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Original article

Risk of sarcopenia: A red flag for cognitive decline in postmenopause?

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ABSTRACT

Objective: To determine if the SARC-F tool, used to screen for sarcopenia risk, can also predict mild cognitive impairment (MCI) diagnosed with the Montreal Cognitive Assessment (MoCA) tool.
Methods: This is a sub-analysis of data from a cross-sectional study carried out in postmenopausal women from Latin America (nine countries) in which sociodemographic, clinical, and anthropometric data were collected, and the SARC-F and MoCA tools administered. From the original sample of 1185 women, analysis was performed only among the 772 with natural menopause.
Results: Overall, mean age, body mass index and years of education were 56.9 years, 26.8 kg/m^2 and 13.6 years, respectively. Women with MCI displayed a higher body mass index, had more children, experienced more severe menopausal symptoms, and were more frequently homemakers and physically inactive. The prevalence of MCI increased from 12.9 % in women with no sarcopenia risk (SARC-F $<$ 4 points) to 35.3 % in those at risk (OR 3.70; 95 % CI 2.36–5.80). According to binary logistic regression analysis, sarcopenia risk (total SARC-F score $\geq$ 4) was associated with MCI (OR: 2.44; 95 % CI 1.50–3.95). Aside from the risk of sarcopenia, being a homemaker (OR 1.97; 95 % CI 1.25–3.10) was also associated with an increased likelihood of MCI. Protective factors included ever use of menopausal hormone therapy (OR 0.26; 95 % CI 0.13–0.54) and having higher educational attainment (OR 0.28; 95 % CI 95 % 0.16–0.47). The SARC-F displayed a sensitivity of 84 % and a specificity of 39 % at diagnosing MCI.

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Conclusion: This study suggests that the SARC-F questionnaire, used to assess sarcopenia risk, could also predict the presence of MCI in postmenopausal women. There is a need for more research to support our preliminary findings.

1. Introduction

The global ageing of the population has significant implications for public health, mainly due to the rise in the prevalence of chronic diseases and the impairment of quality of life. Sarcopenia and cognitive decline are among the primary disabling conditions associated with ageing and are particularly significant [1,2].

In individuals with sarcopenia, there is a well-documented and clear relationship between the loss of muscle mass and the decline of muscle strength [3]. This has significant implications for overall health and well-being. The reduction of muscle strength and mass substantially contributes to the increased risk of falls, which is particularly concerning in older adults [4]. These falls often trigger a cascade of adverse events, with bone fractures being among the most severe consequences. Bone fractures can lead to prolonged periods of immobility, further exacerbating muscle loss and accelerating functional decline [5]. Physical inactivity, malnutrition, smoking, sleep problems, and diabetes are associated with an increased risk of sarcopenia [6].

Traditionally, sarcopenia has been considered primarily as a geriatric problem. However, recently, studies have shown that sarcopenia is not only a concern for the physical health of older adults but also has implications for cognitive health, especially in women [7,8]. The term "Mild Cognitive Impairment (MCI)" refers to the decline in cognitive functions that exceeds what is typically expected for normal ageing, but does not significantly disrupt the daily life of individuals.

The prevalence of MCI varies widely in different studies, with estimates ranging from 3 % to 42 %, depending on the used diagnostic criteria [9]. Despite these disparities, there is a consensus that MCI represents a critical stage of vulnerability, as 10 % to 15 % of individuals diagnosed with MCI progress to dementia each year [10]. Due to the importance of this significant transition, MCI has been extensively researched as a pre-dementia phase, with studies currently aiming to identify early intervention strategies that could delay or prevent progression to dementia, especially Alzheimer's disease. The strongest risk factors associated with MCI include advanced age, a family history of Alzheimer's disease or other forms of dementia, and the presence of conditions that increase the risk of cardiovascular disease, such as hypertension, obesity, and diabetes [11]. Therefore, we decided to investigate whether a simple tool, the so-called SARC-F, used to assess the risk of sarcopenia [12], could also serve to screen for MCI in postmenopausal women, a group particularly vulnerable to cognitive disorders and dementia. Our hypothesis is that the SARC-F, an easy-to-apply test, could also be useful for screening cognitive decline, as both conditions share underlying mechanisms such as chronic inflammation, insulin resistance, and oxidative stress [13]. These factors are exacerbated in the context of menopause and ageing. Unlike other studies that focus on elderly individuals, we were interested in studying middle-aged women (postmenopausal), who may benefit from early preventive measures that could potentially delay further cognitive decline and dementia.

