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Article

Premature Ovarian Insufficiency, Early Menopause and Mild Cognitive Impairment: A Cohort Study

Short Title: Menopause and Cognitive Impairment

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Abstract: Background: Natural menopause (NP) typically occurs around the age of 50. In contrast, premature ovarian insufficiency (POI) and early menopause (EM) refer to the loss of normal ovarian function before the ages of 40 and 45, respectively. Surgical menopause, resulting from bilateral oophorectomy, leads to an abrupt hormonal decline. Emerging evidence suggests that early loss of ovarian function, whether natural or surgical, may impact cognitive performance. **Objective:** This study aimed to clarify the effect of different types of menopauses, POI and EM (spontaneous or surgical) on the risk of mild cognitive impairment (MCI). **Study Design:** This was an observational, cross-sectional, analytical study conducted in women's health outpatient clinics at two university centers in Brazil. **Methods:** Socio-demographic factors, clinical histories, anthropometric measurements, and family histories were studied in a large population of postmenopausal women. MCI and postmenopausal symptoms were assessed using the Montreal Cognitive Assessment (MoCA) test and the Menopause Rating Scale (MRS), respectively. Data were analyzed according to the type of menopause (spontaneous or surgical) and age at menopause (POI, EM and NM) using logistic regression models. **Results:** A total of 519 women were studied. No significant differences were observed between the groups in the different domains and the total score, but a cognitive deficit above 85% was found in the three groups. A higher risk of MCI was observed in women with bilateral oophorectomy [adjusted odds ratio (aOR) 3.21, 95% confidence interval (CI) 1.57 to 7.19, P=0.03], use of sleep inducers (aOR 3.31, 95% CI 1.86 to 5.92, P<0.0001), and higher body mass index (aOR 1.05, 95% CI 1.01 to 1.10, P=0.031). In contrast, more years of education were associated with a lower risk of cognitive impairment (aOR 0.93, 95% CI 0.86 to 0.99, P=0.028). Current or previous use of hormone therapy, parity, smoking, comorbidities, and use of anxiolytics or antidepressants were not significantly associated with MoCA scores. **Conclusion:** POI and EM are not associated with higher MCI risk. Bilateral oophorectomy, use of sleep inducers, and higher BMI are associated with an increased risk of MCI in postmenopausal women, independently of age or time since menopause. Conversely, higher educational attainment appears to be a protective factor. These results highlight the importance of identifying women at greater risk of cognitive decline based on menopausal type and modifiable factors. Longitudinal studies are needed to clarify causality and guide personalized management strategies.

Keywords: cognitive impairment; menopause; oophorectomy; postmenopause

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Introduction

Menopause is a time of transition marked by fluctuating physiologic changes that impact the quality of life of many women in the short term, as it may cause vasomotor symptoms, sleep, and mood disturbances as well as long-term changes such as genitourinary symptoms and decreased bone density [1]. Premature ovarian insufficiency (POI) on the other hand is a condition characterized by the early cessation of ovarian function before the age of 40, whereas early menopause (EM) is defined when the definitive cessation of ovarian function occurs between the ages of 40 and 44 [2,3].

The epidemiologic and social impact of such a diagnosis is evidenced by a recent meta-analysis [4]. The global prevalence of POI was estimated to be approximately 3.5%, with 5.4% in South America, and a trend towards an increase over the last two decades was reported [4]. Most cases of POI are idiopathic in origin, although its occurrence may also be associated with several etiologies, including genetic factors, autoimmune diseases, endocrine disorders, pelvic surgery (bilateral oophorectomy), chemotherapy, radiotherapy, and other less common causes [5].

The onset of menopause is associated with a reduction of quality of life [6]. In fact, the premature loss of ovarian function, which triggers prolonged exposure to hypoestrogenism, is associated with a series of adverse effects [7]. Such drop in estrogen levels increases the risk of developing chronic diseases and other long-term consequences, such as a higher incidence of cardiovascular disease, reduced bone mineral density, psychological impairment, vulvovaginal atrophy, and neurological deficits [8]. On the other hand, the role of estrogens in cognition is well defined since it acts directly on specific brain regions responsible for this function. In addition, estrogens seem to exert neuroprotective and neurotrophic actions preserving and improving memory [9], and modulate the cholinergic system, which is crucial for cognitive functioning [10].

