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Original article

Association between type of menopause and mild cognitive impairment: The REDLINC XII study

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ABSTRACT

Objective: To evaluate the association between type of menopause (spontaneous or surgical) and mild cognitive impairment (MCI).
Study design: This study was a cross-sectional, observational, and sub-analytical investigation conducted within gynecological consultations across nine Latin American countries.
Method: We assessed sociodemographic, clinical, and anthropometric data, family history of dementia, and the presence of MCI using the Montreal Cognitive Assessment (MoCA) tool.
Results: The study involved 1185 postmenopausal women with a mean age of 55.3 years and a body mass index of 26.4 kg/m^2. They had an average of 13.3 years of education, and 37 % were homemakers. Three hundred ninety-nine experienced menopause before 40, including 136 with surgical menopause (bilateral oophorectomy). Out of the 786 women who experienced menopause at 40 or more years, 110 did so due to bilateral oophorectomy. There were no differences in MoCA scores among women who experienced menopause before or after the age of 40. However, lower MoCA scores were observed in women with surgical menopause than in those with spontaneous menopause (23.8 ± 4.9 vs. 25.0 ± 4.3 points, respectively, $p < 0.001$). Our logistic regression model with clustering of patients within countries found a significant association between MCI and surgical menopause (OR 1.47, 95 % CI: 1.01–2.16), use (ever) of menopausal hormone therapy (OR 0.33, 95 % CI: 0.21–0.50), and having >12 years of education (OR 0.21, 95 % CI: 0.14–0.30).
Conclusion: When comparing women who experience spontaneous menopause over the age of 40 with those who undergo it before this age, there was no observed increased risk of developing MCI, while those with surgical

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menopause, independent of age, are more prone to cognitive decline. Women who have ever used menopausal hormone therapy have a lower MCI risk. Further research is warranted to delve deeper into this topic.

1. Introduction

Menopause is a natural biological milestone in a woman's life in which there is the cessation of reproductive function and entails significant hormonal changes that have been associated with ageing and chronic diseases [1]. One aspect that has garnered considerable interest is its potential impact on cognitive function. In 2021, 761 million people worldwide were aged 65 or older, a number projected to reach 1.6 billion by 2050; the population of those aged 80 and over is growing even more rapidly [2]. In this context, age-related diseases such as dementia gain particular significance.

A recent meta-analysis assessing the role of menopause suggests that women experiencing early menopause or premature ovarian insufficiency (POI) may face an elevated risk of dementia compared to women with age at menopause >45 years. However, the study concludes that additional research is warranted to further explore this hypothesis [3].

Another area of contention lies in the correlation between surgical menopause (bilateral oophorectomy) and the risk of dementia. A meta-analysis comprising 11 eligible studies ($n = 18,867$) revealed that while four studies found no significant association between surgical menopause at any age and the risk of dementia (hazard ratio [HR]: 1.16, 95 % CI: 0.96–1.43), early surgical menopause (≤ 45 years of age, 2 studies) was found to be significantly associated with a higher risk (HR: 1.70, 95 % CI: 1.07–2.69) [4]. Moreover, there is a question as to whether the age of menopause (either spontaneous or surgical), could have a varying impact on cognitive function. According to a systematic review [5], there is no evidence to suggest that age at menopause has an impact on cognitive decline. However, most of the reviewed studies focused on early menopause. Additionally, due to the variability among the studies, a meta-analysis could not be conducted [5].

In this context, the present study aimed to investigate the association between the type of menopause and cognitive impairment. Both spontaneous and surgical menopause will be examined to assess their potential impacts on cognitive function, with a specific emphasis on mild cognitive impairment (MCI). By utilizing a standardized cognitive assessment tool and accurately classifying the types of menopause, our goal is to advance the understanding of this relationship, which holds significant implications for the health and well-being of postmenopausal women.

2. Materials and methods

2.1. Study design and participants

This was a cross-sectional, observational and sub-analytic multinational study (REDLINC XII) carried out between January and October 2023 in general gynecological consultations in nine Latin American countries: Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Mexico, Panamá, and Perú. Participants were women under 70 years of age who attended a routine gynecological check-up (convenience sampling). Investigators of the participating centers were asked for 100 surveys with at least a third of them including data of women who had spontaneous or surgical menopause before age 40. The reason for this type of convenience sample was to fulfil the primary goal of the REDLINC XII study: to analyze associations between the type of menopause (premature, surgical or natural) and quality of life, chronic diseases, cognition and longevity. The present sub-analysis explores the association of MCI and type of menopause.

