Maturitas 206 (2026) 108855

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

Physical activity as an alternative or adjunct to menopausal hormone therapy for symptom management in women with primary ovarian insufficiency☆

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☆ This article is part of a Special issue entitled: 'Premature ovarian insufficiency' published in Maturitas.

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https://doi.org/10.1016/j.maturitas.2026.108855
Received 12 September 2025; Received in revised form 18 January 2026; Accepted 23 January 2026
Available online 24 January 2026
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ARTICLE INFO

Keywords:
Primary ovarian insufficiency
Menopause
Physical activity
Menopausal hormone therapy
Symptoms, quality of life

ABSTRACT

Background: Physical activity alleviates menopausal symptoms in women whose menopause occurs after the age of 45; however, its effect in primary ovarian insufficiency, which occurs before the age of 40, remains unknown.
Objective: To examine the association between physical activity, menopausal symptoms, and the use of menopausal hormone therapy in women with primary ovarian insufficiency.
Methods: We analysed data from 4708 participants from two studies conducted in 12 Latin American countries. After applying eligibility criteria, 564 women with primary ovarian insufficiency (351 idiopathic and 213 surgical) were included. Menopausal symptoms were assessed using a validated scale, and severe symptoms were defined according to established cut-offs. Physical activity was classified according to international recommendations for moderate-intensity activity. Logistic regression models were adjusted for sociodemographic, clinical, and lifestyle variables.
Results: The prevalence of severe menopausal symptoms was 39.2%, with no significant difference between idiopathic and surgical primary ovarian insufficiency. Women with severe symptoms were less likely to meet recommended levels of physical activity or to be current users of menopausal hormone therapy. In adjusted models, regular physical activity (OR 0.65; 95% CI 0.45–0.94) and current use of menopausal hormone therapy (OR 0.27; 0.17–0.42) were associated with a lower likelihood of severe symptoms, whereas obesity and use of psychotropic medication were associated with a higher likelihood.
Conclusions: Women with primary ovarian insufficiency who engage in regular physical activity or currently use menopausal hormone therapy report less severe menopausal symptoms. Regular exercise may be an important non-hormonal option for women who cannot or prefer not to use hormone therapy.

1. Introduction

Primary ovarian insufficiency (POI), often referred to as premature ovarian insufficiency in the literature, is a clinical condition characterised by the cessation of ovarian function before the age of 40, manifested by amenorrhoea, elevated gonadotrophin concentrations, and oestrogen deficiency [1]. Globally, POI is estimated to affect approximately 3.7% of women [2], though prevalence varies by geographic and socioeconomic factors. North America reports the highest prevalence (11.3%), followed by South America (5.4%). Rates are 5.3% in low- and middle-income countries compared with 3.1% in high-income settings. Overall, evidence suggests that the burden of POI has increased steadily over the past two decades [3].

POI has wide-ranging physical, psychological, and social consequences that substantially impair quality of life (QoL). A meta-analysis has shown that women with POI experience reduced health-related quality of life (HRQoL), particularly in the physical and sexual domains [4]. The condition is also associated with vasomotor symptoms such as hot flashes and night sweats, mood disturbances, insomnia, fatigue, and sexual dysfunction, often more severe than in women undergoing menopause occurs at a later age [5]. The emotional impact is considerable, with patients reporting confusion, sadness, loss of identity, low self-esteem, and in some cases, stigmatisation or are underestimation by healthcare professionals [6]. Chronic oestrogen deficiency further increases the risk of conditions including cognitive decline [7], osteoporosis [8], cardiovascular disease [9], and autoimmune disorders [10].

Menopausal hormone therapy (MHT) with oestrogens and progestogens, when the uterus is present, remains the primary approach for alleviating menopausal symptoms and preventing long-term complications associated with oestrogen deficiency [11]. Qualitative studies indicate that many women derive psychological and physical benefits from MHT, such as feeling younger or being better able to manage their menstrual cycle. Nevertheless, concerns about side effects persist, with cancer being the most frequently cited worry, followed by monthly bleeding (with MHT) and weight gain [12].