2. Material and methods

2.1. Study design and participants

This is a sub-analysis of the REDLINC XII study that explores the connection between sarcopenia and MCI. The REDLINC XII was a cross-sectional, observational, and multinational study conducted between January 2023 and November 2023 in general gynaecological consultations in nine Latin American countries that primarily aimed at evaluating among 1185 postmenopausal women the association between the type of menopause (spontaneous or surgical) and MCI [14]. The participants were otherwise healthy postmenopausal women aged 40 to 70 years who attended a routine health check-up (convenience sampling). Participants were required to be literate in either Spanish or Portuguese (Brazil) language. Most of the women had moderate incomes and accessed healthcare services from private and state clinical centres. Of the total of 1185 postmenopausal women included in the original REDLINC XII study, data of those who had natural menopause ($n = 722$) were analyzed in the present document.

2.2. Studied variables

The collected data included: age (in years), years of education, body mass index (BMI; weight [kg]/squared height [m]), parity (number of children), sexually active (whether there has been at least one sexual intercourse in the last year), homemaker status, smoker status, physical inactivity (defined as performing <75 min/week of intense aerobic physical activities such as running, gym workouts, tennis, etc., or < 150 min/week of moderate aerobic physical activities such as fast walking, cycling, and dancing) [15], postmenopausal stage (defined according to the STRAW +10 criteria as 12 or more month of amenorrhea), ever use of menopause hormone therapy (MHT) (current or past use), current use of psychotropic medications (including antidepressants, hypnotics, or anxiolytics; indicated as yes or no), and comorbidities (defined as presenting one or more of the following: receiving treatment for dyslipidaemia, diabetes mellitus, or hypertension; indicated as yes or no). A total score obtained with the Menopause Rating Scale (MRS) of 14 or more was defined as severe menopausal symptoms [16].

2.3. Risk of sarcopenia

The risk of sarcopenia was evaluated using the SARC-F tool [12], which is a quick and easy-to-use instrument used to screen for the risk of sarcopenia. This tool assesses five components: strength, assistance with walking, rising from a chair, climbing stairs, and falling (SARC-F). Each component can be scored from 0 to 2 by the participants, hence, providing a total SARC-F score that may range from 0 to 10. A total SARC-F score of 4 or higher indicates an increased risk of sarcopenia, which has been related to poor outcomes [12]. The SARC-F is a valuable test for detecting muscle function impairment and sarcopenia [17].

2.4. Cognitive testing

Cognitive function was assessed with the Montreal Cognitive Assessment (MoCA) tool. This instrument was developed by Nasreddine et al. [18] in Canada to identify individuals with MCI. MCI is considered a potential transitional stage between normal ageing and dementia, particularly Alzheimer's disease.

The MoCA tool assesses six cognitive domains in about 10 min. These domains are memory, visuospatial ability, executive function, attention, language, and orientation, with a maximum obtainable score of 30 points. In its original version, a score of 26 points or lower was used to identify MCI [19]. An additional point is added if the individual has fewer than 12 years of education. Nasreddine et al. [18] suggested that the MoCA is more sensitive (90 %) and specific (87 %) in detecting MCI compared to the Mini-Mental State Examination (MMSE) (sensitivity of 18 % and specificity of 100 %). In the Spanish validation of the MoCA conducted by Lozano Gallego et al. [20], a cut-off value of 21 points was used to identify MCI, with a sensitivity of 71.4 % and a specificity of 74.5 %. In Brazil, the Portuguese language version of the MoCA was used

with a cut-off value similar to that of the Spanish language version (that is 20 points or less positive for MCI) [21].

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

2.5. Sample size calculation

Assuming that 15 % of postmenopausal women have sarcopenia [22], and considering that we aimed to estimate the effect of sarcopenia over cognition, with an odds ratio of 2, at a significance level of 5 % (two-sided test) and 80 % power, to achieve this, with a ratio of 2:1 for cases to controls, we calculated a sample size of 93 cases with sarcopenia and 185 controls.

