.84	<0.001	−1.41	−1.71 to −1.11	<0.001
75–79	−3.36	−3.72 to −3.01	<0.001	−2.35	−2.66 to −2.02	<0.001
80–84	−4.02	−4.50 to −3.53	<0.001	−3.12	−3.59 to −2.65	<0.001
≥85	−4.58	−5.70 to −3.99	<0.001	−3.49	−4.05 to −2.92	<0.001
Sex						
Female	0.00	–	–	0.00	–	–
Male	−0.35	−0.57 to −0.13	0.002	−0.33	−0.53 to −0.14	0.001
Education (years)						
None	–	–	–	0.00	–	–
1–4	–	–	–	1.32	1.09 to 1.55	<0.001
5–8	–	–	–	2.25	1.97 to 2.53	<0.001
>8	–	–	–	3.56	3.28 to 3.82	<0.001

CI: Confidence Interval

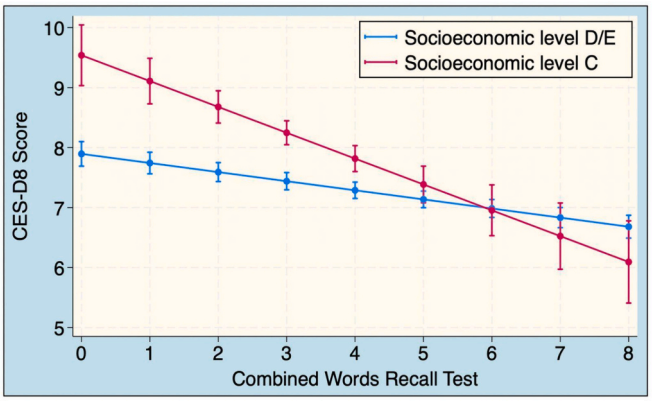

Fig. 2. Effect modification of two socioeconomic levels on the relationship between depression (measured with the Center for Epidemiologic Studies Scale, CES D-8) memory loss (measured with Combined Words Recall test).
Socioeconomic level C: Monthly per-capita income ranging between 2005 and 8640 Brazilian Reals. Socioeconomic level D/E: Monthly per-capita income <2005 Brazilian Reals.

obtained effect size of −0.11 in the combined recall test, an unmeasured confounder that was associated with both the CES D-8 score and the combined recall test by a risk ratio of 1.68-fold each -above and beyond the measured confounders- could explain away the estimated effect size.

5. Discussion

In our study, depressive symptoms were associated with memory loss in adults older than 50 years old, in a population with high prevalence of low educational level and SES. Depressive symptoms were associated with memory loss in adults older than 50 years old. Whereas sex and age were independent predictors of memory in this cohort, educational level was a confounder for the association of depressive symptoms and memory. In addition, educational level was an independent predictor of memory. Compared with no formal education, participants with at least 1 year of education presented a better memory. Furthermore, SES was an effect modifier for the association between depressive symptoms and memory, participants presenting higher SES had a steeper decline for depressive symptoms increasing when compared with individuals with lower SES.

The results of this study should be interpreted from a clinical perspective, as it is well-known that statistical significance does not necessarily imply clinical relevance. While the achievement of statistical significance was facilitated by the large sample size in this study, whether a change of 0.18 words in the CWRT is relevant, needs a clinical interpretation. Stated in a different way, according to our adjusted model, for every 5-points increase in the CES-D8 scale, a reduction of approximately 1 word in the CWRT is expected. To the best of our knowledge, there are no previous studies reporting effect size in terms of CWRT. Thus, the comparison of our effect size with previous literature is limited to existing studies employing similar scores. For example, it has been suggested that a minimal clinically important difference would be represented by a change of 1.6 points in a Mini-Mental State examination, 1.5 points in an Alzheimer's Disease Assessment Scale delayed recall test, and 1.4 points in the animal fluency test. (24) Another study described as meaningful change of 1–3-point decrease in Mini Mental State Examination, 1–2-point increase in Clinical Dementia Scale sum of boxes, and 3–5-point increase in Functional Activities Questionnaire. (25) Accordingly, a decrease of 0.18 words in the CWRT which represents an effect size of 0.11 should be interpreted as a small effect size.

