

REVIEW - SYSTEMATIC

Different regimens of menopausal hormone therapy for improving sleep quality: a systematic review and meta-analysis

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Abstract

Importance: Long-term sleep disturbances in menopausal women are closely related to cardiovascular disorders, metabolic disorders, and cognitive impairment. At present, hormone therapy (HT) is a standard treatment for menopausal symptoms. However, it remains unclear whether HT can improve sleep quality.

Objective: We did a systematic review and meta-analysis to assess the effects of different HT regimens on menopausal sleep quality.

Evidence Review: We systematically searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, PsycINFO, CINAHL, and Web of Science for randomized controlled trials of menopausal HT on sleep disturbances up to June 14, 2021. Information about ongoing and unpublished trials was collected by searching WHOICTRP and ClinicalTrials.gov. Our primary outcome was sleep quality with objective measurements. We estimated the standardized mean difference (SMD) using random-effects models.

Findings: We identified a total of 3,059 studies and finally included 15 studies in the meta-analysis. Compared with placebo, HT improved self-reported sleep outcomes (SMD = -0.13; 95% CI, -0.18 to -0.08, $P < 0.00001$ and $I^2 = 41\%$), but not sleep parameters measured by polysomnography. Subgroup analyses according to the regimen of HT showed that 17 β -estradiol (17 β -E₂) (SMD = -0.34; 95% CI, -0.51 to -0.17, $P < 0.0001$, and $I^2 = 0\%$) and conjugated equine estrogens (SMD = -0.10; 95% CI, -0.12 to -0.07, $P < 0.00001$, and $I^2 = 0\%$) improved sleep quality. Moreover, transdermal administration (SMD = -0.35; 95% CI, -0.64 to -0.06, and $P = 0.02$) was more beneficial than oral (SMD = -0.10; 95% CI, -0.14 to -0.07, and $P < 0.00001$). In addition, the combination of estrogen and progesterone had a positive effect on sleep disturbance (SMD = -0.10; 95% CI, -0.13 to -0.07, $P < 0.00001$, and $I^2 = 0\%$), while estrogen monotherapy did not. The results showed that estrogen/micronized progesterone (SMD = -0.22; 95% CI, -0.37 to -0.06, $P = 0.007$, and $I^2 = 0\%$) and estrogen/medroxyprogesterone acetate (SMD = -0.10; 95% CI, -0.13 to -0.07, $P < 0.00001$, and $I^2 = 0\%$) could alleviate sleep disturbance.

Conclusions and Relevance: HT has a beneficial effect on sleep disturbance to some extent, and the formulations and routes of administration of hormonal agents influence the effect size.

Key Words: Estrogen – Menopause – Progesterone – Sleep.

Sleep disturbance is one of the distinctive features of menopausal symptoms and a well-recognized global health problem.^{1,2} Compared to young women and their male counterparts, premenopausal women have major sleep

disturbances.^{3,4} Self-reported sleep problems were reported to increase by 2 to 3.5 times in women during the menopausal transition.⁵ Forty to sixty percent of women report problems sleeping during perimenopause and postmenopause.⁶

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Menopausal sleep disturbances are significantly associated with vasomotor symptoms, such as hot flashes and night sweats,⁷ and are two to three times more likely to increase the risk of depression.⁸ Furthermore, long-term sleep disturbances are closely related to cardiovascular and metabolic disorders, cognitive impairment, deficits in immune function, and even malignant tumors.^{9,10} Therefore, sleep disturbance is an important issue for menopausal women.

McEwen and Alves¹¹ reported that estrogen acted on the areas of sleep regulation in the brain, and the change of estrogen was the primary factor for sleep disturbance. Progesterone also decreased during menopause, and accumulating clinical data demonstrated its actions on the central nervous system.^{12,13} The close relationship between sleep problems and decreased levels of reproductive hormones in menopausal women has led to consideration of hormone therapy (HT) for their relief.¹⁴ However, there is a lack of effective treatment at present.

Montplaisir et al¹⁵ observed improved sleep efficiency in the oral conjugated equine estrogens (o-CEE) plus micronized progesterone group, but not in the medroxyprogesterone acetate (MPA) group. Cintron et al¹⁶ reported alleviated sleep disturbances in the transdermal 17 β -estradiol (t-17 β -E₂) group and the o-CEE group. However, Heinrich and Wolf¹⁷ did not find beneficial effects of estradiol valerate (EV) or estradiol plus micronized progesterone on sleep quality. Due to the heterogeneity of the participants, different formulations and doses of HT, and different measurements for sleep quality in previous studies,¹⁸ there is no consistent evidence that HT could improve sleep quality. It is also unclear which is the most effective therapeutic regimen for improving sleep quality. Hence, synthesized evidence is needed to help women and clinicians to choose the most appropriate treatment for menopausal women with sleep disorders.

