Research Article

Sociodemographic and clinical profile from the Brazilian very old 90+ study (BRAVO-90+)

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Abstract

Background: Cognitive impairment and disability are frequent among the oldest-old population, particularly in low- and middle-income countries (LMIC), where this population is rapidly increasing. However, studies on people aged 90 or older are scarce in these settings. Here we analyze the characteristics of the Brazilian Very Old 90+ (BRAVO 90+) study, a population-based sample of 90+ older adults who died in Sao Paulo, Brazil.

Objective: To describe clinical and functional characteristics and investigate factors associated with cognitive impairment in Brazilian adults 90 years or older.

Methods: Data were collected at the time of death. Postmortem cognitive evaluation regarding cognitive abilities three months before death was performed using the Clinical Dementia Rating (CDR) scale. We investigated factors associated with cognitive impairment selected by a Lasso regression.

Results: Among 409 participants (mean age = 94 ± 3 years; 72% women; 69% white; average education = 3.3 ± 3.6 years), hypertension, diabetes, and heart failure were prevalent. Most participants had disabilities. The leading causes of death verified by autopsy were pulmonary edema, pneumonia, and ischemic myocardial disease. Although 48% scored a CDR greater or equal to 1, only 51% had a previous dementia diagnosis. Sedentary behavior, osteoarthritis, and depression were associated with higher odds of cognitive impairment, while married status, greater body mass index, hypertension, and neoplasia were related to lower odds.

Conclusions: Cognitive impairment and disability were common among Brazilians aged 90+. The BRAVO 90+ study will provide valuable insights into dementia and resilience in this population.

Keywords

aging, Alzheimer's disease, cognitive impairment, dementia, low- and middle-income countries, oldest-old

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Introduction

The oldest-old (e.g., individuals aged 90 or older) is the age group with the fastest population growth rate worldwide. The number of oldest-old people will grow from 23 to 82 million by 2050.[1] However, longer lifespans are not frequently followed by a healthy life in later years.[2] The oldest-old are vulnerable to multiple comorbidities, functional limitations, sensory and cognitive impairments, mood disorders, and frailty.[3]

Dementia is also common in this age group, where incidence increases from 13% yearly from 90 to 94 to 41% after 100 years old.[4] The incidence in Brazil may be similar, estimated at 39% by one study; however, this rate was found in a sample of individuals 65 or older and included only two new cases of dementia in individuals over 90 years old.[5] In the United States, dementia affects approximately 33% of people between the ages of 90 and 94 and 56% of centenarians.[6] The prevalence in low- to middle-income countries (LMIC) seems to be higher. For example, dementia prevalence for people over 90 was estimated to be 43% in Brazil.[7] Neurodegenerative and cerebrovascular pathologies and the combination of two or more pathologies in the same person are frequently found.[8,9] Evidence suggests people in LMICs are more susceptible to dementia because of a higher prevalence of modifiable risk factors, socioeconomic and environmental challenges, and rapidly aging populations.[10,11]

The lack of region-specific research and interventions exacerbates this situation. Targeted prevention, better healthcare access, and increased research are essential to reduce dementia's growing impact in these regions, including Latin America.[9] Risk factors traditionally associated with a higher risk of dementia in midlife, such as hypertension, higher body mass index (BMI), hypercholesterolemia, and apolipoprotein E allele ϵ4 (*APOE* ϵ4), may become null or protective after the age of 90.[8] Therefore, studies on the oldest old population are important to understand the connections between dementia and factors related to healthy brain aging and longevity.

By 2050, more than 70% of people with dementia will live in LMICs, and the prevalence of dementia in Latin America is expected to increase four times.[12] Additionally, Latin America faces a high burden of chronic diseases, has high rates of less education, and a large rural population, which are factors related to disability and increased healthcare needs.[10]

The Brazilian Very Old 90+ (BRAVO 90+) study aims to investigate the clinical profile and dementia-related neuropathologic changes of the oldest-old participants from the Biobank for Aging Studies (BAS). Here, we described the BRAVO 90+ sample regarding sociodemographic and clinical profiles and investigated factors related to cognitive impairment. We also presented the causes of death determined by a full-body autopsy in this sample.

Methods

Participants

Participants were part of the BAS from the University of São Paulo Medical School in Brazil. Brain donations were collected at the São Paulo Autopsy Service (SPAS), which is responsible for investigating the causes of non-traumatic deaths that occurred without medical assistance or unclear etiology within the city of São Paulo. The deceased's next of kin signed a written informed consent form for brain donation and answered an interview on sociodemographic and clinical variables. BAS inclusion criterion was age at death of 18 years or older. Individuals were excluded in the presence of damage to the brain tissue that caused the material to be unsuitable for analysis, such as brain tumors, macroscopic hemorrhages, and severe acidosis (pH 6.5). For this study, we included all individuals aged 90 years or older who were part of the BAS collection. The exclusion criterion was incomplete data in the Clinical Dementia Rating (CDR).