Our findings are aligned with previous studies investigating the association between depressive symptoms and memory loss. (26–28) For example, in an ongoing longitudinal study, Wilson et.al suggested that the risk of Alzheimer's disease was increased in patients with depressive symptoms, measured with CES D-8 score. (27) More recently, Zollinger et al. suggested that depressive symptoms were associated with a higher prevalence of cognitive decline, in a German population. (26) Finally, in a study involving Brazilian subjects, cognitive and functional impairment were associated with higher levels of depressive symptoms. (28)

In addition, age and self-reported sex were independent predictors of memory decline in the ELSI population. Interestingly, it has been proposed that maintaining a sex-gender perspective is crucial, as, for example, it has been observed that depression in old men is associated with lower cognitive function. (29) On the other hand, a recent meta-analysis found no clear difference in dementia incidence for sex, and the prevalence of dementia was higher in older women probably due to longer lives and inequality in education. (30) In a retrospective study from Brazil, there was a higher odds of dementia in women when compared with men (OR 2.5), which contrasts with our findings. (31) This disparity may be explained by differences in the incidence of episodic memory impairment, higher in males than in females. (32)

5.1. Education level

It has been suggested that the level of education is an essential factor to fully understand the relationship between depression and memory in older individuals. (33) Our study showed that education level was a confounder and independent predictor in the relationship between depressive symptoms and memory. As expected, participants having at least one year of formal education had a better performance in the words-recall test when compared with those with no formal education. In our study, we showed that when education level was introduced in the model, the beta coefficient for the relationship between depression and cognition was reduced by 0.09 points (reduced from 0.27 to 0.18).

Given that subjects with lower education level have higher prevalence of depression and cognitive impairment, and the relationship between these two factors was found to be independent of education level in our study, it is important to consider policies to address preventive and treatment measures for depression and cognition in subjects with lower education level in Latin America. This emphasizes the importance of education policies not only for educational goals, but also as a preventive measure to reduce to some extent depression and cognitive impairment. Indeed, in a large population-based study including individuals from Mexico and Brazil, education was protective against cognitive impairment. Participants with very lower levels of education (1–4 years) compared with those with no formal education presented lower odds of cognitive impairment in both countries. (7)

5.2. Socioeconomic status

In our study, SES was an effect modifier for the relationship between depressive symptoms and memory. Individuals categorized in SES stratum C (Higher SES) exhibited a more pronounced decline in memory, as measured by the CWRT, showing that for every unit increase in depressive symptoms, the decline was greater compared to individuals in SES strata D/E. Furthermore, individuals in the SES stratum C performed on average better in the CWRT, when compared with SES strata D/E (4.0 vs. 3.4, $P < 0.001$).

The interaction found in our study can be explained by the fact that (i) individuals belonging to higher SES may have a better memory reserve, when compared to those belonging to lower SES, and (ii) depression might be a stronger predictor of memory loss in subjects categorized in high SES, when compared with those with lower SES, who may already have reduced memory reserve.

A previous study conducted on European population investigating the association between cognitive decline and childhood socioeconomic condition, demonstrated a better cognitive function among those exposed to higher socioeconomic condition, but stronger cognitive decline among those with older age. (34) Moreover, in a study using the ELSI-Brazil cohort (2015–2016), authors concluded that social isolation and perceived loneliness have a negative impact on cognitive performance. Interestingly, authors found a weak association between social isolation/loneliness and cognitive performance in a sub-population of patients with severe depressive symptoms. In this study, the SES was not included as a covariate in the model, and therefore, the potential interaction of SES in the association between social isolation/loneliness and cognitive performance was not tested. (35)

Another explanation of the SES interaction is that older adults with moderate SES still have an active job or belong to a family with active working activities compared to older adults in low-income families. This different family structures could influence the social support and social networking time of older adults. Previous studies have reported that people with a lower income tend to spend more time socializing with their neighbors and family members than those with a higher income, (36) this socialization time is considered a protective factor to the negative outcomes of depressive symptoms (37). Therefore, social support differences related to different SES categories could explain our findings. However, in the present study this hypothesis was not explored. Future studies should investigate what protective factors present in Latin America lower income communities could explain the effect attenuation of depression symptoms in cognitive outcomes.

