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Meta-analysis exploring the effectiveness and safety of different doses of estrogen in the treatment of osteoporosis in perimenopausal women in China

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Abstract. – OBJECTIVE: This study aims to systematically evaluate the effectiveness and safety of using different doses of estrogen in the treatment of perimenopausal osteoporosis in China.

MATERIALS AND METHODS: Computer searches of the Cochrane Library, PubMed, Embase, CBM, CNKI, WanFang Date, and VIP databases were conducted. Randomized Controlled Trials (RCTs) on different doses of estrogen for the treatment of osteoporosis in Chinese perimenopausal women were searched for the period 01/01/2000-06/09/2022. Document screening and data extraction were completed independently by 2 researchers and assessed using the Cochrane recommended risk bias assessment tool for RCTs. The software used for analysis in this study was Stata, version 16.0.

RESULTS: A total of 10 RCTs with a cumulative total of 804 patients were included. Meta-analysis results showed that low doses of estrogen were more effective in improving patient outcomes [OR=0.521, 95% CI (0.300-0.907), z = 2.31, $p \leq 0.05$] and bone mineral density [SMD = -0.218, 95% CI (-0.42,-0.016), z = 2.11, $p \leq 0.05$] was not superior. For bone metabolism and sex hormone indicators, the standard dose group had a slight advantage, but the difference was small ($p > 0.05$) and not statistically significant. With regard to safety, the incidence of adverse reactions was higher with the standard dose of estrogen.

CONCLUSIONS: In China, standard doses of estrogen are used for clinical effectiveness. However, vigilance must be maintained for potential safety concerns that may arise during treatment.

Key Words:
Estrogen, Perimenopause, Efficacy, Safety, Meta-analysis.

Abbreviations

Randomized Controlled Trials (RCTs), Osteoporosis (OP), Hormone replacement therapy (HRT), estrogen-progestin (EPT), trial registration number (NCT), standardized mean difference (SMD), confidence intervals (CI), Calcium (Ga), Serum alkaline phosphatase (ALP), Urinary calcium/creatinine ratio (Ca/Cr), Follicle stimulating hormone (FSH), Estradiol (E2).

Introduction

Osteoporosis (OP) is a metabolic bone disease characterized by increased bone turnover and decreased bone mass[1]. The main clinical manifestations are bone pain, fatigue, or fractures[2]. The prevalent population is mainly perimenopausal women and older men[3]. The latest US medical guidelines predict that by 2030, the number of people suffering from osteoporosis and bone loss in the US will reach 71 million, with a prevalence of 50% among white women and over 2 million fractures per year[4]. OP has emerged as a significant health concern that necessitates collaborative efforts among nations worldwide for its mitigation. The prevalence of osteoporosis in post-menopausal women over 40 years of age in China is as high as 32.5%[5], which places a heavy burden on national healthcare expenditure and seriously endangers the health and quality of life of middle-aged and elderly women.

Estrogen is a steroid hormone with growth-promoting and bone-metabolizing effects[6]. The NF-κB receptor activator (RANK), (NF-κB receptor)-osteoprotegerin (OPG) axis is disrupted as women enter perimenopause and ovarian function begins to decline, making it an important cause of osteoporosis or bone loss in perimenopausal women[7]. Hormone replacement therapy (HRT) is currently the main treatment for osteoporosis in perimenopausal women[8], but its use is still a topic of controversy in the field

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of medicine[9]. The use of estrogen is associated with an increased risk of intrauterine and breast cancer in women[10]. Therefore, estrogen-progestin (EPT) combinations and lowered estrogen doses are often used clinically to reduce the risk. It is generally accepted in Western medicine that 0.625 mg is the lowest effective dose of estrogen (i.e., the standard dose)[11]. However, the issue of estrogen dosing has been controversial in China due to the enormous differences in genetics, living environment, and body composition between the Chinese and Western populations[12]. There have been calls from Chinese experts for a nationally appropriate exploration of the norms for its use[13]. This study is based on the controversy that there is no uniform standard for the dose of estrogen in China. Our study aims to determine the effectiveness and safety of different doses of estrogen in treating osteoporosis in perimenopausal Chinese women. We collected randomized controlled trials published in the last 20 years and analyzed the data to provide evidence-based recommendations for the appropriate use of estrogen in this population. Our hope is that this study will help inform medical practitioners and improve the quality of care for women suffering from osteoporosis.

Materials and Methods

Literature Search

The search strategy was developed in accordance with the requirements of the Cochrane Collaboration Network System Evaluation. Chinese search terms included "osteoporosis", "bone mineral density", "bone mass", "osteoporosis", "bone mineral density", "bone mineral density", "estrogen", "female hormone", "estradiol", "randomized RCT", "randomized controlled trial", etc. The search was conducted on the Cochrane Library (Cavendish, London, UK), VIP database (Beibu District, Chongqing, China), Embase (Radarweg, Amsterdam, Netherlands), CBM (Dongcheng District, Beijing, China), CNKI (Haidian District, Beijing, China), Wang-Fang Date (Haidian District, Beijing, China) and PubMed (Bethesda, MD, USA).English search terms include "osteoporosis", "bone loss", "age related osteoporosis", "estrogen", "agents", "estrogenic", "compounds", "randomized controlled trial" etc. A combination of manual searches and other methods was also used to collect the literature as comprehensively as possible.

Inclusion Criteria

Inclusion criteria were articles accessible worldwide, RCTs on the use of estrogen for the treatment of osteoporosis in perimenopausal women, with Chinese and English as restricted languages.

Intervention

The intervention included a minimum duration of 6 months, no less than 15 patients in each group, the dose administered was 0.625 mg in the standard dose group and approximately 0.3 mg or lower in the low dose group. Administration is oral or transdermal. No change in drug dose or other medication was allowed during the trial.

Quality Evaluation Criteria

The criteria for evaluating the methodological and literature quality of the included studies in this study were completed by two evaluators. Cochrane (Cavendish, London, UK) version 5.1.0 was used. The main elements were the generation of randomized sequences, allocation concealment, blinding of patients and implementers, blinding of outcome evaluation implementation, completeness of outcome data, and selective reporting; the risk of bias results were classified into three levels: high risk, low risk, unclear risk.

Outcome (observation) indicators: at least one of the following results were reported: (1) bone mineral density measurements at different sites. (2) Kupperman score. (3) Related adverse effects. (4) Bone metabolism-related indicators. (5) Sex hormone-related indicators. (6) Endometrial and breast changes.

Exclusion Criteria

(1) Types of studies not clearly accounted, e.g., non-RCT, irregular experimental design, incorrect relevant evaluation indicators, etc. (2) Literature for which reliable data could not be extracted. (3) Literature with reviews, meta-analyses, abstracts, and duplicate publications. (4) Literature that cannot be downloaded in full. (5) Study subjects with non-perimenopausal osteoporosis or reduced bone mass or study subjects with severe combined organ failure. (6) Study duration < 6 months.

Data Extraction

The procedure involving literature screening, quality evaluation, and data extraction was independently conducted by two evaluators with a professional expertise. In the event of significant disagreement, the decision was resolved by

agreement between the 2 or with the assistance of a third evaluator. The extracted data contained the following: date of publication, authors, duration of treatment, trial registration number (NCT), interventions, and information about the patients included in the study.