A previous meta-analysis found that HT improved sleep quality in postmenopausal women with vasomotor symptoms, nevertheless, it failed to compare the effects of different formulations of HT on sleep disorders with each other owing to the limited number of original studies. Besides, the study was short of the measurement and analysis of objective indicators for sleep disturbances.¹⁹ Therefore, with several newly-published clinical studies, we updated and optimized the previous meta-analysis, and also did a systematic review of randomized controlled trials (RCTs) to evaluate the effects of different formulations and routes of administration of HT on sleep disturbance, aiming to probe into the association between HT therapy and sleep disturbance in menopausal women and consequently take effective measures to promote the physical and mental health of menopausal women.

METHODS

This systematic review adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and was registered with the International Prospective Register of Systematic Reviews (PROSPERO), number CRD42021256551.

Key Points

Question/Objective: What are the effects of different regimens of hormone therapy (HT) on menopausal sleep quality?

Findings: Fifteen randomized controlled trials (n = 27,715) evaluating the effect of different regimens of HT on menopausal sleep quality were included. The present study demonstrated that HT improved subjective sleep quality in 12 randomized controlled trials. More specifically, 17 β -estradiol (17 β -E₂) and conjugated equine estrogens improved sleep quality, whereas estradiol valerate did not. In addition, transdermal regimens were more beneficial than oral.

Meaning: Based on the meta-analysis, HT could improve sleep quality, and the formulations and routes of administration of hormonal agents influence the effect size.

Search strategy and eligibility criteria

We selected relevant studies in the following databases: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials, PsycINFO, CINAHL, and Web of Science. We developed a search strategy from text and MeSH terms related to "hormone replacement therapy," "estrogen," "progesterone," "menopause," "insomnia," and "sleep" up to June 14, 2021. Information about ongoing and unpublished trials was obtained by searching WHOICTRP and ClinicalTrials.gov.

We included studies that considered HT administration as either the treatment or the control group. We identified eligible studies according to the following criteria: participants had to be women during menopause, including perimenopause and postmenopause; minimal intervention length was 4 weeks; the outcomes were related to sleep quality measured with polysomnography or self-reported questionnaires; study design must be double-blind RCTs. Studies with HT at any dose, formulations, and routes of administration, such as oral, subdermal, transdermal, or intravenous, were eligible for inclusion. Exclusion criteria were as follows: observation and retrospective studies; studies in which HT was combined with compounds other than progesterone derived or selective estrogen receptor modulators; studies not published in English. For the overlapped sample sources, we included the report with more information and larger sample sizes.

Two independent investigators reviewed study titles and abstracts, and studies that satisfied the inclusion criteria were retrieved for full-text assessment. The agreement of both investigators determined final eligibility. Disagreements were referred to a third reviewer to reach a consensus.

Data extraction and assessment of risk bias

Two reviewers independently extracted the following data from each included study using a specifically designed form: study design, sample sizes, participant characteristics, details of HT, duration, and sleep outcomes. We extracted the mean

and standard deviation for the result. Disagreements were referred to a third reviewer to reach a consensus.

Two independent reviewers assessed the included studies for risk of bias using the Cochrane risk of bias tool, containing seven specific domains. We resolved any disagreements by consensus or by a discussion with a third author. Each domain was assigned a judgment relating to the risk of bias for that study classified as low, high, or unclear risk.

Statistical analysis

Since the included studies used different scales to evaluate sleep quality, we calculated pooled estimates of the standardized mean differences (SMDs) and 95% confidence intervals (CIs) with a random-effects model. To overcome a unit-of-analysis error for multiarms studies, we combined groups to create a single pair-wise comparison. For most studies, lower scores indicated better sleep quality except five studies,²⁰⁻²⁴ in which we reversed the direction to keep consistent with the others. We assessed statistical heterogeneity using the I^2 statistic, with values greater than 50% regarded as moderate-to-high heterogeneity. We performed prespecified subgroup analyses according to the following

parameters: formulation of HT; routes of administration of HT; andperimenopause or postmenopause. We did Egger tests to assess funnel plot asymmetry, and defined significant publication bias with the P value lower than 0.1. We conducted sensitivity analyses to determine whether the conclusions were robust. We presented the overall quality of the evidence for each outcome using the GRADE criteria. We conducted the statistical analyses with the Review Manager (Revman5.3.3, Cochrane Collaboration, Copenhagen, Denmark, 2014) and Stata software (version 14.0, StataCorp LP, TX, 1985-2015).

RESULTS

Search results

In total, we identified 3,059 studies, and 2,224 studies remained after we removed duplicates. Subsequently, we excluded 2,132 studies after reviewing the titles and abstracts. Of the remaining 92 articles assessed for eligibility, 28 studies met the inclusion criteria. Nineteen studies reported sufficient data,^{16,17,20-36} whereas 15 with placebo arm as comparator were included in the quantitative analysis^{16,17,20-26,28,29,31,33,35,36} (Fig. 1).