5.3. Strengths

The present study, involving Brazilian adults aged 50 and over, ensured reliability through validated memory evaluations, interviewer training, and pre-pilot studies. The findings are applicable to the broader population, allowing comparisons between Brazilian macroregions and other countries. Given the large sample size and the fact that this population had on average low scores of education and SES level, it was possible to truly understand the effects of these two factors on the relationship of depression and cognitive impairment.

5.4. Limitations

The cross-sectional design of this study limits the ability to establish causation, and therefore, the directionality between depressive symptoms and cognitive impairment remains unclear. The implications for every 5-points increase in the CES-D8 scale, a reduction of approximately 1 word in the CWRT is expected of this uncertainty in the directionality of the associations described in this study should not be underestimated. For example, in examining the relationship between (i) physical activity, (ii) conversation with children, and (iii) conversation with relatives, with both the exposure (depression) and the outcome (memory loss), it becomes evident that these potential confounders could also act as colliders, depending on the directionality assumed for these associations. In our study, none of these variables were identified as potential confounders, and consequently, they were not included in our final model. Had they been identified as confounders; the posed paradox could only be solved with a longitudinal study.

In addition, the presence of unmeasured confounders, which is implicit to any observational study, may have distorted the strength of association of our findings. In fact, the reported e-value of 1.68 suggests that it is plausible that our finding may be explained by unmeasured confounders. Thus, further research is needed to explore the association between depression and cognitive decline.

The ELSI-Brazil dataset has been previously used for several research purposes. In our study, the results have not been adjusted for multiple testing, thus increasing the probability of type I error. The problem of multiple testing is ubiquitous in exploratory studies, and there is considerable debate as to whether the level of significance reported should account for the number of tests conducted. For example, concomitant results from similar studies have not been adjusted for the number of tests conducted in previous research. However, the strong level of evidence found for the association between depression and cognitive impairment implies that the probability of type I error remains low, even after adjusting for multiplicity of comparisons. Lastly, it is important to mention that immediate and recall memory scores were based on a single list of 10 words without a second trial, which may potentially limit the validity of the CWRT in this scenario.

6. Conclusion

Among the Brazilian population older than 50 years, depressive symptoms appear to be associated with memory loss, and this association seems to be confounded by educational level and vary among subjects with medium and low SES. The role of SES as an effect modifier for the association between cognitive function and depression, and the education level as a confounder for this relationship underscore their relevance for public health policy makers in Latin America to potentially include them in policies to decrease the burden of depression and cognitive impairment in Latin America. Future longitudinal studies are needed to confirm the directionality of our findings and to test public health programs to detect and prevent cognitive impairment in the

underserved population in Latin America.

Funding source

No funding was necessary for the present study.

Financial disclosure

Nothing to disclose.

CRediT authorship contribution statement

Karla Loss: Writing – original draft, Visualization, Validation, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Wilson Fandino:** Writing – review & editing, Writing – original draft, Visualization, Validation, Methodology, Investigation, Formal analysis, Data curation. **Bassel Almarie:** Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Conceptualization. **Blanca Bazan-Perkins:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Julia Minetto:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Nadine Aranis:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Thiago Monaco:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Aisha Aladab:** Writing – review & editing, Writing – original draft, Methodology, Investigation. **Kevin Pacheco-Barrios:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Felipe Fregni:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dialog.2024.100183.

