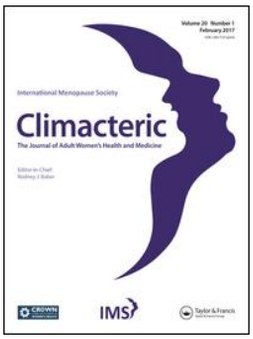

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ORIGINAL ARTICLE

Effect of external sleep disturbance on sleep architecture in perimenopausal and postmenopausal women

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ABSTRACT

Objective: This study aimed to use external sleep disturbance as a model to evaluate sleep architecture in climacteric women before and after menopausal hormone therapy (MHT).

Methods: Seventeen perimenopausal and 18 postmenopausal women underwent a polysomnography protocol: an adaptation night, a reference night and a sleep disturbance night with one hand loosely tied to the bed for blood sampling. The sleep architecture of the reference and disturbance nights were compared. The 24-h urinary free cortisol concentration (UFC) was measured. The procedure was repeated after 6 months on MHT or placebo.

Results: Fifteen perimenopausal and 17 postmenopausal women completed the study. The perimenopausal and postmenopausal groups were combined. During external sleep disturbance, sleep was shorter and more fragmented; with less stage 2, slow-wave and rapid eye movement (REM) sleep and more wake time and awakenings, both at baseline and after the treatment period. Compared to the placebo group, sleep disturbance was minor for women on MHT: sleep was not shortened and the amount of slow-wave sleep did not decrease. Increased 24-h UFC was observed only during MHT.

Conclusions: Sleep in climacteric women is easily disturbed, leading to shorter and more fragmented sleep with less deep sleep and REM sleep. Six months of MHT attenuates the observed sleep disturbance.

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Climacteric; menopause; sleep; sleep disturbance; menopausal hormone therapy

CLINICAL TRIAL REGISTRATION
This trial was not registered because enrollment began prior to 1 July 2005

Introduction

Sleep complaints increase during climacteric [1,2] but the exact influence of climacteric on sleep architecture remains controversial [1,3–7]. Lampio et al. [6] showed age-dependent deterioration in sleep architecture over 6 years in menopausal transition, but higher serum follicle stimulating hormone (S-FSH) concentrations were linked to deeper sleep. Some reports comparing premenopause to postmenopause have also shown an increase in deep sleep and total sleep time [1,5] while others have shown no change [3,4] in sleep architecture. During midlife and climacteric, many women experience several symptoms, such as vasomotor symptoms, depression, anxiety and pain. These symptoms often span a time frame of several years or even decades, and are suggested to interfere with sleep [2].

While climacteric symptoms may induce an internal sleep disturbance, external sleep-disturbing factors (e.g. nocturnal noises or increased psychological stress levels during daytime) also pose a significant problem during climacteric. The increase in self-reported sleep problems in postmenopause is more pronounced during workdays than during leisure days [8]. This suggests that postmenopausal women may be more vulnerable to sleep interference due to work-related psychological strain and its effects on catecholamine levels. Even so, they still have a well-preserved recovery potential after sleep deprivation [9].

Menopausal hormone therapy (MHT) helps women to cope with climacteric symptoms, including insomnia [2]. However, while MHT improves subjective sleep quality, studies on sleep architecture have failed to demonstrate consistent MHT-related sleep changes *per se* or MHT's association with symptom relief [10–13]. It has, however, been proposed that MHT in postmenopausal women may ameliorate sleep architecture and cortisol responses to mild stressors, such as indwelling intravenous catheter and nocturnal blood sampling [14–16], suggesting that sleep laboratory-related stressors can be used as surrogate markers for climacteric sleep disturbance.

Based on the aforementioned rationale, we aimed to investigate whether external sleep disturbance in the form of an intravenous line with one arm loosely tied to the bed for serial blood sampling is associated with deterioration in sleep architecture compared to an undisturbed night of

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sleep in perimenopausal and postmenopausal women. Furthermore, we wanted to evaluate whether 6-month oral MHT influences this response. We analyzed 24-h urinary free cortisol concentration (UFC) as a measure of the hypothalamic–pituitary–adrenocortical axis activity. We hypothesized that external disturbances would involve increased stress hormone levels and difficulties initiating and maintaining sleep, while MHT would counteract this effect.