Participants underwent a full-body autopsy examination. Weight and height were measured before autopsy in the supine position, without clothing or shoes, using an electronic scale and a stadiometer, respectively. The BMI was calculated as kilograms per square of height. The brains were then removed and processed. The causes of death were determined by the autopsy examination and classified using the International Statistical Classification of Diseases and Related Health Problems 10th revision (ICD-10).[13]

Postmortem clinical assessment

Trained gerontologists collected sociodemographic data like age (years), sex (men or women), race (White, Black, or Asian), education (in years), and marital status. The next of kin described the deceased's primary occupation as the one they had during most of their lives. This information was then categorized according to the International Standard Classification of Occupations 2008 (ISCO-2008), which classifies occupations into four skill levels based on the nature of the work and the level of formal education required, from 1 (lowest) to 4 (highest): level 1 included physical or manual tasks like cleaning, building, and farming; level 2 required advanced literacy and numeracy skills and manual dexterity, like butchers, drivers, secretaries, and electricians; level 3 involved complex technical and practical tasks and level 4 required higher educational levels, advanced problem-solving, and decision-making based on specific theoretical and factual knowledge.[14] The Brazilian Criteria score assessed the socioeconomic classification. This instrument includes information on the education level of the person in charge of the household, home structure (number of bathrooms and household staff), access to public services such as

running water and paved streets, and long-term consumer items. Based on this information, participants were classified as having a high, middle, or low socioeconomic level.[15] The use of private health services was also investigated.

The interview also includes the next of kin's report on lifestyle habits (physical activity, smoking, and alcohol consumption) and the presence of previous diagnoses of hypertension, diabetes, heart failure, coronary artery disease, osteoarthritis, stroke, arrhythmia, neoplasia, osteoporosis, peripheral vascular disease (venous and arterial diseases), dyslipidemia, chronic obstructive pulmonary disease, thyroid disease, depression, renal failure, and traumatic brain injury. Medication use was asked as an open question and categorized by the interviewer as treatments for hypertension, diabetes (including insulin), dyslipidemia, heart failure, antidepressants, antipsychotics, cholinesterase inhibitors, and memantine.

In addition, we assessed disabilities like sensory impairments, teething, enteral feeding, waking difficulties, and bedridden status. Teething was the term utilized to describe dentition, in which "normal" denotes the existence of all teeth until edentulism, which is the absence of all teeth. Enteral nutrition involves using a nasoenteral tube or gastrostomy, in contrast to oral feeding. Ultimately, Katz and Lawton scores were implemented to evaluate functionality. The Katz Index for Activities of Daily Living (ADL) measures a person's ability to bathe, dress, use the toilet, transfer, maintain urinary and fecal continence, and feed independently. Grading each activity yields a total score from 0 (dependent) to 6 (independent).[16] The Lawton Instrumental Activities of Daily Living (IADL) scale measures a person's ability to use the telephone, shop, prepare meals, do housekeeping, do laundry, use transportation, self-administer medication, and manage their finances. Scores range from 0 (totally dependent) to 8 (independent).[17] This study classified participants as independent if the ADL or IADL score was 6 or 8, respectively; dependent if ADL or IADL was 0, or partially dependent when scores were between 1 and 5 for the ADL scale or between 1 and 7 for the AIDL scale. A detailed description of the study variables is presented in Supplemental Table 1.

Postmortem cognitive assessment

The cognitive assessment was performed postmortem with the deceased's next of kin using the informant part of the CDR scale.[18] The next of kin was asked to answer questions about the deceased's cognitive status three months before death to avoid delirium or other altered mental states that may be present by the time of death. The BAS informant interview has a sensitivity of 87% and a specificity of 84% for the diagnosis of dementia. The agreement between the CDR acquired by informant interview and the CDR assessed by a team of specialists was 86%.[18] The CDR evaluates six cognitive and functional domains: memory, orientation, judgment and problem-solving, community affairs, home and hobbies, and personal care. These ratings were then used to derive a global CDR score, which indicated dementia presence and severity.[19] Participants were then classified into two groups: normal cognition (CDR 0) or cognitive impairment (CDR greater or equal to 0.5). The CDR sum of boxes (CDR-SB) was calculated by summing the domain scores, which ranged from 0 to 18, with larger values indicating more impairment. Neuropsychiatric symptoms were evaluated using the Neuropsychiatric Inventory (NPI), which evaluates 12 symptoms, such as delusions, hallucinations, dysphoria, anxiety, agitation, euphoria, disinhibition, irritability, apathy, motor disturbances, appetite changes and sleep disturbances.[20]

Statistical analyses

We used the mean and standard deviation (SD) or median and interquartile range (IQR) to describe quantitative data and relative frequencies to describe categorical data. The unpaired t-test or the Wilcoxon Rank Sum test was used for continuous variable, while the chi-square test or Fisher's exact test was employed for categorical data. All sociodemographic and clinical variables from Table 1 were considered potential risk factors for dementia and were included in the LASSO model for variable selection. We used this method because there were several potential risk factors and a limited number of observations.[21] The k-fold cross-validation was conducted to determine the lambda value. The chosen value was the one with the lowest test mean squared error to optimize the model's predictive performance. The selected variables were then used in a logistic regression model to determine their association with cognitive impairment. A sensitivity analysis was performed using the CDR-SB as the outcome to confirm our findings. Finally, stratified analyses by sex were performed to further elaborate on the associations in our results. Data analyses were performed using R v. 4.0.5.6.

