

ORIGINAL STUDY

Severe menopausal symptoms linked to cognitive impairment: an exploratory study

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Abstract

Objective: To evaluate the association between menopausal symptoms and cognitive decline in postmenopausal women.

Methods: This was a subanalysis of a cross-sectional, observational study conducted among women attending gynecological consultations across nine Latin American countries. The survey involved late postmenopausal women who were asked to complete a general questionnaire and the Menopause Rating Scale (MRS) to assess menopausal symptoms, with the Montreal Cognitive Assessment used to evaluate cognitive function as an outcome. A Montreal Cognitive Assessment score of less than 21 was used to define women with mild cognitive impairment (MCI).

Results: The study included 1,287 postmenopausal women with a mean age of 55.5 years and a mean body mass index of 26.3 kg/m². On average, participants had 13.8 years of education and 2.3 ± 1.8 children, with 72.8% reporting having a partner. Additionally, 36.7% ever used menopausal hormone therapy. Regarding lifestyle factors, 50.3% engaged in a sedentary lifestyle, whereas 70.5% had never smoked. 15.3% of women had MCI exhibited significantly more intense menopausal symptoms compared with those without MCI (MRS total score 15.24 ± 12.58 vs 10.53 ± 8.84, respectively, $P < 0.001$). Logistic regression analysis revealed a significant association between severe menopausal symptoms (MRS total score ≥14 points) and MCI (odds ratio [OR], 1.74; 95% CI, 1.25-2.42). Conversely, a lower body mass index (OR, 0.96; 95% CI, 0.95-0.98), sexual activity (OR, 0.70; 95% CI, 0.51-0.96), physical exercise (OR, 0.55; 95% CI, 0.39-0.76), menopausal hormone therapy use (OR, 0.36; 95% CI, 0.24-0.55), and higher educational level (OR, 0.31; 95% CI, 0.21-0.46) were associated with lower odds for MCI.

Conclusion: Severe menopausal symptoms in postmenopausal women were associated with cognitive impairment. This study highlights the intricate interplay between hormonal, lifestyle, and sociodemographic factors and cognitive health.

Key Words: Menopausal hormone therapy – Menopausal symptoms – Menopause Rating Scale – Mild cognitive impairment – Montreal Cognitive Assessment.

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As the global aging population increases, there has been a rise in age-related chronic diseases. Dementia is a particularly concerning condition that is affecting more people worldwide, with a significant impact on medical, social, and economic spheres. Based on recent studies and demographic projections, experts estimate that there are currently 24.3 million people living with dementia globally, with 4.6 million new cases diagnosed every year. This means that approximately one person is diagnosed with dementia every 7 seconds. It is projected that the number of dementia cases will double every 20 years, reaching 81.1 million by the year 2040.¹

Dementia has a significant impact on individuals, their families, and healthcare systems. In order to fight against this disease, it is crucial to implement preventive and nonpreventive effective strategies. As drugs designed to treat dementia have not yet met expectations, the focus has shifted toward primary and secondary prevention. It has been estimated that approximately 40% of cases of Alzheimer disease, the most common form of dementia, can be prevented or delayed.² Among the numerous dementia preventive strategies among older adults, one can mention promoting physical, mental, spiritual, and social health. These include engagement in cognitive activities; controlling body mass index (BMI); adopting a Mediterranean diet; taking vitamin D supplements; abstaining from tobacco and alcohol consumption; controlling glucose, lipid, and blood pressure levels; preventing depression; engaging in regular physical exercise; maintaining a positive mood; and actively participating in social life.³

Recent research has highlighted the importance of estradiol in female cognitive aging.⁴ Studies have demonstrated that menopausal symptoms, particularly vasomotor symptoms, play a significant role in cognition and brain function. Although it is too soon to claim a direct causal relationship between hot flashes and memory dysfunction, studies suggest that women experiencing hot flashes may experience cognitive improvements when these are treated.⁵ The significance of ovarian hormone deficiency in cognitive decline is emphasized by research showing a higher risk of cognitive impairment in women undergoing bilateral oophorectomy. However, this risk appears to decrease with menopausal hormone therapy (MHT).⁶

Menopause is a natural biological process that brings about a range of physical and psychological changes in women. It often leads to menopausal symptoms, which can be significantly prevalent and have severe intensity. These symptoms include vasomotor symptoms, osteomuscular pains, sleep disruptions, mood swings, and cognitive difficulties,⁷ which are related to estrogen deficiency and are indicative of disorders in several systems, including thermoregulation, sleep, circadian rhythms, and sensory processing. They also affect various domains of cognitive function.⁸

