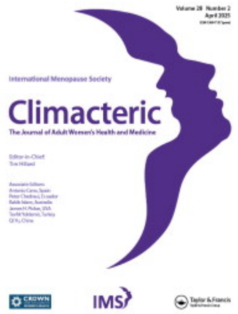

Climacteric

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/icmt20

Severe obesity and menopause symptoms are associated with cognitive impairment in postmenopausal women from Latin America

Juan Enrique Blümel, Maria Soledad Vallejo, Peter Chedraui, Socrates Aedo, Marcia Alexandre Hipolito Rodrigues, Carlos Salinas, Konstantinos Tserotas, Andres Calle, Maribel Dextre, Alejandra Elizalde, Carlos Escalante Gomez, Gustavo Gómez-Tabares, Álvaro de Jesus Monterrosa-Castro, Maria T. Espinoza, Monica Ñañez, Eliana Ojeda, Claudia Rey & Doris Rodríguez-Vidal

To cite this article: Juan Enrique Blümel, Maria Soledad Vallejo, Peter Chedraui, Socrates Aedo, Marcia Alexandre Hipolito Rodrigues, Carlos Salinas, Konstantinos Tserotas, Andres Calle, Maribel Dextre, Alejandra Elizalde, Carlos Escalante Gomez, Gustavo Gómez-Tabares, Álvaro de Jesus Monterrosa-Castro, Maria T. Espinoza, Monica Ñañez, Eliana Ojeda, Claudia Rey & Doris Rodríguez-Vidal (25 Apr 2025): Severe obesity and menopause symptoms are associated with cognitive impairment in postmenopausal women from Latin America, Climacteric, DOI: 10.1080/13697137.2025.2491637

To link to this article: https://doi.org/10.1080/13697137.2025.2491637

Published online: 25 Apr 2025.

CLIMACTERIC
https://doi.org/10.1080/13697137.2025.2491637

ORIGINAL ARTICLE

Severe obesity and menopause symptoms are associated with cognitive impairment in postmenopausal women from Latin America

Juan Enrique Blümel[a], Maria Soledad Vallejo[b], Peter Chedraui[c], Socrates Aedo[d], Marcia Alexandre Hipolito Rodrigues[e], Carlos Salinas[f], Konstantinos Tserotas[g], Andres Calle[h], Maribel Dextre[i], Alejandra Elizalde[j], Carlos Escalante Gomez[k], Gustavo Gómez-Tabares[l], Álvaro de Jesus Monterrosa-Castro[m], Maria T. Espinoza[n], Monica Ñañez[o], Eliana Ojeda[p], Claudia Rey[q] and Doris Rodríguez-Vidal[r]

[a]Medicina Interna Sur, Facultad de Medicina, Universidad de Chile, Santiago de Chile, Chile; [b]Obstetricia y Ginecología, Hospital Clínico, Universidad de Chile, Santiago de Chile, Chile; [c]Escuela de Postgrado en Salud, Universidad Espíritu Santo, Samborondón, Ecuador; [d]Escuela Medicina, Universidad Finis Terra, Santiago de Chile, Chile; [e]Department of Gynecology and Obstetrics, Federal University of Minas Gerais, Belo Horizonte, Brazil; [f]Servicio de Obstetricia y Ginecología, Hospital Ángeles, Puebla, México; [g]Clínica Tserotas, Ciudad de Panamá, Panamá a Unidad de Ginecología Obstétrica, Clínica Los Ángeles, Cochabamba, Bolivia; [h]Centro Integral de Salud Obstétrica y Femenina. Ginecología, Universidad Indoamérica, Academia Ecuatoriana de Medicina, Quito, Ecuador; [i]Ginecología Obstetricia, Clínica Internacional, Clínica Javier Prado, Lima, Perú; [j]Departamento de la Mujer, Niñez y Adolescencia, Facultad de Medicina de la Universidad Nacional del Nordeste, Corrientes, Argentina; [k]Departamento de Ginecología, Facultad de Medicina, Universidad de Costa Rica, Costa Rica; [l]Departamento de Ginecología, Escuela de Medicina, Facultad de Salud, Universidad del Valle, Cali, Colombia; [m]Grupo de Investigación Salud de la Mujer, Universidad de Cartagena, Cartagena, Colombia; [n]Unidad de Ginecología Obstétrica, Clínica Los Ángeles, Cochabamba, Bolivia; [o]II Cátedra de Ginecología, Universidad Nacional de Córdoba, Córdoba, Argentina; [p]Departamento Académico de Medicina Humana, Universidad Andina del Cusco, Cusco, Perú; [q]Asociación Argentina para el Estudio del Climaterio, Buenos Aires, Argentina; [r]Hospital de Clínicas José de San Martín, Universidad de Buenos Aires, Buenos Aires, Argentina