Mild cognitive impairment (MCI), according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), is defined by the presence of subjective complaints of cognitive decline, corroborated by objective evidence of changes in neuropsychological assessments, while maintaining functional independence in activities of daily living [11]. This condition is recognized as an intermediate stage between normal cognitive aging and dementia, highlighting its clinical importance in the early identification of neurocognitive changes [11]. The menopause-related hypoestrogenism may negatively impact cognitive functions, making postmenopausal women more vulnerable to the development of cognitive deficits [12]. Both POI and premature bilateral ovariectomy are associated with long-term negative effects on cognitive function, worse verbal fluency [odds ratio (OR) 1.56, 95% confidence interval (CI) 1.12 to 1.87] and visual memory (OR 1.39, 95% CI 1.09 to 1.77) in later life [13]. Unilateral or bilateral oophorectomy before the onset of menopause increased significantly the risk of cognitive impairment or dementia [hazard ratio (HR) 1.46; 95% CI 1.13 to 1.90] [14].

Even if EM and POI may be suggested as potential causes for impaired cognitive function in postmenopausal patients [15,16], their clinical relationship with MCI remains elusive. In fact, a systematic review did not support a consistent association between EM or shorter reproductive period and dementia risk [15]. Based on these considerations, the current study was designed to test the hypothesis that menopause due to EM and POI (spontaneous or surgical) may present a higher risk of MCI in comparison to natural menopause (NM).

Materials and Methods

Study Design

This was an observational, cross-sectional, analytical study conducted in women's health outpatient clinics at two University centers in Brazil which aimed at studying the effect of different types of menopauses (spontaneous or surgical) and time at menopause (POI, EM, and NM) on the risk of MCI.

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Ethical Aspects

The study protocol was approved by the Ethics Committee of the Hospital das Clinicas of UFMG and Unesp – Botucatu (CAAE: 55412420.5.0000.5149, Opinion Number: 5,287,920). Written Informed consent was obtained from the subjects evaluated after the objectives, importance, and benefits of this study were carefully explained.

Participants

The population consisted of postmenopausal women aged from 50 to 69 years and attending routine gynecological evaluation at the participating centers. Patients who had undergone natural or surgical menopause were included. The population was grouped according to the types of menopause (spontaneous or surgical) and time at menopause (POI, EM, and NM). POI was defined by loss of ovarian activity before the age of 40 years (spontaneous amenorrhea or iatrogenic), whereas EM was defined as the cessation of ovarian function in women aged from 40 to 44 years [2]. Physiologic/natural menopause (NM) was diagnosed in women aged over 45 years who had not had a period for at least 12 months and were not using hormonal contraception [2,3]. Exclusion criteria included: unknown age at menopause; previous ovarian-sparing hysterectomy or unilateral oophorectomy before spontaneous menopause; women who could not read nor write; a diagnosis of dementia that prevented understanding the tests; psychiatric illness that prevented patients from leading a normal life; deafness; blindness; or current chemotherapy or radiotherapy treatment for cancer.

Main Outcome Measures

The following data were collected: age (years), schooling (years), body mass index (BMI, kg/m^2), parity and number of children, having a previous partner or a current one (yes/no), sexual activity (defined as at least one sexual intercourse in the last year, yes/no), physically active (yes/no, if more than 75 minutes per week of intense aerobic physical activities such as running, gym, tennis, etc. or more than 150 minutes per week of moderate aerobic physical activities such as brisk walking, cycling, dancing [18]), role as housewife throughout life (yes/no), smoker (yes/no), postmenopausal stage (defined according to stages of Reproductive Aging Workshop +10 criteria [17]), age at menopause, hysterectomy (yes/no), bilateral oophorectomy (yes/no), current use of menopausal hormone therapy (MHT, including estrogens with or without progestogens and tibolone, yes/no), previous use of MHT (yes/no), current use of antidepressants, anxiolytics, and sleep inducers (yes/no) and/or comorbidities defined as being treated for dyslipidemia, diabetes mellitus or hypertension (yes/no). The time since menopause (years) was defined as the total time in years since the complete cessation of menstruation until the data recording [2,3].

Postmenopausal Symptoms Assessment

The Menopause Rating Scale (MRS) was used to assess climacteric symptoms [19]. This tool evaluates the intensity and presence of eleven symptoms that are divided into three subscales, including somatic-vegetative symptoms (items 1-3 and 11), psychological symptoms (items 4-7), and urogenital symptoms (items 8-10). Each of the eleven items is rated from 0 (absent) to 4 (very severe), allowing for calculating the mean and standard deviation obtained by a population for each item. The mean score of each domain is established by the sum of the mean scores of the defined items, and the total score or overall dimension of the scale is established by the sum of the data obtained in the three dimensions. Severe menopausal symptoms are defined as a score equal to or greater than 14 points [19].

