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Review Article

Effectiveness and safety of hormone replacement therapy in the treatment of menopausal syndrome: a meta-analysis

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Abstract: Objective: To comprehensively evaluate the efficacy and safety of hormone replacement therapy (HRT) in managing menopausal syndrome through a meta-analysis. Methods: A systematic search was conducted across Pubmed, Embase, and Cochrane Library databases utilizing keywords such as "menopause", "hormone replacement therapy", and "menopausal syndrome" from their inception until July 2024. Randomized controlled trials (RCTs) related to HRT's role in treating menopausal symptoms were included. Two researchers independently reviewed literature, extracted data, and assessed study quality. Meta-analysis was performed using RevMan 5.3 software, incorporating calculations of standardized mean difference (SMD) and odds ratio (OR), using either fixed-effects or random-effects models. Results: A total of 24 studies, involving 5089 patients, were included in the analysis. Among these, 3062 patients received HRT as the HRT group, while 2027 patients without HRT comprised the control group. The pooled results: (1) In subgroups with estradiol-containing drugs, the change in Kupperman menopause index (KMI) in the HRT group was significantly smaller than that in the control group [SMD=-1.21 (-1.43, -0.98), *P*<0.001]; while in the subgroups didn't use estradiol as control intervention, the change in KMI in the HRT group was also smaller than that of the control group [SMD=-0.39 (-0.67, -0.10), *P*=0.007]. (2) The change in menopause-specific quality of life questionnaire (MENQOL) scores in the HRT group was significantly smaller than that of the control group [SMD=-0.43 (-0.60, -0.27), *P*<0.001]. (3) The improvement in estradiol (E_2) levels in the HRT group was greater than that of the control group [SMD=1.08 (0.66, 1.49), *P*<0.001]. (4) In the subgroup where the control intervention was placebo, the change in follicle stimulating hormone (FSH) level in the HRT group was significantly lower than that of the control group [SMD=-0.65 (-1.05, -0.24), *P*=0.002]; while in the subgroup where the control intervention was acupuncture, there was no significant difference of the change in FSH level between the HRT group and the control group [SMD=0.13 (-0.21, 0.47), *P*=0.45]. (5) The vaginal pH in the HRT group was significantly lower than that of the control group [SMD=-0.97 (-1.08, -0.87), *P*<0.001]. (6) The maturity change in vaginal exfoliated cells in the HRT group was greater than that of the control group [SMD=0.99 (0.82, 1.16), *P*<0.001]. (7) The improvement in lumbar bone density in the HRT group was significantly greater than in the control group [SMD=1.52 [1.33, 1.71], *P*<0.001]. (8) In the three subgroups with different drug regimens of estradiol plus norethindrone acetate, estradiol, and conjugated equine estrogen/estradiol, the improvements in hip bone density in the HRT group were all greater than in the control group [SMD=1.00 (0.72, 1.27), *P*<0.001/SMD=1.36 (1.11, 1.60), *P*<0.001/SMD=0.57 (0.11, 1.04), *P*=0.02]. (9) No significant difference in the changes in total cholesterol (TC) [SMD=0.20 (-0.25, 0.64), *P*=0.39], low-density lipoprotein (LDL) [SMD=0.29 (-0.16, 0.74), *P*=0.20], and high-density lipoprotein (HDL) [SMD=0.01 (-0.43, 0.46), *P*=0.95] between the two groups. (10) Treatment-emergent adverse events (TEAE) occurred equally in both groups [OR=0.93 (0.78, 1.13), *P*=0.48]. Conclusion: HRT can enhance the quality of life and vaginal health in women experiencing menopausal symptoms, elevate estrogen levels, and improve bone density, while demonstrating a favorable safety profile with no significant increase in adverse events or dyslipidemia risk. Further investigations involving multi-center, large-scale studies with long-term follow-up are warranted to substantiate this conclusion.

Keywords: Menopausal syndrome, HRT, efficacy, safety, randomized controlled trials, meta-analysis

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Introduction

Menopausal syndrome is a natural condition in women of reproductive age, characterized by a constellation of symptoms primarily associated with autonomic nervous system dysregulation and neuropsychological disturbances, which arise from hormonal fluctuations or declines during the peri- and postmenopausal phases [1]. Typically occurring between the ages of 45 and 55; the onset and severity of symptoms can vary significantly among individuals. Common manifestations include irregular menstruation alongside vasomotor symptoms and neuropsychological issues, such as hot flashes, sweating, irritability, anxiety, depression, insomnia, vaginal dryness, urinary frequency, urgency, and pain [2, 3]. These symptoms can profoundly affect both physical health and overall quality of life.

Maintaining physical and mental health during menopause has emerged as one of the foremost health challenges of the 21st century. Hormone replacement therapy (HRT), a widely employed approach for managing menopausal symptoms, regulates menstrual cycles and mitigates clinical manifestations through estrogen supplementation, having historically served as a preferred treatment option for numerous women [4, 5]. However, early 21st-century clinical research by the Women's Health Initiative demonstrated that, over an average follow-up period of 5.2 years, HRT was associated with an increased risk of coronary heart disease and breast cancer, thereby challenging its application and provoking extensive debate regarding its use and administration [6].

As clinical research advances, an increasing body of evidence regarding the risks and benefits of HRT has emerged, rendering discussions in this field more complex and challenging. Presently, controversies surrounding the efficacy and safety of HRT persist. In this context, the current study aims to synthesize high-quality research data through a meta-analysis to comprehensively and systematically evaluate the efficacy and safety of HRT, thereby providing clinicians and patients with critical information on the advantages and disadvantages of this treatment modality, while offering a robust framework for informed decision-making and the development of more rational and effective therapeutic strategies.

Methods

PROSPERO statement

This study has been registered with PROSPERO (CRD42024582282).

Eligibility criteria

Inclusion criteria: (1) Study design: randomized controlled trial; (2) Population: women experiencing menopausal syndrome in good general health; (3) Intervention: HRT, including estrogen, progesterone, or their combination, regardless of hormone type or administration method; (4) Comparator: conventional treatment, placebo, or other non-hormonal drugs for the control group; (5) Outcomes: at least one measurable outcome indicator must be included.

Exclusion criteria: (1) Interventions not involving HRT; (2) Studies focusing on phytoestrogens; (3) Literature unavailable in full text or with unextractable data; (4) Research with incomplete data; (5) Republished literature; (6) Literature based primarily on personal experience, expert opinions, or animal experiments.