ABSTRACT

Objective: This study aimed to evaluate the association between obesity and cognitive impairment.
Methods: This study is a sub-analysis of an observational, cross-sectional study in nine Latin American counties. Sociodemographic, clinical and anthropometric data were collected, and cognition was assessed using the Montreal Cognitive Assessment (MoCA) tool in 722 postmenopausal women.
Results: The mean age, body mass index (BMI) and years of education of the cohort were 56.9 years, 26.8 kg/m^2 and 13.6 years, respectively. Women with cognitive impairment, compared to those without, had a higher BMI (27.8 ± 5.9 vs. 26.6 ± 4.9 kg/m^2, $p = 0.037$), had more children (3.1 ± 2.4 vs. 2.5 ± 1.7, $p = 0.023$), experienced more severe menopausal symptoms (56.3% vs. 31.9%, $p < 0.001$) and presented more comorbidities (60.0% vs. 43.8%, $p = 0.006$). They also had fewer years of study (10.8 ± 5.1 vs. 13.9 ± 4.9 years, $p = 0.001$), were less physically active (35.0% vs. 49.1%, $p = 0.018$) and were less likely to use menopausal hormone therapy (MHT) (11.3% vs. 28.8%, $p = 0.001$). In binary logistic regression analysis, BMI ≥ 35.0 kg/m^2 (odds ratio [OR] 2.27, 95% confidence interval [CI] 1.08–4.76) and severe menopausal symptoms (OR 2.10, 95% CI 1.29–3.43) were associated with cognitive impairment. In the model, factors related to lower risk were ever use of MHT (OR 0.44, 95% CI 0.21–0.92) and having more years of education (OR 0.38, 95% CI 0.20–0.64).
Conclusion: Severe obesity and severe menopausal symptoms increased the risk of cognitive impairment in postmenopausal women, while higher education and ever use of MHT were protective factors.

ARTICLE HISTORY
Received 12 September 2024
Revised 23 March 2025
Accepted 3 April 2025

KEYWORDS
Cognitive impairment; obesity; menopausal symptoms; menopausal hormone therapy

Introduction

The world is currently facing a global epidemic: a significant rise in dementia cases. Worldwide, dementia has become the seventh leading cause of death and a major contributor to disability and dependency among older adults. Recent estimates show that globally more than 55 million individuals are living with dementia, with nearly 10 million new cases occurring every year. This poses substantial challenges for public health systems [1]. In recent decades, a second epidemic has swept across the globe, impacting populations of all ages and regions and claiming the lives of millions. Obesity is currently recognized as one of the most pressing public health challenges, contributing to a range of chronic conditions such as heart disease, diabetes and certain types of cancer. The global spread of this condition has profoundly impacted our health [2]. By 2022, worldwide, approximately 16% of adults aged 18 years and older were affected by obesity, a staggering increase compared to the rates observed in 1990. The prevalence of obesity has more than doubled during this period, underscoring the urgent need for comprehensive strategies to address this growing crisis [3].

In postmenopausal women, there is a convergence of factors that increase the prevalence of both obesity and dementia.

CONTACT Juan E. Blümel jeblumelm@gmail.com Departamento Medicina Sur, Facultad de Medicina, Universidad de Chile, Orquídeas 1068, Departamento 302, P.O. BOX 7510258, Providencia, Santiago de Chile, Chile

Data from the National Health and Nutrition Examination Survey (2015–2016) show that the prevalence of obesity in women aged 20–39 years was 36.5%, a rate that increases to 44.7% among women aged 40–59 years [4]. Postmenopausal women exhibit a higher prevalence of dementia compared to men of similar ages. This disparity is partly attributable to estrogen deficiency following menopause, as well as to women's longer life expectancy. Sex differences influence not only the prevalence of vascular risk factors for dementia, more common in postmenopausal women or those over the age of 60 years, but also the susceptibility to dementia associated with specific risk factors, such as the APOE genotype, vascular conditions and depression [5]. Not only do women have a higher risk of developing dementia, but they also experience higher disability-adjusted life years and mortality due to dementia [6,7].

Cognitive impairment is influenced by various risk factors. A synthesis of 212 meta-analyses identified several risk factors, including body weight, alcohol consumption, depression, diabetes mellitus, poor diet, hypertension, low educational attainment, physical inactivity, sensory loss, sleep disturbances, smoking, social isolation, traumatic brain injuries and vitamin D deficiency [8]. Another study conducted across six Latin American countries pinpointed additional risk factors for cognitive decline: low educational attainment, hypertension, midlife obesity, diabetes mellitus, smoking, excessive alcohol consumption, physical inactivity, depression, limited social interaction, hearing loss and a history of traumatic brain injuries [9]. In Mexico, a study primarily focusing on women revealed several associated risk factors for cognitive decline, such as dependence on basic activities of daily living, lack of cognitive stimulation, being over the age of 75 years, polypharmacy and inadequate blood pressure control [10].