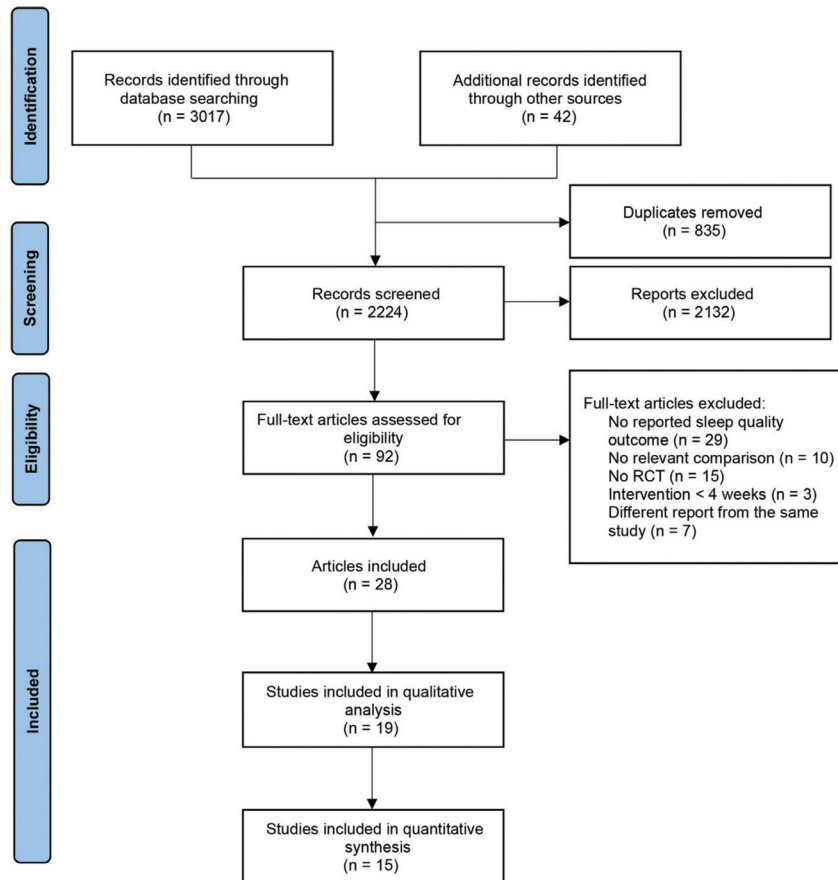


FIG. 1. Flow diagram for study selection.

TABLE 1. Characteristics of included trials

	Y	Study design	Sample sizes	Participant characteristics	Details of HT (/d)	Control	Duration	Sleep outcomes
Brunner et al ²⁰	2005	RCT	10,739	postmenopausal women with hysterectomy, mean age 63.6 y	o-CEE 0.625 mg	placebo	12 mo	WHIIRS
Cintron et al ¹⁶	2018	RCT	727	postmenopausal women, mean age 52.6 y	o-CEE 0.45 mg + micronized progesterone 200 mg, t-17β-E ₂ 50 μg + micronized progesterone 200 mg	placebo	48 mo	PSQI
Ensrud et al ²⁵	2015	RCT	339	menopause, postmenopausal or undergone hysterectomy women, mean age 54.6 y	o-17β-E ₂ 0.5 mg	placebo	8 wk	PSQI
Hachul et al ²⁶	2008	RCT	33	postmenopausal women, mean age 55.9 ± 4.5 y	o-CEE 0.625 mg	placebo	24 wk	polysomnography
Hays et al ²¹	2003	RCT	8,506	postmenopausal women, mean age 63.2 y	o-CEE 0.625 mg + MPA 2.5 mg	placebo	12 mo	WHIIRS
Heinrich and Wolf ¹⁷	2005	RCT	51	postmenopausal women with hysterectomy, mean age 64.1 ± 0.6 y	o-EV 2 mg, o-EV 2 mg + micronized progesterone 200 mg	placebo	24 wk	Sleep item from ADSK and from Menopausal Index
Kagan et al ²⁷	2018	RCT	1,835	postmenopausal women, mean age 55 y	oral TX-001HR (1 mg E ₂ /100 mg P ₄ , 0.5 mg E ₂ /100 mg P ₄ , 0.5 mg E ₂ /50 mg P ₄ , 0.25 mg E ₂ /50 mg P ₄)	placebo	12 mo	MOS-sleep questionnaire
Kalleinen et al ²⁸	2008	RCT	18	postmenopausal women, mean age 62.9 y	o-EV 2 mg + norethisterone 0.7 mg	placebo	6 mo	BNSQ and polysomnography
LeBlanc et al ²⁹	2007	RCT	37	late menopausal or early postmenopause women, mean age 52.3 y	o-E ₂ 2 mg	placebo	8 wk	OHSU SL sleep diary
Leeangkoonsathian et al ³⁰	2017	RCT	100	perimenopause, early menopause or late menopause women, mean age 52.1 ± 4.1 y	o-EV 1 mg + micronized progesterone 10 mg, o-EV 1mg + dydrogesteron 100 mg	none	3 mo	PSQI
Meeuwse et al ³¹	2002	RCT	85	postmenopausal women, mean age 54.2 ± 4.7 y	o-tibolone 2.5 mg	placebo	12 mo	NHP questionnaire
Polisseni et al ³²	2013	RCT	130	postmenopausal women, mean age 52.6 ± 3.6 y	tibolone 2.5 mg, estradiol 1mg + norethindrone acetate 0.5 mg	calcium carbonate 50 mg + VitD ₃ 200IU	12 wk	WHQ sleep item
Polo-Kantola et al ³³	1999	RCT	71	postmenopausal women, mean age 56.4 ± 4.4 y	estrogel 2.5 g, estrogen patch 50 ug	placebo	3 mo	polysomnography
Saletu-Zyhlarz et al ²²	2003	RCT	55	insomniac postmenopausal women, mean age 58 ± 5y	o-EV 2 mg + dienogest 3 mg, o-EV 2 mg	placebo	8 wk	PSQI and polysomnography
Savolainen-Peltonen et al ²³	2014	RCT	150	postmenopausal women, mean age 53.2 y	t-E ₂ 1 mg, o-EV 2 mg, o-EV 2mg + MPA 5 mg	placebo	6 mo	WHQ sleep item
Shulman et al ³⁴	2002	RCT	845	postmenopausal women ≥ 45 y	t-17β-E ₂ /LNG (0.045 mg + 0.015 mg, 0.045 mg + 0.030 mg, 0.045 mg + 0.040 mg), t-17β-E ₂ 0.045 mg o-E ₂ 1mg + trimegestone .125 mg	none	1y	WHQ sleep item
Silva et al ³⁵	2011	RCT	12	postmenopausal women, mean age 49.7 ± 4.4 y	0.045 mg o-E ₂ 1mg + trimegestone .125 mg	placebo	4 wk	polysomnography
Tansupswatdikil et al ²⁴	2015	RCT	40	insomniac postmenopausal women, mean age 54.4 y	t-17β-E ₂ 50 μg	placebo	2 mo	ISI
Welton et al ³⁶	2008	RCT	3,721	postmenopausal women with or without subtotal hysterectomy, mean age 63.8 y	o-CEE 0.625 mg + MPA 2.5 mg, o-CEE 0.625 mg + MPA 5mg	placebo	12 mo	WHQ sleep item