Despite its health benefits, many women decline or avoid MHT because of concerns about perceived side effects, negative perceptions, or misinformation regarding risks [13]. In this context, physical activity represents a valuable non-pharmacological therapeutic option. For women experiencing menopausal symptoms, a meta-analysis shows that exercise, particularly aerobic activity and yoga, can improve physical and psychological quality of life, although evidence for benefits in vasomotor or sexual domains is less consistent [14]. Resistance training increases muscle strength, enhances bone mineral density, and offers protection against osteoporosis [15]. In postmenopausal women, a randomised controlled trial demonstrated that exercise alone, even in the absence of MHT use, can reduce symptoms and improve physical and functional quality of life [16]. Similarly, a longitudinal study with an eight-year follow-up of peri- and postmenopausal women found that maintaining or increasing physical activity is associated with sustained QoL improvements [17].

It is noteworthy that most evidence on the effects of physical activity on menopausal symptoms derives from women undergoing menopause at the typical age. To date, no studies have specifically examined the impact of physical activity in women with POI. To address this evidence gap, the present study examined how habitual (non-structured) physical activity relates to quality of life in women with POI. Specifically, we examined the association between non-structured physical activity [18], MHT use, and menopausal symptoms in women with POI.

[1] Félix Ayala and Juan E. Blümel are joint first authors.

2. Methods

2.1. Study design and participants

This study used data from two REDLINC studies (Red Latinoamericana de Investigación en Climaterio, Latin American Research Network on Menopause) conducted across Latin America. REDLINC XII investigated the association between the type of menopause, spontaneous or surgical (including POI), and mild cognitive impairment (MCI), and included 1185 postmenopausal women (mean age 55.3 years) from nine countries, recruited between January and October 2023 [19]. REDLINC XIII explored the impact of severe menopausal symptoms on occupational well-being in midlife employed women, analysing data from 3523 participants aged 40–60 years, recruited between June 2024 and January 2025 across 30 healthcare centres in twelve Latin American countries [Vallejo et al.; manuscript under review].

For the current analysis, data from both studies were pooled, yielding a total sample of 4708 women. All participants were assessed during routine gynaecological consultations and self-reported being in good health, defined as the absence of clinically manifest disease or disabling conditions, along with adequate physical, mental, and social functioning for their age and social context, allowing them to perform daily activities without significant limitations. Participants were required to be literate in Spanish or Portuguese (Brazil). Most women had middle incomes and received care in either private or state-run clinical centres.

This pooled analysis specifically focused on otherwise healthy women with POI, either idiopathic or surgical. Exclusion criteria included pre- or perimenopausal status, age at menopause $\geq$40 years, history of hysterectomy without bilateral oophorectomy, previous chemotherapy or radiotherapy, body mass index (BMI) <18.5 kg/m^2, and sensory impairments (hearing or vision). Women with dementia, which could interfere with questionnaire comprehension, were also excluded. Eligible participants underwent assessment of general characteristics and menopausal symptoms.

2.2. Studied variables

2.2.1. Sociodemographic and general health variables

A broad range of sociodemographic, gynaecological, and health-related variables were collected. Age (years) and educational attainment (years of formal schooling) were recorded. Anthropometric measures included weight (kg), height (m), and BMI, calculated as weight/height^2 (kg/m^2). Obesity was defined as BMI $\geq$ 30 k/m^2 [20]. Reproductive and sexual health variables included parity (total number of children), partnership status (presence/absence of a stable partner), and recent sexual activity, defined as at least one episode of sexual intercourse in the preceding year (yes/no).

Menopausal status was determined according to STRAW+10 criteria and classified as pre-, peri-, or postmenopausal [21]. Current MHT use was documented (yes/no). Additional dichotomous variables were tobacco use (yes/no); physically active, defined as $\geq$150 min/week of moderate-intensity aerobic activity (i.e. brisk walking, cycling, light sports, dancing) [18,22]; use of psychotropic medication (antidepressants, hypnotics, or anxiolytics); and the presence of comorbidities (yes/no), defined as a current medical diagnosis and treatment for at least one of the following: dyslipidaemia, diabetes mellitus, or arterial hypertension.