Although vasomotor symptoms (ie, hot flashes and night sweats) have been widely examined and recorded, the connection between menopausal symptoms and the risk of cognitive decline is a developing field of research that is gaining attention. Reports

indicate that hormonal changes linked with menopause might impact cognitive function, but the precise nature of this relationship has not been yet thoroughly comprehended.⁹

Cognitive decline is a gradual process that can lead to mild changes in cognitive function or more severe disorders such as dementia.¹⁰ It is important to identify potential risk factors contributing to the development of cognitive decline, such as menopausal symptoms. Early detection of such risk factors can help prevent and timely treat age-related cognitive disorders.

The aim of the present study was to explore the possible association between menopausal symptoms and cognitive decline among postmenopausal women. We analyze epidemiological and clinical data to determine how menopausal symptoms affect cognitive performance in areas such as memory, attention, language, and executive functions.

The results of this study could offer important information regarding the factors that might affect cognitive health in postmenopausal women, which in turn have significant implications for the development of preventive and intervention strategies that may preserve cognitive function and enhance the quality of life of this female population.

METHODS

Study design and participants

The present document is a subanalysis of a multinational observational and cross-sectional study of the Latin American Network for Research of the Climacteric (REDLINC XII) carried out from January 2023 to October 2023 among otherwise healthy postmenopausal women (70 years or younger) attending general gynecological routine consultations in nine Latin American countries: Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Mexico, Panama, and Peru. The recruitment of participants was based on convenience sampling, with participating researchers surveying in their centers at least 100 women, of whom at least a third had spontaneous or surgical menopausal before age 40 years. The overall aims of the REDLINC XII were to analyze associations between the type of menopause (premature, surgical, or natural) and quality of life, chronic diseases, cognition, and longevity. The present subanalysis explores the association of menopausal symptoms and cognition.

All participants were required to be literate in either Spanish or Portuguese (Brazil). Most women had middle incomes and received health care in private or state clinical centers. We excluded women who had undergone chemotherapy or radiotherapy, those declining participation, and those experiencing deafness or blindness or those diagnosed with dementia that hindered their ability to comprehend the questionnaires.

Studied variables

Demographic and health data

The following data were collected: age (in years), BMI (calculated as weight [in kilograms] divided by the square of height [in meters]), parity or the number of children, current partner

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status (yes/no), sexual activity (at least one sexual intercourse in the last year [yes/no]), university graduate (yes/no), age of menopause onset (in years), had natural menopause or premature ovarian insufficiency (POI, spontaneous menopause before the age of 40 years), bilateral oophorectomy (yes/no), ever use of systemic MHT (yes/no), inactive lifestyle (performs less than 75 minutes a week of intense aerobic physical activities such as running, gym, tennis, and so on, or less than 150 minutes a week of moderate aerobic physical activities such as fast walking, cycling, calm sports, dancing, scored as yes/no), smoker (yes/no), current intake of psychotropic drugs (ie, anxiolytic, antidepressants, and hypnotics, yes/no), and comorbidities such as hypertension, diabetes mellitus, and dyslipidemia (yes/no), and/or has a relative with dementia (yes/no).

Assessment of menopausal symptoms

The Menopause Rating Scale (MRS) was used to assess menopausal symptoms.¹¹ It is a tool that evaluates the presence and intensity of 11 symptoms, which are grouped into three subscales. The subscales include somatic-vegetative symptoms (items 1-3 and 11), psychological symptoms (items 4-7), and urogenital symptoms (items 8-10).

The symptoms assessed by the questionnaire include hot flashes, cardiac discomfort, sleep disturbances, muscular and joint discomfort, depressive mood, irritability, anxiety, physical and mental exhaustion, sexual problems, bladder issues, and vaginal dryness. Each of the 11 items can be rated on a Likert scale ranging from 0 (absent), 1 (mild), 2 (moderate), 3 (severe), to 4 (very severe).