17β-E₂,17β-estradiol; ADSK, German short version of the Center for Epidemiological Studies Depression Scale; BNSQ, Basic Nordic Sleep Questionnaire; CEE, conjugated equine estrogens; E₂, estradiol; EV, estradiol valerate; HT, hormone therapy; ISI, Insomnia Severity Index; LNG, levonorgestrel; MOS, Medical Outcomes Study; MPA, medroxyprogesterone acetate; NHP, Nottingham Health Profile; o-, oral; o-CEE, oral conjugated equine estrogen; OHSU SL, Oregon Health and Science University Sleep Laboratory; P₄, progesterone; PSQI, Pittsburgh Sleep Quality Index; RCT, randomized controlled trials; t-, transdermal; TX-001HR, a single, oral softgel capsule that contains hormones that are biologically identical to endogenous 17β-estradiol and progesterone; VitD₃, vitamin D₃; WHIIRS, Women's Health Initiative Insomnia Rating Scale; WHQ, Women's Health Questionnaire.

Description of included studies

The meta-analysis contained 27,715 participants: 14,058 women in the intervention group and 13,657 in the control group. Mean age ranged from 49.7 ± 4.4 to 64.1 ± 0.6 years old. Polysomnography was used in five trials,^{22,26,28,33,35} and subjective sleep questionnaires were used in 12 trials to evaluate sleep disorders.^{16,17,20-25,28,29,31,36} Six studies included women with vasomotor symptoms.^{16,20,21,23,25,35} (Table 1).

Only three studies reported adverse effects. Tansupswatdikil et al²⁴ demonstrated that the t-17β-E₂ group experienced more breast pain and vaginal discharge than the placebo group. Welton et al³⁶ reported 37% of women with vaginal bleeding in the o-CEE plus MPA group and 4% in the placebo group. Meeuwse et al³¹ reported eight women with bleeding and eight with spotting in the tibolone group, and three women with bleeding and one with spotting in the placebo group.

Four RCTs could not be included in the quantitative analysis due to the absence of outcomes in the placebo group. Leeangkoonsathia et al³⁰ reported that both EV combined with micronized progesterone and dydrogesterone improved sleep quality, whereas no significant difference between the two groups. Shulman et al³⁴ demonstrated that both t-17β-E₂ monotherapy and three doses of combined 17β-E₂/levonorgestrel transdermal system improved sleep quality, whereas no significant difference among those groups. Kagan et al²⁷ observed the beneficial effects of TX-001HR, an oral softgel capsule containing hormones that were biologically identical to endogenous 17β-E₂ and progesterone ranging from 0.25 mg E₂/50 mg P₄ to 1 mg E₂/100 mg P₄, on MOS-sleep scores. Polissen et al³² reported alleviated sleep disturbances in the tibolone and the estradiol plus norethindrone acetate groups.