The present sub-analysis aims to explore the association between obesity and cognitive decline in postmenopausal women in Latin America, taking into account the high prevalence of both conditions within this population and existing evidence suggesting a potential relationship between them. It is hypothesized that obesity may increase the risk of cognitive decline.

Methods

Study design and participants

This study is a sub-analysis of the REDLINC XII study, which aimed to assess the association between the type of menopause and cognitive decline. The REDLINC XII study was conducted between January and October 2023 and took place in nine Latin American countries: Argentina, Bolivia, Brazil, Colombia, Costa Rica, Ecuador, Mexico, Panama and Peru. The participants were postmenopausal women under 70 years of age who attended regular gynecological consultations [11].

The present sub-analysis examined the association between cognitive impairment and obesity. The inclusion criteria involved natural postmenopausal women who were native Spanish or Portuguese speakers and were otherwise in normal health. Women who had undergone chemotherapy or radiotherapy, had a bilateral oophorectomy, experienced menopause before the age of 40 years or had a body mass index (BMI) below 18.5 kg/m^2 were excluded from the sub-analysis. Additionally, women with hearing or vision impairments or those diagnosed with dementia that could hinder their comprehension of the questionnaires were also excluded.

Studied variables

The following data were analyzed: age (years), years of education, weight (kilograms), height (meters), BMI (weight/squared height), parity (number of children), partner status (yes/no), sexually active (at least one sexual encounter in the past year; yes/no), smoking habit (yes/no), physically active (more than 150 min a week of moderate aerobic physical activities such as fast walking, cycling, calm sports, dancing; yes/no), natural postmenopausal stage (according to Stages of Reproductive Aging Workshop [STRAW] +10 criteria), years since menopause, ever use (current and/or past) of menopausal hormone therapy (MHT) (yes/no), current use of psychotropic medications (antidepressants, hypnotics or anxiolytics; yes/no) and comorbidities (defined as presenting one or more of treatment for dyslipidemia, diabetes mellitus and/or hypertension; yes/no).

BMI is classified according to the World Health Organization (WHO) criteria as normal (BMI 18.5–24.9 kg/m^2), overweight (BMI 25.0–29.9 kg/m^2), moderate obesity (BMI 30.0–34.9 kg/m^2) and severe obesity (BMI $\geq$ 35.0 kg/m^2) [12].

Menopausal symptoms were evaluated using the Menopause Rating Scale (MRS), a validated tool for assessing the quality of life in middle-aged women. The MRS comprises 11 items that assess menopausal symptoms which are grouped into three subscales: somatic, including hot flashes, heart discomfort, sleep problems, and muscle and joint pain; psychological, including depressive mood, irritability, anxiety, and physical and mental exhaustion; and urogenital, encompassing sexual problems, bladder problems and vaginal dryness. Participants can rate each item from 0 (absent) to 4 (1 = mild; 2 = moderate; 3 = severe; 4 = very severe). The total score for each subscale is the sum of the ratings for the items in that subscale. The total MRS score is the sum of the scores from all the subscales. Severe menopausal symptoms were defined as having a total MRS score of ≥14 points [13]. In this study, the Spanish and Portuguese language versions of the MRS were used [14,15].

For statistical analyses, women were categorized into two groups based on the scores obtained with the Montreal Cognitive Assessment (MoCA) tool (see the 'Cognitive testing' section). Women who were currently using or had previously used MHT were classified as 'ever users', based on previous research indicating that women who used MHT (regardless of type or route of administration) for less than 2 years during early postmenopause showed less cognitive decline [16].

Cognitive testing

Cognitive function was evaluated with the MoCA, a tool developed by Nasreddine et al. in Canada to identify individuals with cognitive impairment, which is a potential transitional stage between normal aging and dementia, particularly Alzheimer's disease [17]. The prevalence of cognitive impairment varies between 3% and 42% in different studies, depending on the diagnostic criteria used [18]. It is estimated that each year, between 10% and 15% of people with cognitive impairment progress to dementia, so numerous studies are investigating cognitive impairment as a pre-dementia phase [19].

The MoCA tool evaluates six cognitive domains in about 10 min. These domains include memory, visuospatial ability, executive function, attention, language and orientation, with a maximum achievable score of 30 points. In its original version, the cut-off value for identifying cognitive impairment was set at 26 points (<26 as positive) [20]. Nasreddine et al. have suggested that the MoCA demonstrates higher sensitivity and specificity for detecting cognitive impairment compared to the Mini-Mental State Examination (MMSE) tool [17], with rates of 90% and 87%, respectively, compared to 18% and 100% for the MMSE.

In the Spanish validation of the MoCA, conducted by Lozano Gallego et al., a cut-off value of 21 points was used to identify cognitive impairment (<21 points), with a sensitivity of 71.4% and a specificity of 74.5% [21]. In Brazil, the Portuguese version of the MoCA has been used with a similar cut-off value to the Spanish version [22].