This allows the calculation of the mean and SD obtained by a population for each item. In addition, mean scores for each subscale can be calculated (sum of rates of each subscale item), and the sum of each subscale score provides a total MRS score. Severe menopausal symptoms are defined as a total MRS score equal to or greater than 14 points.¹² A higher total MRS score indicates a greater deterioration in quality of life. The questionnaire has been validated in both Spanish and Portuguese language.^{13,14}

Evaluation of cognition

Cognitive function was evaluated with the Montreal Cognitive Assessment (MoCA) tool, which is a screening test developed by Nasreddine et al in Canada.¹⁵ This test allows the diagnosis of mild cognitive impairment (MCI), which is a transitional state between normal aging and dementia, particularly Alzheimer disease. The prevalence of MCI varies from 3% to 42% in various studies, depending on the diagnostic criteria used.¹⁶ Several reports indicate that every year between 10% and 15% of individuals with MCI progress to dementia.¹⁷ Currently, there is much research focus on MCI as a precursor of Alzheimer disease.¹⁸

The MoCA evaluates six domains in 10 minutes (memory, visuospatial ability, executive function, attention, language, and orientation), and the maximal score is 30 points. In the original version, a score of 26 points or less defines MCI.¹⁵ According to Nasreddine et al,¹⁵ the MoCA is a better tool than the Mini-Mental State Examination for detecting MCI. The sensitivity and specificity for detecting MCI are 90% and 87% for the MoCA, respectively, compared with 18% and 100% for the Mini-Mental State Examination.

During the Spanish validation of the MoCA, a cutoff value of 21 points for the diagnosis of MCI showed a sensitivity of 71.4% and a specificity of 74.5%.¹⁹ In Brazil, we used the Portuguese version of the MoCA, which uses a similar cutoff value as the Spanish version (20 points or less).²⁰ In this study, the MoCA was administered by a physician who also examined each woman and recorded her personal and family history. A MoCA score of less than 21 points was used to identify those with MCI.¹⁹

Statistical analyses

Statistical analysis was performed using SPSS software (version 21.0 for Windows; SPSS Inc, Chicago, IL). The data are presented as means, SD, or percentages with their respective CI. The Levene test was used to evaluate the homogeneity of the variances, with a $P > 0.05$ indicating homogeneity. The Kolmogorov-Smirnov test was used to assess the normality of the data distribution. Based on the results of these tests, differences between numerical variables were analyzed using the Student t parametric test for normally distributed data or the Mann-Whitney U nonparametric test for nonnormally distributed data.

Logistic regression analysis was performed to determine factors associated with the presence of MCI (MoCA score <21 points). Covariates were introduced as categorical variables, except for age, years of education, and BMI, which were treated as continuous values. A stepwise procedure was used for variable inclusion in the model, with a significance level set at 10%. The variance inflation factor was used to assess multicollinearity in the regression analysis (variance inflation factor <10). The logistic regression model was assessed using Cox and Snell R^2 (which indicates the proportion of variance in the dependent variable explained by the predictor variables), the Hosmer and Lemeshow test (for goodness of fit), and a Durbin-Watson statistic (autocorrelation in a regression model's output). Interactions between variables that were statistically significant upon bivariate analysis were also considered. $P < 0.05$ was considered statistically significant for all calculations.

Ethical considerations

The REDLINC XII study received approval from the Ethics Committee of the Southern Metropolitan Health Service (memorandum 15/2022; June 22, 2022), located in Santiago de Chile, Chile, and adheres to the principles outlined in the Declaration of Helsinki. Before participation, all participants were fully informed about the study objectives and methodologies, and they provided written consent to take part in the research.

RESULTS

The present subanalysis included data of 1,287 women, with a mean age of 55.5 ± 6.8 years and a mean BMI of 26.3 ± 5.2 kg/m². On average, they had 2.3 ± 1.8 children, with 72.8% reporting having a partner and 67.5% engaging in sexual activity in the past 12 months. The average attained educational level was 13.8 ± 5.2 years, with 43.4% identifying themselves as university graduates.

The average age at menopause among the participants was found to be 44.3 ± 5.2 years. Of all the participants, 57.4% had natural menopause ($49.7\% \geq 44$ years and 7.7% from 40

TABLE 1. Characteristics of women according to the presence or not of mild cognitive impairment (MCI)