2.2.2. Menopausal symptoms

Menopausal symptoms were assessed using the Menopause Rating Scale (MRS), a validated and internationally recognised instrument that evaluates both the presence and severity of climacteric symptoms. The MRS includes 11 items grouped into three domains: somatic (hot flushes/sweating, cardiac discomfort, sleep disturbances, joint and muscle pain), psychological (depressed mood, irritability, anxiety, mental or physical exhaustion), and urogenital (sexual problems, bladder dysfunction, vaginal dryness). Each item is rated on a five-point Likert scale (0 = not present to 4 = very severe). Domain scores are calculated by summing item responses, and the total MRS score corresponds to the sum of all domains. For this pooled analysis, severe menopausal symptoms were defined as a total MRS score $\geq$ 14 points [23]. Validated Spanish and Portuguese versions of the MRS were used to ensure cultural and linguistic appropriateness [24,25].

2.3. Statistical analysis

Statistical analyses were conducted using SPSS version 21.0 (SPSS Inc., Chicago, IL, USA). Continuous variables are presented as means $\pm$ standard deviations, and categorical variables as percentages with confidence intervals (CIs). Homogeneity of variances was tested with Levene's test ($p > 0.05$ indicating homogeneity), and data distribution was evaluated using the Kolmogorov–Smirnov test. Depending on distribution, continuous variables were compared using the Student's *t*-test (normal data) or the Mann–Whitney *U* test (non-normal data). Associations between categorical variables were analysed with chi-square tests, expressed as odds ratios (ORs) with 95% CIs.

To identify factors associated with severe menopausal symptoms (MRS $\geq$14 points), a logistic regression model was developed. A stepwise procedure was applied, retaining variables with $p < 0.10$ for inclusion in the final model. Model adequacy was assessed with the Omnibus and Hosmer–Lemeshow tests. Multicollinearity was evaluated using the Variance Inflation Factor (VIF), ensuring all values remained <10 (tolerance $\geq$0.1). Interaction terms were tested for statistically significant variables identified in bivariate analyses. For all analyses, a two-sided p value <0.05 was considered statistically significant.

2.4. Ethical considerations

The REDLINC XII protocol was reviewed and approved by the Ethics Committee of the Southern Metropolitan Health Service, Santiago de Chile, Chile (Memorandum 15/2023; 22 June 2023). The REDLINC XIII protocol was approved by the Ethics Committee of the University of Cartagena, Cartagena, Colombia (reference 178–26–11-24-1-1). Both studies adhered to the principles of the Declaration of Helsinki, and all participants were fully informed about study objectives and procedures and provided written informed consent before enrolment. This manuscript was originally drafted in Spanish and later translated into English. Grammar and style were refined with the assistance of Grammarly (www.grammarly.com), an AI-powered writing tool.

3. Results

Data were derived from the REDLINC XII and XIII studies, yielding a final analytic sample of 564 postmenopausal women with POI after application of exclusion criteria (menopause at $\geq$40 years, pre- or perimenopausal status, or hysterectomy without oophorectomy). Of these, 351 had idiopathic POI and 213 had surgical POI (Fig. 1).

As shown in Table 1, mean total MRS scores were similar between women with idiopathic and surgical POI (12.5 $\pm$ 9.7 vs. 13.1 $\pm$ 10.9; $p = 0.469$). Likewise, the prevalence of severe menopausal symptoms was nearly identical (39.3% vs. 39.0%; $p = 0.934$). Due to these non-significant differences, both POI groups were pooled for subsequent analyses.

When stratified by menopausal symptom severity (Table 2), women with severe symptoms (MRS $\geq$14; $n = 221$) differed significantly in several sociodemographic and clinical variables compared with those without severe symptoms ($n = 343$). They were less likely to be sexually active (61.5% vs. 74.3%; $p = 0.001$), currently use MHT (15.8% vs. 41.7%; $p = 0.001$), or meet World Health Organization (WHO) physical activity recommendations (44.3% vs. 58.6%; $p = 0.001$). Conversely, they had higher BMI (27.1 $\pm$ 5.1 vs. 25.6 $\pm$ 4.7 kg/m^2; $p = 0.001$), were