Results

Of 508 autopsied individuals with +90 years in the BAS, 23 were excluded due to the family's withdrawal or the need to retain the brain to elucidate the cause of death. Seventy-six were destined for other projects and did not have the CDR data collected. The 99 not included cases showed similar sociodemographic characteristics to the final sample (Supplemental Table 2). The final sample comprised 409 individuals, primarily women (72%), aged 94.0 ± 3.4 years old. Most informants were family members who regularly interacted with the deceased: 73% had daily contact, 21% had weekly contact, and 7% had biweekly contact. Most respondents were children (71%) or grandchildren

Table 1. Sociodemographic and clinical characteristics according to the presence of cognitive impairment by CDR global score (n = 409).

	Overall N = 409	Normal cognition N = 162	Cognitive impairment N = 247	p
Age (y), mean (SD)*	94 (3.45)	93.5 (3.23)	94.3 (3.56)	0.01
Women, n (%) †	297 (72.6)	99 (61.1)	198 (80.2)	<0.001
Race, n (%) †				
White	283 (69.5%)	116 (72.0%)	167 (67.9%)	0.24
Black	103 (25.3%)	34 (21.1%)	69 (28.0%)	
Asian	21 (5.2%)	11 (6.8%)	10 (4.1%)	
Married, n (%) †	61 (14.9)	38 (23.5)	23 (9.3)	<0.001
Education (y), median (IQR) ‡	4 (0–4)	4 (0–4)	4 (0–4)	0.45
Socioeconomic classification, n (%) †				
Low income	47 (11.7%)	24 (15.1%)	23 (9.4%)	0.16
Middle income	197 (48.9%)	79 (49.7%)	118 (48.4%)	
High income	159 (39.5%)	56 (35.2%)	103 (42.2%)	
ISCO-08 skill level, n (%) §				0.17
1	228 (55.7)	86 (53.1)	142 (57.5)	
2	118 (28.9)	46 (28.4)	72 (29.1)	
3	4 (1.0)	3 (1.9)	1 (0.4)	
4	15 (3.7)	9 (5.6)	6 (2.4)	
Private health system users, n (%) †	60 (14.7)	19 (11.7)	41 (16.6)	0.22
Body Mass Index (kg/m^2), mean (SD) *	20.1 (4.55)	21 (4.55)	19.5 (4.47)	0.001
Sedentary behavior, n (%) †	295 (72.1)	92 (56.8)	203 (82.2)	0.001
Tobacco use, n (%) †				0.04
Never	283 (69.2)	107 (66.0)	176 (71.3)	
Current	20 (4.9)	13 (8.0)	7 (2.8)	
Previous	98 (24.0)	41 (25.3)	57 (23.1)	
Alcohol use, n (%) †				0.002
Never	299 (73.1%)	111.0 (68.5%)	188.0 (76.1%)	
Current	56 (13.7%)	34.0 (21.0%)	22.0 (8.9%)	
Previous	54 (13.2%)	17.0 (10.5%)	37.0 (15.0%)	
Hypertension, n (%) †	231 (56.5)	104 (64.2)	127 (51.4)	0.02
Diabetes, n (%) †	76 (18.6)	29 (17.9)	47 (19.0)	0.88
Cardiac failure, n (%) †	63 (15.4)	30 (18.5)	33 (13.4)	0.21
Neoplasia, n (%) †	60 (14.7)	33 (20.4)	27 (10.9)	0.01
Osteoarthritis, n (%) †	57 (13.9)	14 (8.6)	43 (17.4)	0.02
Coronary Artery Disease, n (%) †	56 (13.7)	20 (12.3)	36 (14.6)	0.61
Stroke, n (%) †	52 (12.7)	16 (9.9)	36 (14.6)	0.22
Arrhythmia, n (%) †	49 (12.0)	21 (13.0)	28 (11.3)	0.74
Peripheral Vascular Disease, n (%) †	47 (11.5)	24 (14.8)	23 (9.3)	0.12
Osteoporosis, n (%) †	45 (11.0)	13 (8.0)	32 (13.0)	0.16
Dyslipidemia, n (%) †	43 (10.5)	17 (10.5)	26 (10.5)	1.00
Chronic obstructive pulmonary disease, n (%) †	37 (9.0)	15 (9.3)	22 (8.9)	1.00
Thyroid disease, n (%) †	27 (6.6)	9 (5.6)	18 (7.3)	0.45
Depression, n (%) §	26 (6.4)	4 (2.5)	22 (8.9)	0.01
Renal failure, n (%) †	22 (5.4)	10 (6.2)	12 (4.9)	0.72
Traumatic Brain Injury, n (%) §	11 (2.7)	3 (1.9)	8 (3.2)	0.34

*T-test; † Chi-square test; ‡ Wilcoxon Rank Sum Test; **§** Fisher's exact test; ISCO-08: International Standard Classification of Occupations 2008.

(18%). Informants had an average education of 11.0 ± 4.5 years, with only seven illiterates. Seventy percent of participants were declared as white, with a median education of 4 years (Interquartile Range 0–4 years). Sixty percent of individuals had low or middle socioeconomic levels, and 84% worked in unskilled positions. Sociodemographic characteristics like age, race and socioeconomic classification were similar between men and women, except for married status and higher educational attainment, which was more common among men, and lower-skilled jobs, which were more common among women (Supplemental Table 3).