	MCI (no) ^a (<i>n</i> = 1,090 [84.7%])	MCI (yes) ^b (<i>n</i> = 197 [15.3%])	<i>P</i> ^c
Age (y)	55.6 ± 6.6	55.1 ± 7.9	NS ^d
Body mass index (kg/m ²)	26.2 ± 4.9	27.3 ± 6.4	0.0200 ^d
Number of children	2.2 ± 1.6	3.2 ± 2.4	0.0001 ^d
Has a partner	72.8 (70.1-75.4)	72.6 (66.3-78.9)	NS ^e
With sexual activity	69.1 (66.3-71.8)	58.9 (52.0-65.8)	0.0050 ^e
Graduates from universities	48.0 (45.0-51.0)	18.3 (12.8-23.7)	0.0001 ^e
Age at menopause (y)	44.3 ± 7.2	44.0 ± 7.1	NS ^f
Premature ovarian insufficiency	23.5 (21.0-26.0)	18.3 (12.8-23.7)	NS ^e
Oophorectomy	18.9 (16.6-21.2)	25.4 (19.3-31.5)	0.036 ^e
Menopausal hormone therapy (ever used)	40.6 (37.6-43.5)	15.2 (10.2-20.3)	0.0001 ^e
Sedentary lifestyle	47.1 (50.0-44.1)	68.5 (75.0-62.0)	0.0001 ^e
Never smoker	70.0 (77.3-72.7)	73.1 (66.9-79.3)	NS ^e
Psychotropic drugs	33.3 (30.5-36.1)	31.0 (24.5-37.5)	NS ^e
Comorbidities	43.9 (40.9-46.8)	49.2 (42.2-56.3)	NS ^e
Parents with dementia	15.1 (12.9-17.2)	15.7 (10.6-20.9)	NS ^e

Data are presented as mean ± SD or percentages (95% CI). MoCA, Montreal Cognitive Assessment; NS, nonsignificant. ^aMoCA ≥21 points. ^bMoCA score <21 points.

^c*P* value as determined with ^dMann-Whitney *U* test, ^eχ² test or ^fStudent *t* test.

to 44 years), 22.7% experienced POI, 19.9% underwent bilateral oophorectomy at an average age of 41.3 ± 7.1 years, and 36.7% had a history of using MHT at some point in their lives (44.9% oophorectomized vs 34.6% nonoophorectomized, *P* < 0.002). When it comes to lifestyle factors, 50.3% of women led a sedentary lifestyle, whereas 70.5% of them had never smoked, and 32.9% reported using psychotropic drugs. In terms of medical history, 32.9% had some type of cardiometabolic comorbidity, such as high blood pressure, diabetes, or dyslipidemia, whereas 15.2% had relatives diagnosed with dementia.

Characteristics of women according to the presence or not of MCI are presented in Table 1. According to the MoCA test, 15.3% of women (*n* = 197) were diagnosed with MCI, who had higher BMI, more children, have undergone more oophorectomies, and tend to be sedentary. On the other hand, they have lower levels of sexual activity and are less likely to have ever used MHT or be university graduates. No significant differences were observed in terms of age, having a partner, age of menopause, prevalence of POI, smoking habits, use of psychotropic drugs, presence of metabolic comorbidities, or a history of having relatives with dementia.

Women with MCI tend to experience more intense menopausal symptoms, thus more impaired quality of life, when compared with those without MCI. Table 2 shows that the total MRS score was significantly higher in MCI participants as compared with those without MCI (15.24 ± 12.58 vs 10.53 ± 8.84, respectively, *P* < 0.001). Furthermore, a detailed evaluation of the different symptoms evaluated by the MRS highlights that scores for all items were higher among women suffering with MCI. From hot flashes to mood swings and sleep disturbances, each symptom is more intense in this group of women.

Table 3 provides the results of the logistic regression analysis, showing a direct link between the presence of severe menopausal symptoms, as indicated by a total MRS score equal to or greater than 14, and MCI (odds ratio [OR], 1.74; 95% CI, 1.25–2.42). Table 3 also highlights the negative impact of having a higher number of children on cognitive health. On the other hand, factors such as lower BMI, sexual activity, physical

activity, the ever use of MHT, and having higher level education were associated with lower odds for MCI.

This model had a Cox and Snell *R*² of 0.468 (proportion of variance in MCI explained by the predictor variables), Hosmer and Lemeshow of 0.202 (goodness of fit; should be greater than 0.05), and Durbin-Watson of 1.83 (rules out autocorrelation). We did not find interactions between analyzed covariates.