The study included postmenopausal women (one year of amenorrhea) who were otherwise healthy. All participants were required to be literate in either Spanish or Portuguese (Brazil). Most women had middle incomes and received healthcare 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 diagnosed with dementia that hindered their ability to comprehend the questionnaires.

2.2. Studied variables

The following data were collected: age (years), years of education (years), body mass index (BMI; weight [kg]/squared height [m]), parity or the number of children, having a current partner (yes/no), sexual activity (at least one sexual intercourse in the last year, yes/no), homemaker defined as a woman who has primarily assumed that role throughout her life (yes/no), smoker (yes/no), postmenopausal stage (defined according to the STRAW +10 criteria), age at menopause, hysterectomy (yes/no), bilateral oophorectomy (yes/no), current menopausal hormone therapy use (MHT; yes/no), former MHT use (yes/no), current use of antidepressants, hypnotics, or anxiolytics (yes/no), and/or comorbidities defined as being treated for dyslipidemia, diabetes mellitus or hypertension (yes/no).

Surgical menopause was defined in women who had undergone bilateral oophorectomy. For statistical analyses women were divided into 2 groups according to the age at menopause: < 40 years of age or ≥ 40 years; and current and former MHT users were categorized as ever MHT users, based on the fact that our prior research found that women who had ever taken MHT (independent of type or route) for less than two years in early postmenopause was associated with less cognitive decline [6].

2.3. Cognitive test

Cognitive function was evaluated with the Montreal Cognitive Assessment (MoCA), which is a cognitive screening tool developed by Nasreddine in Canada [7]. This assessment identifies those who have MCI, which may be a transitional stage between normal ageing and dementia, particularly Alzheimer's disease. The prevalence of MCI varies between 3 % and 42 % across different studies, depending on the used diagnostic criteria [8]. Research indicates that approximately every year 10–15 % of individuals with MCI progress to dementia. Currently, many studies investigate MCI as a preceding stage of dementia [9].

The MoCA assesses six domains within a 10-min timeframe, including memory, visuospatial ability, executive function, attention, language, and orientation, with a maximum score of 30 points. In its original version, the cut-off point for MCI is set at 26 points [10]. Nasreddine et al. [7] have suggested that the MoCA surpasses the Mini-Mental State Examination (MMSE) in sensitivity and specificity for the detection of MCI, with rates of 90 % and 87 %, respectively, compared to 18 % and 100 % for the MMSE.

During the Spanish validation of the MoCA test, carried out by researchers at Hospitalari Martí i Julià, Girona, Spain led by Lozano Gallego et al. [11], a cut-off of 21 points was used to identify MCI, demonstrating a sensitivity of 71.4 % and a specificity of 74.5 % [11]. In Brazil, the Portuguese version of the MoCA was applied, which uses a similar cut-off value as the Spanish version (20 points) [12].

In our study, a physician administered the general questionnaire and the MoCA tool and also conducted a comprehensive examination of each woman, recording both her personal and family medical history.

2.4. Statistical analysis

Statistical analysis was performed using the SPSS software package (version 21.0 for Windows; SPSS Inc., Chicago, IL). Data are presented as means, standard deviations, medians, interquartile ranges [IQR] or frequencies/percentages. The homogeneity of the variance was evaluated with the Levene test ($p > 0.05$). The Kolmogorov-Smirnov test was used to determine the normality of data distribution. According to this, differences between the studied numeric variables were analyzed with the Mann-Whitney *U* test (non-parametric data) or the Student's *t*-test (parametric data). Comparison of categorical data was performed with the chi-square test. Logistic regression analysis with clustering of patients within countries was performed to evaluate the association between type of menopause and MCI. A MoCA score of <21 points was used to define those with MCI [11]. Categorical covariates were introduced into the model as such, while continuous ones, with their values. The inclusion of different variables in the model was performed through a stepwise procedure, considering a 10 % level as significant. Variance Inflation Factor (VIF) was used to solve multicollinearity in the regression analysis (VIF <10). We also considered the different interactions between the variables found statistically significant in the bivariate analysis. The Omnibus test and the Hosmer–Lemeshow tests were used to determine the adequacy of the regression model. For all calculations, a *p-value* of <0.05 was considered statistically significant.

2.5. Ethical considerations

The study was approved by the ethics committee of the Southern Metropolitan Health Service, Santiago de Chile, Chile (Memorandum 15/2022; June 22, 2022) and complies with the Declaration of Helsinki. All participants were informed of the study, its aims and used tools, after which they provided written consent for participation.