References

[1] Meeks TW, Ropacki SA, Jeste DV. The neurobiology of neuropsychiatric syndromes in dementia. Curr Opin Psychiatry 2006 Nov;19(6):581–6.
[2] Wingo TS, Yang J, Fan W, Min Canon S, Gerasimov ES, Lori A, et al. Brain microRNAs associated with late-life depressive symptoms are also associated with cognitive trajectory and dementia. NPJ Genom Med 2020 Feb 6;5(1):1–8.
[3] Reding M, Haycox J, Blass J. Depression in patients referred to a dementia clinic. A three-year prospective study. Arch Neurol 1985 Sep;42(9):894–6.
[4] Bassuk SS, Berkman LF, Wypij D. Depressive symptomatology and incident cognitive decline in an elderly community sample. Arch Gen Psychiatry 1998 Dec;55(12):1073–81.
[5] Seidman AJ, Yang X, Westbrook A, George CJ, Kovacs M. Effects of current and past depressive episodes on behavioral performance and subjective experience during an N-back task. J Behav Ther Exp Psychiatry 2023 Dec 1;(81):101852.
[6] Larsen EN, Sloth MM, Osler M, Wium-Andersen IK, Jørgensen TSH. Depression in adulthood and risk of dementia later in life: a Danish register-based cohort study of 595,828 men. J Affect Disord 2022 Apr 1;(302):25–32.
[7] Gonçalves NG, Avila JC, Bertola L, Obregón AM, Ferri CP, Wong R, et al. Education and cognitive function among older adults in Brazil and Mexico. Alzheimers Dement Diagn Assess Dis Monit 2023 Sep 27;15(3):e12470.
[8] Murman DL. The impact of age on cognition. Semin Hear 2015 Aug;36(3):111–21.
[9] Mukadam N, Sommerlad A, Huntley J, Livingston G. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. Lancet Glob Health 2019 May 1;7(5):e596–603.
[10] Fiske A, Gatz M, Pedersen NL. Depressive symptoms and aging: the effects of illness and non-health-related events. J Gerontol B Psychol Sci Soc Sci 2003 Nov;58(6):P320–8.
[11] Fiske A, Wetherell JL, Gatz M. Depression in older adults. Annu Rev Clin Psychol 2009;5:363–89.
[12] Zenebe Y, Akele B, WSelassie M, Necho M. Prevalence and determinants of depression among old age: a systematic review and meta-analysis. Ann Gen Psychiatry 2021 Dec 18;20(1):55.
[13] Silva PO, Aguiar BM, Vieira MA, da Costa FM, Carneiro JA. Prevalência de sintomas depressivos e seus fatores associados em idosos atendidos por um centro de referência. Rev Bras Geriatr E Gerontol 2020 Jan 10;(22). e190088.
[14] Morais EP, Rodrigues RAP, Sousa VD. Assessment of depressive symptoms and cognitive impairment in elders from rural areas of the Brazilian State of Rio Grande do Sul. Public Health Nurs Boston Mass 2009;26(3):249–58.
[15] de Ferreira-Filho SF, Borelli WV, Sguario RM, Biscaia GF, Müller VS, Vicentini G, et al. Prevalence of dementia and cognitive impairment with no dementia in a primary care setting in southern Brazil. Arq Neuropsiquiatr 2021 Aug 25;(79):565–70.
[16] Borelli WV, Zimmer ER, Bieger A, Coelho B, Pascoal TA, Chaves MLF, et al. Subjective cognitive decline in Brazil: prevalence and association with dementia modifiable risk factors in a population-based study. Alzheimers Dement Diagn Assess Dis Monit 2022;14(1):e12368.
[17] Lima-Costa MF, de Melo Mambrini JV, Bof de Andrade F, de Souza PRB, de Vasconcellos MTL, Neri AL, et al. Cohort profile: the Brazilian longitudinal study of ageing (ELSI-Brazil). Int J Epidemiol 2023 Feb 8;52(1):e57–65.
[18] Lyness SA, Lee AY, Zarow C, Teng EL, Chui HC. 10-minute delayed recall from the modified mini-mental state test predicts Alzheimer's disease pathology. J Alzheimers Dis JAD 2014;39(3):575–82.
[19] Zivin K, Llewellyn DJ, Lang IA, Vijan S, Kabeto MU, Miller EM, et al. Depression among older adults in the United States and England. Am J Geriatr Psychiatry Off J Am Assoc Geriatr Psychiatry 2010 Nov;18(11):1036–44.
