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ORIGINAL ARTICLE

Sleep during menopausal transition: a 10-year follow-up

Nea Kalleinen[1,2,‡], Jenni Aittokallio[1,3,4,‡,*], Laura Lampio[1,5], Matti Kaisti[6], Päivi Polo-Kantola[1,7], Olli Polo[8], Olli J. Heinonen[9] and Tarja Saaresranta[1,10]

[1]Department of Pulmonary Diseases and Clinical Allergology, Sleep Research Center, University of Turku, Turku, Finland, [2]Heart Center, Turku University Hospital, University of Turku, Turku, Finland, [3]Department of Anesthesiology and Intensive Care, University of Turku, Turku, Finland, [4]Division of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Turku, Finland, [5]Department of Obstetrics and Gynecology, Helsinki University Hospital, Helsinki, Finland, [6]Department of Future Technologies, University of Turku, Turku, Finland, [7]Department of Obstetrics and Gynecology, Turku University Hospital and University of Turku, Turku, Finland, [8]Bragée ME/CFS Center, Stockholm, Sweden, [9]Paavo Nurmi Centre and Unit for Health & Physical Activity, University of Turku, Turku, Finland and [10]Division of Medicine, Department of Pulmonary Diseases, Turku University Hospital, Turku, Finland

[‡]The first two authors have contributed equally to the manuscript and have a dual co-first authorship.

*Corresponding author. Jenni Aittokallio, Department of Anesthesiology and Intensive Care, University of Turku, PO Box 51 (Kiinamyllynkatu 4-8), FI-20521 Turku, Finland. Email: jemato@utu.fi.

Abstract

Study Objectives: A 10-year observational follow-up study to evaluate the changes in sleep architecture during the menopausal transition.

Methods: Fifty-seven premenopausal women (mean age 46 years, *SD* 0.9) were studied at baseline and after a 10-year follow-up. At both time points, polysomnography (PSG) was performed, and the serum follicle-stimulating hormone (S-FSH) concentration was measured. Linear regression models were used to study the effects of aging and menopause (assessed as change in S-FSH) on sleep.

Results: After controlling for body mass index, vasomotor, and depressive symptoms, higher S-FSH level was associated with longer sleep latency (B 0.45, 95% confidence interval [CI]: 0.07 to 0.83). Aging of 10 years was associated with shorter sleep latency (B –46.8, 95% CI: –77.2 to –16.4), shorter latency to stage 2 sleep (B –50.6, 95% CI: –85.3 to –15.9), decreased stage 2 sleep (B –12.4, 95% CI: –21.4 to –3.4), and increased slow-wave sleep (B 12.8, 95% CI: 2.32 to 23.3) after controlling for confounding factors.

Conclusions: This study suggests that PSG measured sleep of middle-aged women does not worsen over a 10-year time span due to the menopausal transition. The observed changes seem to be rather age- than menopause-dependent.

Statement of Significance

Sleep complaints increase markedly during the menopausal transition. However, the studies evaluating sleep architecture have produced conflicting results. Few longitudinal studies with polysomnography parameters have assessed sleep across menopause. This article reports changes in sleep architecture in 57 midlife women across 10 years (mean ages 46 and 56 years). According to the current results, the amount of light sleep decreased over time, but instead sleep latency shortened and the amount of deep sleep increased.

Key words: menopause; sleep architecture; polysomnography (PSG); slow-wave sleep (SWS); sleep latency; follicle stimulating hormone (FSH); aging