Cognitive Evaluation

The cognition was evaluated using the Montreal Cognitive Assessment (MoCA) test [20]. It assesses six domains (memory, visuospatial ability, executive function, attention, language, and orientation) in ten minutes, with a maximum score of 30 points. In the original version [20], the cut-

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off point is 26 points for MCI. In the Brazilian version of the MoCA Test a cutoff point of 25 points was established for the diagnosis of MCI, with a sensitivity of 81% and specificity of 77%. [21]. Moreover, a cut-off ≤ 22 points was used for the MoCA test to improve the accuracy of the screening and to reduce the influence of education on the final scores [22].

Statistical Analysis

The data obtained was inserted in tables divided according to menopause age in POI, EM and NM women. For statistical analyses, women were divided into 3 groups according to the age at menopause: <40 years (POI), between 40-44 years (EM), and ≥45 years (NM); current and former MHT users were categorized as ever MHT users. The Shapiro-Walk test was used to determine whether the variables showed a normal distribution, and the Levene test to determine homogeneity. For data analysis, mean and standard deviation were calculated for quantitative variables, and frequency and percentage for qualitative variables. For comparison between the groups concerning quantitative features, one-way analysis of variance (ANOVA) followed by Tukey multiple comparison test and gamma distribution (asymmetric variables) followed by Wald multiple comparison test were used. The Chi-Square test was used to assess the association between the frequencies of categorical features. In the comparison between the groups for the variables in the MRS and MoCA scores, the Poisson distribution test followed by the Wald multiple comparison test was used.

Additionally, a logistic regression analysis was carried out to determine factors associated with the presence of MCI (MoCA score ≤22 points). Categorical variables were entered into each of the models as they were (tool outcomes according to their cut-off values also), while continuous variables were categorized based on their median. A stepwise procedure was used to include variables in the model, with a significance level of 10%. The odds ratio (OR) and 95% confidence interval (CI) were obtained, adjusting for age and time since menopause (confounders). Bivariate Pearson (r) or Spearman (r) correlations analysis was applied to evaluate the correlations between domains and total score on the MoCA scale and clinical variables. A coefficient (r) of 0.21 to 0.40 was classified as weak correlation, 0.41 to 0.60 as moderate correlation, 0.61 to 0.80 as strong correlation, and > 0.80 as very strong correlation. The statistical tests were bilateral, and a level of significance of 5% was adopted. All analyses were performed using the Statistical Analysis System (SAS) 9.4 program.

Results

This study included 519 women, divided according to the age at menopause into three groups: POI (n=86), EM (n=71), and NM (n=362). The comparison of clinical characteristics between the groups is shown in Table 1. The groups were homogeneous for most of the variables evaluated (P>0.05). The mean age of the participants was not statistically different among groups (59.3 ± 6.3 years vs. 58.2 ± 5.6 years vs. 59.2 ± 5.2 years for the POI group, the EM group, and NM group, respectively; P=0.329). Additionally, the average BMI across all groups was also not statistically different and approximately 27 kg/m². The POI group presented significantly higher current or previous MHT use and a longer duration of MHT use when compared to the EM and NM groups (P<0.05). Moreover, a higher occurrence of bilateral oophorectomy, osteoporosis, and use of sleep inducers was observed in the POI group when compared to the other groups (P<0.05)

Table 1. Comparison of clinical and anthropometric characteristics among women with premature ovarian insufficiency (POI, menopause age < 40 years), early menopause (EM, menopause age 40–44 years), and natural menopause (NM, menopause age ≥ 45 years).

Parameters	POI (n=86)	EM (n=71)	NM (n=362)	*P Value* *	Comparison of Groups
Age (years)	59.3 ± 6.3	58.2 ± 5.6	59.2 ± 5.2	0.329a	POI=EM=NM
Age at menopause (years)	35.4 ± 3.9	42.2 ± 1.2	50.2 ± 3.2	**<.0001 b**	POI<EM<NM
Time since menopause (years)	23.8 ± 7.5	16.0 ± 5.9	9.0 ± 5.6	**<.0001 b**	POI>EM>NM
Years of education (years)	9.6 ± 4.5	8.6 ± 4.2	9.2 ± 4.2	0.287 a	POI=EM=NM