Smoking and alcohol consumption were uncommon. Almost 70% of the participants had never smoked or consumed alcohol (Table 1), and both habits were more common in men than in women (Supplemental Table 3). Cardiovascular comorbidities were prevalent, with hypertension, diabetes, and heart failure being the three most frequent disorders (Table 1). Most of the participants had

Table 2. Frequencies of disabilities according to the presence of cognitive impairment by CDR global score (n = 409).

	Overall N = 409	Normal cognition N = 162	Cognitive impairment N = 247	p
Visual impairment, n (%) †	260 (63.6)	96 (59.3)	164 (66.4)	0.09
Use of Glasses, n (%) †	146 (35.7)	61 (37.7)	85 (34.4)	0.81
Hearing impairment, n (%) †	214 (52.3)	88 (54.3)	126 (51.0)	0.65
Hearing aid use, n (%) †	33 (8.1)	12 (7.4)	21 (8.5)	0.81
Teething, n (%) †				0.25
Normal	22 (5.4)	12 (7.6)	10 (4.3)	
Partially toothless	78 (19.1)	34 (21.5)	44 (18.7)	
Edentulous	293 (71.6)	112 (70.9)	181 (77.0)	
Dental prosthesis, n (%) †	244 (59.7)	96 (59.3)	148 (59.9)	0.47
Dysphagia, n (%) †	65 (15.9)	7 (4.3)	58 (23.5)	<0.001
Enteral feeding, n (%) §	20 (4.9)	4 (2.5)	16 (6.5)	0.10
Urinary incontinence, n (%) †	133 (32.5)	35 (21.6)	98 (39.7)	<0.001
Walking difficulty, n (%) †	285 (69.7)	87 (53.7)	198 (80.2)	<0.001
Bedridden, n (%) †	96 (23.5)	10 (6.2)	86 (34.8)	<0.001
Pressure ulcer, n (%) †	73 (17.8)	9 (5.6)	64 (25.9)	<0.001
ADL Score, n (%) †				<0.001
Independent	117 (28.7)	89 (54.9)	28 (11.3)	
Partially dependent	199 (48.8)	66 (40.7)	133 (53.8)	
Dependent	92 (22.5)	6 (3.7)	86 (34.8)	
IADL Score, n (%) §				<0.001
Independent	2 (0.5)	2 (1.3)	0 (0)	
Partially dependent	150 (36.9)	118 (73.8)	32 (13.0)	
Dependent	255 (62.7)	40 (25.0)	215 (87.0)	

†Chi-square test; § Fisher's exact test; ADL: Activities of Daily Life; IADL: Instrumental Activities of Daily Life.

edentulism (no natural teeth left), sensory impairment, and difficulty walking, with 25% being bedridden. Dysphagia was reported in nearly one-fourth of cognitively impaired participants; however, enteral nutrition was not frequent. Over 70% of the sample had some degree of dependence on ADL, and 99% on IADL (Table 2). Women were more frequently dependent on both ADL and IADL (Supplemental Table 4). Most took at least one type of medication. Antihypertensives, heart disease-related drugs, and antidiabetics were the most frequently prescribed medications, following the most prevalent illnesses (Supplemental Table 5).

Forty percent had a CDR equal to 0, 12% had a CDR equal to 0.5, and 48% had a CDR greater or equal to 1, and therefore considered as having dementia. Fifty-one percent (n = 102) of those with CDR greater or equal to 1 had never been diagnosed with dementia during life (Figure 1). The most common neuropsychiatric symptoms were appetite changes (34%), followed by sleep disorders (25%), apathy (21%), depression (21%), and hallucinations (21%) (Supplemental Table 6).

Cardiovascular diseases were the most frequent cause of death in both groups. The most frequent causes of death in participants with normal cognition were pulmonary edema, pneumonia, ischemic heart disease, thromboembolic diseases, and pericardial effusion. In the cognitive impairment group, the most frequent causes were pulmonary edema, bronchopneumonia, thromboembolic disorders, ischemic heart diseases, and pericardial infusion (Figure 2).

Age, female sex, being married, education, sedentary behavior, BMI, hypertension, peripheral vascular disease, cardiac failure, neoplasia, osteoarthritis, and depression were selected by the Lasso regression. When these variables were entered into a logistic regression model, being married, higher BMI values, hypertension, peripheral vascular disease, and neoplasia were related to lower odds of cognitive impairment. In contrast, sedentary behavior, osteoarthritis, and depression were associated with higher odds (Table 3). The sensitivity analysis using CDR-SB as the outcome showed similar results, except for being married and osteoarthritis, which were no longer associated with cognitive impairment (Supplemental Table 7).

Lastly, stratified analyses were conducted to examine the differences in the sample associated with sex. Sedentary behavior was consistently associated with higher odds of cognitive impairment in men and women alike. Being married and having a cancer history were associated with decreased odds of cognitive impairment in men but not in women. On the other hand, peripheral vascular disease, hypertension, and higher BMI were associated with decreased odds of cognitive impairment only in women. Men had higher odds of cognitive impairment associated with osteoarthritis, while women had a borderline association. Depression was associated with increased odds of cognitive impairment in women and had a borderline association in men (Supplemental Table 8).