2.6. Statistical analysis

The statistical analysis was performed using SPSS software (version 21.0 for Windows; SPSS Inc., Chicago, IL). The data are presented as means, standard deviations, frequencies/percentages, odds ratios (OR), and 95 % confidence intervals (CI). We assessed the homogeneity of the variance using the Levene test with a $p > 0.05$ indicating homogeneity. The normality of data distribution was evaluated with the Kolmogorov-Smirnov test. Based on the results of these tests, differences between numeric variables were analyzed using either the Student's *t*-test for parametric data or the Mann-Whitney *U* test for non-parametric data. Logistic regression analysis was performed to determine factors associated with a higher likelihood for MCI. In addition, we calculated the diagnostic performance of the SARC-F for predicting MCI. A stepwise procedure was used for the inclusion of the variables into the model, considering a significance level set at 10 %. The Variance Inflation Factor (VIF) was used to evaluate multicollinearity in the regression analysis (VIF <10). Interactions between variables found to be statistically significant in the bivariate analysis were also considered. For all calculations, a *p* value of <0.05 was considered statistically significant.

2.7. Ethical considerations

The study protocol was approved by the ethics committee of the Southern Metropolitan Health Service in 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 the tools used. Subsequently, they provided written consent for participation.

3. Results

The average age of the participants of the sample was 56.9 years, with an average educational level of 13.6 years and a mean BMI of 26.8 kg/m^2. Among the participants, 37.0 % were homemakers and had an average of 2.6 children. Additionally, 72.7 % reported being in a relationship. Lifestyle factors included 52.5 % of women being physically inactive, 26.5 % identified as smokers, and 67.6 % reporting being sexually active in the past 12 months. Regarding medication use, 26.9 % had ever used MHT, 19.8 % used hypnotics, 14.7 % antidepressants, and 12.6 % anxiolytics. The main cardiometabolic risk factors for the overall sample were hypertension (31.3 %), hypercholesterolemia (25.1 %), obesity (22.3 %), and diabetes mellitus (12.2 %) (Data not shown in Tables).

Table 1 compares the characteristics of women with and without MCI. Women with MCI have a higher BMI, have more children, experience more severe menopausal symptoms and are more frequently homemakers and physically inactive. They also have fewer years of education and are less likely to have ever used MHT. There were no differences between the two groups in terms of age, partner status, smoking, being sexually active, or the use of psychotropic drugs.

Table 1
Clinical characteristics of postmenopausal women with and without mild cognitive impairment.

Characteristics	MCI (no) ($n = 603$)	MCI (yes) ($n = 119$)	*p* values*
Age (years)	57.0 ± 5.7	56.2 ± 6.6	NS
Body mass index (Kg/m^2)	26.6 ± 4.9	27.8 ± 5.9	0.044
Years of education	14.5 ± 4.4	9.0 ± 5.3	0.001
Homemaker	30.0 (26.4–33.7)	60.5(51.6–69.4)	0.001
Number of children	2.4 ± 1.5	3.4 ± 2.5	0.001
Has a partner	73.1 (69.6–76.7)	70.6 (72.3–68.9)	NS
Sexually active	69.0 (65.3–72.7)	60.5 (51.6–69.4)	NS
Smoker	27.0 (23.5–30.6)	23.5 (15.8–31.3)	NS
Physical inactivity	48.9 (44.9–52.9)	70.6 (62.3–78.9)	0.001
Severe menopausal symptoms	32.5 (28.8–36.3)	45.4 (36.3–54.5)	0.007
MHT ever use	30.7 (27.0–34.4)	7.6 (2.7–12.4)	0.001
Psychotropic drug use	29.9 (26.2–33.5)	27.7 (19.6–35.9)	NS
Comorbidities	44.4 (40.5–48.4)	51.3 (42.2–60.4)	NS

Data are presented as mean ± standard deviations or percentages (95 % confidence intervals).
MCI: Mild Cognitive Impairment; MHT: Menopause Hormone Therapy; NS: non-significant ($p < 0.05$).
Severe menopausal symptoms: total MRS score ≥ 14 points.
* *p* values when women with MCI are compared to those without as determined with the Student's *t*-test; the Mann Whitney *U* test or the chi-square test as appropriate.

Table 2
Mild cognitive impairment in postmenopausal women according to the risk of sarcopenia (SARC-F).

Risk of sarcopenia[1]	MCI[2] *n* (percent)	OR (95 % CI)
No risk ($n = 606$)	78 (12.9 %)	1.00
Increased risk ($n = 116$)	41 (35.3 %)	3.70 (2.36–5.80)

OR, odds ratio; CI, confidence interval.
[1] A total SARC-F score ≥ 4 is indicative of an increased risk of sarcopenia.
[2] MCI, mild cognitive impairment as determined with a total MoCA score of ≤20 points.