Methods

Participants

The study was part of a larger randomized controlled trial (RCT) on the effects of aging, hormonal state and MHT on sleep and cognition performed at the Sleep Research Centre of the University of Turku, Finland, from 2001 to 2004. The women were recruited from the Turku area through announcements in local newspapers. Exclusion criteria consisted of previous cardiovascular (hypertension controlled with medication was accepted), pulmonary, neurological, endocrinological or mental disease as well as alcohol abuse, smoking, excessive caffeine intake and use of medications affecting the central nervous system. Before the study, blood hemoglobin, leucocytes, thrombocytes and serum thyrotropin levels were measured to ensure they fell within normal ranges. Only women with a regular sleep–wake schedule required for inclusion (from 10–11 pm to 6–7 am) were accepted. The reproductive state was defined as perimenopausal if S-FSH levels were lower than 23 IU/ml and the subject had an ongoing regular or irregular menstrual cycle, whereas postmenopausal women were defined by age ($\geq$58 years) and amenorrhea for more than 1 year. The final two study groups comprised 17 perimenopausal women and 18 postmenopausal women. None of the women used MHT upon entering the study. One perimenopausal woman and 13 postmenopausal women had previously used MHT with a washout period of at least 12 months.

Procedure

Polysomnography was performed over three consecutive nights from 11 pm to 7 am. The first night was an adaptation night. The second night served as a reference night to the third, the disturbance night, during which blood samples were drawn from an intravenous line via a tube from the adjacent room every 20 min. To ensure stability of the intravenous line, the subject's arm was loosely attached to the bed, causing continuous external sleep disturbance. For this study, sleep data from the second and third nights were compared. During the sleep phases, only red light was used in the bedroom when needed. The women stayed in the Sleep Research Centre mainly the evenings and nights during the sleep study periods: on the adaption night from 7 pm to 8 am, on the reference night from 7 pm to 1:30 pm and on the sleep disturbance night from 6 pm to 9:30 pm (the ending of the daytime blood collection procedure). The same procedure was repeated at the end of the MHT/placebo treatment period.

S-FSH and serum estradiol were measured in the morning following the adaptation night. The perimenopausal women were studied during the follicular phase of their menstrual cycle. A 24-h urine sample taken during both study nights (reference and disturbance, including daytime collection into a personal container when outside of the Sleep Research Centre) was used to define 24-h UFC. The urine samples were collected without any preservatives, stored at $-70\,^{\circ}C$ until analysis and measured with a liquid chromatography–tandem mass spectrometry system (LC–MS/MS) utilizing an AB Sciex API 3000 LC–MS/MS with an electrospray ionization interface in the negative mode, as described previously [17]. The lowest measurable concentration of free cortisol in urine was 1 nmol/l. The urine samples were analyzed at the Women's Clinic laboratory, HUSLAB, Helsinki, Finland. Height and weight were measured and body mass index (kg/m^2) was calculated accordingly. Demographic data are presented in Table 1.

After the baseline studies, the participants were randomized into either the MHT or placebo group for 6 months in six-person blocks. Perimenopausal women received cyclic MHT (2 mg of estradiol valerate for 16 days and 2 mg of estradiol valerate plus 1 mg of norethisterone for 12 days; Mericomb, Novartis, Basel Switzerland) or a placebo, with administration beginning during the first day of their menstrual cycle. Postmenopausal women received continuous MHT (2 mg of estradiol valerate plus 0.7 mg of noretisterone; Merigest, Novartis) or a placebo. Randomization was performed at the pharmacy of the Turku University Central Hospital, where randomization codes were kept until the data analyses were completed. At the end of the 6-month treatment period, the sleep studies were repeated identically to baseline, and S-FSH, serum estradiol and 24-h UFC concentrations were re-measured. Six women from the postmenopausal group did not complete the 6 months of treatment (four in the MHT group and two in the placebo group) but attended the sleep study after 3–5 months of treatment.

A total of 34 women completed the entire protocol. One perimenopausal (MHT) woman dropped out after randomization for personal reasons. The follow-up studies were performed prior to 6 months of treatment for six postmenopausal women (four on MHT and two on placebo), mainly due to side effects (MHT: bloating and heavy uterine bleeding; placebo: a venous thrombosis of the eye and disturbing climacteric symptoms). Due to insufficient data, one woman from the perimenopausal group and one woman from the postmenopausal group were excluded from the analysis. Thus, final data were taken from 15 perimenopausal and 17 postmenopausal women.