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Introduction

Sleep complaints are more common for women than men at any phase of their life [1], and the incidence of complaints increases markedly in women during the menopausal transition [2–4]. Sleep architecture also changes across the life span [5], but the effect of menopausal transition is controversial. The studies evaluating sleep architecture in menopausal transition are sparse and mainly cross sectional, showing few or no changes [6, 7] or suggesting even better sleep after menopause [2, 8]. There are only two previous longitudinal studies with objective sleep parameters in middle-aged women, and they produced conflicting findings. The first one is our own 6-year follow-up study across the menopausal transition, where polysomnography (PSG) showed worse sleep architecture in terms of shorter total sleep time (TST), lower sleep efficiency, more wake time after sleep onset (WASO), and a higher number of awakenings and transitions from slow-wave sleep (SWS) to wakefulness in association to aging [9]. An increase in serum follicle-stimulating hormone (S-FSH) concentration, a biomarker of menopause, was associated with better sleep architecture by minor increase of SWS [9]. The other one is a wrist actigraphy study with 12 years of follow-up showing an increase in TST and decline in WASO over time [10]. Unlike our study, the latter reported neither S-FSH levels for the menopausal state nor PSG for sleep architecture.

The remarkable changes in hormonal milieu during menopausal transition have been proposed to interact with sleep and explain increased sleep complaints. Few studies have investigated the associations between S-FSH concentration, a commonly used biomarker of menopausal state, and objective sleep parameters in healthy women. Although the results are inconsistent, the majority of the studies have found no association between S-FSH level and sleep architecture [11–13]. However, one study showed a positive association between S-FSH level and WASO in young premenopausal and middle-aged perimenopausal women [14] and another that a more rapid increase in S-FSH level during the preceding 7 years was positively associated with SWS and TST in women aged 48–59 years [15]. All these studies are cross sectional. Moreover, to the best of our knowledge, our previous 6-year follow-up study is so far the only one showing a positive association between S-FSH level and SWS in a longitudinal setting [9].

The primary aim of this study was to evaluate the effects of menopausal hormonal changes and aging on sleep architecture across 10 years in middle-aged women. The longitudinal setting enabled us to separately evaluate the effects of S-FSH level and aging. Since the women were aged 46 years at the baseline, the 10-year time span enabled us to evaluate the changes over menopause. The current study is a continuation of our previous 6-year follow-up study investigating the evolution of sleep during menopausal transition. We hypothesized that the trends in sleep architecture observed at 6-year follow-up (assessed with PSG) would continue to evolve into postmenopausal era.

Methods

This study was conducted during the years 2001–2017 as a part of a larger prospective "Woman 46" study investigating sleep and cardiovascular risk factors in middle-aged women. Altogether, 147 women, aged 46 years, were recruited through newspaper announcements in the Turku city area, Finland. The study had the approval of the Ethics Committee of the Hospital District of Southwest Finland (§231 September 18, 2001, and §275 August 6, 2013). All women gave written informed consent. Participants with coronary heart disease, respiratory insufficiency, sleep apnea, neurological disease, liver disease, malignancies, or alcohol abuse were excluded. The women were studied at baseline, at 6-year follow-up, and at 10-year follow-up time points. The results of the changes in sleep architecture from the baseline to the 6-year follow-up have been reported previously [9]. Of the 147 women studied at baseline, 116 were considered premenopausal (S-FSH < 20 international units/liter [IU/L]) and thus eligible for the present study. Of these women, 32 refused to participate or were missed at the follow-up. Furthermore, 3 women at the baseline and 4 women at the 10-year follow-up had missing data, and 21 women were using menopausal hormone therapy (MHT) at the follow-up and thus they were excluded. The data of the remaining 57 women were included in the present study (Figure 1). Four women were hysterectomized before the baseline study. At the10-year follow-up, all women were postmenopausal defined by S-FSH level > 30 IU/L and amenorrhea > 12 months for those without hysterectomy. In determining the postmenopausal state, we did not only rely on self-reported history of amenorrhea but also used increased S-FSH level as a biomarker of menopause. Five women (8.8%) at the baseline and nine women (15.7%) at the10-year follow-up were using medication with central nervous system effects. The medications used at the baseline were doxepin (n = 1), nortriptyline (n = 1), citalopram (n = 1), amitriptyline (n = 1), and venlafaxine (n = 1). At the10-year follow-up, there was use of pramipexole (n = 2), gabapentin (n = 2), sertraline (n = 1), amitriptyline (n = 3), pregabalin (n = 1), or betahistine (n = 1).