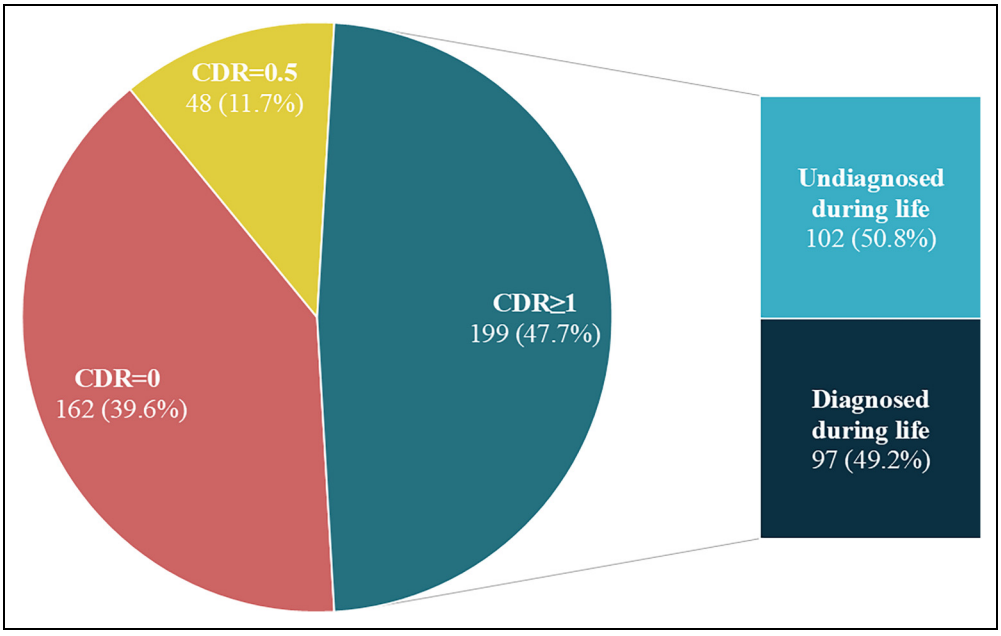

Figure 1. Absolute and relative frequencies of cognitive status according to the clinical dementia rating (CDR). The right bar describes the absolute and relative frequencies of diagnosed and undiagnosed dementia among participants with dementia (CDR equal to or greater than 1).

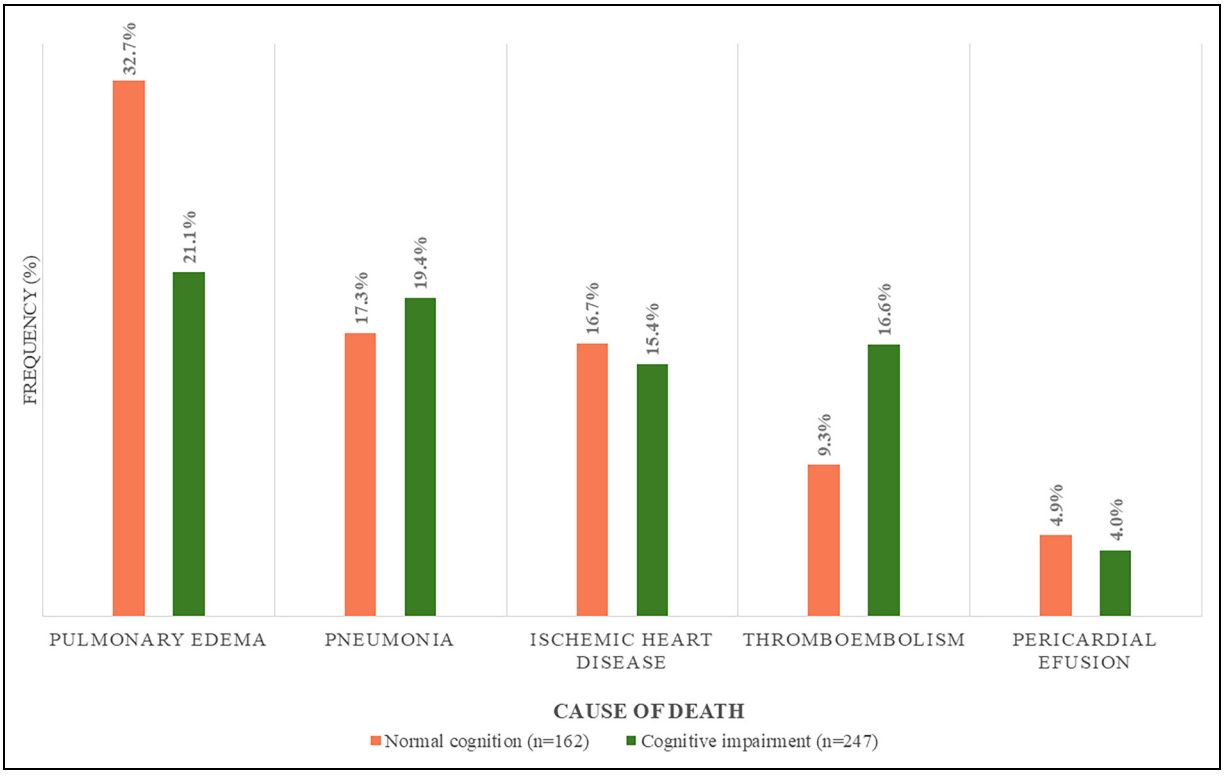

Figure 2. Bar graphs comparing the frequency of causes of death between individuals with normal cognition and those with cognitive impairment. Frequencies were similar between groups in the univariate analysis ($p = 0.31$).