Statistical Analysis

The analysis software used in this study was Stata 16 (College Station, Texas, USA). The statistical analysis for continuous variables employed the standardized mean difference (SMD), while the primary effect measure used was the odds ratio (OR) alongside the SMD value. Additionally, 95% confidence intervals (CI) were provided for each effect measure. Heterogeneity among outcomes was analyzed using Cochrane's Q test, and quantitative I^2 was employed to determine the presence of heterogeneity. If there was heterogeneity ($p > 0.1$ and $I^2 \leq 50\%$), then a fixed-effects model was used. If heterogeneity exceeded a significant threshold ($p \leq 0.1$ or $I^2 > 50\%$), a random-effects model was applied following the exclusion of the impact of pertinent substantial heterogeneity. Conversely, when heterogeneity was within acceptable limits, either a subgroup analysis was conducted, or a descriptive study was performed. For publication bias, the main analyses were performed using funnel plots and Begg's rank correlation test, and differences were considered statistically significant if $p < 0.05$.

Results

Literature Search Results

A total of 9,655 papers were obtained following the initial review, and upon in-depth examination and rigorous evaluation, which entails reading the full text of all 9,655 articles, only 10 RCTs[13,15-23] were ultimately incorporated. These comprised eight articles in the Chinese language and two in English. The screening process is shown in Figure 1, which clearly indicates that

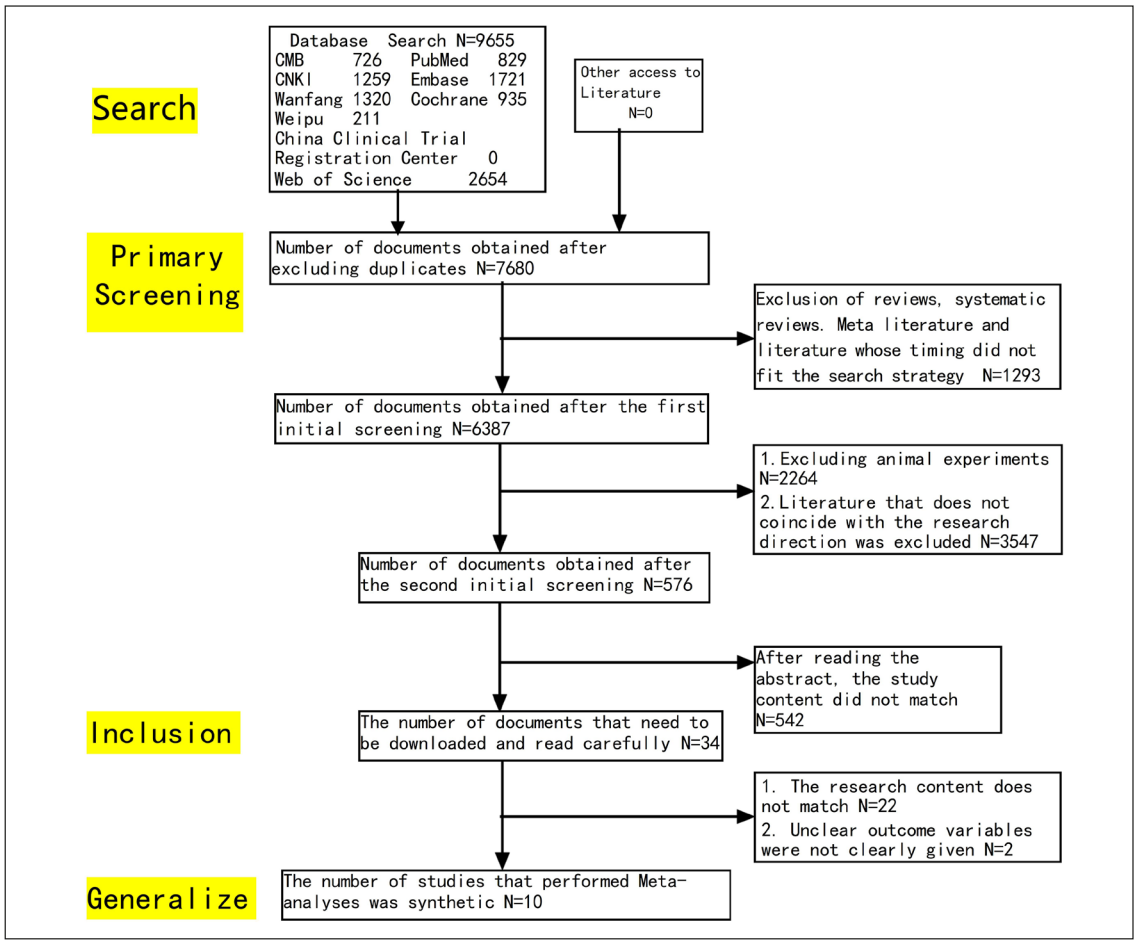


Figure 1. Literature search process.

this research has followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.

Results of the Inclusion Study Table and Risk of Bias Evaluation

The ten papers were published between 2000 and 2022, with a total of 804 patients. The included studies were all RCTs. Treatment cycles were all > 6 months. Among the reviewed studies, seven[12,15,17-20,22] employed oral administration, while three[16,21,23] utilized transdermal administration. It is noteworthy that both oral and transdermal estrogen supplementation demonstrated equivalent efficacy, and the effective dosage remained consistent at 0.625 mg[14]. Furthermore, in nine[12,15-19,21-23] of the studies, a standard dose of approximately 0.625 mg was employed, and a lower dose of approximately 0.3 mg was utilized. The active component of estrogen in the transdermal and other studies aligned with the standard dosage of 0.625 mg and the lower dosage of 0.3 mg. One study employed lower doses of 1 mg and 2 mg, as indicated in Table I. Generation, completeness of outcome data, selective reporting, and other bias were all low risk. The allocation concealment was not explicitly stated in 6 articles[12,16,17,19,21,23] and was low risk in 4 articles[15,18,20,22]; blinding of patients and implementers, and blinding of outcome evaluation were low risk in only 1 article[20] because blinding was difficult in this study and was explicitly stated as double-blind. Thus, only 1 article[20] was low risk, and the rest were high risk; the overall quality of the literature included in this study was high (Figures 2 and 3).

Meta-Analysis

In the assessment of bone mineral density, eight papers were included in this study[12,16,17,19,20]. The analysis for heterogeneity considered $I^2 < 50\%$, Q-test: $p > 0.1$. The results indicated no heterogeneity between studies, so a fixed effect model was chosen.

A sensitivity analysis of the eight papers[15-19,21-23] included in this study revealed that none of the literature significantly influenced the analysis results, as demonstrated in Figure 4. This finding underscores the robustness and stability of the study's outcomes. The combined data from the eight studies[15-19,21-23] produced an SMD = -0.210, 95% Cl (-0.402 - -0.017), z = 2.14, $p < 0.05$, which is statistically significant. The BMD treatment score for the low-dose group was 0.218 points lower than that of the standard-dose group, suggesting an advantage for the standard-dose group in improving BMD (Figure 5). The funnel plot in Figure 6 displays the bias assessment results. Begg's bias test yielded $p > 0.05$. This result indicates the absence of publication bias in this study. Therefore, the standard dose of estrogen was more effective in enhancing the bone density of the patients.

