Research Paper

The comorbidity conditions and polypharmacy in elderly patients with mental illness in a middle income country: a cross-sectional study★☆

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ABSTRACT

Background: Mental disorders increase the risk factor for developing physical comorbidity conditions, such as cardiometabolic diseases. There is a high prevalence of multimorbidity and polypharmacy in the elderly population which hampers clinical response. Studies have shown that this positive correlation between the aging process and enhancement of physical comorbidities is especially high among older adults who live in low or middle income countries.

Objective: To investigate the association between physical disease comorbidities and polypharmacy in older adults with a clinical diagnosis of Alzheimer's disease (AD), mild cognitive impairment (MCI) or major depressive disorder (MDD), living in a middle income country.

Methods: Cross-sectional study of community-dwelling elderly individuals who are cognitively healthy and those with AD, MCI, or MDD. The severity scale of the Charlson Comorbidity Index (CCI) was calculated to classify the severity of comorbidity condition. Logistic regression model (unadjusted and adjusted for age) were used to calculate odds ratios (OR) and 95 % confidence intervals (CI) for cardiometabolic comorbidity (hypertension, diabetes, dyslipidemia and overweight), and polypharmacy.

Results: Although there was not an increased risk of hypertension, diabetes, and obesity among the groups, elderly people with mental disorders presented higher odds for polypharmacy condition. Polypharmacy was significantly higher for all groups in comparison with cognitively healthy participants: AD (OR 22.00, 95 % CI 6.11–79.11), MDD (OR 14.73, 95 % CI 3.69–58.75) and MCI (OR 10.31, 95 % CI 2.44–43.59). Elderly patients with AD presented more severe comorbidities and higher risks for dyslipidemia.

Conclusion: Elderly patients with depression, dementia and mild cognitive impairment have considerably higher odds for polypharmacy. People with dementia also have greater comorbidity severity than those who are cognitively healthy. In middle income countries, there is an urgent need to focus on promoting age-appropriate health approaches for the elderly with mental illness to prevent the development of aggravated cardiometabolic conditions and polypharmacy.

1. Introduction

The increase of life expectancy raises attention to aspects related to longevity, primary and secondary health, social care and policy planning for the elderly. This group represents around 23 % of the total global burden of disease, with the highest expenditures going to chronic and non-communicable diseases (Prince et al., 2015). According to Prince and collaborators (2015), the major burden of the aging process is associated with cardiovascular, respiratory, and musculoskeletal diseases, cancer, and mental and neurological disorders.

Mental disorders, in general, are associated with an increased risk factor for smoking and cardiometabolic diseases, such as hypertension

and diabetes (Prince et al., 2007). A recent Lancet Commission Report showed that people with a mental disorder diagnosis have a 1.4–2.0 increased risk for developing cardiometabolic diseases in comparison with individuals without mental disorders. In major depressive disorder (MDD), for example, the increase for having a physical comorbid diagnosis is around 40 % (Firth et al., 2019). Even though the contributions by this commission to the spectrum of mental illnesses in adults and children are highly recognized, the population of elderly people with Alzheimer's disease (AD) or dementia types were not mentioned in the report.

Besides the high prevalence of dementia among the elderly worldwide, it is important to emphasize that low and middle-income

countries (LMICs) have 62 % of all cases, whereas high-income countries (HICs) have around 38 % of cases. It is also expected that estimates in LMICs should rise to 71 % by 2050 (Alzheimer's Disease International, 2013). Globally, dementia was the fifth-largest cause of death in 2016 (Nichols et al., 2019). This represents the disease burden involving not only the cognitive symptoms but also a poor quality of life for this group, combining physical health and medication misuse. Thereby, it is crucial to consider the highly prevalent multimorbidity in the elderly population, especially in dementia patients (Bunn et al., 2014).

People with dementia are more likely to have five or more physical comorbidity conditions and polypharmacy than those without dementia (Clague et al., 2017). The three most common diseases in this group are hypertension (34.5 %), diabetes (16.3 %) and cardiac arrhythmia (7.3 %). The prevalence of these cardiometabolic conditions is even higher for patients with more severe dementia (Zhu et al., 2017). It is important to highlight that comorbidities are considered risk factors for poor physical and mental health in people with dementia and there is a need to provide greater support and sssintegrated clinical intervention (Nelis et al., 2019).