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Parity (number do children)	2.1 ± 1.7	2.0 ± 1.3	2.2 ± 1.5	0.423 b	POI=EM=NM
BMI (kg/m2)	27.5 ± 5.9	27.0 ± 5.2	27.9 ± 5.5	0.298 a	POI=EM=NM
Current use of MHT (%)	12 (14.0)	3 (4.2)	14 (3.9)	**0.001 c**	POI>EM=NM
Duration of current MHT use (years)	8.9 ± 10.5	6.7 ± 10.7	5.1 ± 4.8	0.297 b	POI=EM=NM
Age at initiation of MHT (years)	39.2 ± 9.4	42.2 ± 4.2	48.5 ± 10.2	**<.0001 b**	POI=EM<NM
Previous use of MHT (%)	22 (25.6)	9 (12.7)	33 (9.1)	**<.0002 c**	POI>EM=NM
Duration of previous MHT use (years)	6.9 ± 6.9	4.2 ± 4.3	2.9 ± 3.6	**0.019b**	POI=EM>NM
Bilateral oophorectomy (%)	18 (20.9)	8 (11.3)	30 (8.7)	**0.003 c**	POI>EM=NM
Age of oophorectomy (years)	34.3 ± 8.2	44.6 ± 7.5	51.9 ± 6.5	**0.040 b**	POI<EM<NM
Current partnership (%)	42 (48.8)	30 (42.6)	202 (55.8)	0.109 c	POI=EM=NM
Sexually active life (%)	43 (50.0)	31 (43.8)	213 (58.8)	0.081 c	POI=EM=NM
Current smoking (%)	9 (10.5)	9 (12.7)	26 (7.2)	0.072 c	POI=EM=NM
Physical activity (%)	38 (44.2)	23 (32.4)	139 (38.4)	0.318 c	POI=EM=NM
Hypercholesterolemia (%)	31 (37.2)	26 (36.6)	136 (37.6)	0.390 c	POI=EM=NM
Hypertension (%)	36 (41.8)	30 (42.2)	208 (57.5)	0.325 c	POI=EM=NM
Diabetes (%)	16 (18.6)	20 (28.2)	88 (24.3)	0.285 c	POI=EM=NM
Coronary Artery Disease (%)	5 (5.8)	2 (2.8)	11 (3.0)	0.220 c	POI=EM=NM
Stroke (%)	3 (3.5)	1 (1.4)	9 (2.5)	0.362 c	POI=EM=NM
Cancer (%)	7 (8.4)	12 (16.9)	44 (12.1)	0.099 c	POI=EM=NM
Osteoporosis (%)	15 (17.4)	5 (7.0)	25 (6.9)	**0.043 c**	POI>EM=NM
Previous fracture (%)	22 (25.9)	19 (26.7)	90 (25.3)	0.496 c	POI=EM=NM
Use of anxiolytics (%)	21 (24.4)	17 (23.9)	78 (21.5)	0.798 c	POI=EM=NM
Use of antidepressants (%)	25 (29.1)	22 (30.9)	104 (28.7)	0.929 c	POI=EM=NM
Use of sleep inducers (%)	28 (32.6)	17 (23.9)	69 (19.1)	**0.023 c**	POI>EM=NM

Values are expressed as mean (± standard deviation) or as number (percentage). BMI, body mass index; EM, early menopause; MHT, hormone therapy; NM, natural menopause; POI, premature ovarian insufficiency. Significant difference if P<0.05 (*a* ANOVA followed by Tukey multiple comparison test; *b* Gamma distribution test followed by Wald multiple comparison test; *c* Chi-square test).

In the evaluation of postmenopausal symptoms using the MRS score, women with POI presented significantly greater intensity of insomnia and depressive mood when compared to EM and NM women (P<0.05). On the other hand, symptoms such as urge incontinence and vaginal dryness were more intense in PM women (P<0.05). There were no significant differences in the comparison of the total MRS score between groups, even if the total score was above 14 suggesting severe postmenopausal symptoms

Table 2. Comparison of menopausal symptoms and total Menopause Rating Scale (MRS) score among women with premature ovarian insufficiency (POI, menopause age < 40 years), early menopause (EM, menopause age 40–44 years), and natural menopause (NM, menopause age ≥ 45 years).