Information sources

We conducted a comprehensive literature search on HRT for the treatment of menopausal syndrome across Pubmed, Embase, and Cochrane Library databases, supplemented with reference tracing. The search period extended from the inception of the databases to July 2024.

Search strategy

The search terms included "menopause", "hormone replacement therapy", "menopausal syndrome", "climacteric syndrome", "efficacy", "safety", and "randomized controlled trial". A combination of subject headings and keywords was used to formulate the search strategy, with adjustments tailored to the specific features of each database. For instance, the detailed search strategy for PubMed is outlined in **Table 1**.

Selection process

Two authors independently conducted the literature search. The titles and abstracts were initially screened to exclude studies that did

Table 1. Search strategies

Steps	
#1	("Menopause"[MeSH Terms] OR menopause* OR climacteric*)
#2	("Hormone Replacement Therapy"[MeSH Terms] OR HRT OR "estrogen replacement" OR "progesterone replacement")
#3	(efficacy OR effectiveness OR safety OR "side effects" OR "adverse events")
#4	(randomized controlled trial[pt] OR RCT OR clinical trial[pt] OR "randomized controlled trials" OR "clinical trials")
#5	#1 AND #2 AND #3 AND #4

not meet the criteria. Subsequently, the full abstracts were thoroughly reviewed to determine their inclusion based on predefined criteria. Upon completion of screening, the authors cross-validated their results, resolving any discrepancies through consultation with a third party if necessary.

Data collection process

Two authors independently extracted data using a standardized form. The collected data encompassed general information such as title, first author, publication year, country and region, and study type; study specifics including sample size, group allocation, drug type, treatment duration, outcome indicators and result measurement; and study characteristics like design details and measures to minimize bias. Following data extraction completion, cross-validation was performed, with any disparities resolved through consultation with a third party.

Data items

The primary outcome measures included changes in the Kupperman Menopause Index (KMI), Menopause-Specific Quality of Life Questionnaire (MENQOL) score, levels of estradiol (E_2), follicle-stimulating hormone (FSH), and treatment-emergent adverse events (TEAE). TEAE refers to serious adverse medical events or worsening of health status experienced by patients during or after hormone replacement therapy, such as vaginal bleeding, breast tenderness, and gastrointestinal reactions. The secondary outcome measures include vaginal pH value, maturity changes in the vaginal exfoliated cells, lumbar spine bone density, hip bone density, total cholesterol (TC), low-density lipoprotein (LDL), and high-density lipoprotein (HDL). For all outcomes except vaginal pH, continuous variable data were extracted, and the difference was calculated to derive the effect size for combined analysis.

Study risk of bias assessment

According to the quality assessment criteria for RCTs outlined in the Cochrane systematic review manual, the following aspects are evaluated: (1) method of random allocation; (2) implementation of allocation concealment; (3) utilization of blinding; (4) management of dropouts or withdrawals. For studies with withdrawals or dropouts, intention-to-treat (ITT) analysis was applied. A (Low Risk of Bias): All quality standards were fully met; B (Moderate Risk of Bias): One or more criteria were partially met, unclear, or not mentioned; C (High Risk of Bias): One or more criteria were not met or completely unmet.

Effect measures

Quantitative data and qualitative data were analyzed using standardized mean difference (SMD) and odds ratio (OR) as effect size statistics, respectively. All effect sizes were reported with 95% confidence intervals (CI).

Synthesis methods

The statistical analysis was conducted using RevMan 5.3 software. The heterogeneity of the included studies was assessed using the I^2 test. If $I^2 \leq 50\%$ or $P \geq 0.05$, studies were considered to show homogeneity, and a fixed-effects model was applied. If $I^2 > 50\%$ or $P < 0.05$, significant heterogeneity among the included studies was indicated. Initially, sources of heterogeneity were examined from both methodologic and clinical perspectives. Subgroup analyses were performed to identify potential sources of heterogeneity, while sensitivity analyses were conducted to address heterogeneity issues. In instances where heterogeneity could not be explained or resolved, a random-effects model was used for statistical analysis.

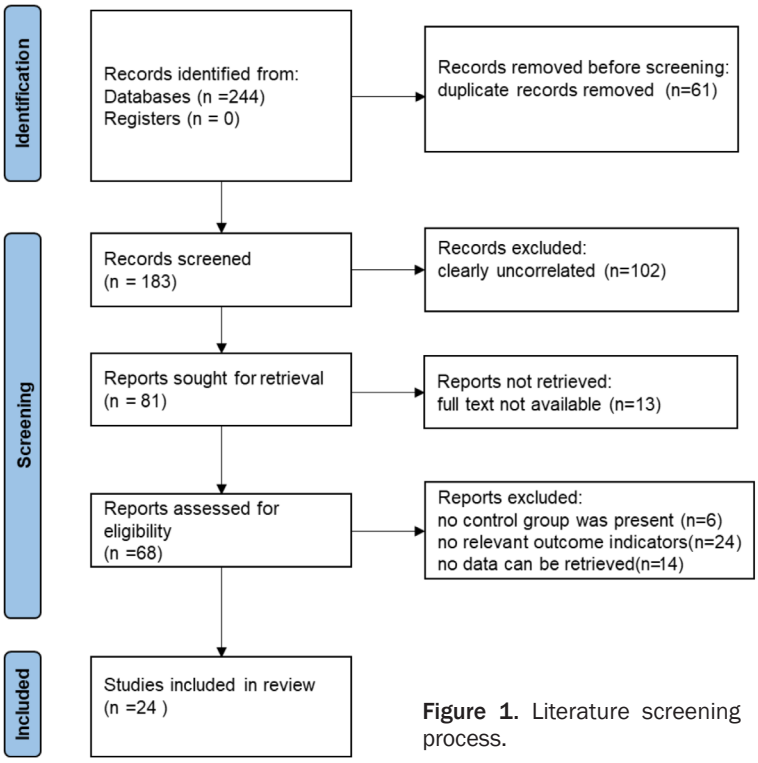

Figure 1. Literature screening process.

Reporting bias assessment

A funnel plot was employed to assess publication bias; asymmetry in the funnel plot was indicative of potential bias.