Table 3. Factors associated with cognitive impairment (n = 409).

	Odds Ratio	95% Confidence Interval	p
Age (y)	1.04	0.97–1.12	0.30
Woman	1.64	0.94–2.84	0.08
Married	0.45	0.22–0.90	0.02
Education (y)	0.96	0.90–1.02	0.20
Sedentary behavior	3.66	2.20–6.16	<0.001
Body Mass Index (kg/m²)	0.94	0.89–0.99	0.02
Hypertension	0.59	0.36–0.96	0.03
Peripheral Vascular Disease	0.41	0.19–0.87	0.02
Cardiac Failure	0.64	0.33–1.22	0.17
Neoplasia	0.52	0.27–0.98	0.04
Osteoarthritis	2.27	1.11–4.87	0.03
Depression	6.36	1.92–26.97	0.01

Logistic Regression model.

Discussion

In our sample of 409 Brazilians who died over 90 years, most participants were women, had low education, and belonged to low and medium socioeconomic levels. Most had functional limitations and cardiovascular diseases, such as hypertension, diabetes, and heart failure. Although 48% of the sample scored a CDR greater or equal to 1, and only 51% had a previous dementia diagnosis. Higher BMI, hypertension, peripheral vascular disease, and neoplasia were related to lower odds of cognitive impairment, while physical inactivity, osteoarthritis, and depression were associated with higher odds.

Organ donation programs are prone to several biases due to socioeconomic status, cultural and religious beliefs, family dynamics, and geographic disparities of potential donors. Several studies report that donors tend to be disproportionately white, highly educated, and from affluent neighborhoods. Even cognitive factors can introduce biases such as the "healthy volunteer bias", where cognitive deficits might reduce participation and favor individuals with preserved cognition.[22] However, our study design mitigates these biases by originating from the SPAS, which encompasses the entire city of São Paulo and includes individuals from all neighborhoods and socioeconomic backgrounds, regardless of cognitive status. We observe a similar composition when comparing our sample to the 85+ population of São Paulo (n = 20,177), based on the general mortality data for the city of São Paulo available for 2020[23] and the data of individuals with 90+ years old autopsied at the SVO in 2023 (n = 1636).[24] There is a similar female predominance: 60% in São Paulo, 71% in the SVO, and 73% in our sample. The racial composition is also consistent, with 78% white individuals in São Paulo, 76% in the SVO, and 69% in our sample. These similarities suggest that our sample represents the population of São Paulo.

Our sample stands out from other autopsy studies on the oldest-old due to its diversity. While most participants were white, there was a significant representation of black and Asian individuals. The educational level was notably low. Most individuals were from the lower or middle classes, had unskilled occupations, and only a minority had private health coverage. Other autopsy studies were conducted in the United States and Europe and comprised most white participants with at least a high school education.[25–27]

Brazilians live an average of 76 years,[28] and those who survive above 90 are considered to have exceptional longevity. Hypertension, diabetes, and coronary artery disease were the main comorbidities in our sample. Despite their extremely long life, most of our sample had several disabilities, including walking difficulties, bedridden status, urinary incontinence, and dysphagia, and they were dependent on others for everyday activities. The prevalence of dementia in this sample was also high, and 49% of the participants who had dementia (CDR greater or equal to 1) were not diagnosed during their life. Dementia underdiagnosis is common in high-income and low- and middle-income countries, which may occur due to inadequate healthcare access, stigma, and lack of awareness.[7,29,30] We can suppose that the diagnosis gap may be even larger since the BAS postmortem cognitive evaluation was performed with an informant. A previous study showed that our cognitive evaluation had a sensitivity of 87% and a specificity of 84% for dementia diagnosis compared to dementia evaluation during life, and we might not have diagnosed some dementia cases since we interviewed only the next of kin.[18]

Compared to the oldest old in HIC, those in LMIC have more disabilities. A review showed 44% independence in ADL in the USA and Europe versus 28% in our sample.[31] For IADLs, a French study found 68% dependence, defined as any impairment in instrumental activities,[32] whereas nearly 100% of our sample was dependent since only two participants were independent. Family members provide most of the care in LMIC, which can strain family resources and lead to inconsistent care quality.[33] Current evidence suggests that women present more disabilities than men in the oldest old, in line with our findings.[31,34] In the same way, socioeconomic disparities, including gender inequalities and access to healthcare, can contribute.[31] It is also possible that survival bias may present since higher morbidity rates are observed in older women than in men of the same age,[35,36] and women tend to live longer than men, both in total life span and in years living with disabilities.[31,34]

While "old age" has often been reported as a cause of death, it is nonspecific and vague. Autopsy studies showed that organ failure is the leading cause of death in the oldest old.[37] Our results show that cardiovascular disease and pneumonia are the leading causes of death in

this sample. In line with these findings, the primary causes of death for those over 80 years old in Brazil are cardiovascular diseases, followed by pulmonary diseases and neoplasia,[38] and this trend is also observed in the oldest-old in Europe and North America.[39,40] However, the leading cause of death in our study was pulmonary edema, a nonspecific term that does not accurately reflect the underlying cause of death.[37]