Parameters	**POI (n=86)**	**EM (n=71)**	**NM (n=362)**	***P Value*** *	**Comparison of Groups**
Hot flashes	1.62 ± 1.59	2.11 ± 1.70	1.89 ± 1.55	0.071	POI=EM=NM
Tachycardia	1.12 ± 1.35	1.08 ± 1.30	0.88 ± 1.13	0.064	POI=EM=NM
Insomnia	2.01 ± 1.69	1.69 ± 1.55	1.46 ± 1.46	**0.002**	POI>EM=NM
Arthralgia/Myalgia	2.23 ± 1.55	2.32 ± 1.52	2.02 ± 1.45	0.176	POI=EM=NM
Depressed mood	1.79 ± 1.89	1.14 ± 1.33	1.38 ± 1.42	**0.003**	POI>PM>NM
Irritability	1.55 ± 1.36	1.63 ± 1.47	1.54 ± 1.40	0.857	POI=EM=NM
Anxiety	1.93 ± 1.59	1.75 ± 1.47	1.89 ± 1.48	0.664	POI=EM=NM
Physical/mental exhaustion	1.67 ± 1.50	1.44 ± 1.38	1.67 ± 1.36	0.348	POI=EM=NM
Lack of sexual desire	1.53 ± 1.56	1.68 ± 1.50	1.79 ± 1.57	0.251	POI=EM=NM

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Urgency incontinence	0.80 ± 1.26	0.51 ± 1.11	0.89 ± 1.33	**0.002**	POI=PM>NM
Vaginal dryness/Dyspareunia	1.38 ± 1.53	0.97 ± 1.36	1.42 ± 1.47	**0.008**	POI=PM>NM
Score total	17.64 ± 9.7	16.32 ± 9.33	16.84 ± 9.11	0.120	POI=EM=NM

Values are expressed as mean (standard deviation). Significant difference if P<0.05 (Poisson distribution test followed by Wald multiple comparison test).

Cognition assessment using the MoCA test revealed no significant differences between the groups in the different domains and in the total score (*P*>0.05), even if a cognitive deficit above 85% was found in the three groups. Some domains of cognitive function, including short-term memory, visuospatial construction, executive function, attention and concentration, were significantly (*P*<0.01) worse in those with EM and POI when compared to those in the NM group.

Table 3. Comparison of domains and total score on the Montreal Cognitive Assessment (MoCA) scale among women with premature ovarian insufficiency (POI, menopause age < 40 years), early menopause (EM, menopause age 40–44 years), and natural menopause (NM, menopause age ≥ 45 years).

Domain (score 0 to 30, worst to best cognition)	**POI (n=86)**	**EM (n=71)**	**NM (n=362)**	***P Value*** *	**Comparison of Groups**
Short-term memory	2.59 ± 1.44	2.53 ± 1.34	2.61 ± 1.39	0.931	POI=EM=NM
Visuospatial construction	2.38 ± 1.08	2.14 ± 1.17	2.54 ± 1.23	0.126	POI=EM=NM
Executive function	1.89 ± 1.11	1.61 ± 1.04	1.95 ± 1.00	0.166	POI=EM=NM
Attention and concentration	4.12 ± 1.57	3.97 ± 1.57	4.31 ± 1.44	0.383	POI=EM=NM
Language	3.76 ± 1.02	3.74 ± 1.07	3.65 ± 1.10	0.854	POI=EM=NM
Temporal and spatial orientation	5.91 ± 0.29	0.99 ± 0.12	0.95 ± 0.21	0.987	POI=EM=NM
Total score	20.65 ± 4.00	19.87 ± 3.63	20.91 ± 4.02	0.207	POI=EM=NM
Mild cognitive impairment **				0.189	
Yes (%)	74 (86.0)	64 (90.1)	334 (92.3)		
No (%)	12 (14.0)	7 (9.9)	28 (7.7)		

Values are expressed as mean (standard deviation) or as number (percentage). * Significant difference if P<0.05 (Poisson distribution test followed by Wald multiple comparison test). ** Total MoCA score ≤ 22 points (Chi-square test).

Considering overall population, only years of schooling showed a significant (*P*<0.01) correlation with all MoCA domains, and the use of sleep inducers a negative correlation with the total MoCA test score

Table 4. Correlation between domains and total score on the Montreal Cognitive Assessment (MoCA) scale and clinical variables in 519 postmenopausal women.