Results

Study selection

The search yielded a total of 244 articles, from which 61 duplicate articles were excluded using NoteExpress software. Following a preliminary review of titles and abstracts, 102 articles were discarded due to content mismatch. A subsequent full-text examination resulted in the exclusion of 57 articles: 13 lacked full text, 6 did not include a control group, 24 failed to present relevant outcome indicators, and 14 had data extraction limitation. Ultimately, 24 studies were included in the meta-analysis. The selection process is depicted in **Figure 1**.

Study characteristics and quality

The HRT group comprised sample sizes ranging from 8 to 575 cases, totaling 3062 cases; while the control group had sample sizes ranging from 6 to 240 cases, totaling 2027. Estradiol was the most frequently used drug in the HRT group, whereas placebo was the predominant comparator in the control group. The treatment duration varied from 4 weeks to 57 months, with a majority being 12 weeks. The minimum number of outcome indicators described was one, and the maximum was five. Six articles were classified as A level and eighteen articles as B level based on quality evaluation criteria for RCTs. The characteristics of the included articles are presented in **Table 2**.

Results of syntheses

Five studies provided data on KMI changes, with a total of 600 patients enrolled, including 347 in the HRT group and 253 in the control group. Significant heterogeneity was observed among the studies (I^2=83%, P<0.001). Subgroup analysis indicated that the presence of estradiol in HRT drugs was the primary source of heterogeneity. A fixed-effects model was used for the meta-analysis. Stratifying by interventions with or without estradiol-containing drugs, the results showed that HRT groups both using estradiol-containing drugs or not were associated with smaller KMI change compared to that of the control group [with: SMD=-1.21 (-1.43, -0.98), P<0.001; without: SMD=-0.39 (-0.67, -0.10), P=0.007], as shown in **Figure 2**.

Four studies reported data on MENQOL changes, involving 1019 patients (540 in the HRT group and 479 in the control group). Significant heterogeneity was found among the studies (I^2=74%, P=0.009). Yet no specific sources of this heterogeneity were identified. Employing a sequential exclusion method, it was found that excluding Sun's study reduced the I^2 value to 26%, with the P value exhibiting a consistent directional change, indicating greater robustness of the results. Consequently, a fixed-effects model was applied for the meta-analysis. The results showed that the change in MENQOL scores in the HRT group was significantly smaller than that of the control group [SMD=-0.43 (-0.60, -0.27), P<0.001]. See **Figures 3**, **4**.

Table 2. Study characteristics and quality

Study	Sample size		Drugs/measures		Treatment time	Outcome index	Quality evaluation
	HRT group	Control group	HRT group	Control group			
Wiklund 1993 [7]	112	111	Estradiol	Placebo	12 weeks	a, c	B
Bech 1998 [8]	68	37	Estradiol + Norethisterone acetate	Placebo	12 months	a	B
Delmas 2000 [9]	90	45	Estradiol + Norethisterone acetate	Placebo	24 months	h, i	B
Sørensen 2001 [10]	8	6	Estradiol + Norethinone acetate	Placebo	12 weeks	c, h	B
Rubinacci 2003 [11]	52	55	Estradiol + Norethisterone acetate	Placebo	96 weeks	h, i	B
Nielsen 2004 [12]	217	118	Estradiol	Placebo	24 months	h, i	A
Mizunuma 2010 [13]	45	15	Estradiol	Placebo	24 months	h	B
Cano 2012 [14]	105	48	Estriol	Placebo	12 weeks	e, f, g	B
Griesser 2012 [15]	264	132	Estriol	Placebo	12 weeks	e, f	B
Karp 2012 [16]	22	43	Estradiol	Placebo	12 weeks	e, f	A
Farr 2013 [17]	45	31	Conjugated equine estrogen/Estradiol	Placebo	48 months	h, i	A
Carmignani 2015 [18]	20	20	Estradiol + Norethinone	Placebo	16 weeks	c, d, e, f	A
Paoletti 2015 [19]	80	20	Norethisterone acetate/Drospirenone	Placebo	12 months	a, b	B
Honisett 2016 [20]	10	12	Estradiol	Placebo	20 weeks	c, d	B
Panazzolo 2016 [21]	21	19	Estradiol	Placebo	3 months	a, j, k, l	B
Constantine 2017 [22]	575	192	Estradiol	Placebo	12 weeks	e, g	B
Sun 2016 [23]	196	194	Conjugated estrogen	He Yan Kuntai capsule	12 months	b	B
Archer 2018 [24]	248	240	Estradiol	Placebo	12 weeks	e, g	B
Femandes 2018 [25]	18	20	Conjugated estrogen	Placebo	12 weeks	c, d, j, k, l	A
Kroll 2018 [26]	239	233	Estradiol	Placebo	12 weeks	e, g	B
Sriprasert I 2019 [27]	125	123	Estradiol	Placebo	57 months	c	A
Sriprasert II 2019 [28]	172	176	Estradiol	Placebo	57 months	c	A
Diem 2019 [29]	101	100	Estradiol	Placebo	12 weeks	b	B
Jiang 2020 [30]	66	66	Tibolone	Acupoint massage	4 weeks	a, d	B
Ren 2022 [31]	163	165	Estradiol + Dydrogesterone	Placebo	12 weeks	b, g	B

Note: HRT: hormone replacement therapy; a: Kupperman menopause index; b: menopause-specific quality of life questionnaire score; c: estradiol levels; d: follicle stimulating hormone levels; e: vaginal pH value; f: maturity changes in the vaginal exfoliated cells; g: treatment-emergent adverse events; h: lumbar spine bone density; i: hip bone density; j: cholesterol; k: low-density lipoprotein; l: high-density lipoprotein.