3. Results

Of the 1250 postmenopausal women invited to participate, 1185 (or 94.8 %) agreed to participate. The mean age of the whole sample was 55.3 ± 6.9 years, years, and their average BMI was 26.4 ± 5.2 kg/m^2. Of the participants, 23.7 % were homemakers with an average of 10.4 ± 4.2 years of education. On the other hand, those who worked outside the home had an average education of 14.9 ± 4.8 ($p < 0.001$).

Overall, women with spontaneous menopause, compared to those with surgical menopause, were older (median 55 [IQR: 9] vs 53 [9] years, $p < 0.0001$), were older at menopause onset (48 [13] vs 39 [8] years, $p < 0.0001$), and had fewer years since menopause onset (9 [11] vs 14 [15] years, $p < 0.0001$). They were also less frequently identified as homemakers (35.5 % vs 42.7 %, $p < 0.04$), and were less likely to have ever used MHT (33.8 % vs 43.9 %, $p < 0.003$), only 4 women out of 1185 had started MHT after age 60. There were no differences observed in terms of BMI, number of children, years of study, having a partner, smoking status, sexual activity, use of psychotropic drugs, comorbidities, or having parents with dementia (Data not shown in Tables).

As shown in Table 1, out of the total of participants, 399 women (33.7 %) experienced menopause before the age of 40 of which 136 had undergone bilateral oophorectomy. Out of the 786 who underwent menopause at 40 or more years, 110 did so due to oophorectomy. In addition, there were significant differences in various parameters when we compared women who experienced spontaneous menopause before the age of 40 with those who experienced it after the age of 40. These included age (with a median of 52 [55] years for the former and 56 [32] years for the latter), years since menopause onset (17.4 ± 7.9 years for the former and 7.7 ± 5.3 years for the latter), BMI (25.7 ± 4.8 kg/m^2 for the former and 26.6 ± 5.1 kg/m^2 for the latter), number of children (1.8 ± 1.5 for the former and 2.6 ± 1.8 children for the latter), and ever use of MHT or current use of psychotropic drugs (52.9 % for the former and 26.3 % for the latter, and 42.6 % for the former and 28.7 % for the latter, respectively). However, we did not observe any significant differences in terms of years of education, percentage of homemakers, having a partner, sexual activity, tobacco consumption, or presence of comorbidities.

Table 1
Clinical characteristics of studied women according to age and type of menopause.

	Spontaneous menopause		Surgical menopause	
	Age ≥ 40 years	Age < 40 years	Age ≥ 40 years	Age < 40 years
Parameters	($n = 676$)	($n = 263$)	($n = 110$)	($n = 136$)
Age (years)	56 [32]	52 [55] $^{0.001}$	53 [28] $^{0.001}$	53 [41] $^{0.001}$
Age at menopause (years)	49.1 ± 3.5	35.5 ± 3.7 $^{0.001}$	46.3 ± 4.4 $^{0.001}$	36.0 ± 3.0 $^{0.001}$
Years since menopause	7.7 ± 5.3	17.4 ± 7.9 $^{0.001}$	7.5 ± 6.6	17.8 ± 8.3 $^{0.001}$
Body mass index (Kg/m^2)	26.6 ± 5.1	25.7 ± 4.8 $^{0.02}$	26.6 ± 5.6	27.2 ± 5.6
Years of education	13.4 ± 5.1	13.3 ± 4.5	12.8 ± 5.3	12.7 ± 4.3
Homemakers (%)	35.5	35.4	45.5 $^{0.04}$	40.4
Number of children	2.6 ± 1.8	1.8 ± 1.5 $^{0.01}$	2.7 ± 1.7	2.2 ± 1.7 $^{0.03}$
With a partner (%)	72.1	71.9	72.7	69.9 $^{0.001}$
With sexual activity (%)	68.0	66.5	66.4	63.2 $^{0.001}$
Never smoker (%)	73.7	73.8	79.1	64.0 $^{0.02}$
Ever MHT users (%)	26.3	52.9 $^{0.001}$	30.0	55.1 $^{0.001}$
Use of psychotropic drugs (%)	28.7	42.6 $^{0.001}$	23.6	46.3 $^{0.001}$
Comorbidities (%)	44.1	43.7	39.1	55.9 $^{0.01}$
Parents with dementia (%)	15.2	12.5	19.1	13.2

Data are presented as medians [interquartile ranges], means ± standard deviations or percentages.
Note: Only significant *p* values are presented in superscript which were calculated when comparisons were made with spontaneous menopausal women aged ≥40 years using the Mann Whitney *U* test (medians), the Student's *t*-test (means), or the chi-square test (%).
MHT, menopause hormone therapy.