MoCA Domain/ Variables	**Memory**	**Visuo spatial**	**Executive**	**Attention**	**Language**	**Orientation**	**Total score**
Age	-0.07	-0.08	-0.03	-0.05	-0.07	-0.03	-0.08
Age at menopause	-0.01	0.08	0.10	0.07	-0.01	-0.01	-0.06
Time since menopause	-0.04	-0.12	-0.10	-0.08	-0.03	-001	-0.01
Years of education	**0.20***	**0.35***	**0.41***	**0.40***	**0.29***	0.05	-0.04
BMI	0.001	-0.03	-0.06	-0.01	-0.05	0.01	0.11
Current MHT use	0.05	0.09	0.08	0.06	0.07	0.06	0.01
Previuos MHT use	-0.01	0.03	0.02	0.09	0.05	-0.06	0.03
Bilateral Oophorectomy	0.02	0.04	-0.01	0.02	0.002	0.01	0.07
Current smoking	-0.08	-0.06	-0.04	-0.01	-0.01	-0.04	0.05
Physical activity	0.003	-0.03	0.02	0.04	0.05	-0.05	-0.05
Use of anxiolytics	0.02	0.03	-0.03	-0.01	0.01	-0.14	-0.15
Use of antidepressants	-0.05	0.01	0.01	0.04	0.06	-0.07	0.10
Use of sleep inducers	-0.02	0.01	-0.04	-0.02	0.03	0.10	**-0.22****

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BMI, body mass index; MHT, menopausal hormone therapy. * Pearson correlation coefficient (r), $P<0.05$. ** Spearman correlation coefficient (r), $P<0.05$.

When evaluating the main clinical factors associated with cognitive deficit, in the logistic regression analysis adjusted for age and time since menopause, a higher risk of MCI (i.e., MoCA score ≤ 22 points) was demonstrated in women with bilateral oophorectomy (OR 3.21, 95% CI 1.57 to 7.19, $P=0.03$), use of sleep inducers (OR 3.31, 95% CI 1.86 to 5.92, $P\leq0.0001$) and with higher BMI (OR 1.05, 95% CI 1.01 to 1.10, $P=0.031$). Current or previous MHT use did not show a significant association with cognition ($P>0.05$). Other variables analyzed, such as parity, smoking, comorbidities, and use of anxiolytics or antidepressants, were also not significantly associated ($P>0.05$) (data not shown).

Table 5. Logistic regression analysis of factors associated with mild cognitive impairment (MCI) on the Montreal Cognitive Assessment (MoCA score ≤22 points) scale.

Factors	OR	95% CI	P value
Bilateral Oophorectomy	3.21	1.52 - 7.19	0.003
Use of sleep inducers	3.31	1.86 - 5.92	<.0001
High BMI *	1.05	1.01 - 1.10	0.031
Longer years of education	0.93	0.86 - 0.99	0.028

BMI, body mass index. * Higher BMI: means overweight and/or obesity (BMI >25). *Note:* Only statistically significant results are present. BMI and years of education were continuous variables. Other variables did not show significance. Logistic regression with calculation of odds ratio (OR) and 95% confidence interval (CI), adjusted for age and time since menopause.

Discussion

The present study demonstrated that bilateral oophorectomy and the use of sleep inducers, regardless of age or time since menopause, were associated with a higher risk of MCI, whereas a higher number of years of education was a protective factor for MCI. Women diagnosed with POI had a higher incidence of osteoporosis (self-reported), greater severity of insomnia, more frequent use of sleep inducers, and a higher prevalence of depressive symptoms. Symptoms associated with genitourinary symptoms were more prevalent among women who experienced menopause at or after 45 years of age. Furthermore, regardless of whether they had undergone bilateral oophorectomy, women with POI presented significantly lower scores in the cognitive domains of short-term memory, visuospatial construction, executive function, attention, and concentration compared to those with spontaneous menopause at ≥45 years. Similar results were observed in women with EM.

The average MRS score exceeded 14 in all groups (ranging from 16 to 17), indicating the presence of severe postmenopausal symptoms. When evaluating specific MRS symptoms, women with POI had significantly more severe insomnia and depressive mood compared to women with EM and NM. These findings are generally consistent with existing literature. In fact, a recent cross-sectional study conducted in Shanghai with women aged 40 to 60 years identified the five most reported symptoms as hot flushes/sweating, fatigue, sleep disturbance, mood swings, and joint/muscle pain [23]. Another cross-sectional study involving 293 women with POI reported that the most prevalent symptoms were mood swings, insomnia, sexual problems, and fatigue, with moderate to severe mood swings being the most frequent [24]. Compared with women with natural menopause, those with POI had significantly higher risks of fatigue, melancholy, mood swings, and insomnia, but a lower risk of moderate to severe sexual problems [24].

Urogenital symptoms are known to be significantly bothersome and frequently underreported, which underscores the need for improved screening and management. In the current study, symptoms such as urge incontinence and vaginal dryness were more intense among women with NM. On the contrary, our previous data demonstrated a greater severity of urogenital symptoms in women with POI [25]. A plausible explanation for this apparent discrepancy may explained with the

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higher prevalence of MHT use among women with POI than in NM patients (14% *vs*. 3.9% in the POI and NM group, respectively).