According to recent estimates from high income countries, medical expenditures for people living with dementia is particularly high. From 2010 to 2015 there was an increased burden of 35 % in Alzheimer's disease in the United States, with approximated medical costs of $818 million dollars (Nichols et al., 2019). The costs of medical care for patients with moderate/severe dementia are twice as expensive ($19,604) than for people without dementia ($9108) (Zhu et al., 2017).

Despite the high costs cited above, the number of comorbidity conditions in patients with dementia has the strongest association with expenditures in medical care, reporting that for people with more than three comorbidities, the treatment cost is around $30,244. This amount is more than ten times higher in comparison with those without comorbidities ($2612) (Zhu et al., 2017).

Prospective cohort studies investigating cognitively healthy elderly people have already found that vascular risk factors such as diabetes, heart failure, stroke, high levels of obesity and chronic multimorbidity conditions are associated with the incidence of mild cognitive impairment (MCI) (Vassilaki et al., 2015; Ganguli et al., 2013; Luck et al., 2010). There is also a consensus in the literature that MCI is not necessarily a precursor to Alzheimer's disease, but there is a strong association between an MCI diagnosis and the increased risk for developing AD (Sanford, 2017; Bennett et al., 2002). A recent paper found that vascular systemic diseases, among other clinical comorbidities, were the most prominent risk factor that influences the transitional stage from MCI to dementia and highlighted the importance of monitoring these physical conditions during MCI treatment (Panpalli Ates and Yilmaz Can, 2020).

A scoping review investigating the prevalence of comorbidity in people with dementia found a suggestive diabetes rate of around 13–20 % and of stroke between 16–29 %. These include 74 papers from 12 countries, 63 % of the studies were from the United Kingdom and the United States of America, and the remaining 37 % were spread among Australia, Canada, Japan and other countries in Europe (Bunn et al., 2014). Despite the large volume of evidence about comorbidities in this population, the majority of studies show data from high income countries whereas there are relatively few data from middle income countries to estimate the prevalence of physical conditions in the elderly with mental illness (Prince et al., 2011; Prina et al., 2019).

Therefore, considering the relevant issues with physical health conditions for the target group, the aim of this study was to investigate the association between physical disease comorbidities and polypharmacy in older adults with a clinical diagnosis of AD, MCI or MDD living in a middle income country.

2. Material and methods

2.1. Study design, setting and participants

In this cross-sectional study, cognitively healthy elderlies from community and patients with the diagnosis of Major Depressive Disorder, Mild Cognitive Impairment and Alzheimer Disease (both sexes, ages > 60 years old) from the Center of Alzheimer Disease (CDA) of the Psychiatry Institute of the Federal University of Rio de Janeiro were recruited. The sample was composed by elderly living in Brazil, a country grouped according to the World Bank economy classification as a Middle Income Country (MIC). The MICs are a varied group defined by territorial extension, population and income level (Lower and Upper), which comprehends in general 75 % of the world's population and 62 % of the world's poor (The World Bank Group, 2019). The diagnostic assessments were performed by clinical staff, using a structured clinical interview to assess mental disorders according to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (American Psychiatric Association, 2000) and Petersen criteria (Winblad et al., 2004) for dementia, MDD, and MCI, respectively. Exclusion criteria included: illiterate; functional classes III and IV according to the New York Heart Association standards; with mental or physical comorbidities that impaired performance during the tests; severe visual and/or auditory impairments; mixed dementia, with evidence of cerebrovascular infarction in neuroimage; and other comorbid psychiatric disorders. All participants agreed to be part of this research, and all of them signed the written consent form. The Research Ethics Committee of the IPUB-UFRJ approved this study, under registration permit CAAE: 42349815.0.0000.5263.

2.2. Procedures and data analyzed

Anamnesis was performed with participants and their caregivers to assess the number of daily medications use and cardiometabolic diseases, such as hypertension, diabetes and dyslipidemia. Body Mass Index (BMI) was calculated according to defined cut points (< 25 normal weight; ≥ 25 overweight). The Charlson Comorbidity Index (10-year survival $= 0.983\hat{\ }(e^{CCIx0.9})$) was calculated according to reported comorbidities (Charlson et al., 1987, 2008). In the present study, dementia was not accounted for the classification score. Polypharmacy was defined as taking four or more medications daily, after excluding supplements and vitamins (Bushardt et al., 2008).