In the same Table 1, we observed few differences when comparing women who underwent surgical menopause with those who experienced spontaneous menopause after 40 years. On the other hand, there were significant differences when comparing women who had surgical menopause before the age of 40 with women who had spontaneous menopause after the age of 40 in terms of years since menopause (17.8 ± 8.3 vs 7.7 ± 5.3 years), number of children (2.2 ± 1.7 vs 2.6 ± 1.7 children), ever MHT users (55.1 % vs 26.3 %), use psychotropic drugs (46.3 % vs 28.7 %), and comorbidities (55.9 % vs 44.1 %) (Table 1).

MoCA score and percentage of women with MCI by the type of menopause, independent of age is presented in Table 2. Women who had surgical menopause displayed lower mean MoCA scores compared to those who had spontaneous menopause (23.8 ± 4.9 vs 25.0 ± 4.3 points, respectively, $p < 0.001$). Although there was a higher rate of women with MCI among those undergoing surgical menopause compared to women experiencing spontaneous menopause (20.3 % vs 15.5 %), the difference did not reach statistical significance. There were

Table 2
MoCA score and percentage of women with mild cognitive impairment in accordance to the type of menopause independent of age.

Parameters	Spontaneous menopause	Surgical menopause
	$n = 939$	$n = 246$
MoCA (Score)	25.0 ± 4.3	23.8 ± 4.9 $^{0.001}$
MCI	146 (15.5)	50 (20.3)

Data are presented as mean ± standard deviations or frequencies *n* (%).
In superscript only significant *p* value is presented which was calculated with the Mann-Whitney *U* test (mean). MCI: Mild cognitive impairment is defined as a MoCA score < 21 points.

no significant differences in MoCA scores or rates of MCI among women who experienced spontaneous menopause before or after the age of 40 (MoCA 25.0 ± 4.5 vs 25.0 ± 4.3 points; MCI 13.4 % vs 16.4 %, respectively). Similarly, there were no significant differences among women who had surgical menopause before or after age 40 (MoCA 23.9 ± 4.9 vs 23.8 ± 5.0 points; MCI: 19.9 % vs 20.9 %, respectively) (Data not shown in Table 2).

We constructed a logistic regression model to evaluate the association between the type of menopause (surgical menopause [yes] or spontaneous [no]) and the likelihood of presenting MCI while adjusting for confounding covariates: age, history of surgical menopause (at any age), age of menopause onset, years since menopause onset, have >12 years of study (median), and ever use of MHT (Table 3). After analysing the data, we found that only three of these factors were significantly associated with MCI. These factors were surgical menopause (OR 1.47, 95 % CI: 1.01–2.16), ever use of MHT (OR 0.33, 95 % CI: 0.21–0.50), and having >12 years of study (OR 0.21, 95 % CI: 0.14–0.30) (Table 3). We did not find interactions in the analyzed model.

4. Discussion

The current study shows that women undergoing spontaneous menopause before the age of 40 do not exhibit greater cognitive decline compared to those experiencing spontaneous menopause after this age. However, irrespective of the age at which menopause occurs, undergoing surgical menopause and having lower education was associated with more cognitive deterioration. Conversely, ever use of MHT was associated with less decline. While most studies assessing cognitive decline and menopause focus on women over 70 years [4], our study examined women with an average age of 55.3 ± 6.9 years. This allowed us, to some extent, to distinguish between the effects of menopause and those of ageing.

Our results could be explained in part by the differences described in previous studies in ovarian hormone levels between women who experience spontaneous menopause and those who undergo surgical menopause. One study has shown that in both groups, estrogen levels decrease, but the decline is more significant in women who have undergone bilateral oophorectomy [13]. Premenopausal women under the age of 40 have an average estradiol blood level of 34.30 pg/mL (with a range of 25.3–44.9), while women of similar age undergoing surgical menopause have an average level of only 7.15 pg/mL (with a range of 5.0–20.5). Moreover, older women who undergo surgical menopause at 46 years of age have significantly lower estradiol (E2) levels (11.1 pmol/L) than 56-year-old women who had natural menopause. Additionally, testosterone levels also decrease more in women who undergo bilateral oophorectomy than in those who undergo spontaneous menopause. Surgically postmenopausal women experience a decline of 0.04 nmol/L per year from an initial level of 0.97 nmol/L, whereas naturally postmenopausal women maintain a stable level of 0.89 nmol/L [14].