Efficacy

The present investigation, which included three papers[16,21,22], exhibited minimal heterogeneity, as indicated by an $I^2 < 50\%$. Additionally, the Q-test resulted in a $p > 0.1$, confirming the absence of significant heterogeneity among these studies. Therefore, the fixed effects model was chosen. The results of the sensitivity analysis showed that no study was seen to cause significant interference with the results of the analysis, as shown in Figure 7, which had excellent stability. The OR was 0.521, 95% CI (0.300-0.907) z = 2.31, $p < 0.05$, which was statistically significant. It is suggested that the efficacy of using standard doses of estrogen is more significant. Due to the limited number of studies, a funnel plot was not generated, as depicted below. However, Begg's bias test yielded $p > 0.05$, indicating the absence of publication bias among the selected literature for this study (Figure 8).

Bone Metabolism-Related Indicators

Calcium (Ca)

The two selected papers[15,22] were not heterogeneous ($I^2 = 0\%$, $p = 0.757$), so a fixed effects model was used, showing that the low dose of estrogen was 0.017 points lower than the standard dose score, $p > 0.05$ and was not statistically significant (Figure 9).

Serum alkaline phosphatase (ALP)

There was no heterogeneity between the three selected[16,20,21] papers ($I^2 = 0\%$, $p = 0.976$), so a fixed effects model was used. The results showed that the MD of estrogen at the low dose was 1.642 points lower than the standard dose. The difference was small, $p > 0.05$, and not statistically significant (Figure 10).

Urinary calcium/creatinine ratio (Ca/Cr)

there was no heterogeneity between the three selected[16,20,21] papers ($I^2 = 0\%$, $p = 0.999$), so a

Table I. Basic characteristics of the included studies.

Inclusion in the study	Age (T/C)	N	Course of disease	Interventions	Pharmaceutical industries	Method of administration	Closing indicators
Chen and Zhu[12] 2003	54 ± 6	40	1.8 ± 1.0	Estrogen 0.3 mg + MPA 2.5 mg + Ca-D1 600 mg	Wyeth harmaceutical P Co., Ltd (Wuzhong District, Jiangsu China)	Oral	(1)(5)(6)
	54 ± 6	40	1.8 ± 1.0	Estrogen 0.625 mg + MPA 2.5 mg + Ca-D1 600 mg		Oral	
Wu[15] 2021	50.2 ± 4.39	42	0.2 ± 0.17	Estradiol Valerate Tablets 0.5 Tablets + 200 mg Progesterone Capsules	Estradiol: Bayer Ltd. (Huangpu District, Guangdong, China) Progesterone: Xianju Pharmaceutical Co., Ltd (Xianju, Zhejiang, China)	Oral	(1)(2)(3)(4)
	49.0 ± 3.78		42	0.3 ± 0.12 1 tablet + 200 mg progesterone capsules	Estradiol Valerate	Oral	
Zhang et al[16] 2002	55 ± 3.4	19	1.9 ± 0.8	Demesol 25 + MPA 2 mg + Calcium carbonate tablets 500 mg	Rottapharm Biotech S.r.l. (Via Valosa di Sopra, Monza, Italy)	Transdermal	(1)(2)(5)(6)
	53.3 ± 2.8	18	2.2 ± 1.0	Demesol 50 + MPA 2 mg + calcium carbonate tablets 500 mg		Transdermal	
Zhao et al[17] 2011	54.4 ± 4.27	30	2.5 ± 1.05	Estrogen 0.3 mg + MPA 2 mg + Ca-D1 1 g	Wyeth Pharmaceutical Co., Ltd (Wuzhong District, Jiangsu China)	Oral	(2)(3)(6)
	55.3 ± 5.12	30	2.6 ± 0.99	Estrogen 0.625 mg + MPA 2 mg + Ca-D1 1 g		Oral	
Zhang et al[18] 2020	48.5 ± 3.56	28	4.1 ± 1.34	Estrogen 0.3 mg + 400 mg progesterone	Estrogen: Newbridge Co. (Kildare, Leinster, Estrogen: Newbridge Ireland); MPA: Aisheng Pharmaceutical Co., Ltd (Qiantang District, Zhejiang, China); Ca-D1: Solvay Pharmaceuticals (Schepersweg, Herten, Netherlands)	Oral	(2)(4)(6)
	49.8 ± 3.68	26	3.4 ± 1.08	Estrogen 0.625 mg + 400 mg progesterone		Oral	

Continued

Table I *(Continued)*. Basic characteristics of the included studies.

Inclusion in the study	Age (T/C)	N	Course of disease	Interventions	Pharmaceutical industries	Method of administration	Closing indicators
Weng[19] 2007	52.0 ± 6.2	46	6.2 ± 4.1	Estrogen 0.3 mg + MPA 2 mg + Ca-D1 1 g	Estrogen: Wyeth Pharmaceutical Co., Ltd (Wuzhong District, Jiangsu China); MPA: Xianju Junye Pharmaceutical Co., Ltd (Xianju District, Zhejiang, China); Ca-D1: Wyeth Pharmaceutical Co., Ltd (Wuzhong District, Jiangsu China)	Oral	(2)(3)(4)(6)
	52.0 ± 6.2	46	6.2 ± 4.1	Estrogen 0.625 mg + MPA 2 mg + Ca-D1 1 g		Oral	
Haines et al[20] 2003	49.2 ± 5.1	50	> 6 months	Estrogen 1 mg	Novo Nordisk A/S (Smørmosevej, Bagsværd, Denmark)	Oral	(2)
	48.2 ± 4.7	52	> 6 months	Estrogen 2 mag		Oral	
Yang et al[21] 2007	49.1	20	-—	0.75 mg 17-betaE2 gel + calcium carbonate 500 mg	Besins Healthcare France (besins-lscovesco, Paris, France)	Transdermal	(2)
	51.3	21	-—	1.5 mg 17-betaE2 gel + calcium carbonate 100 mg		Transdermal	
Zuo et al[22] 2018	53.7 ± 4.2	35	4.4 ± 1.5	Estrogen 0.3 mg + Progesterone Capsules 50 mg	Estrogen: Tefeng Pharmaceutical Co., Ltd (Urumqi,Xinjiang, China); Progesterone: Xianju JunyePharmaceutical Co., Ltd (Xianju District, Zhejiang, China)	Oral	(2)(3)(4)
	53.1 ± 3.1	37	3.9 ± 1.3	Estrogen 0.625 mg + Progesterone Capsules 50 mg		Oral	
Sun et al[23] 2001	—	15	1 to 5 years	0.75 mg E2 transdermal with 17-betaE2 gel + MP 100 mg	Besins Healthcare France (besins-lscovesco, Paris, France)	Transdermal	(2)(3)(4)(6)
	—	15	1 to 5 years	1.5 mg E2 transdermal with 17-betaE2 gel + MP 100 mg		Transdermal	

(1) Efficacy, Kupperman score, (2) Bone mineral density, (3) Bone metabolism index, (4) Sex hormone index, (5) Endometrial and breast changes, (6) Other adverse effects.

fixed effects model was used. The results showed that the low dose of estrogen had an SMD value 0.004 points lower than the standard dose. The difference was small, $p > 0.05$, and not statistically significant (Figure 11).

In summary, there were no significant differences in bone metabolism-related indicators between the use of standard or low doses of estrogen for the treatment of perimenopausal women with osteoporosis.