2.3. Statistical analysis

A descriptive analysis of the demographic data was conducted. To verify normality and homoscedasticity, Kolmogorov-Smirnov and Levene were applied, respectively. Demographic characteristics, comorbidity and polypharmacy prevalence, CCI, and frequency of severity scale of CCI were compared among groups using ANOVA or Kruskal-Wallis test. Bonferroni and Tamhane´s T2 post hoc analyses were performed to parametric and non-parametric variables, respectively.

For assessing differences among prevalence in cognitively healthy, MDD, MCI and AD groups, a chi-squared test was used. Logistic regression model (unadjusted and adjusted for age) were used to calculate odds ratios (OR) and 95 % confidence intervals (CI) for cardiometabolic comorbidity (hypertension, diabetes, dyslipidemia and overweight), and polypharmacy. All statistical analyses were performed using SPSS® version 26.0 and GraphPad Prism version 5.01. $p \leq 0.05$ was considered to indicate statistical significance.

3. Results

Two hundred and twelve elderly people were included in this study (102 cognitively healthy, 30 MDD, 26 MCI and 54 AD). For all groups, female participants prevailed (healthy = 89.2 % n = 91; MDD = 83.3

Table 1
Demographic and clinical characteristics by groups.

	H (n = 102)	MDD (n = 30)	MCI (n = 26)	AD (n = 54)	F/X^2 (p value)	Post Hoc
Age (y)[a]	72.7 (7.9)	73.7 (8.4)	76.7 (6.3)	79.6 (7.9)	9.52 (< 0.001)	ADxH** ADxMDD*
Sex(%)					26.30 (< 0.001)	–
Male	10.8	16.7	38.5	44.4		
Female	89.2	83.3	61.5	55.6		
BMI (kg/m²)[b]	26.3 (5.0)	26.3 (5.0)	25.6 (5.6)	24.9 (5.1)	6.16 (0.104)	–
Marital Status n (%)					11.99 (0.213)	–
Single	8 (17 %)	6 (20 %)	7 (27 %)	3 (6%)		
Married	21 (45 %)	11 (37 %)	9 (35 %)	26 (48 %)		
Divorced	5 (11 %)	3 (10 %)	5 (19 %)	4 (7%)		
Widower	13 (28 %)	10 (33 %)	5 (19 %)	21 (39 %)		
Scholarship (%)						
0 − 4y	7.8	3.4	3.8	17.3	11.94 (0.008)	–
5 − 9y	20.6	41.4	11.5	34.6	14.00 (0.003)	–
10 − 12y	41.2	17.2	34.6	28.8	47.02 (< 0.001)	–
> 12y	30.4	37.9	50.0	19.2	18.13 (< 0.001)	–
MMSE (score)[b]	28 (3.0)	29 (3.0)	29 (1.3)	20.5 (6.8)	92.02 (< 0.001)	ADxH** ADxMDD** ADxMCI**
CCI severityn(%)					20.06 (0.003)	–
Mild	27 (27 %)	6 (20 %)	2 (8%)	3 (6%)		
Moderate	63 (62 %)	21 (70 %)	17 (65 %)	35 (65 %)		
Severe	11 (11 %)	3 (10 %)	7 (27 %)	16 (29 %)		
CCI (score)[c]	3.0 (2.9–3.3)	3.5 (3.0–3.7)	4.0 (3.3–4.3)	4.0 (3.8–4.3)	27.68 (< 0.001)	ADxH** ADxMDD*
Comorbidities (%)						
Hypertension	56.9	70.0	53.8	51.9	2.75 (0.430)	–
Diabetes	16.7	16.7	7.7	25.9	4.34 (0.227)	–
Dyslipidemia	18.6	40.0	26.9	38.9	9.81 (0.020)	–
Medications (n)[d]	2.0 (0–8.0)	3.5 (1.0–11.0)	2.5 (0–11.0)	4.0 (0–11.0)	35.12 (< 0.001)	ADxH** MDDxH
Polypharmacy (%)	3.4	34.5	27	44	34.69 (< 0.001)	–

Note. H: Healthy; MCI: Mild Cognitive Impairment; AD: Alzheimer's Dementia; MDD: Major Depressive Disorder; BMI: Body Mass Index; MMSE: Mini-Mental State Exam; CCI: Charlson Comorbidity Index; *p < 0.05; **p < 0.01.
[a] parametric variables: mean (std deviation).
[b] non-parametric variables: median (interquartile range).
[c] non-parametric variables: median (95 % confidence interval, lower bound – upper bound).
[d] non-parametric variables: median (minimum – maximum).