In the REDLINC XII study, a physician administered the general questionnaire and the MoCA tool and performed a comprehensive examination of each woman, recording her personal and family medical history.

Statistical analysis

Statistical analysis was performed with SPSS software, version 21.0 for Windows (SPSS Inc., Chicago, IL, USA). Numerical variables are presented as means and standard deviations, and categorical variables are presented as frequencies and percentages. The homogeneity of variance was assessed using Levene's test ($p > 0.05$), and the normality of data distribution was determined using the Kolmogorov–Smirnov test.

The results of these tests were used to analyze differences between numerical variables. Non-parametric data were analyzed with the Mann–Whitney *U*-test, whereas parametric data were analyzed with the Student *t*-test. The chi-square test was used to compare categorical data. Additionally, one-way analysis of variance was employed to determine whether there were statistically significant differences between the means of three or more groups.

A logistic regression analysis examined the relationship between obesity and cognitive impairment, with cognitive impairment defined as a MoCA score of <21 [21]. Categorical variables were entered into the model as found, whereas continuous variables were categorized based on their median, except BMI, which was categorized according to the WHO definition. The stepwise procedure included variables in the model with a significance level of 10%. The variance inflation factor (VIF) was used to address multicollinearity in the regression analysis, ensuring that all VIF values were <10. Additionally, interactions between statistically significant variables in the bivariate analysis were considered. $p < 0.05$ was considered statistically significant for all analyses.

Ethical considerations

The protocol of the REDLINC XII study was revised and approved by the Ethics Committee of the Southern Metropolitan Health Service (Memorandum 15/2022; 22 June 2022), located in Santiago de Chile, Chile, and the study adheres to the principles outlined in the Declaration of Helsinki. Before participation, all participants were fully informed about the study aims and methodologies, after they provided written consent to take part in the research.

Results

A total of 1185 postmenopausal women under the age of 70 years were recruited in the REDLINC XII study. Figure 1 shows the participant flowchart from which the cases needed for this sub-analysis were obtained. Cases due to menopause before the age of 40 years or previous bilateral oophorectomy, both of which can impact cognition, were excluded [23,24]. Additionally, 11 women were excluded due to having a BMI below 18.5 kg/m^2, which has also been linked to dementia [25]. Finally, the present sub-analysis included data from 722 women with an average age of 56.9 years and a mean BMI of 26.8 kg/m^2. On average, they had 2.6 children, 72.7% reported having a partner and 67.6% had been sexually active in the past 12 months. The mean educational level was 13.6 years, and 46.0% identified themselves as college graduates.

Table 1 presents the characteristics of women with and without cognitive impairment. The results show no significant differences in age, cigarette smoking, having a partner, being sexually active, years postmenopausal and the use of psychotropic drugs. However, women with cognitive impairment had a higher BMI compared to women without cognitive impairment (27.8 ± 5.9 vs. 26.6 ± 4.9 kg/m^2, $p = 0.037$), had more children (3.1 ± 2.4 vs. 2.5 ± 1.7, $p = 0.023$), experienced severe menopausal symptoms at a higher rate (56.3% vs. 31.9%, $p = 0.001$) and had a higher prevalence of comorbidities (60.0% vs. 43.8%, $p = 0.006$). Additionally, women with cognitive impairment had fewer years of education (10.8 ± 5.1 vs. 13.9 ± 4.9 years, $p < 0.001$), were less physically active (35.0% vs. 49.1%, $p < 0.018$) and were less likely to have ever used MHT (11.3% vs. 28.8%, $p = 0.001$).

The average MoCA score for women with a normal weight (BMI 18.5–24.9 kg/m^2) was 25.7 ± 4.0, for those overweight (BMI 25.0–29.9 kg/m^2) was 24.8 ± 4.7, for those with moderate obesity (BMI 30.0–34.9 kg/m^2) was 24.0 ± 4.5 and for those with severe obesity (BMI ≥35 kg/m^2) was 22.7 ± 4.5 (analysis of variance $p < 0.0001$).

Table 2 presents data showing that the percentage of women with cognitive impairment was significantly higher in those with severe obesity (defined by the WHO as a BMI ≥ 35.0 kg/m^2), with the prevalence rising from 6.9% in women with normal weight to 26.8% in those with a BMI of ≥35 kg/m^2 (odds ratio [OR] 4.88, 95% confidence interval [CI] 2.20–10.82).