In Table 2, one can observe that there was a significant increase in the percentage of women with MCI among those at higher risk of sarcopenia (total SARC-F score 4 or more). The prevalence of MCI increased from 12.9 % in women with no sarcopenia risk to 35.3 % among those at high risk, resulting in an OR of 3.70 (95 % CI: 2.36–5.80) for women with a total SARC-F score of 4 or higher. The SARC-F displayed a sensitivity of 84 %, specificity of 39 %, positive predictive value of 88 %, and a negative predictive value of 33 % at diagnosing MCI.

In a binary logistic regression model, MCI (MoCA ≤20 points) was used as the dependent variable, with the characteristics analyzed in Table 1 included as covariates. Quantitative variables were categorized based on the median. Table 3 indicates that having a total SARC-F score

Table 3
Risk factors associated with mild cognitive impairment in postmenopausal women: Binary logistic regression.

	Mild cognitive impairment
Characteristics	OR (95 % CI)
Risk of sarcopenia (SARC-F ≥ 4 points)	2.44 (1.50–3.95)
Homemaker	1.97 (1.25–3.10)
Years of education (≥ 14 years, median)	0.28 (0.16–0.47)
Menopause hormone therapy (ever use)	0.26 (0.13–0.54)

Variables introduced into the regression model: age, obesity, years of education, homemaker, number of children, partner, sexually active, smoker, physical inactivity, severe menopausal symptoms, MHT ever use, psychotropic drug use, comorbidities.
OR, odds ratio; CI, confidence interval.

≥ 4 was associated with a higher risk of MCI, with an OR of 2.44 and a 95 % CI of 1.50–3.95. Collinearity between the variables was dismissed, as all VIF values ranged from 1.046 to 1.258 (collinearity is considered present with VIF values >10). Apart from sarcopenia, being a homemaker was also associated with an increased likelihood of MCI. Protective factors in the model included MHT ever use and having a higher educational attainment.

4. Discussion

The present study found a significant link between the risk of sarcopenia (total SARC-F score ≥ 4 points) and MCI, indicating a potential cause-effect relationship. However, since this was a cross-sectional study, we cannot definitively establish a causal association. Our findings strengthen the hypothesis that sarcopenia could be an independent risk factor for cognitive impairment in postmenopausal women. It's important to note that even after thorough adjustment for other variables, the risk of MCI remains >2-fold in women at risk of sarcopenia compared to those without it.

Women could be at a higher risk for cognitive disorders such as dementia due to the decrease in estrogen levels after menopause [23]. This decrease in estrogen levels is linked to an increase in pro-inflammatory cytokines and a decline in muscle estrogen receptors, which can affect muscle strength and power. Estrogen also helps regulate carbohydrate and lipid metabolism, impacting skeletal muscle composition by mobilizing muscle glycogen and inducing lipid oxidation. Moreover, estrogen can directly influence muscle metabolism by binding to estrogen receptors in skeletal muscle, and indirectly by altering the secretion of growth hormone and insulin-like growth factor 1 [24].

The relationship between sarcopenia and cognitive decline is bidirectional. Loss of muscle mass can lead to reduced physical activity, which decreases the brain stimulation required to maintain optimal cognitive function [25]. Systemic inflammation, which is common in sarcopenia, may also contribute to the deterioration of brain functions. On the other hand, cognitive decline can limit the ability to engage in physical activities, which can exacerbate sarcopenia [26].

Sarcopenia has been suggested as a potential predictor of cognitive impairment in older adults. A study that monitored cognitively healthy individuals over five years found that those with poor muscle function had a 2.22 OR (95 % CI 1.05–4.72) for developing cognitive impairment [27]. Similarly, a study from Taiwan concluded that sarcopenia was a predictor for both global and specific domains of cognitive impairment in older adults [28]. Our study rendered similar results. We found that the SARC-F displayed a sensitivity of 84 %, specificity of 39 %, positive predictive value of 88 %, and a negative predictive value of 33 % at diagnosing MCI; thus, detecting at a higher rate of those ill but not those who are healthy. These results align with those reported by Lee et al. [29].

The present study found that besides sarcopenia, several other factors were associated with a higher risk of MCI. Women who were homemakers were at a greater risk of cognitive decline, possibly due to their lower education levels compared to women who work (9.0 ± 5.3 vs. 14.5 ± 4.4 years, $p = 0.001$). Educational attainment significantly influences cognitive test performance, which could explain in our study the lower MoCA scores observed among homemakers; situation that has been observed by others [30]. Additionally, socioeconomic factors, limited access to higher education, and less participation in mentally stimulating activities have been previously reported to be linked to a higher risk of cognitive decline [31]; supporting our results.