% n = 25; MCI = 61.5 % n = 16; AD = 55.6 % n = 30) with a mean age of 75.14 (SD = 8.32). The elderly with AD were significantly older than the cognitively healthy (*p* < 0.001) and MDD (*p* = 0.007) groups, but there were no significant differences for the MCI group (*p* = 0.756). There was also no difference for the MDD group in comparison with the healthy one (*p* = 1.000). There was no significant difference for marital status (*p* = 0.213) and BMI (*p* = 0.104).

In the scholarship analyses, significant statistical differences were observed among the compared ranges (< 4 years, X^2 = 11.94; *p* = 0.008; 5 − 9 years, X^2 = 14.00; *p* = 0.003; 10 − 12 years, X^2 = 47.02; *p* < 0.001; > 12 years; X^2 = 18.13; *p* < 0.001). As expected, global cognition (MMSE) was worse in the AD group (*p* < 0.001).

The Charlson Comorbidity Index results showed that patients with AD have more physical comorbidities than MDD (*p* = 0.015) and healthy older (*p* < 0.001) groups, but there was no difference when compared with MCI patients (*p* = 0.932). MDD and AD groups take more medications than the elderly without mental illness. Descriptive analysis is shown in Table 1.

Among the four cardiometabolic comorbidities examined, odds ratio

(OR) analyses showed that MDD (OR 2.91, 95 % CI 1.20–7.05; p = 0.026) and AD (OR 2.78, 95 % CI 1.32–5.82; p = 0.007) had higher odds for dyslipidemia. However, the odds for hypertension are not increased (MDD OR 1.77, 95 % CI 0.73–4.24; p = 0.213, MCI OR 0.88, 95 % CI 0.37–2.10; p = 0.827 and AD OR 0.81, 95 % CI 0.42–1.58; p = 0.613). Similar results were observed for diabetes (MDD OR = 1.00, 95 % CI 0.33–2.98; p = 1.000, MCI OR 0.41, 95 % CI 0.90–1.93; p = 0.360 and AD OR 1.75, 95 % CI 0.78–3.89; p = 0.206) and for overweight (MDD OR 1.22, 95 % CI 0.45–3.28; p = 0.689, MCI OR 0.62, 95 % CI 0.25–1.51; p = 0.296 and AD OR 0.51, 95 % CI 0.25–1.05; p = 0.068).

Since the Post Hoc analyses showed a significant difference in the ages for AD x Healthy and AD x MDD, we also calculated the adjusted odds ratio (AOR), adjusted by age, in order to obtain more reliable results.

The AOR analyses presented similar results, with higher odds only for dyslipidemia (MDD AOR 2.89, 95 % CI 1.19–7.01; p = 0.019; AD AOR 3.93, 95 % CI 1.68–9.23; p = 0.002). There were no increased odds for hypertension (MDD AOR 1.77, 95 % CI 0.73–4.25; p = 0.199,
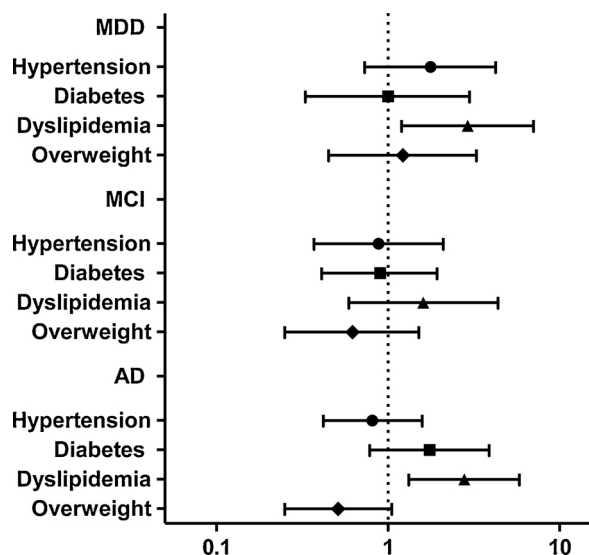
Fig. 1. Odds ratio of hypertension, diabetes, dyslipidemia and overweight for each diagnosed group.

MCI AOR 0.91, 95 % CI 0.38–2.22; $p = 0.851$ and AD AOR 0.91, 95 % CI 0.44–1.88; $p = 0.816$), diabetes (MDD AOR 0.99, 95 % CI 0.33–2.97; $p = 0.995$, MCI AOR 0.38, 95 % CI 0.08–1.79; $p = 0.222$ and AD AOR 1.50, 95 % CI 0.63–3.57; $p = 0.354$) and overweight (MDD AOR 1.21, 95 % CI 0.45 – 3.27; $p = 0.701$, MCI AOR 0.65, 95 % CI 0.26–1.61; $p = 0.357$ and AD AOR 0.52, 95 % CI 0.24–1.11; $p = 0.093$).