Sleep parameters

The polysomnography recordings were scored offline by experienced scorers (initially by N.K., rescored by P.P.-K. and later by I.V., all blinded from the treatment) using the Rechtschaffen and Kales criteria [18], valid during data

Table 1. Demographic data at baseline.

Variable	*Perimenopausal* (N = *15*)	*Postmenopausal* (N = *17*)	p-*Value*
Age (years)	47.9 ± 0.5	62.7 ± 0.7	<0.001
BMI (kg/m^2)	24.0 ± 0.6	27.8 ± 1.2	<0.05
P-FSH (IU/l)	11.7 ± 1.2	76.4 ± 9.0	<0.001
Serum estradiol (nmol/l)	0.27 ± 0.08	0.03 ± 0.003	<0.05

BMI, body mass index; P-FSH, follicle stimulating hormone.

gathering. The variables calculated were total sleep time, sleep efficiency as the percentage of sleep during time spent in bed, sleep latency to first 30 s of sleep, latency to slow-wave sleep (SWS), latency to rapid eye movement (REM) sleep, percentages of each sleep stage (stage 1 [S1], stage 2 [S2], SWS and REM) of total sleep time, number of sleep stage transitions, wake after sleep onset (WASO), number of awakenings of at least 30 s and number of arousals of at least 3 s. An awakening was determined as entering a wake stage from sleep and the criteria of the American Sleep Disorders Association were used to score arousals [19]. The results of the main effects of MHT on the reference night sleep parameters in both perimenopausal and postmenopausal women have been published previously [12].

Statistical analysis

As the distributions of the variables were skewed and uneven, the between-group, between-night and MHT (MHT vs. placebo at 6 months) effects on demographic and sleep parameters were analyzed using the Kruskal–Wallis *H* test (a non-parametric test for independent samples using Dunn–Bonferroni adjusted significances for each comparison and interaction) both at baseline and at 6 months. As the sleep parameters were observed to be mainly similar between perimenopausal and postmenopausal groups at baseline (see Results; Baseline; Group differences) and no night and group interaction was found, the data for the perimenopausal and postmenopausal groups were combined, and the night effect at baseline as well as the night and MHT versus placebo effects at 6 months were analyzed using these combined groups. The statistical analyses were carried out with Statistical Package for Social Sciences (SPSS) version 24 (IBM Corp., Armonk, NY, USA). All of the results are presented as means and standard errors of the mean. Values of $p < 0.05$ were considered significant.

Ethics

The study was approved by the Ethical Committee of Turku University Central Hospital. All study subjects gave their written informed consent after receiving oral and written study information.

Results

Baseline

Group differences

At baseline, postmenopausal women had more arousals during both reference and disturbance nights and more awakenings during the disturbance night than perimenopausal women. All other sleep parameters were similar between the groups, and there was no night and group interaction. Therefore, for further analyses, the groups were combined (Table 2).

Sleep disturbance effect

The sleep disturbance effect was analyzed using the combined groups. The sleep disturbance night showed less total sleep time and lower sleep efficiency and more WASO and awakenings. Furthermore, the women had more S1 sleep and less S2, SWS and REM sleep during the disturbance night. Additionally, 24-h UFC did not differ between the nights (Table 3).

Six months

Sleep disturbance effect

Using combined perimenopausal and postmenopausal groups, the reference and disturbance nights were first compared separately in the placebo and MHT groups. In the placebo group, the sleep disturbance effect was similar to that observed at baseline, with reduced total sleep time and sleep efficiency; more WASO; and less S2, SWS and REM sleep. The 24-h UFC was unchanged. In contrast, in the MHT group, there were fewer differences in sleep architecture between the nights: WASO, awakenings and S1 sleep increased, and REM sleep decreased during sleep disturbance. In addition, 24-h UFC increased compared to the reference night (Table 4).

MHT effect

When evaluating the sleep architecture during the 6-month disturbance night, the women in the MHT group had longer total sleep time, higher sleep efficiency, shorter SWS latency and less WASO than women in the placebo group. No night and treatment interaction was observed.