The complex association between the variables under investigation and cognitive impairment among the oldest individuals in a cross-sectional study is influenced by reverse causation and survival bias. Survival bias occurs because 90+ studies included those who survived to advanced age or presented milder manifestations of risk factors.[41] Therefore, the sample may appear healthier only because those at higher risk may have died before the study.[28] Another contributor is reverse causation, as dementia itself could affect some conditions, such as hypertension, depression, and BMI.[42] It is essential to consider all these factors to interpret the findings accurately. Cognitive reserve can also explain some of our findings since individuals who live to advanced ages despite having cardiovascular risk factors probably have protective factors against cognitive decline.[8] Age remains the primary risk factor for neurodegenerative diseases, especially Alzheimer's disease.[6] However, our model did not show an association, probably due to the narrow range of age of the participants. Likewise, education is a known predictor of dementia,[43,44] but most participants had low educational attainment in our sample.

Research indicates that women typically exhibit a greater prevalence of dementia, particularly Alzheimer's disease,[4] mostly attributable to increased life expectancy and hormonal changes such as menopause.[45,46] Additionally, women have increased vulnerability to Alzheimer's disease neuropathologic changes.[47,48] Genetic factors such as *APOE* ϵ4 status seem to affect both sexes equally.[49] However, the genetic influence decreases with older age.[4] Biological differences, education, and social roles are other contributing factors.[48,50] Though, we did not find an association between sex and cognitive impairment. This finding could provide additional evidence supporting the lack of association described in previous studies[45,50] but also may indicate that our sample size was not large enough to establish a conclusive association.

Married status may be related to a lower risk for dementia for a variety of reasons. In addition to enjoying higher social interaction and support, married individuals frequently had healthier lifestyles and lower death rates.[51] Although previous research suggests that marriage may have a more robust protective impact against dementia in men than in women, our stratified analyses revealed no difference. This could be attributed to societal patterns among the older population, such as the fact that widowed women remarry less frequently than widowed men, which could impact the risk profiles given that women are already at higher risk of having dementia.[52]

Previous research has demonstrated that regular physical activity in mid-life decreases the probability of developing cognitive impairment[53] and that sedentary behavior is a risk factor for dementia.[54] Still, these results are unclear in the oldest old, since no specific studies exist on this age group. The fact that cognitive impairment reduces mobility and physical activity[54,55] suggests that the findings could be interpreted as reverse causality.

Depression and dementia are both prevalent illnesses among older people, exhibiting considerable overlap. In a nationwide Brazilian study relying on self-reported diagnosis, depression may impact as much as 13% of individuals aged over 60,[56] and another study showed a prevalence of 13% of those 90+ years.[57] Depression prevalence was 7% among those with cognitive impairment and over 60 years old,[7] but rates as high as 46% in patients with Alzheimer's disease were described previously.[58] Multiple studies indicate that depression is associated with an increased risk of developing dementia, including Alzheimer's disease and all-cause dementia.[59,60] However, it is unclear how this causal mechanism occurs and whether depression is an actual risk factor for dementia or a prodromic symptom of the condition.[59]

Osteoarthritis also showed increased odds of cognitive impairment but no significant association in the sensitivity analysis. Decreased daily physical activity due to osteoarthritis may contribute to the onset of dementia. Both diseases share inflammatory pathways, and it has also been suggested that osteoarthritis-induced inflammation may contribute to the development of Alzheimer's disease and other dementias, as well as chronic pain and depression, which are commonly present in osteoarthritis.[61,62] Structural neuroimaging markers, such as hippocampal, entorhinal, ventricular, and grey matter volumes, indicate that cerebral atrophy may be a mechanism underlying the association,[63] while another study demonstrated that knee osteoarthritis accelerated amyloid beta deposition and neurodegeneration in a mouse model of Alzheimer's disease.[64]

Consistent with recent literature, our results indicate a greater BMI,[65] hypertension,[66] and peripheral vascular disease[67] are associated with lower odds of cognitive impairment. As discussed above, to accurately interpret the causal relationships between cardiovascular risk factors and cognitive impairment in the oldest old, it is essential to consider survival bias, cognitive reserve and reverse causation.

Hypertension in mid to late life correlates with an increased risk of dementia, linked to impaired cerebral perfusion and neuroinflammation. However, the age of onset seems significant, as the occurrence of hypertension after the age of 80 is likely to confer a protective effect.[68,69] In the oldest old, hypotension has been associated with worse cognitive function.[69] Dementia can cause weight

loss up to ten years before clinical symptoms appear, providing a better cognitive outcome for people with a higher BMI at the time of death.[65] Neuropathological changes associated with dementia in the oldest old are often related to multiple diseases other than Alzheimer's disease and vascular dementia that may not be affected by cardiovascular risk factors.[70] The mechanisms underlying peripheral vascular disease in this setting are less apparent; however, this association has been previously described.[71]