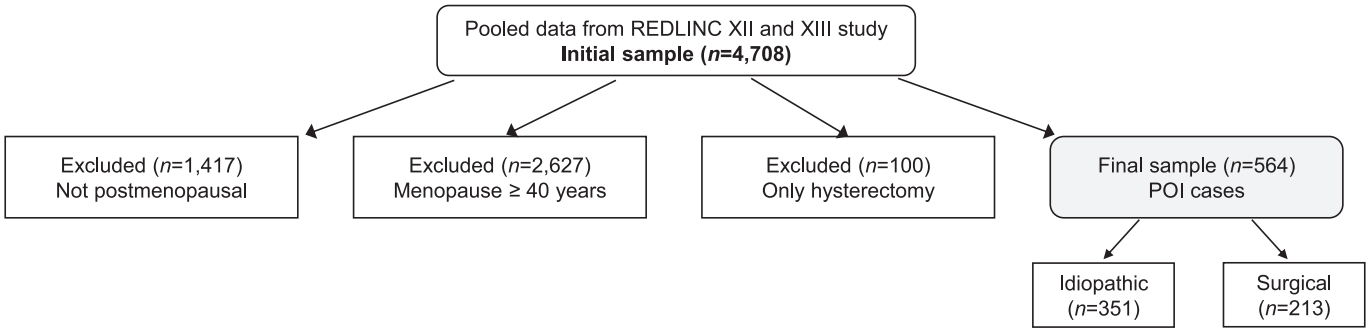


Fig. 1. PRISMA flow chart of included and excluded women with premature ovarian insufficiency.

Table 1
Total MRS scores and prevalence of severe symptoms among women with POI (idiopathic and surgical).

POI Types	N° women	Total MRS score	Severe menopausal symptoms*
Idiopathic POI	351	12.5 ± 9.7	39.3 (34.2–44.5)
Surgical POI	213	13.1 ± 10.9	39.0 (32.4–45.6)
Total	564	12.7 ± 10.1	39.2 (35.2–43.3)
p value		0.469[a]	0.934[b]

Data are presented as mean ± standard deviations or percentages (95% confidence intervals).
p values were determined with the Mann–Whitney *U* test[a] or the chi-square test[b].
POI, primary ovarian insufficiency; MRS, Menopause Rating Scale.
*Total MRS score ≥14 points.

Table 2
Sociodemographic and clinical characteristics of participants with POI according to severity of menopausal symptoms (*n*=554).

	Severe menopausal symptoms		
	No	Yes[1]	
Characteristics	n = 343	n = 221	*p* value*
Age (years)	51.2 ± 6.9	51.8 ± 8.2	0.324[a]
Postmenopausal (years)	**14.9 ± 7.7**	**15.2 ± 9.1**	**0.659[a]**
Years of education	**13.6 ± 4.8**	**13.1 ± 4.6**	**0.225[b]**
Number of children	**1.8 ± 1.6**	**2.0 ± 1.5**	**0.057[b]**
BMI (Kg/m^2)	**25.6 ± 4.7**	**27.1 ± 5.1**	**0.001[b]**
Has a partner	74.9 (70.3–79.5)	68.8 (62.6–74.9)	0.110[c]
Sexually active	74.3 (69.7–79.0)	61.5 (55.1–68.0)	0.001[c]
Current MHT use	41.7 (36.5–46.9)	15.8 (11.0–20.7)	0.001[c]
Physically active[2]	58.6 (53.4–63.8)	44.3 (37.7–50.9)	0.001[c]
Smoker	19.2 (15.1–23.4)	32.1(25.9–38.3)	0.001[c]
Current psychotropic drug use	36.2 (31.0–41.3)	49.8 (43.1–56.4)	0.001[c]
Presence of comorbidities	35.9 (30.8–41.0)	49.8 (43.1–56.4)	0.001[c]

Data are presented as mean ± standard deviations or percentage (95% confidence interval). [1]Total MRS score ≥ 14 points; Physically active was defined as ≥150 min of moderate-intensity physical activity per week. **p* values as determined with the Mann-Whitney *U* test[a], the Student's *T* test[b] or the chi-square test[c]. MHT, menopausal hormone therapy; BMI, body mass index; POI, primary ovarian insufficiency.

more frequently smokers (32.1% vs. 19.2%; $p = 0.001$), and reported greater use of psychotropic medications (49.8% vs. 36.2%; $p = 0.001$) and comorbidities (49.8% vs. 35.9%; $p = 0.001$). No significant differences were observed in age, years of education, parity, or years since menopause.

Multivariate logistic regression (Table 3) identified independent factors associated with severe menopausal symptoms. Current use of psychotropic medications (OR 2.40; 95% CI 1.64–3.51) and obesity (OR 1.78; 95% CI 1.11–2.86) were positively associated with severe symptoms. In contrast, being physically active (OR 0.65; 95% CI 0.45–0.94) and currently using MHT (OR 0.27; 95% CI 0.17–0.42) were associated with a lower likelihood of severe symptoms. Sexual activity demonstrated borderline protective effect (OR 0.70; 95% CI 0.47–1.02).