In a binary logistic regression model (Table 3), cognitive impairment (MoCA < 21 points) was used as the dependent variable, with the factors presented in Table 1 included as covariates. Quantitative variables were grouped based on the

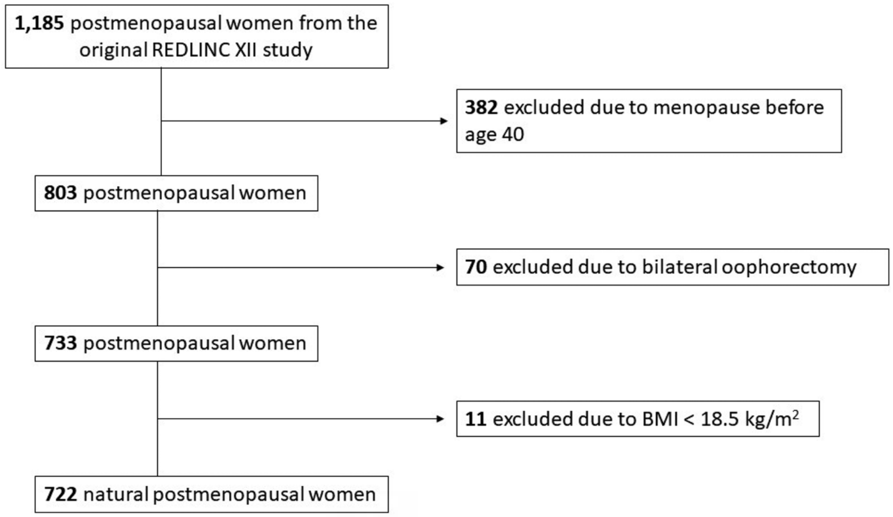

Figure 1. Participant flowchart for the present sub-analysis originated from the original REDLINC XII cohort [11]. BMI, body mass index.

Table 1. Characteristics of women based on the presence or absence of cognitive impairment.

	Cognitive impairment[a]		
Characteristic	*No* (n = 642)	*Yes* (n = 80)	p-*Value*
Age (years)	56.9 ± 5.7	56.1 ± 6.2	NS[b]
BMI (kg/m²)	26.6 ± 4.9	27.8 ± 5.9	0.037[b]
Years of education	13.9 ± 4.9	10.8 ± 5.1	0.001[b]
Physically active	49.1 (45.2–52.9)	35.0 (24.3–45.7)	0.018[c]
Smoker	27.8 (23.5–30.6)	23.5 (15.8–31.3)	NS[c]
Number of children	2.5 ± 1.7	3.1 ± 2.4	0.023[b]
Has a partner	72.7 (69.3–76.2)	72.5 (62.5–82.5)	NS[c]
Sexually active	68.4 (64.8–72.0)	61.3 (50.3–72.2)	NS[c]
Years since menopause	7.8 ± 5.5	8.6 ± 6.3	NS[d]
Severe menopausal symptoms (total MRS score ≥ 14)	31.9 (28.3–35.6)	56.3 (45.1–67.4)	0.001[c]
Ever use of MHT	28.8 (25.3–32.3)	11.3 (4.2–18.3)	0.001[c]
Psychotropic drug use	28.5 (25.0–32.0)	37.5 (26.7–48.3)	NS[c]
Comorbidities	43.8 (39.9–47.6)	60.0 (49.0–71.0)	0.006[c]

[a]Defined as a total MoCA score of <21 points.
[b]Determined with the Mann–Whitney *U*-test.
[c]Determined with the chi-square test.
[d]Determined with Student's *t*-test[3].
Data presented as mean ± standard deviation or percentage (95% confidence interval). BMI, body mass index; MHT, menopausal hormone therapy; MoCA, Montreal Cognitive Assessment; MRS, Menopause Rating Scale; NS, non-significant.

Table 2. Cognitive impairment in postmenopausal women according to BMI.

BMI (kg/m²)	*Cognitive impairment*[a], n *(%)*	*OR (95% CI)*[b]
18.5–24.9 (*n* = 303)	21 (6.9%)	1.00
25.0–29.9 (*n* = 258)	33 (12.8%)	1.97 (1.11–3.50)
30.0-34.9 (*n* = 116)	14 (12.1%)	1.84 (0.90–3.76)
≥35.0 (*n* = 45)	12 (26.8%)	4.88 (2.20–10.82)

[a]Defined as a MoCA score <21 points.
[b]Compared to normal-weight women with a BMI of 18.5–24.9 kg/m².
BMI, body mass index; CI, confidence interval; MoCA, Montreal Cognitive Assessment; OR, odds ratio.

median (except for BMI which was categorized according to the WHO definition). Table 3 indicates that severe obesity (BMI ≥ 35.0 kg/m²) was significantly associated with cognitive impairment (OR 2.27, 95% CI 1.08–4.76). The model included an interaction between severe menopausal symptoms (total MRS score of ≥14) and BMI ≥ 35 kg/m², but this was not statistically significant and was therefore removed. Collinearity between variables was ruled out because all VIF values ranged between 1.026 and 1.049 (collinearity is present when the VIF is >10). In addition to obesity, the presence of severe menopausal symptoms was also associated with cognitive impairment (OR 2.10, 95% CI 1.29–3.43). Protective factors in the model included ever use of MHT (OR 0.44, 95% CI 0.21–0.92) and having more years of education (OR 0.38, 95% CI 0.20–0.64). Another logistic regression model showed that having BMI > 25 kg/m² did not emerge as a factor related to cognitive impairment.