We also found an inverse association between neoplasia and cognitive impairment. This association has been previously described in other studies and is not entirely explained by reverse causation or selection bias.[72] This is particularly notable in Alzheimeŕs disease, which is associated with a lower frequency of cancer in the oldest old, in contrast to vascular dementia, which has been linked to a higher cancer risk.[73] The biological mechanisms of apoptosis and cell survival may explain this inverse relationship. Increased apoptosis may decrease cancer risk but can contribute to neurodegeneration, while enhanced cell survival reduces neurodegeneration but encourages tumor growth. Metabolic dysregulation, especially via the Warburg effect – the observation that most cancers utilize exclusively aerobic glycolysis – underscores contrasting metabolic processes in cancer and Alzheimer's disease. The shared genetic pathways that include genes, such as Pin1 and p53, highlight the intricate nature of these diseases, while genetic factors like *APOE4* can affect the risk of both cancer and Alzheimer's disease.[72,74]

In the stratified analyses by sex, being married was associated with lower odds of cognitive impairment only in men, which is in line with previous findings.[75] Sedentary behavior was associated with cognitive impairment in both men and women, as previously shown.[53] Hypertension was associated to lower cognitive impairment odds in women but not in men. The literature on sex-specific differences in late-life hypertension and the risk of dementia is inconsistent, with a systematic review indicating that there were no sex differences.[76] However, hormonal variations across the life cycle, particularly estrogen in pregnancy and menopause, may help explain a shift in risk in women.[76] Similarly, the hormonal influence may explain the decreased odds of cognitive impairment of peripheral vascular disease for women.[46] However, we did not find studies that specifically address the risk of peripheral vascular disease by sex in late life. The odds of cognitive impairment associated with neoplasia was significant in men but not women. We were unable to locate any additional studies that specifically addressed this association by sex, but the literature establishes that men present a higher incidence of cancer at older age.[77] Indeed, the prevalence of cancer was higher among men in our sample, which could help to explain these findings. Osteoarthritis seems to have higher odds for cognitive impairment in men; however, the correlation for women was borderline. Previous studies did not find sex differences in the association between osteoarthritis and dementia.[61,62] Depression was associated with an increased odd of dementia only in women, but the association was borderline in men. The literature on this topic is inconsistent. Some studies found a higher risk for women, and others found a higher risk for men.[78] Our study suggests that depression may increase the odd of dementia in both sexes.

Our study has strengths. It includes a racially and socioeconomically diverse sample and provides valuable insights into cognitive health among the oldest-old in an LMIC. The comprehensive clinical and functional assessment, the full-body autopsy, and stratified analysis by sex enhance the depth of our findings. However, our study had limitations. Firstly, there was no longitudinal follow-up of the sample before death, which limits our ability to establish causal relations. We also lacked access to health records or a unified medical registry. Additionally, we did not conduct any in vivo assessment of clinical (e.g., measurements of blood pressure or weight), functional, or cognitive evaluations. In this context, we could not evaluate potential changes in BMI over time or any weight changes resulting from neoplasia or other factors. Yet, assessments with a proxy were previously validated and largely accepted as a reliable source of information.[18] The absence of *APOE* data in our study is a limitation. *APOE* ϵ4 is a significant genetic risk factor for late-onset Alzheimer's disease and can modify the associations between risk factors and dementia.[79] For example, midlife hypertension, followed by late-life hypotension possibly resulting from a reduced concentration of norepinephrine in the brain due to neurodegeneration, enhances amyloidogenesis and tauopathy. Higher systolic and diastolic blood pressure levels were associated with better cognitive performance, particularly in *APOE* ϵ4 carriers, whereas hypertension was associated with increased dementia risk in non-carriers.[80,81] Future research aims to incorporate genetic investigation into the BAS sample.

In conclusion, our study of oldest-old Brazilians provides insights into the health, socioeconomic, and lifestyle challenges faced by this age group in an LMIC. Less education, high rates of disability, and significant levels of cognitive impairment without medical diagnoses were present in our sample. Moreover, we described factors associated with cognitive impairment in 90+ older adults. Future studies on the neuropathologic changes associated with dementia in this oldest-old sample will enhance the understanding of cognitive aging in diverse populations.

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Statements and declarations

Ethical considerations

The local ethical committee approved this study (protocol number 52180321.2.0000.0068).

Consent to participate

Written informed consent was obtained from the deceased's next of kin for brain donation and information use.

Consent for publication

Not applicable.

Author contributions/CRediT

Aline Maria Macagnan Ciciliati (Data curation; Formal analysis; Methodology; Writing – original draft); Renata Elaine Paraizo Leite (Methodology; Resources; Writing – review & editing); Lea T. Grinberg (Methodology; Resources; Writing – review & editing); Carlos Augusto Pasqualucci (Methodology; Resources; Writing – review & editing); Vitor Ribeiro Paes (Investigation; Methodology; Resources; Writing – review & editing); Alberto Fernando Oliveira Justo (Investigation; Methodology; Resources; Writing – review & editing); Renata Eloah de Lucena Ferretti-Rebustini (Methodology; Resources; Writing – review & editing); Eduardo Ferrioli (Methodology; Resources; Writing – review & editing); Claudia Kimie Suemoto (Conceptualization; Investigation; Methodology; Resources; Visualization; Writing – original draft; Writing – review & editing).

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Conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Data availability

Data is available upon request to the corresponding author (CKS).

Supplemental material

Supplemental material for this article is available online.

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