DISCUSSION

The findings of this study underscore an association between menopausal symptoms and cognitive health, particularly in the context of MCI among postmenopausal women. Our analysis revealed that women with MCI exhibit greater menopausal symptom severity, overall (higher total MRS scores) and across each item assessed by the MRS. Additionally, logistic regression modeling demonstrated a significant association between the presence of severe menopausal symptoms and increased odds for MCI. However, intriguingly, certain factors emerged as

TABLE 2. MRS scores (total and per subscale) in women with and without mild cognitive impairment (MCI)

Symptoms	MCI (no) ^a (<i>n</i> = 1,090 [84.7%])	MCI (yes) ^b (<i>n</i> = 197 [15.3%])	<i>P</i> ^c
Somatic subscale			
Hot flushes, sweating	1.04 ± 1.23	1.51 ± 1.45	0.001 ^d
Heart discomfort	0.65 ± 0.97	1.03 ± 1.35	0.002 ^d
Sleep problems	1.08 ± 1.27	1.50 ± 1.52	0.001 ^d
Joint and muscular discomfort	1.24 ± 1.26	1.67 ± 1.56	0.001 ^d
Psychological subscale			
Depressive mood	0.82 ± 1.14	1.67 ± 1.56	0.001 ^d
Irritability	1.00 ± 1.17	1.37 ± 1.47	0.009 ^d
Anxiety	0.91 ± 1.16	1.35 ± 1.45	0.001 ^d
Physical/mental exhaustion	1.28 ± 1.23	1.48 ± 1.49	0.050 ^e
Urogenital subscale			
Sexual problems	1.35 ± 1.31	1.55 ± 1.57	0.048 ^e
Bladder problems	0.63 ± 1.07	1.02 ± 1.48	0.010 ^d
Dryness of vagina	1.20 ± 1.29	1.49 ± 1.58	0.001 ^e
Total score	10.53 ± 8.84	15.24 ± 12.58	0.001^d

Data are presented as mean ± SD. MoCA, Montreal Cognitive Assessment; MRS, Menopause Rating Scale. ^aMoCA ≥21 points. ^bMoCA score <21 points. ^c*P* value as determined with ^dMann-Whitney *U* test or ^eStudent *t* test.

TABLE 3. Factors associated with MCI: logistic regression analysis

Factors	OR (95% CI)
Severe symptoms (total MRS score ≥ 14)	1.74 (1.25-2.42)
Number of children	1.11 (1.03-1.20)
Low body mass index	0.96 (0.95-0.98)
With sexual activity	0.70 (0.51-0.96)
Not sedentary lifestyle	0.55 (0.39-0.76)
Menopausal hormone therapy (ever used)	0.36 (0.24-0.55)
Graduates from universities	0.31 (0.21-0.46)

Variables discarded in the model: has a partner, never smoker, years of postmenopause, surgical menopause, use of psychotropic drugs, parents with dementia, and comorbidities. MCI, mild cognitive impairment; MRS, Menopause Rating Scale; OR, odds ratio.

potential protective factors against MCI, including ever use of MHT, higher level of education, lower body weight, engagement in sexual activity, and regular physical exercise. Despite this, important to note is that our study is observational (a known limitation), which means that it cannot establish causal relationships.

The heightened severity of menopausal symptoms observed among postmenopausal women with MCI aligns with existing literature linking hormonal levels during menopause to cognitive changes.²¹ Estrogen regulates a wide range of neuronal functions in the brain, such as dendritic spine formation, remodeling of synaptic plasticity, cognition, neurotransmission, and neurodevelopment.²² Compared with reproductive women, postmenopausal women have lower cerebellostriatal and cerebellocortical connectivity, particularly in frontal regions, along with lower connectivity within the cerebellum.²³ These changes suggest a potential mechanism underlying the observed association between menopausal symptoms and cognitive impairment.

The protective effects shown in this study associated with ever use of MHT, higher educational level, lower body weight, sexual activity, and physical activity merit further exploration. From a theoretical perspective, these results can be understood within the framework of the “critical window hypothesis, or timing hypothesis”²⁴ and the concept of cognitive reserve,²⁵ which refers to brain's ability to develop new communication pathways between various regions through mental activity, which finally mitigate MCI.