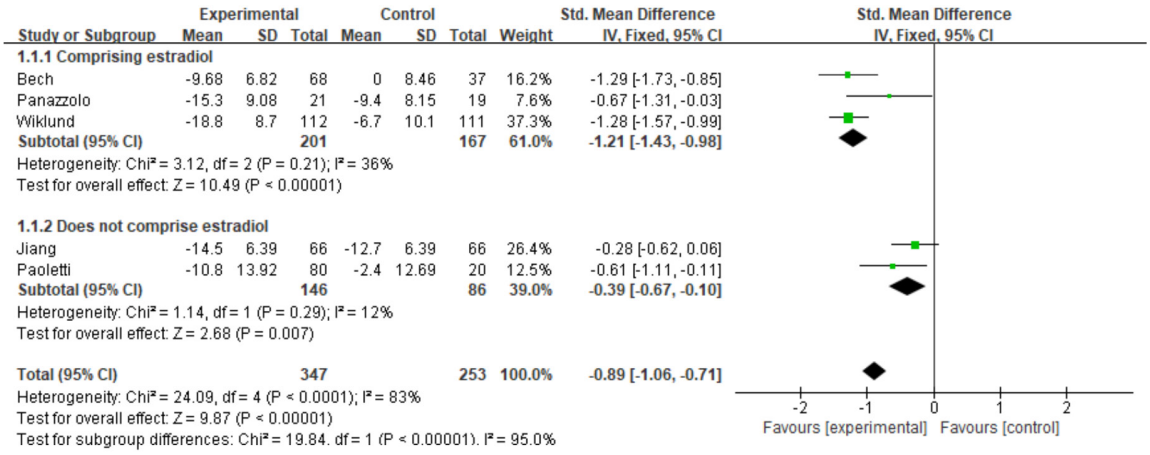

Figure 2. Forest plot of the comparison of changes in kupperman menopause index.

Six studies reported the changes in E_2 levels, involving 933 patients (465 in the HRT group and 468 in the control group). Significant heterogeneity was observed among the studies (I^2=84%, P<0.001), yet no specific sources of this heterogeneity were identified. The I^2 value exhibited minimal variation when individual studies were sequentially excluded, and the P values demonstrated a consistent directional change, as presented in **Table 3**, indicating that

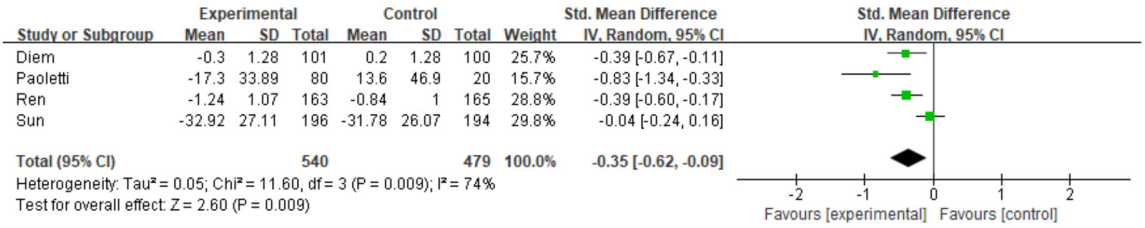

Figure 3. Forest plot of the comparison of changes in menopause-specific quality of life questionnaire scores.

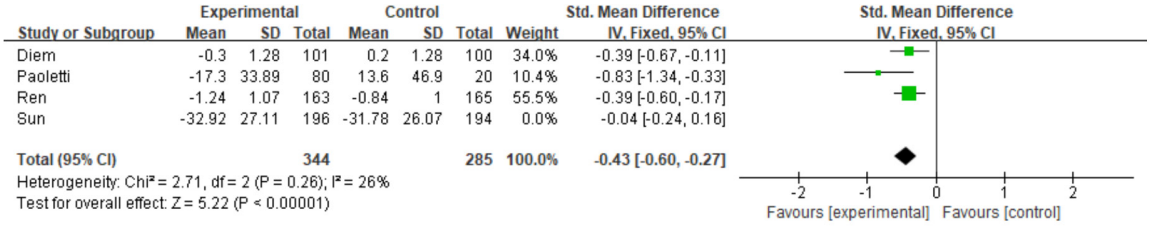

Figure 4. Forest plot of the comparison of changes in menopause-specific quality of life questionnaire scores (after exclusion).

Table 3. Sensitivity analysis

Elimination Study	I^2	SMD	*P*
Carmignani	86%	1.08 (0.61, 1.54)	<0.001
Femandes	77%	1.25 (0.89, 1.62)	<0.001
Honisett	86%	1.13 (0.69, 1.57)	<0.001
Sriprasert I	85%	0.99 (0.46, 1.52)	<0.001
Sriprasert II	78%	0.95 (0.50, 1.40)	<0.001
Sørensen	86%	1.03 (0.59, 1.46)	<0.001
Wiklund	81%	1.13 (0.66, 1.60)	<0.001

the results were relatively robust. Consequently, a random effects model was used for the meta-analysis. The results showed that the improvement in E_2 levels in the HRT group was greater than that of the control group [SMD=1.08 (0.66, 1.49), *P*<0.001], as shown in **Figure 5**.

Four studies reported data on FSH level changes, involving 232 patients (114 in the HRT group and 118 in the control group). There was significant heterogeneity among the studies (I^2=72%, *P*=0.01). Subgroup analysis indicated that the type of control intervention was the main source of heterogeneity, so a fixed-effects model was used for the meta-analysis. Subgroup analysis of the studies using placebo as control showed that the change in FSH level in the HRT group was significantly smaller than that of the control group [SMD=-0.65 (-1.05, -0.24), *P*=0.002]; while in the subgroup analysis of the studies using acupuncture as control intervention demonstrated that there was no significant difference in the change in FSH level between the HRT group and the control group [SMD=0.13 (-0.21, 0.47), *P*=0.45], see **Figure 6**.

Six studies examined vaginal pH value, involving 1,614 patients (898 in the HRT group and 716 in the control group). The heterogeneity among the studies was not significant (I^2=43%, *P*=0.12), so a fixed effects model was applied. The results showed that the vaginal pH value in the HRT group was lower than that of the control group [SMD=-0.97 (-1.08, -0.87), *P*<0.001], as shown in **Figure 7**.

Four studies reported data on maturity changes in vaginal exfoliated cells, involving 650 patients (408 in the HRT group and 242 in the control group). The heterogeneity among the studies was not significant (I^2=22%, *P*=0.28), so a fixed effects model was adopted. The results showed that the maturity change in vaginal exfoliated cells in the HRT group was significantly greater than that of the control group [SMD=0.99 (0.82, 1.16), *P*<0.001], as shown in **Figure 8**.