Risk of bias in included studies

We assessed the risk of bias in all included studies, as demonstrated in Figure 2. Ten studies reported adequate methods for random sequence generation.^{16,20,21,24,25,28,29,33,35,36} Seven studies did not specify whether data collectors and outcome assessors were masked to treatment allocation.^{17,22,23,26,28,33,35} Two studies rated at low risk of bias,^{16,35} and four were judged to be at high risk because of incomplete outcome data or funded by industry.^{17,21,31,36}

Primary outcomes

Meta-analysis of polysomnography studies showed no significant improvement in sleep parameters in the HT group, including total sleep time (SMD = -0.14; 95% CI, -0.48 to 0.20, *P* = 0.43, and *I*² = 10%), sleep latency (SMD = -0.22; 95% CI, -0.57 to 0.13, *P* = 0.23, and *I*² = 0%), sleep efficiency (SMD = -0.09; 95% CI, -0.39 to 0.20, *P* = 0.54, and *I*² = 0%), and arousals number (SMD = -0.07; 95% CI, -0.42 to 0.28, *P* = 0.69, and *I*² = 0%) (Fig. 3). These studies did not show any heterogeneity. However, we downgraded the evidence to low quality using GRADE criteria due to the few participants of the included studies (Supplemental Digital Content 1, <http://links.lww.com/MENO/A904>).

Pooled analysis of self-reported sleep outcomes of the 12 included studies showed the significant improvement of sleep quality in the HT group (SMD = -0.13; 95% CI, -0.18 to -0.08, and *P* < 0.00001) (Fig. 4), with moderate between-study heterogeneity (*I*² = 41%). We downgraded the evidence to moderate quality because of some included studies' unclear risk for allocation concealment (Supplemental Digital Content 2, <http://links.lww.com/MENO/A905>).

Subgroup analysis

In the postmenopausal subgroup, HT improved self-reported sleep quality (SMD = -0.10; 95% CI, -0.13 to -0.08, and *P* < 0.00001) (Fig. 4), and there was no significant heterogeneity between studies (*I*² = 20%). Subgroup analysis on the basis of sample size suggested a favorable sleep quality

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Brunner, R. L. 2005	+	+	+	+	?	+	+
Cintron, D. 2018	+	+	+	+	?	+	+
Ensrud, K. E. 2015	+	+	+	+	+	+	+
Hachul, H. 2008	?	?	?	?	+	+	+
Hays, J.2003	+	+	+	+	+	?	-
Heinrich, A. B.2007	?	?	?	?	-	?	+
Kalleinen, N.2008	+	?	?	?	+	+	+
LeBlanc, E. S.2007	+	+	+	+	?	?	?
Meeuwssen, I. B. 2002	?	+	+	+	+	?	-
Polo-Kantola, P. 1999	+	?	?	?	+	+	+
Saletu-Zyhlarz, G.2003	?	?	?	?	?	+	+
Savolainen-Peltonen, H.2014	?	?	?	?	+	+	?
Silva, B. H. 2011	+	?	?	?	?	+	+
Tansupswatdikul, P. 2015	+	+	+	+	+	+	+
Welton, A. J.2008	+	+	+	+	-	+	+

FIG. 2. Risk of bias summary: review authors' judgments about each risk of bias item for each included study.

improvement of HT in the large sample subgroup (SMD = -0.12; 95% CI, -0.17 to -0.08, *P* < 0.00001, and *I*² = 46%). We also conducted subgroup analysis based on the duration of studies and found that more than 6 months of HT improved sleep quality (SMD = -0.10; 95% CI, -0.13 to -0.08, *P* < 0.00001, and *I*² = 6%). Subgroup analyses by different regimens of HT showed that 17β-E₂ (SMD = -0.34; 95% CI, -0.51 to -0.17, *P* < 0.0001, and *I*² = 0%) and CEE (SMD = -0.10; 95% CI, -0.12 to -0.07, *P* < 0.00001, and *I*² = 0%) improved sleep quality, but EV had no positive effect (Fig. 4). Both oral and transdermal subgroup showed beneficial effects on sleep disturbances (oral: SMD = -0.10; 95% CI, -0.14 to -0.07, *P* < 0.00001, and *I*² = 17%;