A randomized clinical trial found that percutaneous estradiol gel and micronized progesterone attenuated cognitive decline in women with MCI.²⁶ In contrast, another study has shown that MHT has a deleterious effect on cognition. The WHI-MS study that used oral estrogens plus progestin therapy showed an increased risk (hazard ratio, 2.05; 95% CI, 1.21–3.48) for probable dementia in postmenopausal women 65 years or older.²⁷ However, another study suggests that MHT initiated at a younger age in closer temporal proximity to menopause may reduce the risk of Alzheimer disease.²⁸ A later subanalysis of the same WHI-MS concluded that MHT based on conjugated equine estrogens delivered near the time of menopause provides neither cognitive benefit nor detriment; if administered in older women, it results in small decrements in several cognitive domains.²⁹

According to the theory of the “critical window,” women who initiate MHT early in the menopausal transition may leverage

estrogen's neuroprotective properties, potentially reducing the risk of cognitive decline in later life. For instance, several studies have shown that women receiving MHT during the early years of menopause have lower rates of cognitive decline compared with those who initiate therapy later in menopausal life.³⁰ This temporal perspective on the therapeutic efficacy of MHT underscores the importance of timely intervention strategies in menopausal health care. By targeting the neuroprotective effects of estrogen during this critical window, it may be possible to establish a foundation for sustained cognitive health throughout the aging process. Moreover, recognizing the significance of early intervention aligns with a broader paradigm shift toward proactive approaches in women's health, emphasizing the potential long-term benefits of timely hormone therapy initiation.

Cognitive reserve has been hypothesized as a protective factor in disease pathology by using existing neural networks more efficiently to compensate for brain damage. Higher educational level may confer cognitive reserve, allowing individuals to better withstand the pathological processes associated with cognitive decline. Mental activity increases the “cognitive reserve” of an individual and promotes the formation of new communications between brain cells. Because it is not possible to influence the genetic components of Alzheimer dementia, preventive interventions such as encouraging regular engagement in mental and physical activities are extremely important.³¹

Lower body weight, sexual activity, and physical exercise are known to be correlated with enhanced cardiovascular health, a factor that has been extensively linked to improved cognitive outcomes. The mechanisms underlying this association are multifaceted. First, maintaining a lower body weight reduces the risk of cardiovascular diseases such as hypertension and atherosclerosis, which are known contributors to cognitive decline.³² Furthermore, regular sexual activity has been shown to stimulate the release of neurotransmitters and hormones such as dopamine, oxytocin, and endorphins, which play crucial roles in mood regulation, stress reduction, and neuroplasticity, thereby potentially enhancing cognitive function.³³ Moreover, engaging in physical exercise promotes increased cerebral blood flow, neurogenesis, and the release of neurotrophic factors, all which are essential for maintaining cognitive health. Additionally, exercise has been demonstrated to reduce systemic inflammation and oxidative stress, processes that have been implicated in neurodegenerative diseases.³⁴ Thus, by positively impacting cardiovascular health and promoting various neurobiological mechanisms supportive of cognitive function, these lifestyle factors may collectively contribute to the preservation of cognitive abilities in aging individuals.

Summarizing, the concept of cognitive reserve suggests that individuals with higher levels of cognitive reserve, such as those with higher educational level, may have greater neuronal resilience and compensatory mechanisms, enabling them to maintain cognitive functions despite underlying pathology. Similarly, engaging in activities that promote cardiovascular health, such as physical exercise and sexual activity, may enhance cerebral blood flow, neurogenesis, and synaptic plasticity, thereby supporting cognitive resiliency.

This study has some limitations, but it also has several strengths. Indeed, it takes into account the common characteristics of Latin American women, such as their ethnicity, cultural and socioeconomic factors, and female social roles. The multinational sample was evaluated with tools validated specifically for this population, and to ensure the accuracy of the results, all women were evaluated by physicians who specialize in women's health. Also, we used valid statistical methods to control for various potential confounding factors. Despite this, as mentioned, it is important to note that our study is a secondary analysis of an observational study, which means that it cannot establish causal relationships, a known limitation. However, its significance lies in generating hypotheses.

Additionally, we included women from gynecological care settings, resulting in the participation of many women with early menopause and gynecological surgery. This secondary analysis is part of a project that aimed to study the effects of different types of menopause on quality of life. Hence, we included a greater number of women with bilateral oophorectomy and with early menopause than what is typically found in the general population. This was because we were seeking associations rather than looking at the prevalence of the different types of menopause. Moreover, cognitive function evaluation with a one-time assessment alone has its own drawbacks and must be interpreted with some caution. This study included only women who have access to private health care, which is not representative of all Latin American women. Therefore, the findings of this study cannot be generalized to the entire Latin American population, as most of them rely on the public health sector. It is also worth mentioning that the lack of widespread access to preventive health screenings in Latin America introduces a potential selection bias. Despite these limitations, to the best of our knowledge, the present study is the first to associate menopausal symptoms and cognition in a Latin American postmenopausal population.