The risk of developing four common cardiometabolic conditions (hypertension, diabetes, dyslipidemia, overweight) and polypharmacy in patients (MDD, MCI and AD) compared with elderly people without mental disorders are presented in Figs. 1 and 2, respectively.

Polypharmacy was significantly higher for groups with morbidity in comparison with cognitively healthy participants. The polypharmacy OR showed higher odds for DA (OR 22.00, 95 % CI 6.11–79.11; $p < 0.001$), MDD (OR 14.73, 95 % CI 3.69–58.75; $p < 0001$) and MCI (OR 10.31, 95 % CI 2.44–43.59; $X^2 = 13.67$; $p = 0001$) (Fig. 2). Similar results were observed when controlled by age (MDD AOR 14.52, 3.59–58.62; $p < 0.001$, MCI AOR 10.40, 95 % CI 2.31–46.87; $p = 0.002$ and AD AOR 45.98, 95 % CI 10.33–204.69; $p < 0.001$).

4. Discussion

The aim of this study was to investigate possible associations between physical disease comorbidities and polypharmacy conditions in older adults with mental disorders living in an MIC. Our findings show
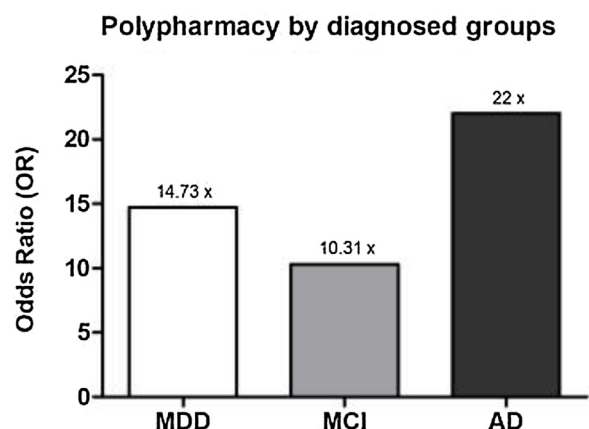
Polypharmacy by diagnosed groups

Fig. 2. Odds ratio of polypharmacy (takes 4 or more medications) by each diagnosed group.

that, compared to cognitively healthy and depressive elderly people, dementia and MCI patients have a significantly higher number of comorbidities and greater comorbidity severity. This is indicated by a higher Charlson Comorbidity Index and by the greater proportion of severe CCI, as seen in previous studies (Silay et al., 2017; Panpalli Ates and Yilmaz Can, 2020; Luck et al., 2010). However, it is important to highlight that Dementia and MCI groups were significantly older than the cognitively healthy and depressive disorder groups. This reinforces the correlation between the aging process and advancement of physical comorbidities in the elderly population, especially among those who live in low and middle-income countries (LMICs) (Prince et al., 2015).

Among the investigated cardiometabolic conditions, only dyslipidemia showed statistically significant results for groups with dementia and depression. Unlike other studies, we did not find greater risks for hypertension, diabetes or being overweight associated with mental illness in the elderly (Bunn et al., 2014; Vassilaki et al., 2015). A possible explanation is that older people who live in MICs are more vulnerable to develop chronic medical conditions, even with no preexisting mental illness. It is expected that the prevalence of cardiometabolic diseases increase during the aging process. Also, it is known that older adults living in low and middle income regions are more susceptible to the development of vascular diseases (Prince et al., 2015).

In our study, we found a high prevalence of hypertension among elderly participants with and without mental disorders, similar to the literature for middle income countries, where hypertension affects 50 % or more of the elderly (Prince et al., 2015). Results show that older people that live in an MIC are more vulnerable to developing chronic medical conditions, even with no preexisting mental illness. This is largely supported in literature, which shows that risk behaviors, such as diets rich in saturated fats, smoking, physical inactivity, low socioeconomic class, and low levels of education, are a strong predictor of chronic and non-communicable diseases. Therefore, our findings corroborated Shubert's study (Shubert et al., 2006), which evaluated 3013 patients, with and without dementia diagnosis, from primary care centers in Indianapolis. After adjusting for age, sex and race, they found no differences in the overall chronic medical condition assessed, suggesting that older people have similar comorbidity profiles, independent of a dementia diagnosis.