Six studies analyzed the changes in lumbar spinal bone density, involving 727 patients (457 in the HRT group and 270 in the control group). The heterogeneity among the studies was not

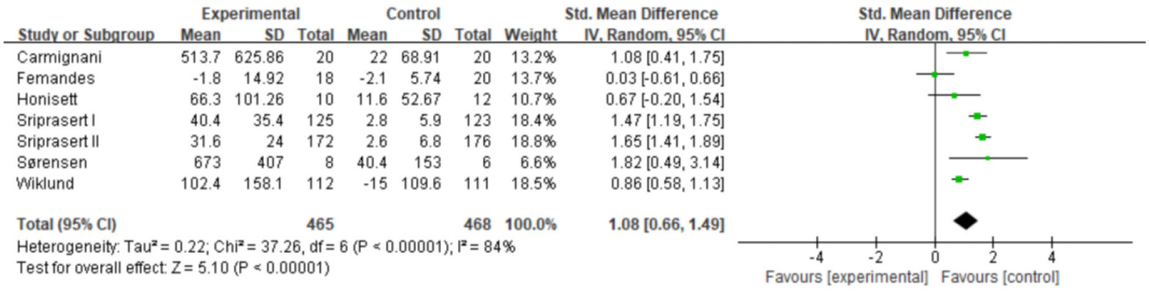

Figure 5. Forest plot of the comparison of changes in estradiol (E_2) levels.

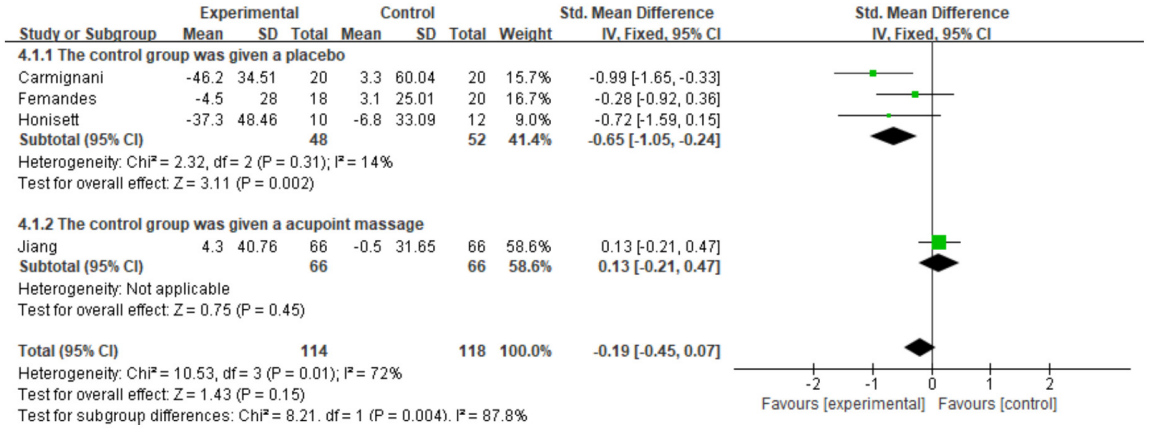

Figure 6. Forest plot of the comparison of changes in follicle stimulating hormone (FSH) levels.

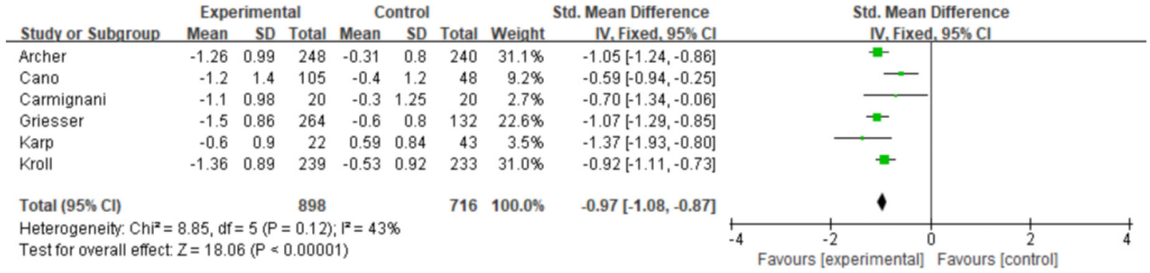

Figure 7. Forest plot of comparisons of vaginal pH values.

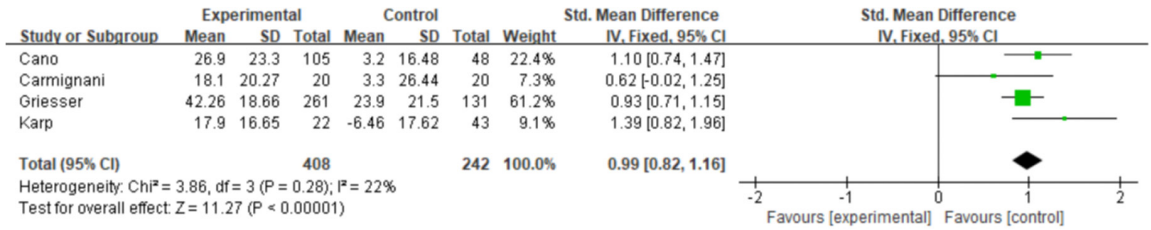

Figure 8. Forest plot of the comparison of maturity changes in vaginal exfoliated cells.

significant (I^2=64%, P=0.02). However, no specific sources of this heterogeneity were identified. Employing a stepwise exclusion method, we found that excluding Rubinacci's study reduced the I^2 value to 35%, and the P value exhibited a consistent directional change, indicat-

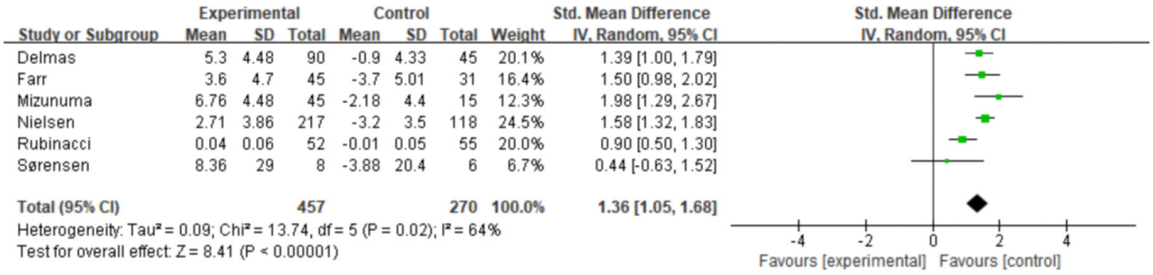

Figure 9. Forest plot of the comparison of changes in lumbar spinal bone density.