Our study has some limitations. They include observational design, the absence of follow-up cognitive assessments, and the lack of detailed data on MHT types, doses, and administration routes. Nonetheless, it also presents several strengths. It is the first Brazilian study to objectively assess cognitive impairment in women with EM and POI using a validated cognitive tool, i.e. MoCA test, applied with standardized training and a conservative cutoff to reduce educational bias. In fact, MoCA test according to Nasreddine is probably superior to the Mini-Mental State Examination (MMSE), as its sensitivity and specificity for detecting MCI is 90% and 87% versus 18% and 100% for the MMSE, respectively [20]. In addition, we used a more conservative threshold of ≤22 provides a better balance between sensitivity and specificity for MCI diagnosis because a cutoff of ≤25 may result in many false positives [26] and the addiction of 1 point for individuals with less than 12 years of education does not adequately adjust for Brazil's socioeconomic heterogeneity [22]. In our study, the average MoCA score for all three groups was below 22, indicating the presence of MCI. On the other hand, the use of a cutoff ≤25 would have resulted in an excessive number of women being classified as cognitively impaired.

Using the ≤22 threshold for MoCA test, a very high proportion of postmenopausal patients were defined as having MCI. In particular, we found that 86%, 90%, and 92% of women with POI, EM, and NM, respectively, met the criteria for MCI. No statistically significant difference between groups. While our data did not reveal a significant association between menopause type and MCI, the high overall prevalence of MCI in this population is noteworthy. Cognitive difficulties are most pronounced during the menopausal transition and may improve in postmenopause [27]. However, high levels of stress and depression can prolong cognitive decline into the postmenopausal phase [28]. POI is associated with a greater risk of comorbidities, including depression and cognitive decline [29]. Similarly, the hypoestrogenism seen in EM is also linked to increased risk for several comorbid conditions, some of which overlap with those seen in POI [29]. Another Brazilian study on 1,218 women with EM demonstrated low performance on cognitive assessments, suggesting that EM is an independent risk factor for cognitive impairment [30]. Despite the limitations of our cross-sectional design and sample size, our findings highlight the need for longitudinal studies and further reassessment of cognitive assessment tools to improve diagnostic accuracy, particularly in women with POI and EM. Moreover, the low use of MHT across all three groups studied reinforces the need for improved care.

Cognitive testing may also be influenced by the symptoms present at the time of evaluation. A recent meta-analysis showed that POI is associated with an increased risk of dementia compared to women with NM (OR 1.18; 95% CI 1.15 to 1.21), and a similar association was observed for EM only in cohorts (OR 1.41; 95 % CI 1.13 to 1.76) but not in case-control studies (OR 0.97; 95 % CI 0.62 to 1.52) [31]. However, when excluding retrospective cohort studies from the analysis, the association for EM was no longer statistically significant (OR 1.07; 95% CI 0.78 to 1.48) [31]. Recently, a close and direct relationship between postmenopausal symptoms (irrespectively from the specific symptoms) and cognitive function was detected, and each additional year of postmenopause was linked to more consistent signs of cognitive dysfunction [32]. These findings align with our results and the literature [31–33], suggesting a link between cognitive dysfunction and menopause, particularly in women who enter menopause before age 45 and remain untreated, potentially due to long-term hypoestrogenism. Moreover, although the total MoCA score did not significantly differ between groups, our study did find that women with POI and EM performed worse in specific cognitive domains—short-term memory, visuospatial construction, executive function, attention, and concentration—than those with menopause ≥45 years. Similarly, poorer verbal fluency and visual memory resulted closely associate to EM, both natural and surgical [16], suggesting that some cognitive domains may result more severely impaired.

Estrogen likely plays a central role in cognitive function, as cognitive deficits are more prominent in women than in men [34]. An observational cross-sectional study of 117 middle-aged women found that declines in attention, working memory, verbal learning, verbal memory, and motor speed were

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most noticeable within the first year after the final menstrual period [35]. That data emphasized the importance of considering age, duration of hypoestrogenism, and symptom severity when assessing cognitive changes across menopause types.

In younger postmenopausal women, the decline in estrogen, acetylcholine, and serotonin lead to episodic memory deficits, which may be reversed with estrogen therapy [36]. On the other hand, estrogen initiation during midlife is associated with neural protection, whereas initiation later in life may be neutral or harmful [36]. Therefore, different cognitive domains may be affected at different stages of reproductive aging, and the timing of MHT initiation appears to be critical.