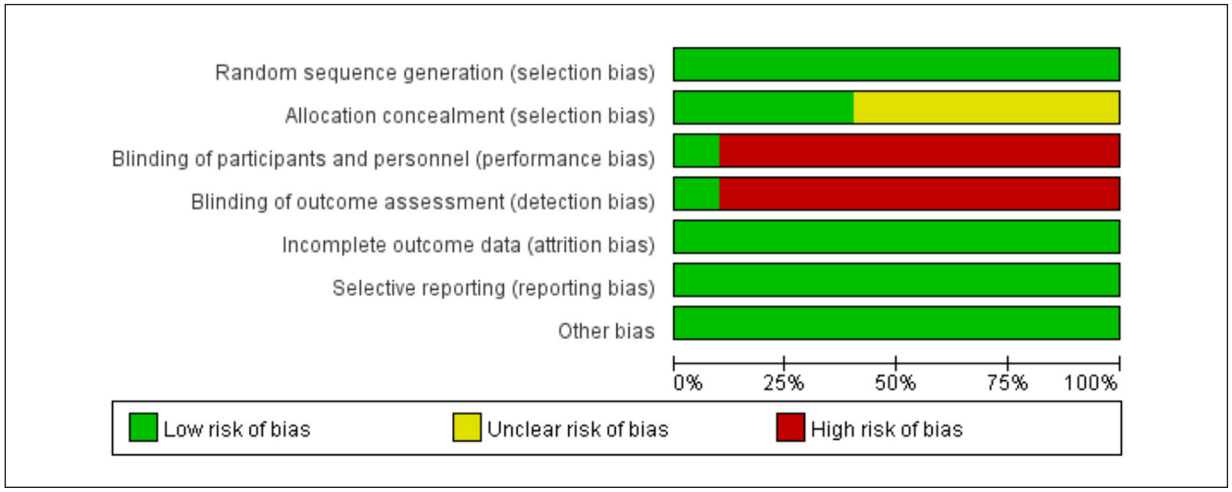


Figure 2. Risk of bias assessment (1).

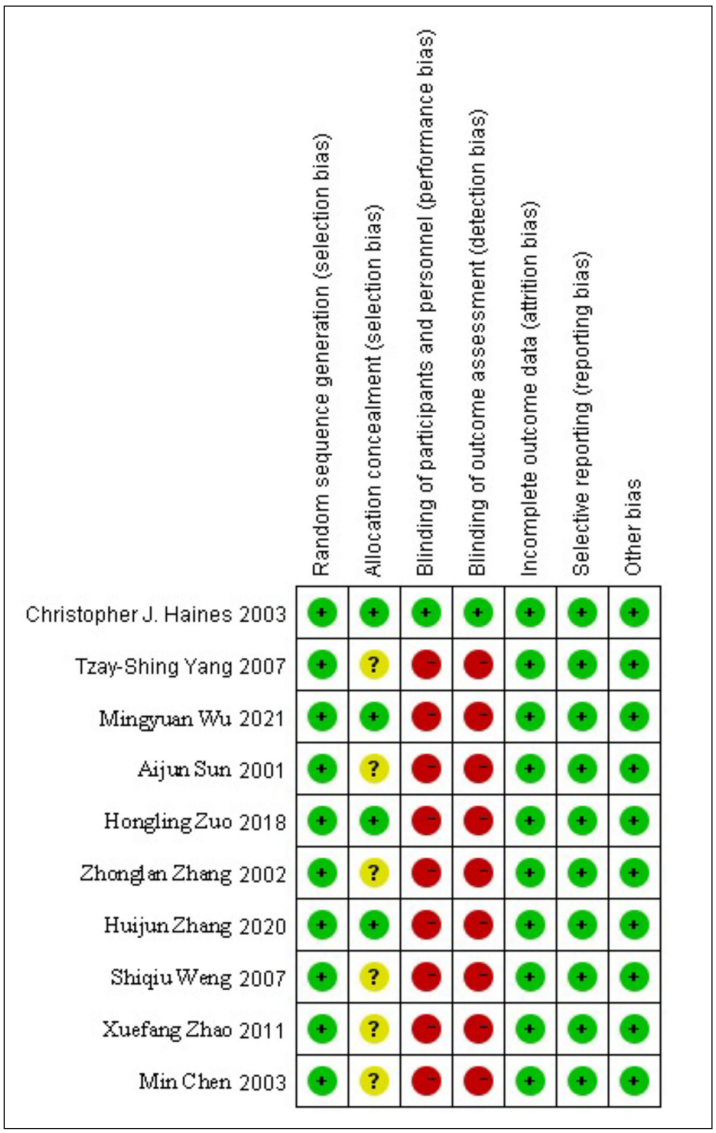


Figure 3. Risk of bias assessment (2).

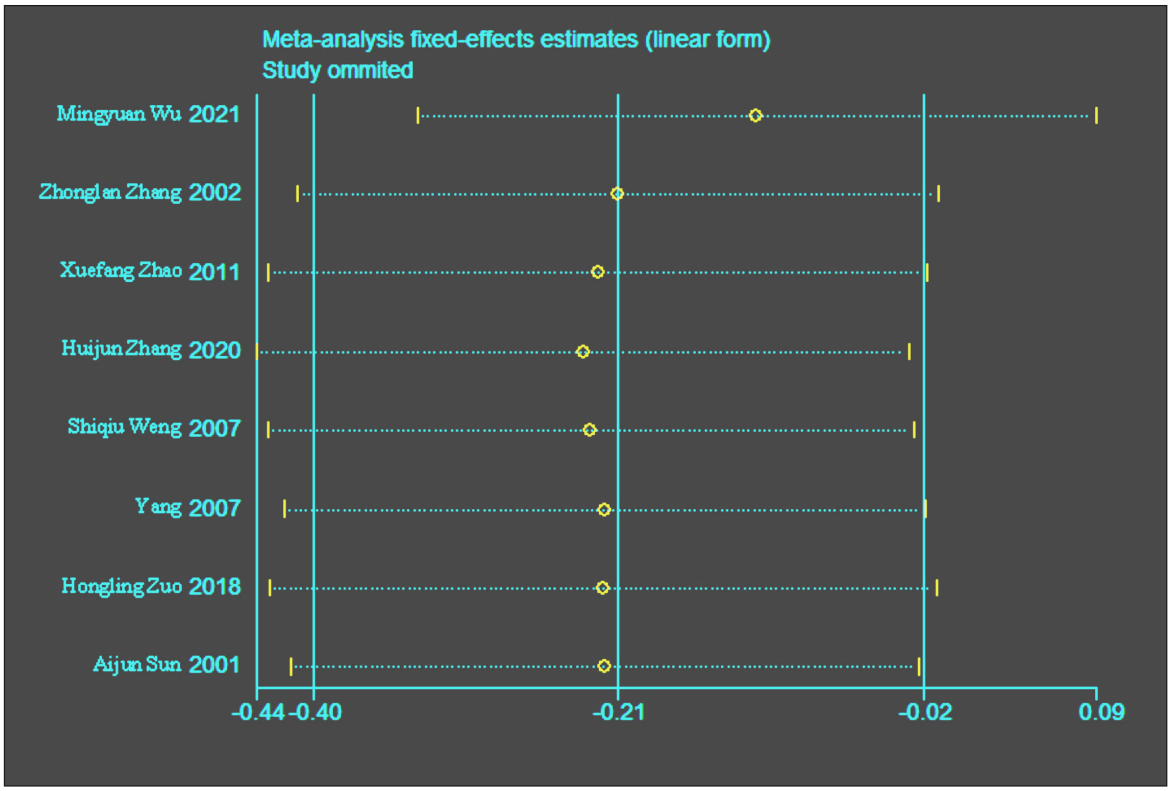


Figure 4. Sensitivity analysis for bone densitometry.