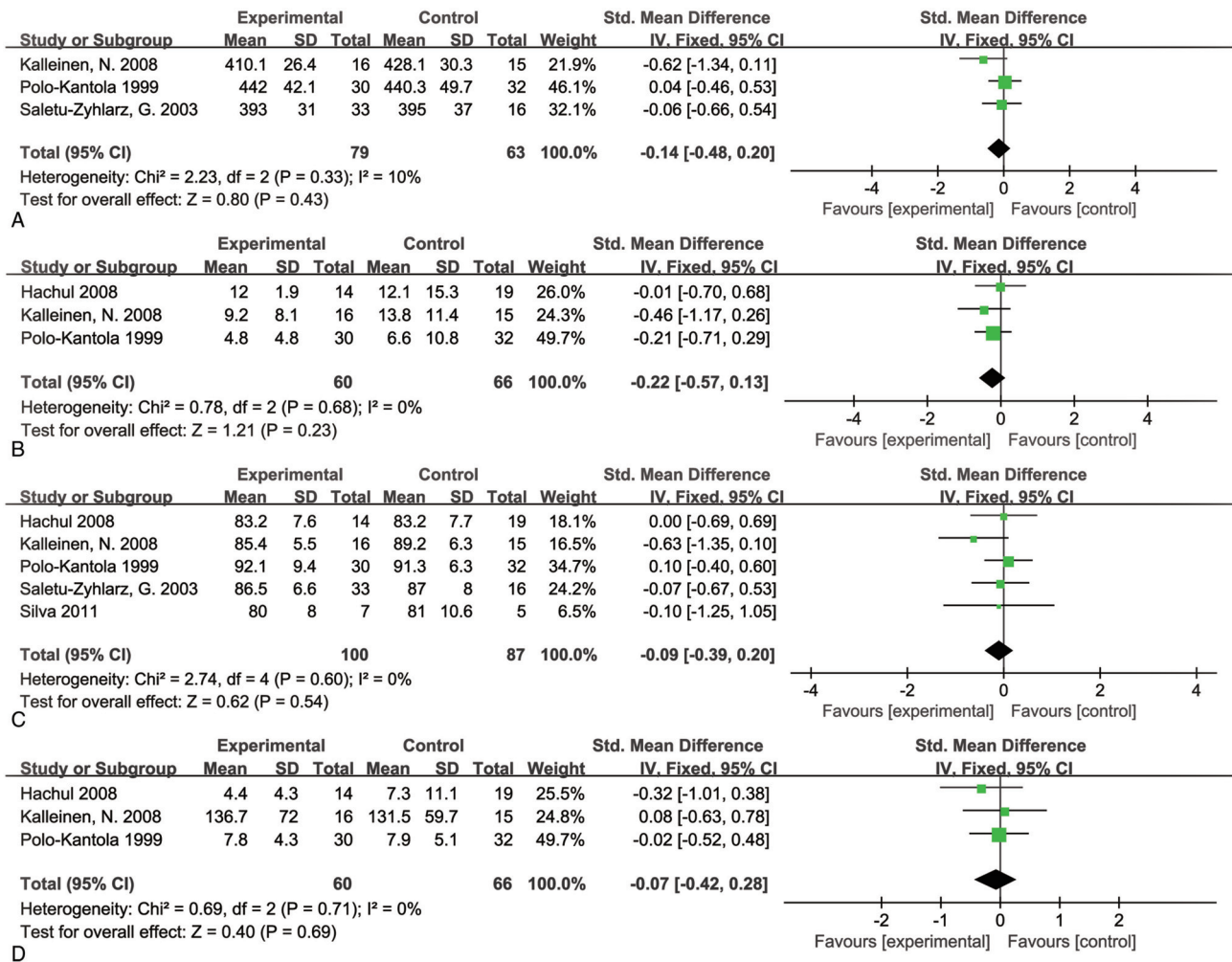


FIG. 3. Forest plot showing individual and combined effect size estimates and 95% confidence intervals (CIs) in studies that evaluated the effect of hormone therapy using polysomnography. Horizontal lines indicate 95% CIs, boxes show the study-specific weight, diamond represents combined effect size. (A) Total sleep time; (B) sleep latency; (C) sleep efficiency; and (D) arousals number.

transdermal: $\text{SMD} = -0.35$; 95% CI, -0.64 to -0.06 , $P = 0.02$, and $I^2 = 18\%$), and the transdermal subgroup had a larger effect (Fig. 4). In addition, estrogen plus progesterone was an adequate intervention ($\text{SMD} = -0.10$; 95% CI, -0.13 to -0.07 , $P < 0.00001$, and $I^2 = 0\%$), whereas estrogen monotherapy was not ($\text{SMD} = -0.14$; 95% CI, -0.40 to 0.12 , $P = 0.29$, and $I^2 = 57\%$) (Fig. 4). Furthermore, subgroup analysis of estrogen combined with different progesterone showed that both estrogen plus micronized progesterone ($\text{SMD} = -0.22$; 95% CI, -0.37 to -0.06 , $P = 0.007$, and $I^2 = 0\%$) and estrogen plus MPA ($\text{SMD} = -0.10$; 95% CI, -0.13 to -0.07 , $P < 0.00001$, and $I^2 = 0\%$) positively associated with sleep disturbances, whereas other progesterone did not (Fig. 4).

Sensitivity analysis

Tansupswatdikul et al²⁴ measured subjective sleep quality with Insomnia Severity Index, which is quite different from other sleep questionnaires. We conducted a sensitivity analysis to assess the contribution of this study to the synthesized

outcome. We generated similar pooled SMD and 95% CI with the removal of this study ($\text{SMD} = -0.12$; 95% CI, -0.17 to -0.08 , $P < 0.00001$, and $I^2 = 36\%$), thus indicating no significant influence of the trial on the overall estimation of self-reported sleep quality.

Publication bias

The funnel plots for self-reported sleep quality models and regression analyses of Egger’s test suggested publication bias in this analysis (Supplemental Digital Content 3, <http://links.lww.com/MENO/A906>; Supplemental Digital Content 4, <http://links.lww.com/MENO/A907>).