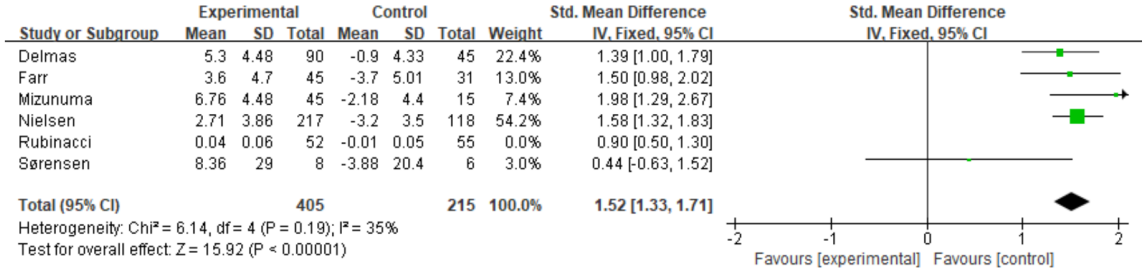

Figure 10. Forest plot of the comparison of changes in lumbar spinal bone density (after exclusion).

ing greater robustness of the results. Consequently, a fixed-effects model was used for the combined analysis. The results showed that the improvement in lumbar bone density in the HRT group was significantly greater than that in the control group [SMD=1.52 (1.33, 1.71), *P*< 0.001], as shown in **Figures 9**, **10**.

Four studies reported changes in hip bone density, involving 653 patients (404 in the HRT group and 249 in the control group). Significant heterogeneity was observed among these studies (I^2=69%, *P*=0.02). Subgroup analysis revealed that the type of hormone replacement therapy was the primary source of heterogeneity. Consequently, a fixed-effects model was employed for the meta-analysis. The results showed that in the three subgroups with different drug regimens - estradiol plus norethindrone acetate, estradiol, and conjugated equine estrogen/estradiol, the improvement in hip bone density in the HRT group were all greater than those of the control group [SMD=1.00 (0.72, 1.27), *P*<0.001; SMD=1.36 (1.11, 1.60), *P*<0.001; SMD=0.57 (0.11, 1.04), *P*=0.02], as shown in **Figure 11**.

Two studies analyzed changes in TC, LDL, and HDL levels, involving 78 patients (39 in the HRT group and 39 in the control group). The heterogeneity among these studies was not significant (I^2=0%, *P*=0.44/0.32/0.77), so a fixed-effects model was employed. The results indicated no significant difference in TC change [SMD=0.20 (-0.25, 0.64), *P*=0.39], LDL change [SMD=0.29 (-0.16, 0.74), *P*=0.20], or HDL change [SMD=0.01 (-0.43, 0.46), *P*=0.95] between the two groups, as shown in **Figures 12**-**14**.

Five studies reported on TEAE, involving 953 patients (569 in the HRT group and 384 in the control group). The heterogeneity among the studies was not significant (I^2=12%, *P*=0.34), so a fixed effects model was used. The results showed that TEAE occurred equally in both groups [OR=0.93 (0.78, 1.13), *P*=0.48], as shown in **Figure 15**.

Bias assessment

Funnel plots were created for studies reporting vaginal pH value, the maturity of vaginal exfoliated cells, and the results of TEAE analysis, as shown in **Figure 16A-C**. Most of the included studies were located within the 95% CI. However, there was noticeable asymmetry in the distribution of studies between the left and right sides, which suggests a potential for publication bias.

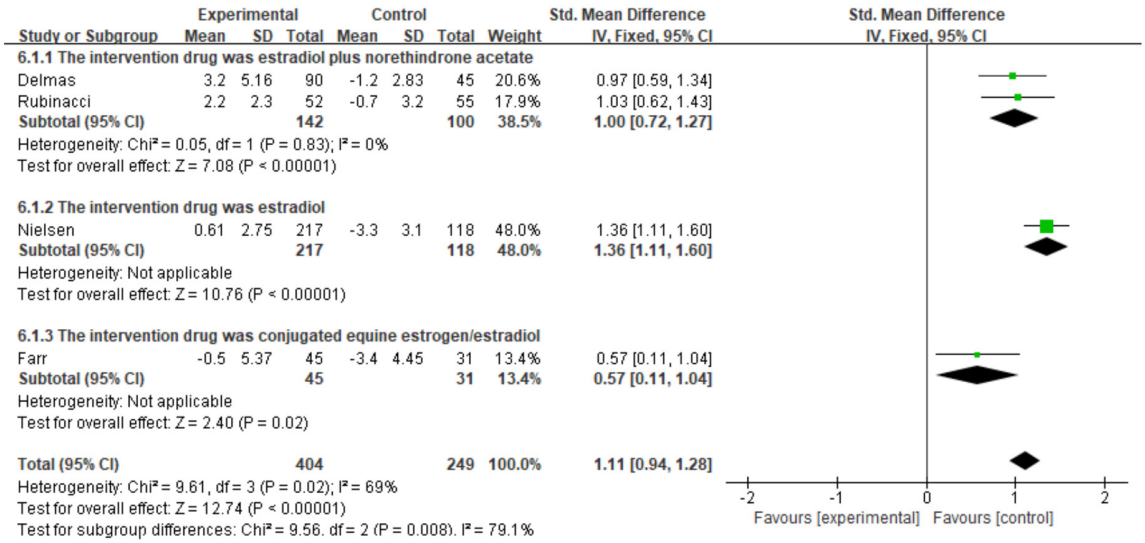

Figure 11. Forest plot of the comparison of changes in hip spinal bone density.

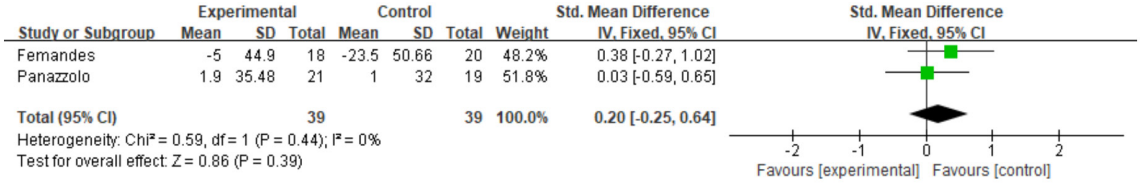

Figure 12. Forest plot of the comparison of changes in total cholesterol (TC).