The present study showed a critical risk of polypharmacy for all diagnostic groups. This was particularly expressive among dementia patients whose risk was considerably higher (22 times). The AD and MDD patients were the most susceptible to polypharmacy. These results are probably influenced by typical treatments, different from MCI, which usually does not require pharmacological interventions. A systematic review and meta-analysis with seven studies, all derived from High Income Countries (HICs), showed that polypharmacy is observed in more than 50 % of dementia patients. The review also indicates that there is a proportional increase risk of dementia with medication numbers and a strong association between dementia and polypharmacy (AOR 1.30) (Leelakanok and D'Cunha (2019)). Furthermore, other studies have shown that depressed elderly patients have higher odds for polypharmacy when compared with cognitively healthy ones, and that there is a positive association between polypharmacy and depressive symptoms in elderlies' women (Holvast et al., 2017; Bazargan et al., 2019).

It is important to note that even in HICs polypharmacy is a common condition among elderly people without dementia. A recent study with 34,232 older participants from 17 European countries identified a polypharmacy prevalence of 32.1 %. However, it was observed that socioeconomic variables such as economic difficulties and low number of years of education are associated with higher prevalence for polypharmacy (Midão et al., 2018). There is a positive association between old age and elevated drug consumption, which increases the risk of adverse drug reactions and multimorbidity (Sergi et al., 2011; Jyrkka et al., 2011). Furthermore, polypharmacy and medication misuse are negatively related to health decline, worsening of functional ability,

cognitive capacity, nutritional aspects, and quality of life outcomes in the elderly population (Bonfiglio et al., 2019; Umegaki et al., 2019; Jyrkka et al., 2011). The impacts on health-related outcomes in elderly people with mental illness are possibly even more important since depression and neurocognitive disorders already lead to similar unfavorable outcomes associated with pharmacological treatments and medication misuse (Bonfiglio et al., 2019). Sanford (2017) highlighted the need to focus on controlling polypharmacy and treating depression in MCI patients, and also reducing risk factors such as diabetes and hyperlipidemia, which may contribute to reverse mild impairment to normal cognition or to slow down the possibility of progression to dementia. Furthermore, mental health care providers must be aware of polypharmacy risk to reduce the prescription of inappropriate medications, drug-drug interactions and adverse consequences (Prince et al., 2015).

The complex multimorbidity characteristic of this population includes frailty, chronic diseases, social difficulties, and even age discrimination. All of these aspects require attention from policymakers to establish accessibility requirements and high-quality treatment, since access to age-appropriate care in the health services systems is still lacking for older people (Prince et al., 2015). As pointed out by the recent blueprint report, access to proper health care is also negatively influenced by the stigmatization of mental disorders (Firth et al., 2019) and this issue may be even more critical for the mentally ill elderly, especially in LMICs. The most effective care will most likely be holistic and patient-centered, with higher investment in primary and secondary prevention for cardiometabolic disorders. Investing in a healthy lifestyle, such as consuming a nutrient rich diet and regular physical exercise, contribute to the treatment of various mental disorders and also prevent the clinical worsening in physical and cognitive parameters.

5. Conclusion

Among the clinical conditions investigated, there were higher odds for dyslipidemia and polypharmacy, but not for diabetes, hypertension, and being overweight. The Charlson Comorbidity Index showed that dementia and MCI patients have more physical comorbidities when compared with depressive and cognitively healthy elderlies. Multimorbidity and polypharmacy conditions are commonly observed in the general elderly population, however, our study found dementia patients at a considerable risk with twenty-two times higher polypharmacy, ten times higher for mild cognitive impairment and fourteen times higher for the elderly with depression. In low and middle income countries, there is an urgent need to focus on promoting age-appropriate health approaches for the elderly with mental illness to prevent the development of aggravated cardiometabolic conditions.

Limitations

The difference of age among groups might be influenced by the prevalence of cardiometabolic risk observed in the present study. Moreover, considering the lack of studies in LMICs, it is important to highlight that most studies do not separate the analyses into lower and upper classification of MICs, usually allocating all the regions in the same classification of low and middle income countries (LMICs). However, Brazil was ranked as an upper middle income country within the middle income countries (MICs) major group (The World Bank Group, 2019). Future studies should investigate the differences between upper and lower MICs.

Conflict of interest

The authors declare that they have no conflicts of interest.

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