Discussion

Our results showed that external sleep disturbance during climacteric deteriorated sleep profoundly. Total sleep time shortened; sleep efficiency and time spent in S2, SWS and REM sleep decreased; and nocturnal wake time and awakenings increased. This effect was similar in both perimenopausal and postmenopausal women. Six months of oral MHT seemed to attenuate the sleep disturbance effect, which partly supported the previously proposed positive effect of MHT on sleep during climacteric [10,11,20,21]. Although

Table 2. Sleep parameters and 24-h UFC at baseline during the reference and disturbance nights.

	Perimenopausal (N = *15*)		*Postmenopausal* (N = *17*)	
Variable	*Reference night*	*Disturbance night*	*Reference night*	*Disturbance night*
Total sleep time (min)	407.9 ± 11.2	355.3 ± 20.6	393.2 ± 11.4	358.4 ± 16.9
Sleep efficiency (%)	85.0 ± 2.3	74.0 ± 4.3	81.9 ± 2.4	74.6 ± 3.5
Sleep latency (min)	17.3 ± 4.6	18.9 ± 3.8	16.4 ± 3.6	17.9 ± 2.8
SWS latency (min)	20.8 ± 3.9	17.9 ± 4.0	18.7 ± 4.9	16.9 ± 3.8
REM latency (min)	73.8 ± 5.8	85.3 ± 13.9	71.5 ± 7.2	98.3 ± 18.5
S1 sleep (%)	7.9 ± 0.9	8.8 ± 0.8	8.1 ± 0.8	10.1 ± 0.8
S2 sleep (%)	43.4 ± 2.3	38.3 ± 2.9	39.3 ± 1.5	35.5 ± 2.3
SWS (%)	12.2 ± 1.5	10.0 ± 1.2	14.9 ± 1.7	12.3 ± 1.3
REM sleep (%)	21.4 ± 1.8	16.9 ± 2.0	19.5 ± 1.3	16.6 ± 1.5
WASO (%)	11.4 ± 1.9	22.0 ± 4.1	14.7 ± 1.9	21.7 ± 3.3
Sleep stage transitions (*N*)	161.9 ± 8.2	159.3 ± 11.9	172.5 ± 10.5	177.2 ± 10.2
Awakenings (*N*)	17.4 ± 1.8	21.3 ± 3.0	20.9 ± 2.2	25.4 ± 1.7$^{\#}$
Arousals (*N*)	97.9 ± 11.6	97.1 ± 15.1	153.7 ± 18.1*	142.8 ± 14.6$^{\#\#}$
24-h UFC (nmol)	76.6 ± 8.1	79.7 ± 10.8	70.2 ± 10.1	75.8 ± 10.4

$^{*}p < 0.05$ for group (perimenopausal vs. postmenopausal) difference during the reference nights.
$^{\#}p < 0.05$ and $^{\#\#}p < 0.01$ for group (perimenopausal vs. postmenopausal) difference during the disturbance nights.
For 24-h UFC, $N = 13$ for both perimenopausal and postmenopausal women. REM, rapid eye movement; S1, stage 1; S2, stage 2; SWS, slow-wave sleep; UFC, urinary free cortisol concentration; WASO, wake after sleep onset.

Table 3. Sleep parameters and 24-h UFC at baseline during the reference and disturbance nights (perimenopausal and postmenopausal groups combined).

Variable	*Reference night* (N = *32*)	*Disturbance night* (N = *32*)	p-*Value*
Total sleep time (min)	400.1 ± 8.0	357.0 ± 13.0	0.004
Sleep efficiency (%)	83.3 ± 1.7	74.3 ± 2.7	0.004
Sleep latency (min)	16.8 ± 2.8	18.4 ± 2.3	ns
SWS latency (min)	19.7 ± 3.1	17.4 ± 2.7	ns
REM latency (min)	72.6 ± 4.6	92.2 ± 11.7	ns
S1 sleep (%)	8.0 ± 0.6	9.5 ± 0.6	0.005
S2 sleep (%)	41.3 ± 1.4	36.8 ± 1.8	0.015
SWS (%)	13.6 ± 1.2	11.2 ± 0.9	0.009
REM sleep (%)	20.4 ± 1.1	16.8 ± 1.2	0.019
Sleep stage transitions (*N*)	167.5 ± 6.7	168.8 ± 7.8	ns
WASO (%)	13.2 ± 1.4	21.9 ± 2.6	0.003
Awakenings (*N*)	19.3 ± 1.4	23.4 ± 1.7	0.015
Arousals (*N*)	127.5 ± 12.0	121.4 ± 11.1	ns
24-h UFC (nmol)	73.5 ± 6.4	77.7 ± 7.4	ns