[20] Centro de Politicas Sociais FGV. Centro de Políticas Sociais. 2015 [cited 2023 Nov 12]. Qual a faixa de renda familiar das classes?. Available from: https://cps.fgv.br/qual-faixa-de-renda-familiar-das-classes.
[21] Cuschieri S. The STROBE guidelines. Saudi J Anaesth 2019 Apr;13(Suppl. 1):S31–4.
[22] Textor J, Van Der Zander B, Gilthorpe MS, Liśkiewicz M, Ellison GTH. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. Int J Epidemiol 2017 Jan 15:dyw341.
[23] VanderWeele TJ, Ding P. Sensitivity analysis in observational research: introducing the E-value. Ann Intern Med 2017 Aug 15;167(4):268–74.
[24] Borland E, Edgar C, Stomrud E, Cullen N, Hansson O, Palmqvist S. Clinically relevant changes for cognitive outcomes in preclinical and prodromal cognitive stages. Neurology 2022 Sep 13;99(11):e1142–53.
[25] Andrews JS, Desai U, Kirson NY, Zichlin ML, Ball DE, Matthews BR. Disease severity and minimal clinically important differences in clinical outcome assessments for Alzheimer's disease clinical trials. Alzheimers Dement Transl Res Clin Interv 2019;5(1):354–63.
[26] Zöllinger I, Bauer A, Blotenberg I, Brettschneider C, Buchholz M, Czock D, et al. Associations of depressive symptoms with subjective cognitive decline in elderly people-a cross-sectional analysis from the AgeWell.de-study. J Clin Med 2023 Aug 10;12(16):5205.
[27] Wilson RS, Barnes LL, Mendes de Leon CF, Aggarwal NT, Schneider JS, Bach J, et al. Depressive symptoms, cognitive decline, and risk of AD in older persons. Neurology 2002 Aug 13;59(3):364–70.
[28] Barcelos-Ferreira R, Pinto JA, Nakano EY, Steffens DC, Litvoc J, Bottino CMC. Clinically significant depressive symptoms and associated factors in community elderly subjects from Sao Paulo. Brazil Am J Geriatr Psychiatry 2009 Jul 1;17(7):582–90.
[29] Calatayud E, Marcén-Román Y, Rodríguez-Roca B, Salavera C, Gasch-Gallen A, Gómez-Soria I. Sex differences on anxiety and depression in older adults and their relationship with cognitive impairment. Semergen 2023;49(4):101923.
[30] Huque H, Eramudugolla R, Chidiac B, Ee N, Ehrenfeld L, Matthews FE, et al. Could country-level factors explain sex differences in dementia incidence and prevalence? A systematic review and meta-analysis. J Alzheimers Dis JAD 2023;91(4):1231–41.
[31] de Souza RKM, Barboza AF, Gasperin G, Garcia HDBP, Barcellos PM, Nisihara R. Prevalence of dementia in patients seen at a private hospital in the southern region of Brazil. Einstein Sao Paulo Braz 2019;18:eAO4752.
[32] The prevalence of mild cognitive impairment in Latin America and the Caribbean: a systematic review and meta-analysis. Aging Ment Health [Internet]. [cited 2023 Nov 10]; Available from: https://doi.org/10.1080/13607863.2021.2003297.
[33] Alagoa João A, Maroco J, Ginó S, Mendes T, de Mendonça A, Martins IP. Education modifies the type of subjective memory complaints in older people. Int J Geriatr Psychiatry 2016 Feb;31(2):153–60.
[34] Aartsen MJ, Cheval B, Sieber S, Van der Linden BW, Gabriel R, Courvoisier DS, et al. Advantaged socioeconomic conditions in childhood are associated with higher cognitive functioning but stronger cognitive decline in older age. Proc Natl Acad Sci U S A 2019 Mar 19;116(12):5478–86.
[35] Souza JG, Farias-Itao DS, Aliberti MJR, Bertola L, de Andrade FB, Lima-Costa MF, et al. Social isolation, loneliness, and cognitive performance in older adults: evidence from the ELSI-Brazil study. Am J Geriatr Psychiatry 2023 Aug 1;31(8):610–20.
[36] Zhang S, Xiang W. Income gradient in health-related quality of life—the role of social networking time. Int J Equity Health 2019 Dec;18(1). 1–0.
[37] Werner-Seidler A, Afzali MH, Chapman C, Sunderland M, Slade T. The relationship between social support networks and depression in the 2007 National Survey of Mental Health and Well-being. Soc Psychiatry Psychiatr Epidemiol 2017 Dec;52(5):1463–73.