Table 3
Logistic regression analysis of factors associated with severe menopausal symptoms.

Factors	Severe menopausal symptoms* Odds ratio (95% CI)
Psychotropic drug use	2.40 (1.64–3.51)
Obesity (BMI ≥ 30 kg/m^2)	1.78 (1.11–2.86)
Sexually active	0.70 (0.47–1.02)
Physically active	0.65 (0.45–0.94)
Current MHT use	0.27 (0.17–0.42)

MHT, menopausal hormone therapy; CI, confidence interval. *MRS total score ≥ 14.

4. Discussion

In this cross-sectional study of women with POI, regular physical activity (≥150 min/week) and current MHT use were associated with lower odds of severe menopausal symptoms. In contrast, obesity and psychotropic medication use were linked to greater symptom severity, while sexual activity showed a trend toward reduced symptom severity.

Physical activity alleviates menopausal symptoms through multiple physiological pathways. A key pathway involves neuroendocrine and thermoregulatory regulation: exercise modulates autonomic nervous system activity, favouring parasympathetic dominance and reducing sympathetic overactivity, which contributes to vasomotor symptom reduction [26]. Resistance training increases β-endorphin release, which stimulate KNDγ neurons to secrete neurokinin B, thereby improving hypothalamic thermoregulation [27]. Exercise also enhances serotonergic, dopaminergic, and noradrenergic signalling, improving mood, sleep quality, and overall psychological well-being [28]. Additionally, physical activity modulates the hypothalamic–pituitary–adrenal axis, lowering cortisol levels and attenuating stress responses [29,30].

Oestrogen deficiency in POI accelerates bone and muscle loss, increasing risk of pain and frailty [31]. Resistance and impact exercise stimulate osteoblastic activity via IGF-1 and Wnt/β-catenin pathways while strengthening muscle, reducing musculoskeletal pain, and enhancing overall physical function [32]. These improvements may foster a more positive perception of general health among postmenopausal women and women with POI.

Physical activity also benefits cardiovascular and metabolic health. Regular exercise enhances insulin sensitivity, optimises lipid profiles, lowers blood pressure [33], and improves endothelial function and cerebral perfusion, collectively reducing fatigue, improving sleep quality, and preserving cognitive function [34,35]. These effects likely converge to improve health-related quality of life and alleviate the overall burden of menopausal symptoms.

While the benefits of physical activity in women experiencing

spontaneous menopause after age 40, such as improvements in cardiovascular health [27], bone density [36], and physical and psychological well-being, are well established [37], evidence regarding its effect on vasomotor and sexual symptoms remains inconsistent. For instance, a meta-analysis showed that aerobic exercise and yoga can enhance general health-related quality of life [38]; however, studies focusing specifically on women with POI are still lacking.

Our study reinforces the critical role of MHT in women with POI. The European Society of Human Reproduction and Embryology (ESHRE), American Society for Reproductive Medicine (ASRM), Centre for Research Excellence in Women's Health in Reproductive Life (CRE WHIRL), and the International Menopause Society (IMS) Guideline Group recommend continuing physiologic hormone replacement, ideally until the natural age of menopause (around 50 years), to mitigate long-term health risks [39]. Evidence suggests that conventional MHT risk observed in older postmenopausal women may not directly apply to women with POI, as the benefit-risk profile differs by age and timing. Current data support MHT's effectiveness in alleviating menopausal symptoms and highlight a potential window of opportunity in midlife for optimizing long-term health outcomes [40]. The use of psychotropic medications correlated with greater symptom severity, which may reflect the neuropsychiatric impact of oestrogen deficiency. Oestrogen acts by modulating key neurotransmitters (GABA, serotonin, and, dopamine), neurosteroids (allopregnanolone), and neuropeptides (kisspeptin, neurokinin B) that govern thermoregulation, mood, and cognition [41]. Disruption of these pathways can present as hot flushes, depressed mood, and anxiety—symptoms that often lead to psychotropic prescribing. Importantly, menopausal symptoms (including in POI) may be misclassified as primary depression, with antidepressants initiated without adequate consideration of MHT. Our data support systematic endocrine evaluation before—or alongside—psychotropic treatment in women with POI and severe symptoms.