For 24-h UFC, $N = 27$, perimenopausal and postmenopausal groups combined.
REM, rapid eye movement; S1, stage 1; S2, stage 2; SWS, slow-wave sleep; UFC, urinary free cortisol concentration; WASO, wake after sleep onset.

Table 4. Sleep parameters and 24-h UFC values at 6 months during the reference and disturbance nights (perimenopausal and postmenopausal groups combined).

	Placebo (N = *16*)		*MHT* (N = *16*)	
Variable	*Reference night*	*Disturbance night*	*Reference night*	*Disturbance night*
Total sleep time (min)	410.1 ± 6.6$^{\#\#}$	350.7 ± 12.8	426.3 ± 7.5	390.2 ± 15.2*
Sleep efficiency (%)	85.4 ± 1.4$^{\#\#}$	73.1 ± 2.7	88.8 ± 1.6	81.3 ± 3.2*
Sleep latency (min)	9.2 ± 2.0	12.6 ± 2.9	13.6 ± 2.8	16.8 ± 3.2
SWS latency (min)	19.7 ± 3.8	21.6 ± 3.1	25.4 ± 7.2	13.7 ± 2.0*
REM latency (min(	74.3 ± 6.4	97.3 ± 13.6	68.9 ± 4.5	67.9 ± 4.7
S1 sleep (%)	7.6 ± 0.5	8.0 ± 0.9	6.2 ± 0.6$^{\#}$	8.8 ± 1.2
S2 sleep (%)	45.2 ± 1.7$^{\#}$	39.6 ± 2.1	45.8 ± 1.9	42.0 ± 1.8
SWS (%)	10.1 ± 1.6$^{\#}$	7.6 ± 1.4	11.9 ± 2.0	10.2 ± 1.3
REM sleep (%)	22.5 ± 1.3$^{\#}$	17.9 ± 2.1	24.9 ± 1.4$^{\#\#}$	20.3 ± 1.8
Sleep stage transitions (*N*)	169.8 ± 9.9	154.9 ± 10.2	150.9 ± 7.9	168.3 ± 12.5
WASO (%)	12.7 ± 1.5$^{\#\#}$	24.3 ± 2.4	8.4 ± 1.4$^{\#}$	15.2 ± 3.2
Awakenings (*N*)	24.8 ± 2.4	29.4 ± 4.5	17.4 ± 1.6$^{\#\#}$	23.1 ± 2.3*
Arousals (*N*)	136.6 ± 18.0	118.6 ± 14.8	127.6 ± 15.0	133.4 ± 16.9*
24-h UFC (nmol)	64.3 ± 9.7	75.7 ± 11.8	63.0 ± 7.0$^{\#}$	85.5 ± 9.8

$^{*}p < 0.05$ for MHT effect.
$^{\#}p < 0.05$, $^{\#\#}p < 0.01$ for sleep disturbance effect.
Perimenopausal and postmenopausal groups combined. For dU-cortisol, $N = 9$ in placebo and $N = 11$ in MHT group. MHT, menopausal hormone therapy; REM, rapid eye movement; S1, stage 1; S2, stage 2; SWS, slow-wave sleep; UFC, urinary free cortisol concentration; WASO, wake after sleep onset.

disturbed sleep presumably causes distress, 24-h UFC was increased only for the MHT group.

Sleep disruption is a common problem in modern society. Importantly, sleep loss, originating either from curtailed sleep or from sleep fragmentation, is detrimental for health, having negative effects on glucose and lipid metabolism as well as the immune system [22]. Considering also the possible sex differences in vulnerability to sleep disturbance elements, research in this field is warranted. For instance, middle-aged and older women have been shown to be more sensitive to sleep fragmentation induced by night-time traffic noise than men of the same age [23]. However, an earlier study by our team showed that recovery response to a sleep deprivation challenge (40 h) is relatively well preserved also in older women [9].