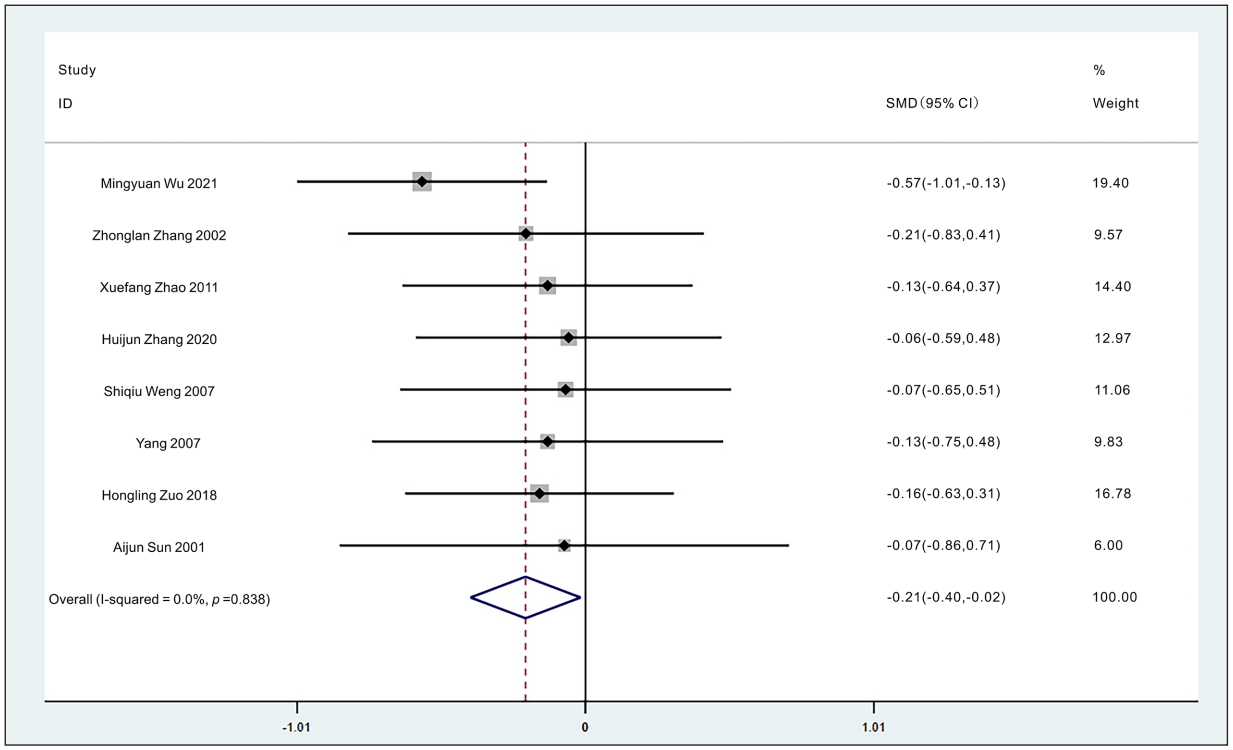


Figure 5. Meta-analysis on improvement in bone mineral density after 6 months of perimenopausal women treated with different doses of estrogen.

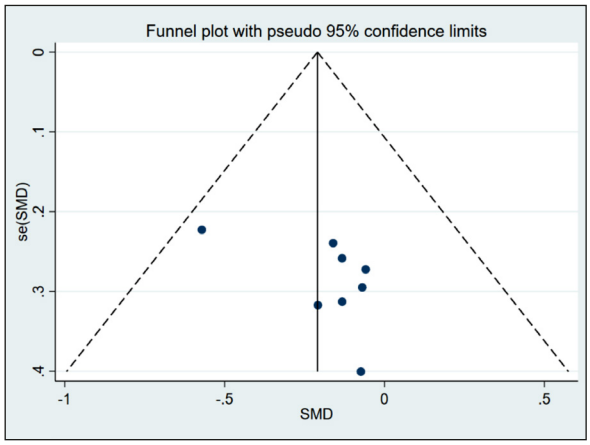


Figure 6. Funnel plot for bone densitometry.

Sex Hormone-Related Indicators

Follicle stimulating hormone (FSH)

2 selected[18,20] papers had strong heterogeneity, so a random effects model was used. The results showed that the low dose of estrogen had an SMD value 0.213 points higher than the standard dose. $p \geq 0.05$, not statistically significant.

Estradiol (E2)

There was no heterogeneity between the 2 selected[18,20] papers ($I^2 = 0\%$, $p = 0.624$), so a fixed effects model was used, and the results showed that the low dose of estrogen had an SMD value of 2.209 points lower than the standard dose, $p \leq 0.05$ was statistically significant.

In summary, when standard and low doses of estrogen were used to treat perimenopausal women with osteoporosis, the standard dose of estrogen significantly elevated estrogen levels in patients, as shown in Figures 12 and 13. However, the advantage was not statistically significant in the results for FSH.

Exploring Lower Doses

A study by Haines et al[20] explored the feasibility of lower doses of estrogen for the treatment of osteoporosis in Chinese women. Separate doses of 1 mg and 2 mg of estrogen were used. The results of the study showed that the 1 mg and 2 mg doses of estrogen still had the effect of increasing bone mineral density. This provides new insights into the safety and efficacy of the optimal dose of estrogen for the treatment of perimenopausal women with osteoporosis.

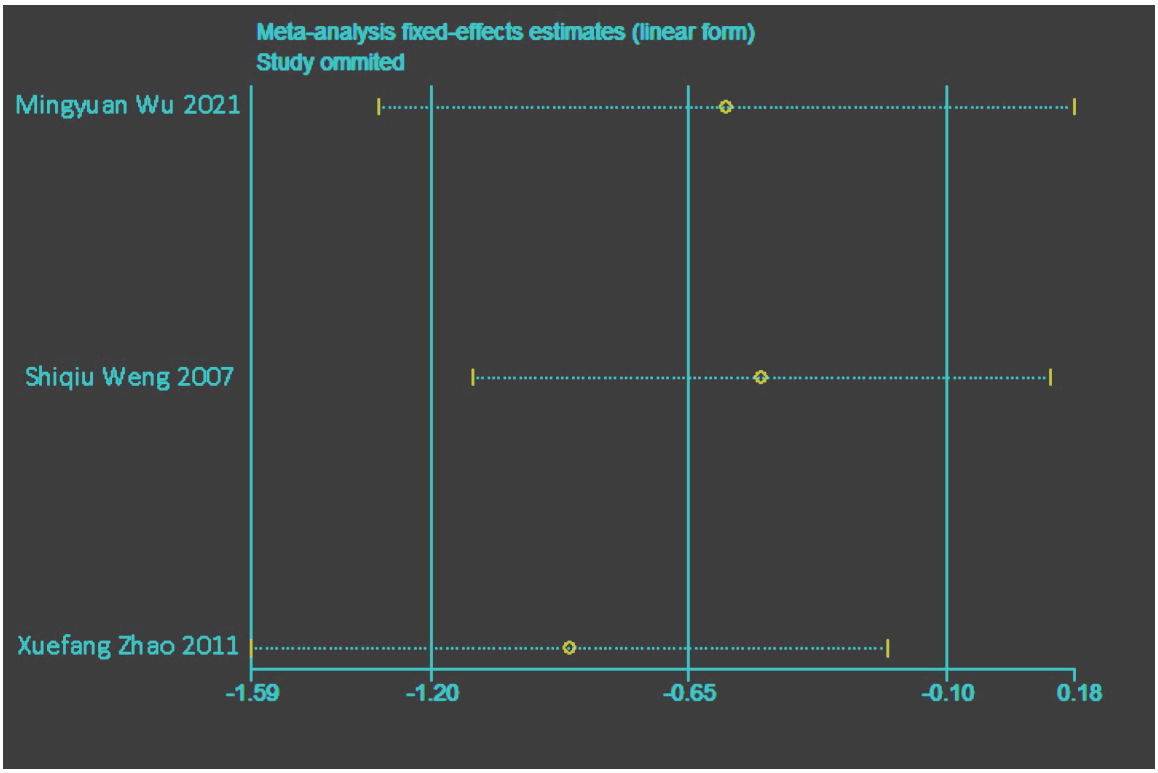


Figure 7. Efficacy sensitivity analysis.