The lower levels of estradiol found in women with surgical menopause could be one of the factors that explain our results. Studies suggest that E2 is essential for promoting the growth of new brain cells, regulating neuronal activity, and modulating synaptic plasticity. E2 appears to promote cell proliferation by activating nuclear receptors and inhibiting specific neuroinflammatory signalling pathways that are linked to IL-1β. Furthermore, E2 impacts various neurotransmitter systems such as the dopaminergic or glutamatergic, while also reducing the levels of reactive oxygen species and enhancing nitric oxide production. Additionally, E2 influences the expression of genes that regulate transcriptional activity and enhances the ERK/MAPK signalling pathway that regulates cell growth and differentiation [15].

Table 3
Factors associated with MCI: Logistic regression.

Factor	Odds ratio (CI 95 %)
Surgical menopause	1.47 (1.01–2.16)
Ever MHT use	0.33 (0.21–0.50)
Education of >12 years	0.21 (0.14–0.30)

CI, confidence interval; MHT, menopause hormone therapy.

Our study has found no significant differences in cognitive function among women who experience spontaneous menopause before or after the age of 40. This suggests that the timing of hypoestrogenism may not be a determining factor in the risk of cognitive impairment, as long as certain minimal levels of estradiol are maintained. Our results indicate that women with surgical menopause, where estrogen levels fall below those seen in spontaneous postmenopause [14], have an increased likelihood of cognitive decline.

The results of our study support the idea that even modest levels of estrogen can play a protective role in preventing cognitive decline. It has been reported that the use of MHT, as oral E2 1 mg, leads to moderate E2 blood levels of 65 pg/mL [16]. These levels may be sufficient to mitigate cognitive deterioration. Concordantly our study demonstrates that ever MHT users have lower odds of cognitive function deterioration.

In a study we conducted previously, we found evidence that supports the idea that hormone therapy containing estrogen may have cognitive benefits for menopausal women. We observed a significantly lower prevalence of cognitive impairment among women who used hormone therapy and had intact ovaries, compared to those who did not use hormone therapy (11.7 % vs. 29.3 %). Similarly, among women who had their ovaries removed, we found that those who used hormone therapy had a significantly lower prevalence of MCI compared to non-hormone therapy users (12.8 % vs. 45.2 %) [6]. These findings suggest that even moderate levels of estrogen supplementation may provide cognitive benefits for menopausal women.

Our findings, indicating a reduced likelihood of MCI among ever MHT users, sharply contrast with those of the WHI Memory Study [17]. The WHI Memory Study documented a non-significant increase in the risk of MCI associated with MHT use in both the estrogen-alone and estrogen-progestin groups, with HRs of 1.34 (95 % CI, 0.95–1.89) and 1.25 (95 % CI, 0.97–1.60), respectively. Discrepancies between our study and the WHI Memory Study could potentially be attributed to the differing demographics of participants. Notably, the majority of women in the WHI Memory Study began therapy after the age of 60, in contrast to our study, where the majority of women began therapy before that age threshold. The divergent results between our study and the WHI Memory Study are compatible with the theory of the window of opportunity, according to which the MHT would protect against cognitive deterioration if it is used before the age of 60; however, its efficacy may diminish if therapy is started after that age, potentially resulting in adverse effects [18]. A meta-analysis that including 13 studies showed that if therapy is initiated in early-postmenopause, the risk of Alzheimer's decreases, but if it is initiated in late postmenopause, the risk does not decrease and even increases in some studies [19]. Postmenopausal hypoestrogenism may impair mitochondrial function and induce neuronal senescence. Early initiation of estrogen therapy may prevent the senescent phenomenon, whereas late initiation may be ineffective in re-estrogenizing the senescent mitochondria [20].

It seems that not only estrogens play a role in women's cognitive decline but also testosterone. It has been reported that women who have undergone surgical menopause display lower testosterone levels compared to those who undergo spontaneous menopause [14]. Studies on animals have shown that testosterone can have neuroprotective effects by reducing the production of amyloid-beta, enhancing synaptic signalling, and mitigating neuronal death [21]. A study by Lee et al. [22] revealed that higher levels of free testosterone in both females and males were associated with reduced cerebral beta-amyloid deposition and decreased cognitive impairment. In contrast, free E2 levels were not found to correlate with beta-amyloid deposition or neurodegeneration in either sex [22].