Our study found that obesity was significantly associated with more severe menopausal symptoms in women with POI. Elevated BMI may aggravate vasomotor disturbances, limit physical activity, and thereby intensify the overall symptom burden while reducing quality of life [42]. Although not unique to POI, this finding underscores the importance of lifestyle interventions, particularly weight control and structured exercise, which remain promising strategies given the protective effect of physical activity observed in our cohort.

Although not statistically significant, sexual activity showed a trend toward reducing the risk of severe menopausal symptoms. This aligns with evidence from systematic reviews linking sexual health to overall physical and psychological well-being [43]. This observation may reflect better general well-being among sexually active women, or conversely, more severe menopausal symptoms contributing to reduced libido and sexual dysfunction. Given the bidirectional natures of this relationship, quality of life domains related to sexuality deserve closer attention. Interventions such as MHT and structured exercise may improve sexual function [44,45]. But further research is needed to clarify the impact of different types of physical activity, whether aerobic, resistance, or mind-body, on sexual health and overall well-being.

Several strengths should be highlighted. First, the relatively large sample size, covering participants from 12 Latin American countries, enhances generalizability and provides data from an underrepresented population. Second, the use of validated and culturally adapted instruments, including the MRS, strengthens the reliability of symptom assessment. Third, the application of robust multivariable logistic regression models, adjusted for key sociodemographic, behavioural, and clinical confounders, supports internal validity. Additional checks for collinearity and model fit (Hosmer-Lemeshow test), further underscore methodological rigour. Clinically, the study also suggests that hot flashes may serve not only as symptomatic indicator but also as potential markers of chronic disease risk.

Despite the above, several limitations must be acknowledged. First, the cross-sectional design precludes causal inference. Second, symptom evaluation relied on self-reported data, raising concerns about recall and social desirability bias. Third, selection bias may also be present, as participants were recruited from routine gynaecological visits and women with severe health conditions were excluded, potentially underrepresenting more vulnerable groups. Moreover, the lack of objective biomarkers (i.e. hormonal levels, inflammatory markers, or epigenetic age estimations) limits biological validation of the observed associations. Furthermore, it was not possible to determine whether the use of psychotropic medications was related to menopausal symptoms or to formally diagnosed psychiatric disorders. Finally, while physical activity showed a protective association, other interacting factors, particularly obesity and correlates, may have confounded its impact on symptom burden; additionally, the type of performed physical activity was not assessed, representing a relevant limitation for interpreting its impact on symptom burden.

In conclusion, this study is among the first to examine physical activity and menopausal symptom severity in POI. Future research should employ longitudinal or interventional designs to determine whether increased activity directly alleviates menopausal symptoms. Further investigation into the role of different exercise modalities (aerobic, resistance, or mind-body) on sexual health and quality of life is also warranted. In parallel, randomised trials comparing MHT modalities, doses, and durations, with outcomes such as quality of life, fractures, cardiovascular events, and cognition, are urgently needed, given the current reliance on surrogate endpoints and heterogeneous evidence.

Contributors

Félix Ayala contributed to study conception and design, text preparation and revision.

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

Ethical approval

This study involved the pooled data of participants of two studies of the REDLINC Network (Red Latinoamericana de Investigación en Climaterio, Latin American Research Network on Menopause) conducted across Latin America. The REDLINC XII protocol was reviewed and approved by the Ethics Committee of the Southern Metropolitan Health Service, Santiago de Chile, Chile (Memorandum 15/2023; 22 June 2023). The REDLINC XIII protocol was approved by the Ethics Committee of the University of Cartagena, Colombia (reference 178–26–11-24-1-1). Both studies complied with the principles of the Declaration of Helsinki. All participants were fully informed about study objectives and procedures and provided written informed consent before enrolment.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Declaration of Generative AI and AI-assisted technologies in the writing process

This manuscript was initially written in Spanish and subsequently translated into English. Grammar and style were refined with the assistance of Grammarly (www.grammarly.com). After using Grammarly, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Funding

This research received no specific grant from funding agencies in the public, commercial, or non-for-profit sectors.

Declaration of competing interest

The authors declare that they have no competing interest.

Data availability

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

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