DISCUSSION

We performed the systematic review and meta-analysis to comprehensively analyze the effect of HT on sleep disturbance with both subjective and objective sleep outcomes. We included 15 RCTs with similar interventions and sufficient quantitative data for statistical pooling. The pooled effects of subjective sleep quality showed a significant improvement in

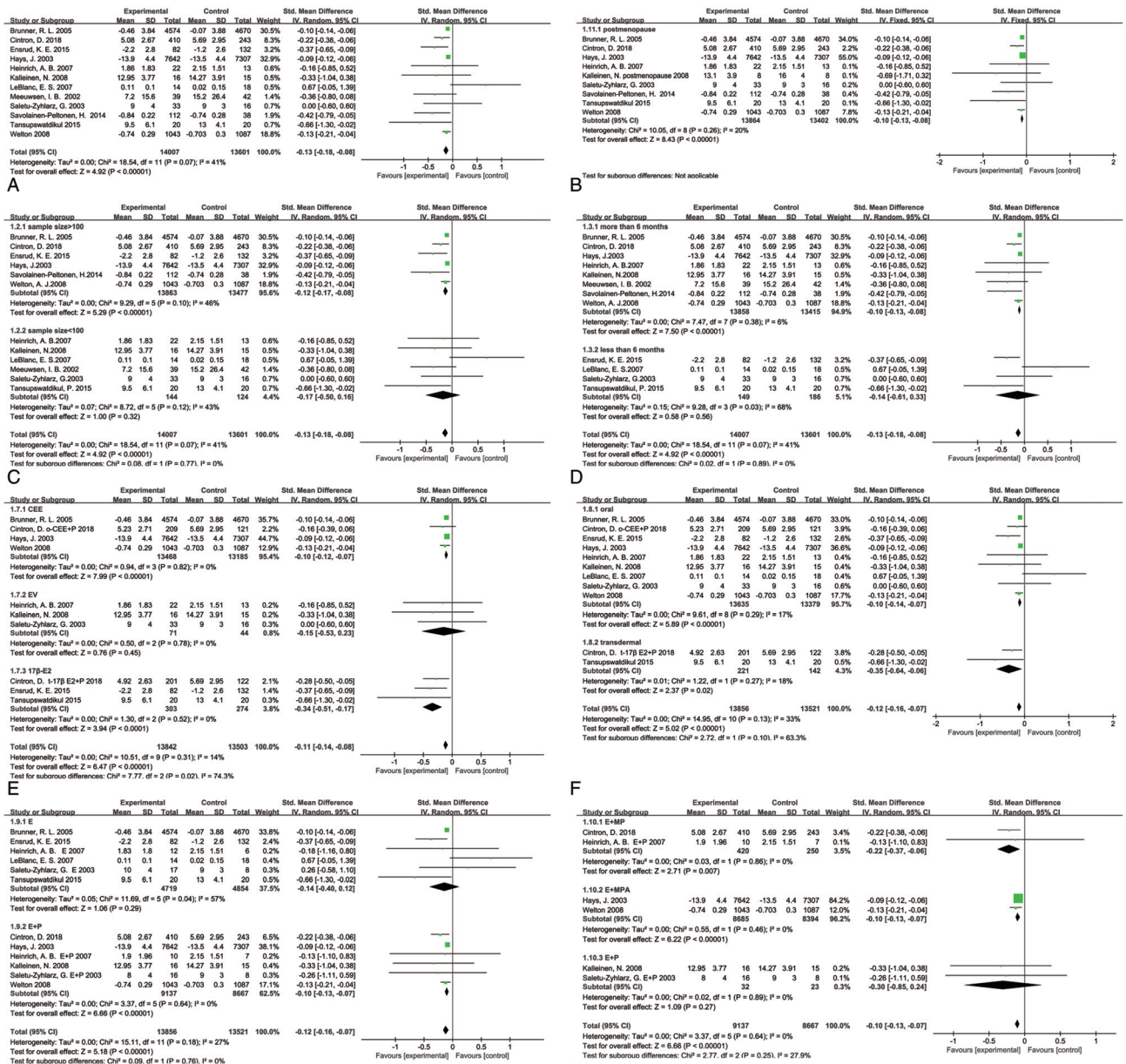


FIG. 4. Self-reported scores of subjective sleep questionnaire and subgroup analysis. (A) Self-reported scores of subjective sleep questionnaire among participants receiving hormone therapy versus placebo; (B) postmenopausal subgroup analysis; (C) sample size subgroup analysis; (D) duration subgroup analysis; (E) different estrogen regimens subgroup analysis; (F) oral and transdermal subgroup analysis; (G) ET and EPT subgroup analysis; and (H) estrogen combined with different progesterone subgroup analysis. 17 β -E₂, 17 β -estradiol; CEE, conjugated equine estrogens; E, estrogen; EPT, estrogen plus progestogen therapy; ET, estrogen therapy; EV, estradiol valerate; MP, micronized progesterone; MPA, medroxyprogesterone acetate; P, progesterone.

the HT group. Our pooled results were stable, and the heterogeneity among studies was moderate.