Table 3. Factors associated with cognitive impairment in postmenopausal women: logistic binary regression.

Factor	*Cognitive impairment, OR (95% CI)*
BMI ≥ 35.0 kg/m²	2.27 (1.08–4.76)
Severe menopausal symptoms (MRS total score ≥ 14)	2.10 (1.29–3.43)
Ever use of MHT	0.44 (0.21–0.92)
Years of education (above a median of 14 years)	0.38 (0.20–0.64)

BMI, body mass index; CI, confidence interval; MHT, menopausal hormone therapy; MRS, Menopause Rating Scale; OR, odds ratio.

Discussion

The present study found a significant association between severe obesity (BMI ≥ 35 kg/m²) and cognitive impairment, suggesting a potential causal relationship. Obesity is recognized as a significant risk factor for cognitive impairment. Recent evidence suggests that excessive body fat, especially during midlife, may increase the risk of cognitive decline later in life. An analysis involving five million participants found a significant association between obesity and a higher risk of cognitive decline and dementia, with a hazard ratio (HR) of 1.10 (95% CI 1.05–1.15) [26]. Additionally, a global study that synthesized data from 72 investigations, and included a total of 2,980,947 older adults, reported a prevalence of 32.5% for mild cognitive impairment among individuals who were overweight or obese [27]. The same study identified a 12.6% prevalence of decline in obese individuals for Latin America [27].

Supporting the theory that obesity negatively impacts cognition, a meta-analysis revealed that bariatric surgery can improve cognitive function in patients with obesity [28]. These findings highlight the importance of addressing obesity as a crucial factor in preventing and managing cognitive impairment.

As the present study is cross-sectional, a definitive causal relationship between obesity and cognitive impairment cannot be established. In addition to the association between obesity and cognitive decline, our study found that severe menopausal symptoms, as assessed with the MRS, were associated with a higher risk of cognitive impairment. Consistent with our findings, a systematic review of 33 studies concluded that menopausal symptoms, such as hot flashes, depression, anxiety and brain fog, are directly associated with cognitive decline [29]. Another study analyzing the association between menopausal symptoms and cognition (assessed with the MMSE) showed that women with severe menopausal symptoms (higher total score on the Greene Climacteric Scale) exhibit significantly lower mean scores in orientation, registration, attention, memory and linguistic/visuospatial abilities compared to those with mild menopausal symptoms [30].

Our findings, showing a reduced likelihood of cognitive impairment among MHT ever users, contrast with the WHI Memory Study [31], which reported a non-significant increase in cognitive decline risk with MHT use in both the estrogen-alone group (HR 1.34, 95% CI 0.95–1.89) and the estrogen–progestin group (HR 1.25, 95% CI 0.97–1.60). However, important to mention is that HRs for probable dementia were increased in the estrogen-alone trial (HR 1.77, 95% CI 0.74–4.23) and in the pooled trials (HR 2.19, 95% CI 1.25–3.84). These differences may stem from participant demographics, as most WHI participants started therapy after age 60 years whereas in our study most participants were younger than 60 years. This aligns with the 'window of opportunity' theory, suggesting that MHT protects against cognitive decline when initiated before 60 years, while late initiation may reduce efficacy or cause harm [32]. A meta-analysis of nine studies found that early-postmenopause MHT initiation decreases Alzheimer's risk, but late initiation may have no effect or increased risk [33]. Postmenopausal hypoestrogenism may impair mitochondrial function and induce neuronal senescence, and while early estrogen therapy could prevent this, late therapy may fail to restore senescent mitochondria [34]. However, several studies following the aforementioned meta-analysis have revealed different results. A White Paper from the International Menopause Society, addressing cognitive changes during menopause, reviews several studies on MHT and cognition, concluding that using estrogen therapy seems safe even in late menopause [35]. Nevertheless, using MHT late in postmenopause carries risks if the formulation is conjugated equine estrogens/medroxyprogesterone acetate, although it appears to be neutral if the formulation is oral 17β-estradiol plus vaginal progesterone. Nonetheless, the literature reporting on the magnitude of the effect of MHT on dementia, whether beneficial or adverse, is small.

The present study found that a higher level of education was linked to reduced cognitive decline. A meta-analysis of 23 prospective cohort studies involving more than 75,000 individuals showed that each additional year of education was associated with a 7% decrease in the risk of dementia. The effect of education on cognitive decline is consistent with the concept of 'cognitive reserve', a theoretical idea that helps reduce the impact of age-related decline over brain damage. Cognitive reserve involves the brain's structural and dynamic capacities, acting as a defense mechanism against degeneration and injury. The brain's compensatory mechanisms, such as redistributing cognitive tasks across different neural networks, may contribute to maintaining cognitive function despite localized damage [36].