In our study, one of the protective factors associated with MCI was the ever use of MHT. Estrogen may prevent cognitive decline by augmenting hippocampal and prefrontal cortex function, reducing neuroinflammation, preventing degradation of estrogen receptors, decreasing oxidative damage to the brain, and increasing cholinergic and serotonergic function [32].

Our results demonstrating a lower association between MCI and MHT ever users are completely different from the results of the WHI Memory Study, which reported an increased, although not significant, risk of MCI associated with the use of MHT in both the estrogen-alone and estrogen-progestin groups, being ORs 1.34 (95 % CI, 0.95–1.89) and 1.25 (95 % CI, 0.97–1.60), respectively [33]. These findings align with a meta-analysis of six RCTs that used transdermal estrogens and progesterone, concluding that their use decreases cognitive decline in women with MCI [34]. The difference between our results and those of the WHI Memory Study may be due to the fact that most women in the latter study started their therapy after the age of 60, in contrast to our series in which only 8 women were over the age of 60. The divergent results between our study and the WHI Memory Study are compatible with the theory of the window of opportunity, according to which MHT would protect against cognitive deterioration if it is used before the age of 60; later on, it could be deleterious [35].

Our study also found that education can help protect against MCI. Educational level has been implicated epidemiological studies as one of the most widely accepted risk factors for dementia [36]. The effect of education on the risk of cognitive impairment has been explained with the paradigm of the “cognitive reserve”, a hypothetical construct that moderates the effects of age-related decline and pathological damage. It refers to the structural and dynamic capacities of the brain that buffer against atrophies and lesions. Tissue or functional loss in a particular brain region may be compensated by other neurons working harder to maintain, as much as possible, the same level of functioning. Cognitive activity strengthens the functioning and plasticity of neural circuits (software or dynamic cognitive reserve), increasing cognitive reserve and decreasing the risk of dementia [37].

The present study has strengths: first, it uses two validated and widely accepted instruments used to assess the probability of sarcopenia and cognitive impairment. Second, the fact that it is a multi-centre study neutralizes the local biases that a protocol carried out in one place could have. Participants from various healthcare settings, including both public and private sectors, were included, which enhances the generalizability of the findings. Third, all participants were assessed by physicians specializing in women's health, and rigorous statistical methods were used to control for various potential confounding factors.

However, it is important to note that while the results are valuable, they may not be representative of the Latin American population as a whole due to limited access to preventive health check-ups in the region. This introduces the possibility of selection bias.

The present study has several weaknesses. Firstly, its cross-sectional design does not allow us to draw conclusions about causality. Secondly, the study did not evaluate diet, which is known to be associated with cognitive health [38]. In addition, the focus on women in the late postmenopausal period (60.9 % of the total) may have led to inaccuracies in determining the age of menopause or certain aspects of their clinical history, given that the analyzed condition (MCI) is uncommon in premenopausal women. Lastly, the study lacked specificity regarding the type of used MHT (estrogens or progestogens), the route of administration, and the duration of this therapy.

Despite the mentioned limitations, the present study underscores the significance of using the SARC-F, a simple questionnaire to assess sarcopenia risk, as a way to predict cognitive decline in postmenopausal women. It also highlights the need to consider other contributing factors, such as being a homemaker, experiencing severe menopausal symptoms, and the number of children, as these factors may increase the risk of cognitive decline. The study identifies protective factors, including the ever use of MHT and higher educational attainment, which could be potential interventions to reduce cognitive decline in this population.

Contributors

María S. Vallejo contributed to study conception and design, and text preparation and revision.

Juan E. Blümel contributed to study conception and design, statistical analysis, and text preparation and revision.

Peter Chedraui contributed to study design, statistical analysis and text preparation and revision.

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Claudia Rey contributed to data collection and text revision.

Eliana Ojeda contributed to data collection and text revision.

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Carlos Escalante contributed to data collection and text revision.

Alejandra Elizalde contributed to data collection and text revision.

Maribel Dextre contributed to data collection and text revision.

Andrés Calle contributed to data collection and text revision.

Sócrates Aedo contributed with statistical analysis and text revision.

All authors reviewed and approved the final version and no other person made a substantial contribution to the paper.

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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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 interests.

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