We did subgroup analyses to eliminate heterogeneity and evaluate the effect of different regimens of HT on sleep quality. The results showed that both oral and transdermal regimens positively impacted sleep disturbance, and transdermal administration was more helpful. Both 17 β -E₂ and CEE improved sleep quality, whereas EV did not. Furthermore, we found more favorable sleep quality improvement in the 17 β -E₂ subgroup. Considering the 17 β -E₂ subgroup contained three RCTs and two of them compared transdermal 17 β -E₂

to placebo, we speculated that transdermal 17 β -E₂ administration led to better effects. The underlying mechanism may be that transdermal estrogen delivery avoids the first-pass effect, resulting in more stable serum estradiol level and higher bioavailability comparing with oral administration.

In the subgroup analysis, the large sample subgroup showed improved sleep quality. Since large sample studies were more likely to avoid sampling error and better represent the actual effect, this result revealed a beneficial effect of HT on sleep disturbance. Furthermore, in the subgroup analysis of the duration of studies, we found that more than 6 months

of HT improved sleep quality. Our results provide evidence for the clinical application of HT on menopausal sleep disturbances.

A previous study has proved the sedative and hypnotic effects of progesterone.³⁷ Lancel et al³⁸ demonstrated that progesterone metabolites could produce similar changes to sleep architecture as benzodiazepines. We conducted subgroup analyses to estimate the effect of progesterone on sleep quality. Estrogen plus progesterone alleviated sleep disturbance, but estrogen monotherapy did not. Furthermore, both the estrogen plus micronized progesterone group and the estrogen plus MPA group improved sleep quality, and the former showed a better effect. However, formulations of estrogen may be a confounding factor. Consistent with the study, Leeangkoonsathia et al³⁰ reported improved sleep quality in the EV plus micronized progesterone group and the EV plus dydrogesterone group. Montplaisir et al observed improved sleep efficiency in the micronized progesterone group. In postmenopausal women taking estrogen, they also observed increased subjective sleep quality in the micronized progesterone and the MPA group.¹⁵ Together with our results, the evidence indicated the critical role of progesterone on sleep.

A previous meta-analysis favored oral micronized progesterone for sleep onset latency but not total sleep time or sleep efficiency.³⁹ We also analyzed the effects of HT on different sleep parameters of polysomnography. Because previous studies showed significant improvements in other menopausal symptoms in women who received estrogen therapy for four weeks,^{40,41} we excluded the studies with HT less than four weeks. Our pooled results indicated that HT had no beneficial effects on sleep parameters in postmenopausal women, including total sleep time, sleep latency, sleep efficiency, and arousals.

In addition, the pooled-analysis outcomes of polysomnography were inconsistent with that of subjective sleep scores. The possible reasons may be as follows: first, the studies measured with polysomnography were conducted in small samples on one or few nights, the polysomnography without long-term monitoring might not always correlate with perceived sleep quality.^{42,43} Second, objective sleep outcomes were assessed only in a few studies. Therefore, the pooled analysis results may be dubious. Mansikkamaki et al⁴⁴ demonstrated that subjective symptoms were vital to assess sleep quality. A previous systematic review also showed that patients reported measurements were highly predictive of sleep quality.⁴⁵ A clinical guideline-recommended subjective sleep measurements as instruments to diagnose and evaluate chronic insomnia.⁴⁶ However, self-reported sleep quality items have some defects, such as a lack of standardized assessment tools. It is of importance for standardizing sleep assessments tools in further study.

Limitations

There are several limitations of this systematic review and meta-analysis. First, the studies included in our meta-analysis may have publication bias. One of the underlying reasons may

be that some studies meeting the eligibility criteria did not report sufficient data for quantitative analysis. The attempts to communicate with authors to obtain missing data were unsuccessful. Second, some of the evidence in this review cannot discern the magnitude of effect on sleep quality through indirect reduction of vasomotor symptoms, which was known to affect sleep quality. Third, since lacking original studies, our meta-analysis could not directly estimate the effects of different routes of administration and formulations of HT on sleep quality. Fourth, we found that more than 6 months of HT improved sleep quality, but the ideal timing for the duration of HT on sleep disturbance remains vague. Finally, several studies carried potential risks of bias, such as attrition bias and pharmaceutical industry funding. Despite this, our study provides a comprehensive review of the current literature guided by a prospectively registered protocol. Overall, the conclusions drawn from this review represent a current collation of best evidence.

CONCLUSIONS

In conclusion, HT has a beneficial effect on sleep disturbance to some extent, and the formulations and routes of administration of hormonal agents influence the effect size. Our findings from indirect evidence support the use of transdermal 17 β -estradiol combined with micronized progesterone for at least 6 months in menopausal women with sleep disturbance. However, further head-to-head RCTs with multicenter and larger sample sizes are needed to evaluate the effects of different routes of administration and formulations of HT on sleep quality to provide direct evidence.

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