One of the limitations of this study is that, as an observational study, causal relationships cannot be established. Therefore, our study justifies the need for longitudinal studies to evaluate whether obesity is indeed associated with cognitive impairment, as our results seem to indicate. This study excluded women with BMI < 18.5 kg/m^2 because this group has also been linked to cognitive decline. Furthermore, since the condition being evaluated is rare in premenopausal women, we focused on studying women in the late postmenopausal period. However, the passage of time may have led to inaccuracies in determining the age of menopause or specific details of the clinical history. Another limitation could stem from the lack of details about the MHT used (estrogens or progestogens), the method of administration or the duration of this therapy. However, the study has some important strengths. Firstly, it used a validated and widely accepted tool to assess cognitive function. Secondly, the study was conducted across multiple centers, which helps reduce biases if the study was conducted in a single location. Thirdly, participants from various healthcare settings, including both public and private sectors, were included, enhancing the findings' generalizability. It is important to note that while the results are valuable, they may not represent the whole Latin American population due to the region's limited access to preventive health check-ups. This introduces the possibility of selection bias. Additionally, all participants were assessed by physicians specializing in women's health, and rigorous statistical methods were used to control for various potential confounding factors.

In conclusion, the present study suggests that natural postmenopausal women with severe obesity are at a higher risk of experiencing cognitive decline. Similarly, women with severe menopausal symptoms also face an increased risk. On the other hand, higher education levels and ever use of MHT were associated with a reduced risk. Future longitudinal studies are needed to reveal the intricate relationship between the risk factors determined in the current research (known or unknown) and cognitive decline.

Acknowledgements

The authors alone are responsible for the content and writing of the article.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

None.

ORCID

Claudia Rey http://orcid.org/0000-0002-0853-300X

Data availability statement

There are no linked research datasets for this article. The data for this study are not publicly available. However, the data can be requested for research collaboration projects according to ethical, privacy and legislation issues.