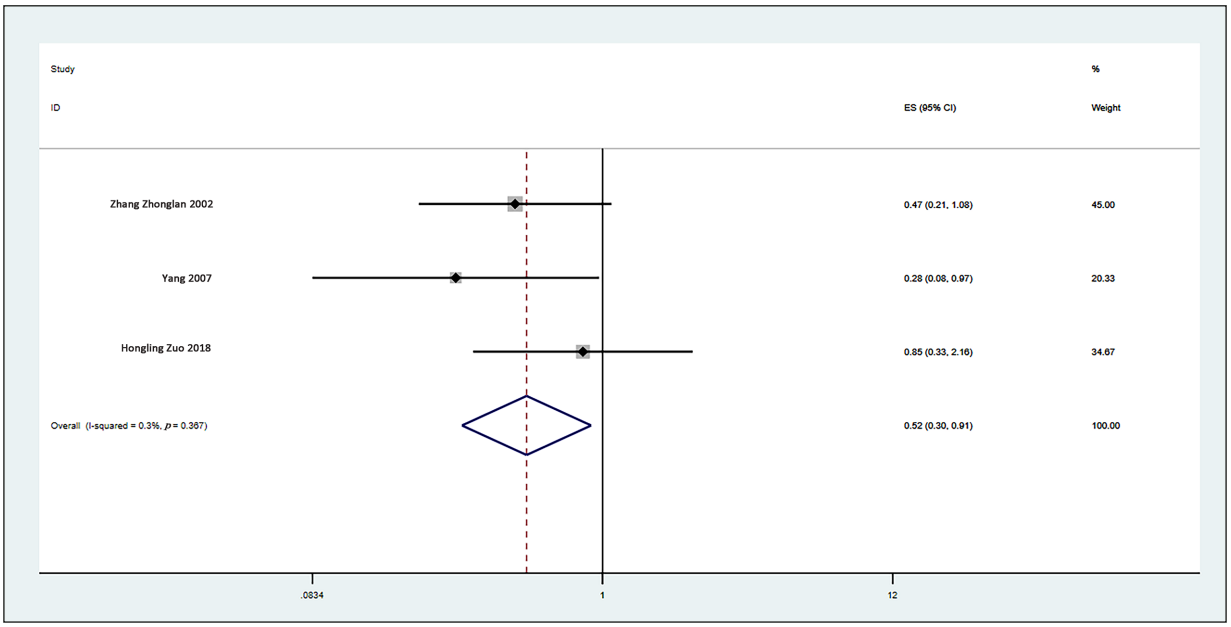


Figure 8. Meta-analysis on the efficacy of different doses of estrogen in perimenopausal women after 6 months of treatment.

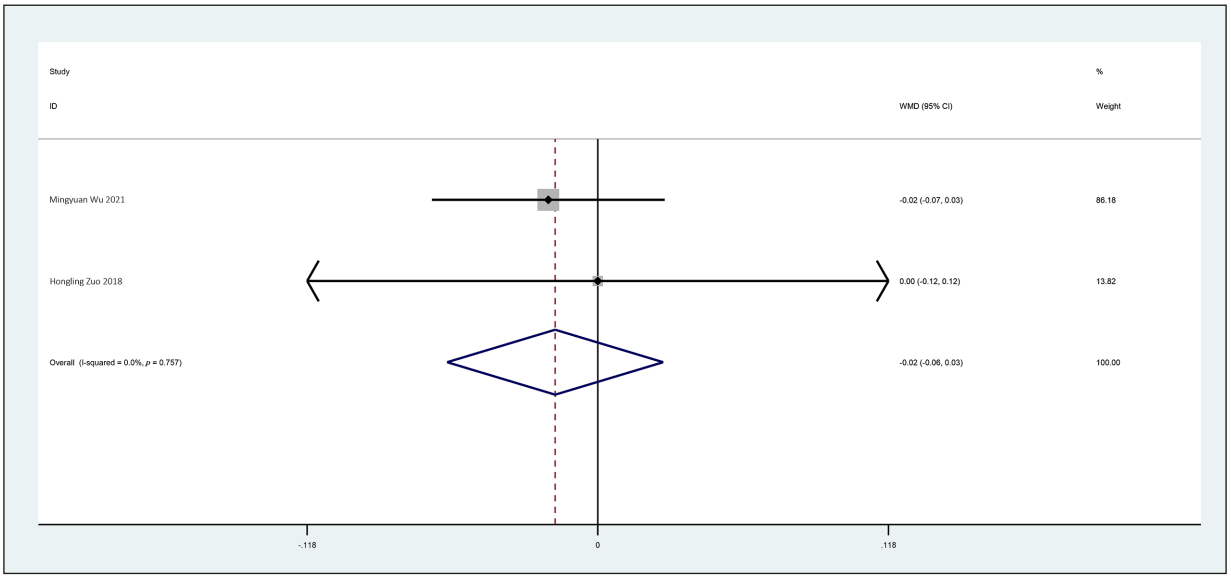


Figure 9. Meta-analysis on bone metabolism indicator (Ga) after 6 months of different doses of estrogen treatment in perimenopausal women.

Adverse Effects

Six of the included papers[12,16-19,23] counted indicators of adverse effects, with a cumulative total of 361 patients. The number of times patients experienced vaginal bleeding, endometrial thickening (≥ 5 mm), breast disease, and other adverse effects were counted for comparison by calculating the probability of the occurrence of different doses of estrogen in perimenopausal women who were treated with the intervention for more than 6 months. The probability of adverse events in the included studies was approximately 4% in the low-dose group and up to over 13% in the high-dose group. The likelihood of adverse events was higher in the standard dose group. The results are shown in Table II and Figure 14.