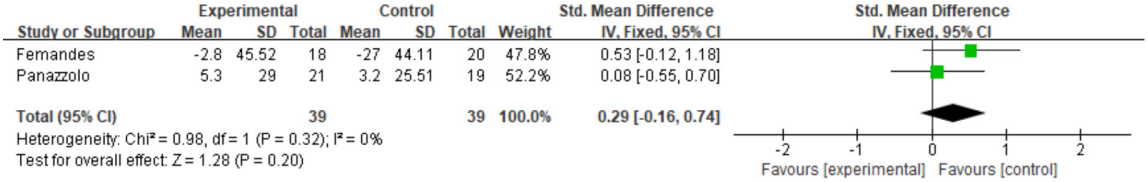

Figure 13. Forest plot of the comparison of changes in low-density lipoprotein (LDL) levels.

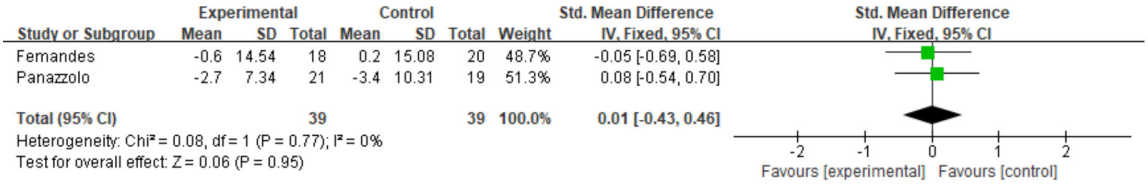

Figure 14. Forest plot of the comparison of changes in high-density lipoprotein (HDL) levels.

Discussion

The concept of quality of life is multifaceted and subject to diverse interpretations across different academic fields. In this study, we used two widely recognized questionnaires, modified KMI and MENQOL, to assess the quality of life in women experiencing menopausal syndrome symptoms. The KMI comprises 13 items encompassing a wide range of symptoms commonly associated with menopause, such as hot flashes, sensory disturbances, insomnia, anxiety, depression, dizziness, weakness, joint and muscle pain, headaches, palpitations, skin sen-

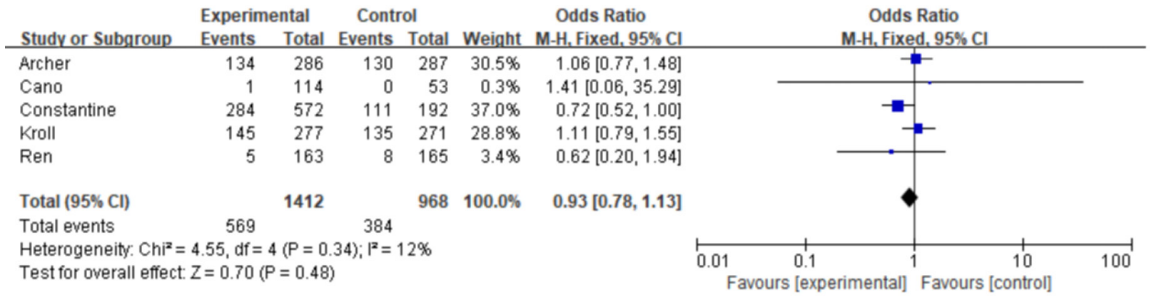

Figure 15. Forest plot of comparisons of treatment-emergent adverse events (TEAE).

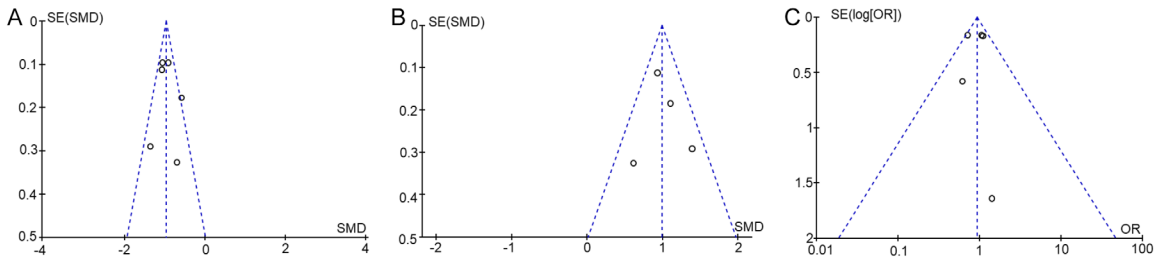

Figure 16. Funnel plot. A: A funnel chart based on the analysis results of vaginal pH; B: A funnel chart based on the analysis results of vaginal exfoliated cell maturity; C: A funnel chart based on the analysis results of treatment-emergent adverse events (TEAE).

sations, sexual dysfunction, and urinary system symptoms [32]. Meanwhile, the MENQOL questionnaire encompasses various dimensions including cardiovascular vasoconstrictive symptoms, psychosocial state, sexual function, and physiological state; each dimension further incorporates multiple specific symptoms or issues [33]. Our findings indicate that the HRT group exhibited smaller changes in KMI and MENQOL scores compared to the control group, suggesting a significant positive impact of HRT on alleviating menopausal symptoms and maintaining quality of life for women undergoing menopause. Nevertheless, quality of life is inherently subjective and influenced by a multitude of factors, including individual variability, cultural context, and social environment. Consequently, future efforts should aim to refine QoL evaluation tools to better capture the multifaceted nature of menopausal experiences.