References

[1] World Health Organization; 2024. https://www.who.int/news-room/fact-sheets/detail/dementia. August 19.
[2] Williams EP, Mesidor M, Winters K, et al. Overweight and obesity: prevalence, consequences, and causes of a growing public health problem. Curr Obes Rep. 2015;4(3):363–370. doi: 10.1007/s13679-015-0169-4.
[3] World Health Organization. Obesity. 2024, August 19. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight.
[4] Hales CM, Carroll MD, Fryar CD, et al. Prevalence of obesity among adults and youth: United States, 2015–2016. NCHS Data Brief. 2017;(288):1–8.
[5] Ferretti MT, Iulita MF, Cavedo E, et al. Sex differences in Alzheimer disease – the gateway to precision medicine. Nat Rev Neurol. 2018;14(8):457–469. doi: 10.1038/s41582-018-0032-9.
[6] Kolahchi Z, Henkel N, Eladawi MA, et al. Sex and gender differences in Alzheimer's Disease: genetic, hormonal, and inflammation impacts. Int J Mol Sci. 2024;25(15):8485. doi: 10.3390/ijms25158485.
[7] Li R, Singh M. Sex differences in cognitive impairment and Alzheimer's disease. Front Neuroendocrinol. 2014;35(3):385–403. doi: 10.1016/j.yfrne.2014.01.002.
[8] Jones A, Ali MU, Kenny M, et al. Potentially modifiable risk factors for dementia and mild cognitive impairment: an umbrella review and meta-analysis. Dement Geriatr Cogn Disord. 2024;53(2):91–106. doi: 10.1159/000536643.
[9] Mukadam N, Sommerlad A, Huntley J, et al. Population attributable fractions for risk factors for dementia in low-income and middle-income countries: an analysis using cross-sectional survey data. Lancet Glob Health. 2019;7(5):e596–e603. doi: 10.1016/S2214-109X(19)30074-9.
[10] Moreno-Noguez M, Castillo-Cruz J, García-Cortés LR, et al. Risk factors associated with cognitive impairment in aged: cross-sectional study. Rev Med Inst Mex Seguro Soc. 2023;61(Suppl 3):S395–S406. doi: 10.5281/zenodo.8319815).
[11] Espinoza MT, Blümel JE, Chedraui P, et al. Association between type of menopause and mild cognitive impairment: the REDLINC XII study. Maturitas. 2024;189:108110. doi: 10.1016/j.maturitas.2024.108110.
[12] World Health Organization. Obesity and overweight: preventing and managing the global epidemic: report of a WHO consultation; 2024, August 18. https://iris.who.int/handle/10665/42330.
[13] 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.
[14] Zentrum für Epidemiologie und Gesundheitsforschung. August 18, 2024.https://zeg-berlin.de/wp-content/uploads/2017/01/MRS_Spanish.pdf.
[15] Berlin ZEG. 2024; [cited 2024 Aug 30]. Available from: https://zeg-berlin.de/expertise/diagnostics-tools/%20menopause-rating-scale/languages/.
[16] 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(2):195–202. doi: 10.1080/13697137.2021.1951203.
[17] 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(4):695–699. doi: 10.1111/j.1532-5415.2005.53221.x.
[18] Ward A, Arrighi HM, Michels S, et al. Mild cognitive impairment: disparity of incidence and prevalence estimates. Alzheimers Dement. 2012;8(1):14–21. doi: 10.1016/j.jalz.2011.01.002.
[19] Petersen RC, Doody R, Kurz A, et al. Current concepts in mild cognitive impairment. Arch Neurol. 2001;58(12):1985–1992. doi: 10.1001/archneur.58.12.1985.
[20] 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(8):633–644. doi: 10.1176/appi.ajgp.13.8.633.
[21] Lozano-Gallego M, Hernández-Ferrándiz M, Turró-Gárriga O, et al. Validación del Montreal Cognitive Assessment (Moca): test de cribado para el deterioro cognitivo leve. Datos Preliminares. Alzheimer Real Inves Demenc. 2009;43:4–11.
[22] Freitas S, Simões MR, Martins C, et al. Estudos de adaptação do Montreal Cognitive Assessment (MoCA) para a população portuguesa. Avaliação. Psicológica. 2010;9(3):345–357.
[23] Karamitrou EK, Anagnostis P, Vaitsi K, et al. Early menopause and premature ovarian insufficiency are associated with increased risk of dementia: a systematic review and meta-analysis of observational studies. Maturitas. 2023;176:107792. doi: 10.1016/j.maturitas.2023.107792.
[24] Georgakis MK, Beskou-Kontou T, Theodoridis I, et al. Surgical menopause in association with cognitive function and risk of dementia: a systematic review and meta-analysis. Psychoneuroendocrinology. 2019;106:9–19. doi: 10.1016/j.psyneuen.2019.03.013.
[25] Wang C, Fu W, Cao S, et al. Weight loss and the risk of dementia: a meta-analysis of cohort studies. Curr Alzheimer Res. 2021;18(2):125–135. doi: 10.2174/1567205018666210414112723.
[26] Tang X, Zhao W, Lu M, et al. Relationship between Central Obesity and the incidence of cognitive impairment and dementia from Cohort Studies Involving 5,060,687 Participants. Neurosci Biobehav Rev. 2021;130:301–313. doi: 10.1016/j.neubiorev.2021.08.028.
[27] Wei J, Zhu X, Liu J, et al. Estimating global prevalence of mild cognitive impairment and dementia in elderly with overweight, obesity, and central obesity: a systematic review and meta-analysis. Obes Rev. 2025;26(5):e13882. doi: 10.1111/obr.13882.
[28] Tao B, Tian P, Hao Z, et al. Bariatric surgery improves cognition function in the patients with obesity: a meta-analysis. Obes Surg. 2024;34(3):1004–1017. doi: 10.1007/s11695-024-07086-8).
[29] Zhu C, Thomas N, Arunogiri S, et al. Systematic review and narrative synthesis of cognition in perimenopause: the role of risk factors and menopausal symptoms. Maturitas. 2022;164:76–86. doi: 10.1016/j.maturitas.2022.06.010.
[30] Kaur M, Kaur M. Is cognitive performance of women sensitive to the severity of menopausal symptoms? Menopause. 2022;29(2):170–177. doi: 10.1097/GME.0000000000001910.
[31] Shumaker SA, Legault C, Kuller L, et al. Conjugated equine estrogens and incidence of probable dementia and mild cognitive impairment in postmenopausal women: women's health initiative memory study. JAMA. 2004;291(24):2947–2958. doi: 10.1001/jama.291.24.2947.
[32] Koebele SV, Bimonte-Nelson HA. Trajectories and phenotypes with estrogen exposures across the lifespan: What does Goldilocks have to do with it? Horm Behav. 2015;74:86–104. doi: 10.1016/j.yhbeh.2015.06.009.
[33] 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.
[34] Turner RJ, Kerber IJ. A theory of eu-estrogenemia: a unifying concept. Menopause. 2017;24(9):1086–1097. doi: 10.1097/GME.0000000000000895.
[35] Maki PM, Jaff NG. Brain fog in menopause: a health-care professional's guide for decision-making and counseling on cognition. Climacteric. 2022;25(6):570–578. 10.1080/13697137.2022.2122792 36178170
[36] Cheng ST. Cognitive reserve and the prevention of dementia: the role of physical and cognitive activities. Curr Psychiatry Rep. 2016;18(9):85. doi: 10.1007/s11920-016-0721-2.