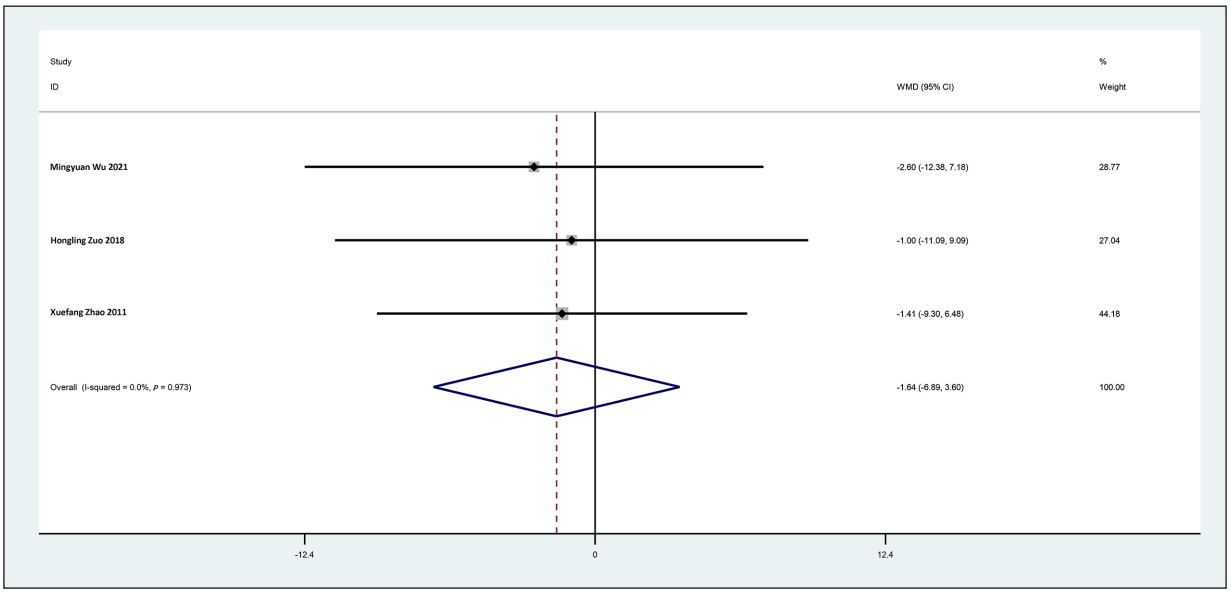


Figure 10. Meta-analysis on bone metabolism indicators (ALP) after 6 months of different doses of estrogen treatment in perimenopausal women.

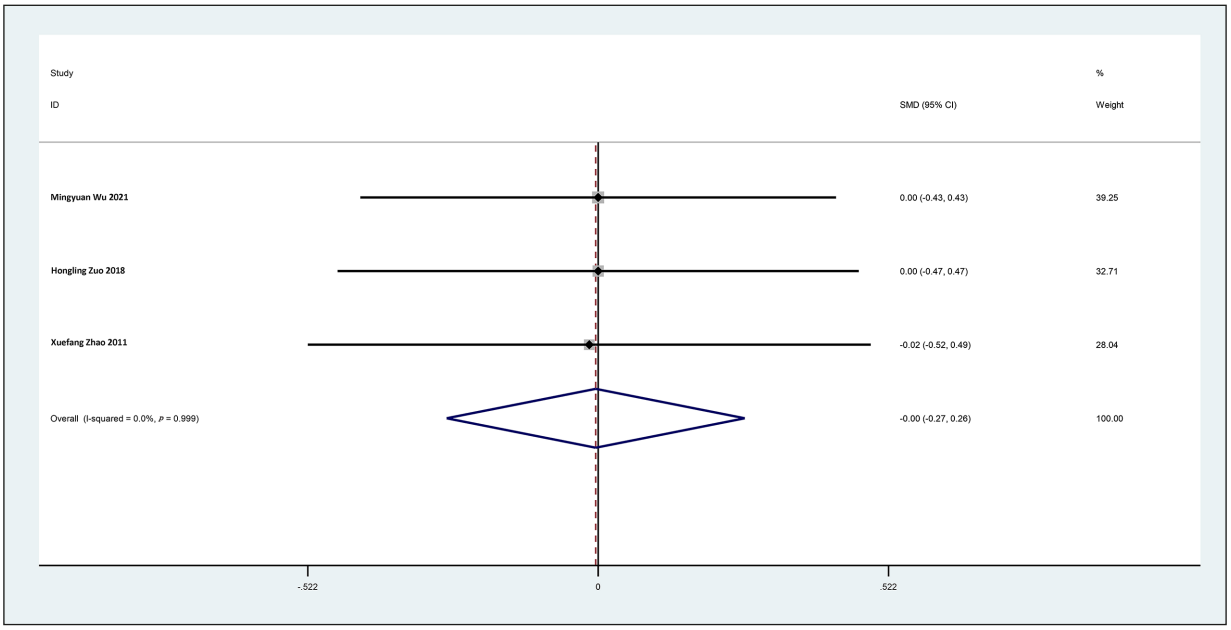


Figure 11. Meta-analysis on bone metabolism indicators (Ca/Cr) after 6 months of different doses of estrogen treatment in perimenopausal women.

Discussion

After collecting and analyzing the results of several similar studies, this research aimed to address the issue of dosing estrogen for the treatment of perimenopausal osteoporosis in China, where there is currently no uniform standard. A total of 10 randomized controlled trials were included to assess the efficacy and safety of multiple doses of estrogen in the treatment

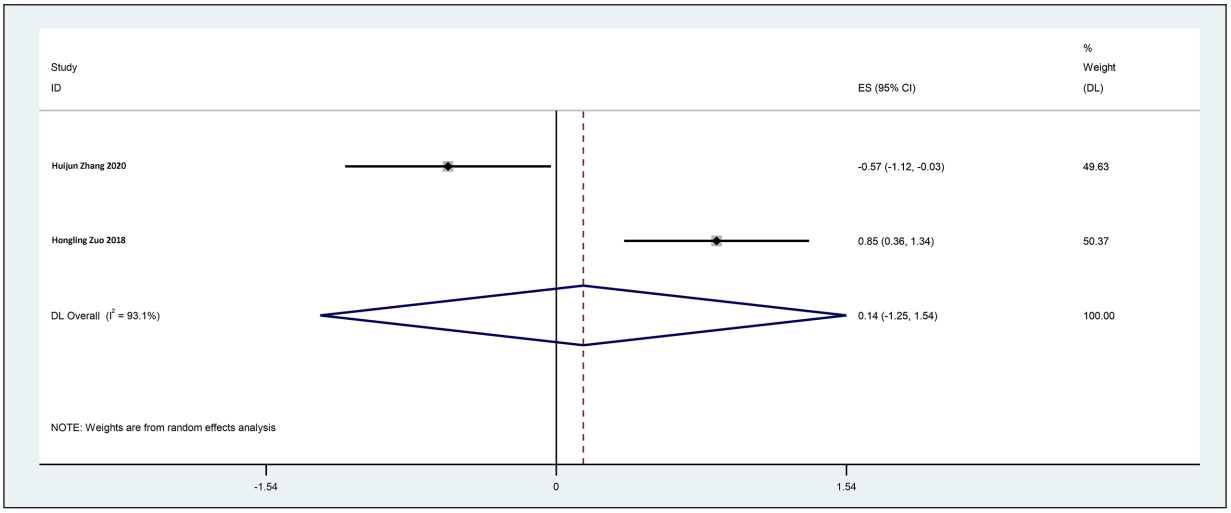


Figure 12. Meta-analysis on sex hormone indicators (FSH) after 6 months of different doses of estrogen treatment in perimenopausal women.