The pathogenesis of menopausal syndrome is intricate and primarily driven by hormonal fluctuations resulting from diminished ovarian function. As estrogen levels decline, the equilibrium among the hypothalamus, pituitary gland, and ovaries becomes disrupted. This disruption leads to a reduction in pituitary feedback inhibition and an increase in gonadotropin secretion from the pituitary gland, causing dysregulation of both hypothalamic-pituitary axis and pituitary-endocrine gland regulatory mechanisms. Consequently, this imbalance results in disturbances of autonomic nervous system function, manifesting as various physiological and psychological adverse symptoms [34-36]. E_2 is the most significant and biologically active form of estrogen, primarily secreted by the ovaries, follicles, and placenta during pregnancy. The decline in ovarian function associated with menopause results in a decreased secretion of E_2 [37]. FSH is an essential for the maturation of follicles and the proliferation and differentiation of granulosa cells within the ovaries. In menopausal women, FSH levels are usually elevated [38]. Our study found that E_2 levels in the HRT group were significantly higher than that in the control group, indicating that HRT can effectively restore E_2 levels in women experiencing menopausal syndrome. In the studies with placebo as the control intervention, the change in FSH levels in the HRT group was lower than that in the control group, supports the notion that HRT can help normalize FSH levels by restoring the hormonal balance disrupted during menopause. However, in the studies

using acupuncture as the control, there was no significant difference in the FSH changes between the HRT group and the control group, which may be due to the small number of included studies and limited sample size, which are not sufficient to detect the difference between the two groups.

Menopausal women often experience changes in the appearance of the vaginal epithelium, characterized by a shift from a thick, wrinkled texture to a thin, pale appearance due to declining estrogen levels. Cytological analysis of vaginal smears, particularly from the upper 1/3 of the vagina, shows a reduced surface cell count and increased basal-apical cell proliferation in postmenopausal women. The assessment of vaginal epithelial maturation is commonly employed to quantify these cytologic alterations. As estrogen-dependent glycogen content gradually diminishes, there is a reduction in normal lactobacillus bacterial flora and an alteration in vaginal pH, leading to an elevated risk of urinary and genital tract infections known as postmenopausal urinary and genital tract syndrome [39, 40]. This investigation observed lower vaginal pH and greater epithelial maturation in the HRT group compared with the control group, suggesting that HRT can ameliorate urinary and genital tract symptoms in menopausal women. In a network meta-analysis conducted by Li et al. [41] on 29 randomized controlled trials and 8311 postmenopausal women with urinary and genital symptoms, vaginal estrogen was found to be less effective than laser therapy in improving symptoms such as vaginal dryness, sexual intercourse difficulty, and urinary incontinence, as well as in normalizing pH levels. The difference may be attributed to the predominantly placebo-based treatment given to the control group in this study. Therefore, it is essential to comprehensively consider various factors when interpreting these results and avoid drawing one-sided or absolute conclusions.

Estrogen plays a crucial role in maintaining bone health, acting as a receptor for bone cells and influencing bone metabolism by promoting the synthesis and deposition of the bone matrix while inhibiting bone resorption, thereby increasing bone density and enhancing bone strength [42, 43]. A decrease in E_2 levels is believed to be the main cause of postmenopausal osteoporosis [44]. With the decline in estrogen levels, the bone turnover rate increases, leading to an imbalance between bone resorption and formation, resulting in a decrease in bone volume, bone density, and ultimately, osteoporosis [45]. Our study found that the changes in lumbar spine and hip bone density observed in the HRT group were significantly greater than those in the control group, suggesting that HRT can effectively enhance bone density levels in postmenopausal women. A meta-analysis conducted by Szybiak W et al. [46] corroborated these findings, revealing that estrogen replacement therapy demonstrated more pronounced effects on increasing bone mass and reducing fracture risk compared to growth hormone in patients with osteoporosis associated with Turner syndrome. Additionally, another meta-analysis [47] indicated that postmenopausal hormone therapy can substantially improve bone density and recommended initiating treatment as early as possible for women without contraindications.

Menopausal lipid metabolic disorders are common physiologic changes associated with declining estrogen levels, characterized by an increase in TC and LDL levels, and a decrease in HDL levels. These changes may lead to a series of health problems, such as metabolic syndrome and cardiovascular diseases [48]. Estrogen plays a pivotal role in lipid metabolism by affecting lipid synthesis and regulation in the liver. It can promote the reverse transport of cholesterol, thereby lowering TC levels, increase HDL synthesis, and reduce the oxidative modification of LDL [49]. In this study, no significant differences were observed in TC, LDL, and HDL between the two groups. Although no significant advantage was found in improving the body's lipid metabolic disorders with HRT, this result indicates that the therapy does not cause abnormal lipid levels, showing a certain degree of safety.

The assessment of safety holds paramount importance when evaluating HRT for managing menopausal syndrome. This investigation revealed comparable incidences of TEAE across both groups, suggesting favorable safety profiles associated with HRT. However, Du et al. [50] conducted a meta-analysis comprising 15 RCTs involving 1243 patients and observed that the incidence of adverse reactions in patients treated with Kuntai capsule was lower than that in those receiving HRT. He et al. [51]

also demonstrated through a meta-analysis that the side effects of acupuncture therapy for menopausal syndrome were fewer compared to those associated with HRT. Therefore, considering individual variations and potential risks, it is imperative to cautiously select patients and closely monitor them during treatment. It is noteworthy that many risks do not directly impact a patient's life; however, in clinical practice, serious life-threatening issues such as increased risk of venous thrombosis and certain cancers should be taken into consideration. Nevertheless, this study lacks a comprehensive evaluation of this aspect.

Despite the rigorous methodology employed in this study, certain limitations should be acknowledged. First, while multiple RCTs were incorporated, potential heterogeneity among studies regarding patient characteristics, treatment regimens, and follow-up duration may influence the aggregated outcomes. Second, due to incomplete data reporting or missing information in some studies, the depth and precision of the study may be somewhat constrained. Furthermore, this investigation primarily concentrated on TAEA incidence; hence further exploration and monitoring are imperative for other potential side effects or long-term safety concerns. Last, it is essential to note that the findings of this study predominantly rely on existing literature with most studies possessing B-level quality. To confirm and extend these findings, high-quality, multi-center, large-sample, and long-term follow-up studies are needed in the future.

Conclusion

This study evaluated the effects of hormone replacement therapy compared to a control group on various aspects, including menopausal symptoms, hormone levels, urinary and reproductive system symptoms, bone density, lipid profiles, and complications. The findings indicate that hormone replacement therapy significantly enhances the quality of life for menopausal women, improves hormonal balance, alleviates urinary and reproductive system symptoms, and increases bone density. Importantly, it does not lead to abnormal lipid levels or an increase in TEAE, demonstrating both efficacy and safety. However, individual differences and cultural contexts must be considered when interpreting these results. Future research should focus on high-quality studies to validate and expand upon these findings to provide more precise guidance for clinical practice.

Disclosure of conflict of interest

None.

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