The research paradigm of using a tied arm facilitating frequent blood sampling as a sleep-disturbing factor could be considered to simulate the sleep disturbance caused by other everyday means, such as outside stressors or nocturnal menopausal symptoms in climacteric women. Few previous studies have used a comparable study set-up with similar findings [14–16]. In concordance with our findings, those previous studies showed a decrease in REM sleep and an increase in wake time [14–16]; a decrease in sleep efficiency, SWS and S2 sleep [15,16]; and an increase in awakenings [15] during the disturbed sleep. In the study by Moe et al. [14], sleep latency increased during the catheter night, which was not demonstrated in our study nor in the others [15,16]. In our study, the findings of shorter and lighter sleep with increased sleep fragmentation during disturbed conditions were successfully repeated after 6 months.

The rather unanimous beneficial effect of MHT on subjective sleep quality described in the literature [2] has been disputed by studies on sleep architecture, where the effect was at most minor [1,2,10–16,20,24–26]. Previous RCTs were conducted with a moderately small number of women and different climacteric symptomologies [10–13,16,24,25]. Cross-sectional studies with a greater sample size have shown more deep sleep in postmenopausal women compared to premenopausal women and a favorable effect of MHT during normal conditions [1,26]; less wake time [26] and less S1 sleep; and more deep sleep [1] on MHT. However, after 40 h of total sleep deprivation, MHT use was not beneficial for the recovery response in our previous cross-sectional study [9].

Previous studies with similar disturbed conditions to our study (i.e. nocturnal blood sampling) have shown that MHT use after menopause induces less proneness to external disturbances as compared to non-users [14,15] or a placebo group [16]. We found that the group of women taking MHT had longer sleep, higher sleep efficiency and less awakenings during the disturbed night compared to the group taking placebo, although there was no night and treatment interaction. Our results are mostly in line with the study by Caufriez et al. [16], which showed longer sleep, higher sleep efficiency, more time spent in SWS and less time awake on MHT compared to a placebo during the disturbance night. Prinz et al. [15] demonstrated a treatment interaction in sleep efficiency and SWS; these sleep parameters deteriorated less in MHT users compared to non-users during the disturbed condition. Likewise, Moe et al. [14] found less impairment in sleep parameters, especially SWS, in MHT users compared to non-users. The aforementioned studies had some differences in their designs, which could partly explain the variations in outcomes. The studies by Moe et al. [14] and Prinz et al. [15] were cross-sectional (i.e. MHT use was self-selected before the study), whereas the study by Caufriez et al. [16] was an RCT similar to ours, but also a cross-over with only eight subjects.

Acute stress, both physiological and psychological, leads to a rapid increase in cortisol secretion, while chronic stress can trigger either an increase or decrease in cortisol levels [27,28]. Research shows that hypothalamic–pituitary–adrenocortical axis and autonomic nervous system responses to stress differ according to sex and menopausal status [29]. Studying different phases of menopause, Woods et al. [30] observed increased morning urine cortisol concentrations in the late menopausal transition stage in association with more severe vasomotor symptoms. In our previous study, we were unable to demonstrate any effect of menopause or postmenopausal MHT on 24-h serum cortisol levels although perimenopausal MHT increased the serum cortisol concentration [31]. In our present RCT, 24-h UFC increased from the reference night to the disturbance night but only in the MHT group, even if the sleep disturbance effects were minor while on MHT. However, the concentrations seemed to increase in all groups (combined group at baseline; MHT and placebo groups after treatment), but reached significance only in the MHT group. In contrast, an observational study with a similar set-up of external disturbance demonstrated elevated 24-h UFC in a combined group of postmenopausal women with or without self-chosen MHT. These elevated concentrations were only associated with impaired sleep in women without self-chosen MHT. In line with our RCT, this previous study also failed to show a difference in 24-h UFC between the study groups (with MHT and without MHT) [15]. Most previous evidence in the field also suggests that MHT attenuates the hypothalamic–pituitary–adrenocortical axis response to acute stress rather than enforcing it [29], as our present study might suggest. Recent data on menopausal women has shown an association specifically between psychological stress and 24-h UFC [32]. Accordingly, it is also plausible that the stress created with our sleep disturbance was not psychologically demanding.