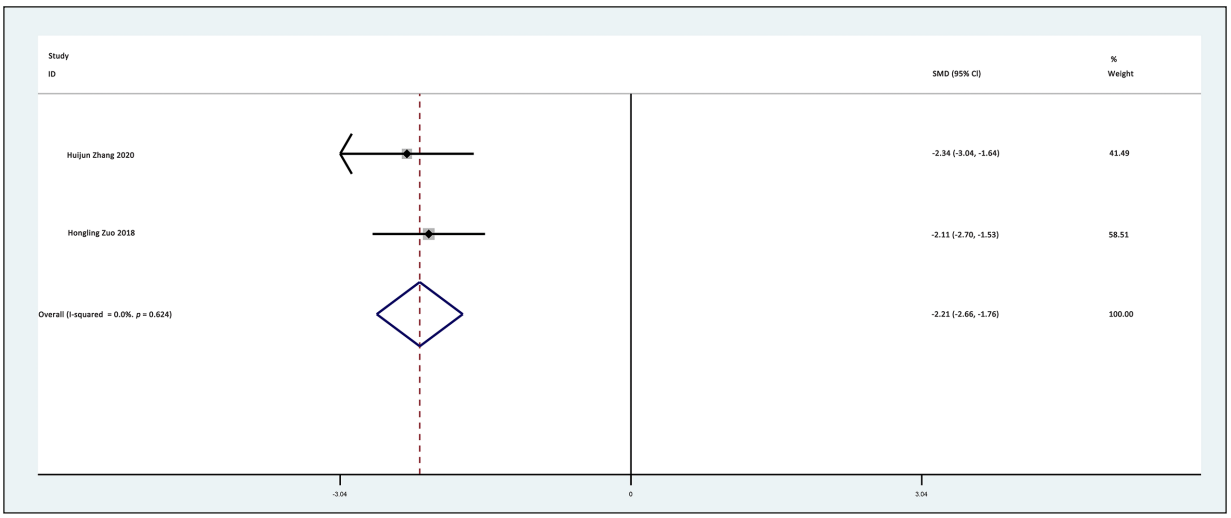
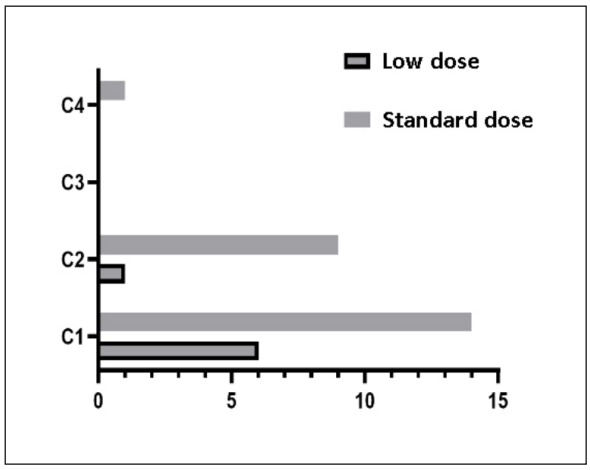


Figure 13. Meta-analysis on sex hormone indicators (E2) after 6 months of different doses of estrogen treatment in perimenopausal women.

Table II. Summary of adverse results.

Author	Low dose group					Standard dose group				
	Event 1	Event 2	Event 3	Other	N	Event 1	Event 2	Event 3	Other	N
Chen and Zhu[12] 2003	0	0	0	0	40	1	1	0	1	40
Zhang et al[16] 2002	2	1	-	-	18	3	4	-	-	16
Zhao et al[17] 2011	2	0	0	0	30	0	4	0	0	30
Zhang et al[18] 2020	0	0	0	0	28	0	0	0	0	26
Weng[19] 2007	1	0	0	-	46	5	0	0	-	46
Sun et al[23] 2001	2	-	-	-	15	> 5	0	0	-	26
Total	6	1	0	0	177	> 14	9	0	1	184

Event 1: vaginal bleeding; event 2: endometrium ≥ 5 mm; event 3: breast disease; other: fracture, headache or other medical condition. (Treatment period 6-12 months), "-" indicates not mentioned.



Figur 14. Comparison chart without good events.

of osteoporosis in perimenopausal women. Meta-analyses of common indicators of the impact of clinical perimenopausal osteoporosis were conducted by expanding the sample size and improving test performance. Treatment status, bone mineral density, bone metabolism indicators, and sex hormone indicators were extracted in terms of efficacy[24,25]. In terms of safety, indicators such as changes in the endometrium and mammary glands, and adverse effects were extracted[26]. The aforementioned parameters were incorporated into the study because estrogen deficiency has historically been a significant factor contributing to osteoporosis in women[27]. Furthermore, bone mineral density serves as a crucial measure for clinically assessing the severity of osteoporosis[28]. Bone metabolism indicators, such as Ca, ALP, and Ca/Cr, are highly sensitive markers for assessing the effectiveness of medication in osteoporosis patients. They not only reflect the rate of bone loss but also provide insights into bone turnover rates[29]. FSH, a sex hormone, rises significantly after women enter perimenopause, so changes in FSH can predict the decrease in bone mass before and after menopause[30], while estrogen levels tend to decrease[31]. Estrogen supplementation is the main treatment for osteoporosis in perimenopausal women, but long-term use of estrogen is associated with an increased risk of endometrial and breast cancer in women[32]. Therefore, post-treatment endometrium $\geq$ 5 mm, breast disease and other discomfort are considered important indicators of adverse effects.

The perimenopause is an important and long transition in women's life course. Estrogen receptors are expressed in bone, skin, and brain[33], and play a major role in improving bone turnover, inhibiting bone resorption, and increasing bone mass. The decline in estrogen levels can, therefore, lead to accelerated bone loss in women during this period and continue into old age. According to the 2010 China census, there are over 40 million perimenopausal women with osteoporosis in China[34]. The extensive patient population presents challenges in the clinical application of estrogen therapy, including issues related to personalization, suboptimal effectiveness, and the occurrence of adverse effects. The results of this analysis show that in the treatment of perimenopausal women with osteoporosis, standard doses of estrogen have a significant advantage in terms of bone mineral density and therapeutic efficacy. And it can increase the estrogen level in the patient's body more quickly. The standard dose of estrogen was slightly better than the lower dose when it came to improving bone metabolic parameters (Ca, ALP, Ca/Cr) and sex hormones (FSH) in patients, but the difference was not statistically significant. In terms of safety, the probability of adverse effects was significantly higher with the standard dose of estrogen than with the low dose, but the small sample size did not allow for a more progressive statistical description. More high-quality trials are needed to verify the poor safety profile of standard doses.

Limitations and Prospective

The meta-analysis has some limitations. First, none of the included studies gave a minimum dose of estrogen that met the efficacy and safety requirements for the Chinese population. The lowest dose of 0.625 mg of estrogen accepted in Western countries is superior in terms of efficacy, but the appropriate dose for both efficacy and safety is still unclear. Secondly, the small sample sizes included in some of the studies may have led to some bias. Finally, the overall small number of studies included in this study, and the inclusion of variation in outcome indicators and different background treatments may have contributed to the heterogeneity of the results of this study. Higher-quality clinical trials are therefore needed to further explore the appropriate dose of estrogen for perimenopausal women in China, with a view to achieving maximum efficacy and minimum risk in the treatment of osteoporosis.

Conclusions

In summary, the use of standard doses of estrogen (0.625 mg) has been shown to be clinically superior to lower doses. However, in terms of safety, there is a need to be alert to the possible risks associated with the use of standard doses of estrogen and higher-quality clinical trials are needed to provide the basis for an optimal balance of benefit and risk.

Conflict of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, or publication of this article.

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Ethics Approval

This article does not involve animal or human experiments; this article is a meta-analysis, and the data involved are retrieved through databases. Therefore, this study does not deal with ethical issues, and ethical review and approval are not applicable.

Informed Consent

The informed consent was waived because there is no patient or subject involved in this study.

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Authors' Contribution

Weikang Sun was responsible for the design and writing of this article. Zichen Shao and Weikang Sun are responsible for proofreading. Qipeng Yuan participated in data collection and analysis.

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Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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