In the present study, our logistic regression model found that having >12 years of study is a protective factor of cognitive impairment. Level

of education has been reported as an important aspect related to the validation of cognitive and dementia tests [23]. In this sense, lower educational attainment has consistently been identified as one of the most prevalent risk factors for dementia in epidemiological research. A meta-analysis of 23 prospective cohort studies that included over 75,000 individuals revealed a 7 % reduction in dementia risk for each additional year of education [24]. The impact of education on the risk of cognitive decline aligns with the concept of "cognitive reserve," which is a theoretical construct that mitigates the effects of age-related decline and pathological damage. The cognitive reserve encompasses both structural and dynamic brain capacities that serve as a buffer against atrophy and injury. Compensatory mechanisms within the brain, such as redistributing cognitive tasks among different neural networks, can help maintain functional abilities despite localized damage. Engaging in cognitive activities reinforces neuronal circuitry, bolstering both functional plasticity and cognitive reserve, thus lowering the risk of dementia [25].

The present study emphasizes that the type of menopause is associated with distinct clinical characteristics that may contribute to variations in the rate of cognitive impairment. For instance, women experiencing surgical menopause after the age of 40 had a higher proportion of women with lower levels of education compared to those who undergo spontaneous menopause at the same age threshold. Furthermore, the rate of ever MHT use differs significantly between the two groups, with ever MHT users accounting for 26.3 % of women with spontaneous menopause after 40 years of age and 55.1 % among those undergoing surgical menopause before 40 years of age. These demographic and treatment differences may explain the varying prevalence of cognitive impairment reported in studies investigating the impact of different types of menopause on cognitive risk [5].

It is necessary to emphasize that not all women with cognitive impairment will progress to dementia. The present study specifically evaluates the association of certain risk factors with MCI, not with dementia. It is important to note that the present study has some limitations. Firstly, its observational design means that it cannot establish causal relationships. Additionally, the study focused on investigating the effects of menopause among older women. To ensure this, we only included individuals who had elapsed several years since menopause. However, this may have led to inaccuracies in determining the age of menopause or certain aspects of clinical history. Another limitation could be related to the lack of specification regarding the type of ever used MHT (estrogens or progestogens), the route of administration, or the duration of this therapy. Without previously precising this information, in a previous study we showed a decrease in the risk of MCI among women who had ever used less than two years of MHT [6]. Given that this study aimed to establish the association between the type of menopause and MCI, our findings include a higher proportion of women with menopause before the age of 40 (convenience sample) than the prevalence of this condition in the general population [26]; which can be seen as a limitation. We compared women who had menopause before the age of 40 with those who experienced it after that age, instead of comparing them with women whose menopause occurred at 45 years or older, which is considered the normal age of menopause. We made this decision because the average age of menopause in Latin America is about three years earlier [26].

On the other hand, the study also has some significant strengths. Firstly, it utilized a validated and widely accepted tool for the evaluation of cognitive function. Secondly, it was conducted across multiple centers, which helps reduce biases that could occur if the study was conducted in just one location. Thirdly, participants from diverse healthcare settings (including private and public sectors) were included, which adds to the generalizability of the findings. However, it's important to keep in mind that while the results are valuable, they may not be representative of the broader Latin American population because of the limited access to preventive health check-ups in the region. This introduces the possibility of selection bias. Additionally, all participants were evaluated by physicians specializing in women's health, and rigorous statistical methods were used to control for various potential confounders.

In conclusion, this study suggests that women with spontaneous menopause before age 40, compared to those having menopause over 40, have no increased MCI risk, while those with surgical menopause, independent of age, are more prone to cognitive decline. Ever MHT users have a lower MCI risk. These findings suggest that residual ovarian function, typical of postmenopause, plays a role in cognitive impairment. There is a need for further research to confirm our findings.

Contributors

María T. Espinoza contributed to study conception and design, and text preparation and revision.

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Ethical approval

The present study was approved by the ethics committee of the Southern Metropolitan Health Service, Santiago de Chile, Chile (Memorandum 15/2022; June 22, 2022) and complies with the Declaration of Helsinki. All participants were informed of the study, its aims and used tools, after which they provided written consent for participation.

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This article was not commissioned and was externally peer reviewed.

Data sharing and collaboration

There are no linked research data sets for this paper. The data of this study are not publicly available but can be requested for research collaboration projects according to ethical, privacy and legislation issues.

Declaration of competing interest

The authors declare that they have no competing interest.

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