There are some limitations to our study. First, the total sample size was small but comparable to other RCT polysomnographic studies in the field. Second, six women from the postmenopausal group did not complete the 6 months of treatment. However, all of them had at least 3 months of treatment, which can be considered sufficient to draw conclusions on the treatment efficacy in clinical practice. Third, the improvement in sleep parameters during MHT was observed when combining the groups of the study, but not when analyzing the perimenopausal and postmenopausal groups separately probably due to the small number in subgroups. Fourth, since the sleep data were collected and analyzed between 2001 and 2004, the sleep stage analysis was

performed using the Rechtschaffen and Kales criteria [18], instead of the American Academy of Sleep Medicine criteria [33]. This may lead to overestimation of S2/N2 sleep and underestimation of S1/N1 sleep and SWS in our data [34]. As the difference was consistent across all groups and nights, it is unlikely that this could form an error in the interpretation. Fourth, we recruited only generally healthy women; therefore, we cannot extrapolate our results to women with chronic diseases. Furthermore, while we did not enroll women with previous diagnoses of sleep apnea and restless legs syndrome, we did not use leg electrodes or nasal pressure transducers during the polysomnography sessions. Therefore, undiagnosed diseases could not be ruled out. The most important strength of the study was the double-blinded RCT design.

Conclusions

Sleep architecture during climacteric is easily disturbed by external disturbances, leading to a shorter sleep, decreased amounts of deep sleep and REM sleep and increased sleep fragmentation. However, after 6 months of MHT, women showed fewer sleep disturbance effects compared to those found in the placebo group, and had a better sleep efficiency overall on the sleep disturbance night than the placebo group, suggesting that MHT may play a role in stabilizing sleep architecture.

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References

[1] Young T, Rabago D, Zgierska A, et al. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin sleep cohort study. Sleep. 2003; 26(6):667–672.
[2] Polo-Kantola P. Sleep probems in midlife and beyond. Maturitas. 2011;68(3):224–232.
[3] Shaver J, Giblin E, Lentz M, et al. Sleep patterns and stability in perimenopausal women. Sleep. 1988;11(6):556–561.
[4] Kalleinen N, Polo-Kantola P, Himanen S-L, et al. Sleep and the menopause – do postmenopausal women experience worse sleep than premenopausal women? Menopause Int. 2008;14(3): 97–104.
[5] Hachul H, Frange C, Bezerra AG, et al. The effect of menopause on objective sleep parameters: data from an epidemiologic study in São Paulo, Brazil. Maturitas. 2015;80(2):170–178.
[6] Lampio L, Polo-Kantola P, Himanen S-L, et al. Sleep during menopausal transition: a 6-Year follow-up. Sleep. 2017;40(7):zsx090.
[7] Kalleinen N, Aittokallio J, Lampio L, et al. Sleep during menopausal transition: a 10-year follow-up. Sleep. 2021;44(6):zsaa283.
[8] Lampio L, Saaresranta T, Polo O, et al. Subjective sleep in premenopausal and postmenopausal women during workdays and leisure days: a sleep diary study. Menopause. 2013;20(6):655–660.
[9] Kalleinen N, Polo O, Himanen S-L, et al. Sleep deprivation and hormone therapy in postmenopausal women. Sleep Med. 2006; 7(5):436–447.
[10] Polo-Kantola P, Erkkola R, Irjala K, et al. Effect of short-term transdermal estrogen replacement therapy on sleep: a randomized, double-blind crossover trial in postmenopausal women. Fertil Steril. 1999;71(5):873–880.
[11] Scharf MB, Berkowitz DV, Reape KZ. Effects of synthetic conjugated estrogens A on sleep quality in postmenopausal women with nocturnal diaphoresis and/or hot flushes: a pilot study. Fertil Steril. 2007;88(3):654–656.
[12] Kalleinen N, Polo O, Himanen S-L, et al. The effect of estrogen plus progestin treatment on sleep: a randomized, placebo-controlled, double-blind trial in premenopausal and late postmenopausal women. Climacteric. 2008;11(3):233–243.
[13] Hachul H, Bittencourt L, Andersen M, et al. Effects of hormone therapy with estrogen and/or progesterone on sleep pattern in postmenopausal women. Int J Gynaecol Obstet. 2008;103(3):207–212.
[14] Moe KE, Larsen LH, Vitiello MV, et al. Estrogen replacement therapy moderates the sleep disruption associated with nocturnal blood sampling. Sleep. 2001;24(8):886–894.
[15] Prinz P, Bailey S, Moe K, et al. Urinary free cortisol and sleep under baseline and stressed conditions in healthy senior women: effects of estrogen replacement therapy. J Sleep Res. 2001;10(1): 19–26.
[16] Caufriez A, Leproult R, L'Hermite-Balériaux M, et al. Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women. J Clin Endocrinol Metab. 2011;96(4):E614–23.
[17] Katainen R, Kalleinen N, Teperi S, et al. The relationship between diurnal cortisol secretion and climacteric-related symptoms. Maturitas. 2018;115:37–44.
[18] Rechtschaffen A, Kales A. A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects. Los Angeles, California: Brain Information Service/Brain Research Institute, University of California; 1968.
[19] The Atlas Task Force: Bonnet M, et al. ASDA report. [100] EEG arousals: scoring rules and examples. Sleep. 1992;15:173–184.
[20] Montplaisir J, Lorrain J, Denesle R, et al. Sleep in menopause: differential effects of two forms of hormone replacement therapy. Menopause. 2001;8(1):10–16.
[21] Baker FC, Lampio L, Saaresranta T, et al. Sleep and sleep disorders in the menopausal transition. Sleep Med Clin. 2018;13(3): 443–456.
[22] Potter GD, Skene DJ, Arendt J, et al. Circadian rhythm and sleep disruption: causes, metabolic consequences, and countermeasures. Endocr Rev. 2016;37(6):584–608.
[23] Gerbase MW, Dratva J, Germond M, et al. Sleep fragmentation and sleep-disordered breathing in individuals living close to main roads: results from a population-based study. Sleep Med. 2014; 15(3):322–328.
[24] Purdie DW, Empson JA, Crichton C, et al. Hormone replacement therapy, sleep quality and psychological wellbeing. Br J Obstet Gynaecol. 1995;102(9):735–739.
[25] Saletu-Zyhlarz G, Anderer P, Gruber G, et al. Insomnia related to postmenopausal syndrome and hormone replacement therapy:

sleep laboratory studies on baseline differences between patients and controls and double-blind, placebo-controlled investigations on the effects of a novel estrogen-progestogen combination (Climodien, Lafamme) versus estrogen alone. J Sleep Res. 2003; 12(3):239–254.

[26] Hachul H, Andersen M, Bittencourt L, et al. Does the reproductive cycle influence sleep patterns in women with sleep complaints? Climacteric. 2010;13(6):594–603.

[27] Hannibal KE, Bishop MD. Chronic stress, cortisol dysfunction, and pain: a psychoneuroendocrine rationale for stress management in pain rehabilitation. Phys.Ther. 2014;94(12):1816–1825.

[28] Miller GE, Chen E, Zhou ES. If it goes up, must it come down? Chronic stress andthe hypothalamic-pituitary-adrenocortical axis in humans. Psychol Bull. 2007;133(1):25–45.

[29] Kajantie E, Phillips DI. The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology. 2006;31(2):151–178.

[30] Woods NF, Carr MC, Tao EY, et al. Increased urinary cortisol levels during the menopausal transition. Menopause. 2006;13(2):212–221.

[31] Kalleinen N, Polo-Kantola P, Irjala K, et al. 24-hour serum levels of growth hormone, prolactin, and cortisol in pre- and postmenopausal women: the effect of combined estrogen and progestin treatment. J Clin Endocrinol Metab. 2008;93(5):1655–1661.

[32] Cagnacci A, Xholli A, Fontanesi F, et al. Treatment of menopausal symptoms: concomitant modification of cortisol. Menopause. 2021;29(1):23–27.

[33] Iber C, Ancoli-Israel S, Chesson A, et al. The AASM manual for the scoring of sleep and associated events: rules, terminology, and technical specifications, 1st ed. Westchester, Illinois: american Academy of Sleep Medicine; 2007.

[34] Moser D, Anderer P, Gruber G, et al. Sleep classification according to AASM and Rechtschaffen & Kales: effects on sleep scoring parameters. Sleep. 2009;32(2):139–149.