CONCLUSION

Overall, our findings underscore the complex interplay between hormonal, lifestyle, and sociodemographic factors in shaping cognitive health outcomes during the postmenopausal period. Further research is warranted to elucidate the underlying mechanisms and inform targeted interventions, aimed at preserving cognitive function in aging women.

REFERENCES

1. Venketasubramanian N, Sahadevan S, Kua EH, Chen CPL, Ng T-P. Interethnic differences in dementia epidemiology: global and Asia-Pacific perspectives. *Dement Geriatr Cogn Disord* 2010;30:492-498. doi: 10.1159/000321675
2. Niotis K, Akiyoshi K, Carlton C, Isaacson R. Dementia prevention in clinical practice. *Semin Neurol* 2022;42:525-548. doi: 10.1055/s-0042-1759580
3. Tsai FJ, Shen SW. Concepts of dementia prevention in the health promotion among older adults: a narrative review. *Medicine (Baltimore)* 2022;101:e32172. doi: 10.1097/MD.00000000000032172
4. Cervera-Juanes R, Zimmerman KD, Wilhelm L, et al. Modulation of neural gene networks by estradiol in old rhesus macaque females. *Geroscience* 2024. doi: 10.1007/s11357-024-01133-z
5. Maki PM, Thurston RC. Menopause and brain health: hormonal changes are only part of the story. *Front Neurol* 2020;11:562275. doi: 10.3389/fneur.2020.562275

6. Blümel JE, Arteaga E, Vallejo MS, et al. Association of bilateral oophorectomy and menopause hormone therapy with mild cognitive impairment: the REDLINC X study. *Climacteric* 2022;25:195-202. doi: 10.1080/13697137.2021.1951203
7. Blümel JE, Chedraui P, Baron G, et al. Collaborative Group for Research of the Climacteric in Latin America (REDLINC). Menopausal symptoms appear before the menopause and persist 5 years beyond: a detailed analysis of a multinational study. *Climacteric* 2012;15:542-551. doi: 10.3109/13697137.2012.658462
8. Brinton RD, Yao J, Yin F, Mack WJ, Cadenas E. Perimenopause as a neurological transition state. *Nat Rev Endocrinol* 2015;11:393-405. doi: 10.1038/nrendo.2015.82
9. Jett S, Schelbaum E, Jang G, et al. Ovarian steroid hormones: a long overlooked but critical contributor to brain aging and Alzheimer's disease. *Front Aging Neurosci* 2022;14:948219. doi: 10.3389/fnagi.2022.948219
10. Cozza M, Boccardi V. A narrative review on mild behavioural impairment: an exploration into its scientific perspectives. *Aging Clin Exp Res* 2023;35:1807-1821. doi: 10.1007/s40520-023-02472-1
11. Heinemann K, Ruebig A, Potthoff P, et al. The Menopause Rating Scale (MRS) scale: a methodological review. *Health Qual Life Outcomes* 2004;2:45. doi: 10.1186/1477-7525-2-45
12. Blümel JE, Arteaga E, Parra J, et al. Decision-making for the treatment of climacteric symptoms using the Menopause Rating Scale. *Maturitas* 2018;111:15-19. doi: 10.1016/j.maturitas.2018.02.010
13. Chedraui P, Aguirre W, Hidalgo L, Fayad L. Assessing menopausal symptoms among healthy middle-aged women with the Menopause Rating Scale. *Maturitas* 2007;57:271-278. doi: 10.1016/j.maturitas.2007.01.009
14. ZEG Berlin. Available at: <https://zeg-berlin.de/expertise/diagnostics-tools/%20menopause-rating-scale/languages/> Accessed April 12, 2024.
15. Nasreddine ZS, Phillips NA, Bédirian V, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;53:695-699. doi: 10.1111/j.1532-5415.2005.53221
16. Ward A, Arrighi HM, Michels S, Cedarbaum JM. Mild cognitive impairment: disparity of incidence and prevalence estimates. *Alzheimers Dement* 2012;8:14-21. doi: 10.1016/j.jalz.2011.01.002. PMID: 22265588
17. Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. *Arch Neurol* 2001;58:1985-1992. doi: 10.1001/archneur.58.12.1985
18. Panza F, D'Introno A, Colacicco AM, et al. Current epidemiology of mild cognitive impairment and other predementia syndromes. *Am J Geriatr Psychiatry* 2005;13:633-644. doi: 10.1176/appi.ajgp.13.8.633
19. Lozano Gallego M, Hernández Ferrández M, Turró Garriga O, Pericot Nierga I, López-Pousa S, Vilalta FJ. Validación del Montreal Cognitive Assessment (MoCA): test de cribado para el deterioro cognitivo leve. Datos preliminares. *Alzheimer Real Invest Demenc* 2009;43:4-11.
20. Freitas S, Simões MR, Martins C, Manuela V, Santana I. Estudos de adaptação do Montreal Cognitive Assessment (MoCA) para a população portuguesa. *Aval Psicol* 2010;9:345-357. Available at: http://pepsic.bvsalud.org/scielo.php?script=sci_arttext&pid=S1677-04712010000300002
21. Khattar D, Sodhi C, Parmod J, Dutta A. Correlating estrogen levels and cognitive functions in regularly menstruating females of reproductive age group and post menopausal women of North India. *J Family Reprod Health* 2015;9:83-88.
22. Iqbal J, Huang GD, Xue YX, Yang M, Jia XJ. Role of estrogen in sex differences in memory, emotion and neuropsychiatric disorders. *Mol Biol Rep* 2024;51:415. doi: 10.1007/s11033-024-09374-z
23. Ballard HK, Jackson TB, Hicks TH, Bernard JA. The association of reproductive stage with lobular cerebellar network connectivity across female adulthood. *Neurobiol Aging* 2022;117:139-150. doi: 10.1016/j.neurobiolaging.2022.05.014
24. Speth RC, D'Ambra M, Ji H, Sandberg K. A heartfelt message, estrogen replacement therapy: use it or lose it. *Am J Physiol Heart Circ Physiol* 2018;315:H1765-H1778. doi: 10.1152/ajpheart.00041.2018
25. Jammula VR, Leeper H, Gilbert MR, Cooper D, Armstrong TS. Effects of cognitive reserve on cognition in individuals with central nervous system disease. *Cogn Behav Neurol* 2021;34:245-258. doi: 10.1097/WNN.0000000000000282
26. Yoon BK, Chin J, Kim JW, et al. Menopausal hormone therapy and mild cognitive impairment: a randomized, placebo-controlled trial. *Menopause* 2018;25:870-876. doi: 10.1097/GME.0000000000001140
27. Shumaker SA, Legault C, Rapp SR, et al, WHIMS Investigators. Estrogen plus progestin and the incidence of dementia and mild cognitive impairment in postmenopausal women: the Women's Health Initiative Memory Study: a