In our study, women with POI had been postmenopausal for an average of 23 years, reflecting a longer period of hypoestrogenism than those with EM or NM. The role of estrogens in the cholinergic system, which is vital for learning and memory, provides a potential biological basis for our findings [37], as suggested by meta-analytic data [38]. The mean age of our population was lower than observed in other studies reporting cognitive decline, which may partially explain our lack of statistically significant findings. Nonetheless, their MoCA scores were consistent with MCI. MCI, by definition, involves biomarker abnormalities and mild deficits that do not yet meet the criteria for dementia [39]. MHT use during midlife may offer preventive benefits against Alzheimer's disease if initiated within the so-called "window of opportunity," a critical period in which intervention may halt or slow disease progression [39].

In the present study, the small proportion of MHT users and the relatively young age of participants could explain the lack of group differences. It's also important to consider the socioeconomic diversity, different assessment tools, and variations in MHT use when interpreting results. Among women with POI, 32.6% used sleep inducers compared to 19.1% of PM women, a statistically significant difference. This likely reflects the high prevalence of sleep disturbances in women with POI, consistent with recent studies [40,41]. POI and circadian regulation share key genetic and neurobiological pathways, involving stress response circuits and the hypothalamic-pituitary-gonadal axis [42].

A Brazilian study from 2012–2013 reported an MHT prevalence of 19.5% in NM women and a 50% decrease from 2002 [43]. Our current data, collected roughly a decade later, reveal even lower rates, only 14% of POI women were using MHT, compared to fewer than 5% in the EM and NM groups. This trend is consistent with international data. In fact, in Israel, only 29.1% of women received MHT, and just 12.6% reported current or past use [44]. Similar findings have been observed in other countries [45–47], reflecting widespread MHT underuse. The decline in MHT use may be attributed to ongoing concerns stemming from the Women's Health Initiative (WHI) publications [47], which continue to influence prescribing behaviors. Following the WHI, global MHT use dropped from 85% to 18% [49], and enhanced education and training in this field are probably needed [50].

Finally, in our analysis, bilateral oophorectomy and the use of sleep inducers were both independently associated with a threefold increase in the likelihood of MCI. These findings are consistent with previous clinical studies showing that oophorectomy before menopause increases the risk of cognitive decline, also after adjusting data for MHT use [51]. A study of 24,851 Danish nurses found an 18% increased risk of dementia after bilateral oophorectomy [relative risk (RR) 1.18; 95% CI 0.89 to 1.56] [52] with faster declines in verbal and semantic memory, as well as processing speed [15].

Additionally, higher educational attainment was protective against MCI in our study. This finding agrees with previous data [53,54]. More than 12 years of education was associated with a lower risk of MCI (OR 0.21; 95% CI 0.14 to 0.30) [53] and each additional year of education reduces the risk of dementia by 9.0% [54]. Similarly, data from the U.S. National Alzheimer's Coordinating Center showed that college education is associated with a lower risk of dementia [risk differences (RD) -1.5%; 95% CI -2.8 to -0.3] [55], and continuous adult education further reduces that risk [hazard risk (HR) 0.82; 95% CI 0.74 to 0.90] [56]. This protective effect may be explained by cognitive reserve, as well as associated benefits like healthier lifestyles, increased social engagement, and reduced stress.

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In current study, no significant association between current or past MHT and cognitive performance was found. This lack of association may be attributed to the small number of MHT users in our sample and the limitation of a single cognitive assessment. The literature reveals heterogeneous results on this topic, with randomized trials indicating mostly neutral effects and observational studies suggesting potential benefits when MHT is initiated early in the postmenopausal period [57–61]. In our study, this assessment is hampered by at least two major reasons. The first refers to the small number of women undergoing MHT, and, second, because we only performed one cognitive assessment test upon admission of the patients involved in the present study.

Conclusion

Our data indicated that bilateral oophorectomy and the use of sleep inducers is associated with an increased risk of MCI, while higher educational attainment was protective. Women with POI demonstrated poorer performance in cognitive domains such as short-term memory, attention, executive function, and visuospatial construction. These findings highlight the importance of early cognitive screening in women with POI and EM and suggest the need for targeted preventive strategies, including improved access to education and non-pharmacological management of sleep disturbances. Longitudinal studies are guaranteed to better understand the underlying mechanisms and to clarify the potential role of MHT for cognitive protection.

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