- randomized controlled trial. *JAMA* 2003;289:2651-2662. doi: 10.1001/jama.289.20.2651
28. Henderson VW. Alzheimer's disease: review of hormone therapy trials and implications for treatment and prevention after menopause. *J Steroid Biochem Mol Biol* 2014;142:99-106. doi: 10.1016/j.jsbmb.2013.05.010
 29. Espeland MA, Rapp SR, Manson JE, et al, WHIMSY and WHIMS-ECHO Study Groups. Long-term effects on cognitive trajectories of postmenopausal hormone therapy in two age groups. *J Gerontol A Biol Sci Med Sci* 2017;72: 838-845. doi: 10.1093/gerona/glw156
 30. Khadilkar SS. Post-reproductive health: window of opportunity for preventing comorbidities. *J Obstet Gynaecol India* 2019;69:1-5. doi: 10.1007/s13224-019-01202-w
 31. Radić B, Blažeković A, Duraković D, Jurišić-Kvesić A, Bilić E, Borovečki F. Could mental and physical exercise alleviate Alzheimer's disease? *Psychiatr Danub* 2021;33(Suppl 4):1267-1273.
 32. O'Donnell M, Teo K, Gao P, et al. Cognitive impairment and risk of cardiovascular events and mortality. *Eur Heart J* 2012;33:1777-1786. doi: 10.1093/eurheartj/ehs053
 33. Wright H, Jenks RA. Sex on the brain! Associations between sexual activity and cognitive function in older age. *Age Ageing* 2016;45:313-317. doi: 10.1093/ageing/afv197
 34. Pahlavani HA. Exercise therapy to prevent and treat Alzheimer's disease. *Front Aging Neurosci* 2023;15:1243869. doi: 10.3389/fnagi.2023.1243869