The blood sample for S-FSH measurement was taken in the morning on the day of the sleep study and measured with time-resolved immunofluorometric assay (AutoDELFIA;

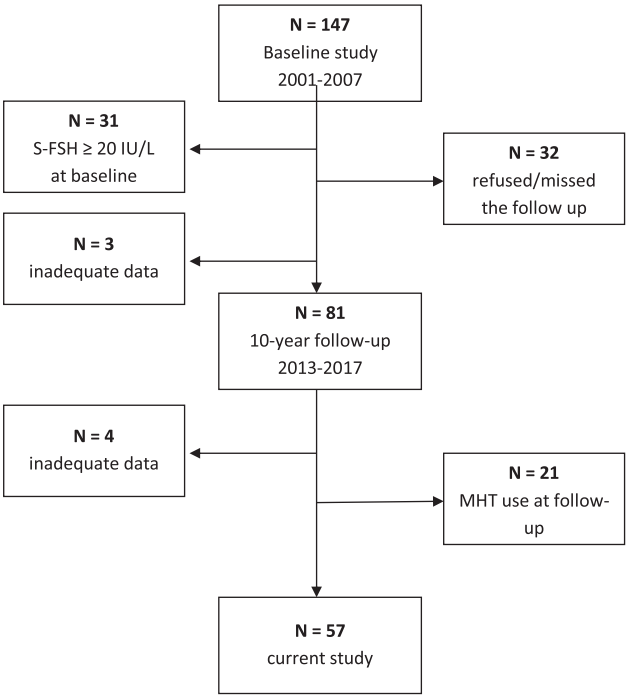

Figure 1. Flow chart of the study.

PerkinElmer Life and Analytical Sciences, Wallac Oy, Turku, Finland). The FSH laboratory assays of our study were solid phase, two-site fluoroimmunometric assays based on the direct sandwich technique (two monoclonal antibodies directed against two separate antigenic determinants on the hormone molecules). At the baseline, menstruating women were studied at the beginning of their follicular phase (days 1–7 of the menstrual cycle). Body mass index (BMI, kg/m^2) was calculated from height and weight measurements at the baseline and the follow-up. Other background variables were assessed with questionnaires at the baseline and the follow-up. Vasomotor symptoms during the past 6 months were scored with two questions (night sweats and hot flashes). The frequency of the symptoms was determined on a four-point scale: one ("seldom or never"), two ("approx. once a month"), three ("approx. once a week"), and four ("almost every day"). Depressive symptoms were screened by the Beck Depression Inventory (BDI) [16]. Marital status/committed relationship was classified as yes or no, and education was categorized into lower (elementary school to middle school) or higher (middle school + college-level training to academic education).

Sleep recordings

Sleep studies were carried out in the sleep laboratory of The Turku Sleep Research Centre both at baseline and at 10-year follow-up with the same device. PSG recordings at both time points comprised continuous monitoring of electroencephalograms (EEG; C3/A2, C4/A1, O1/A2, and O2/A1), two electrooculograms, and a mandibular electromyogram (Embla, Medcare Flaga hf. Medical Devices, Reykjavik, Iceland). Nasal inspiratory airflow was measured with nasal prongs connected to a pressure transducer. Arterial oxyhemoglobin saturation (SaO_2) was measured with a finger probe pulse oximeter (Nonin oximeter built in with Embla/Somnologica system; MedcareFlaga hf, Reykjavik, Iceland). All recordings were visually scored in 30-second epochs off-line by an experienced technician according to conventional R–K criteria [17]. The American Academy of Sleep Medicine (AASM) criteria were not used since they were not published at the time of the study initiation. Five sleep stages (stage 1 [S1], stage 2 [S2], stages 3 and 4 [S3 and S4, SWS], and rapid eye movement sleep [REM] sleep), as well as wake after sleep onset (WASO), were classified. Sleep stages were expressed as percentages of TST and WASO as minutes. Sleep onset was defined as the time to the occurrence of three consecutive epochs of stage 1 or the first epoch of any other sleep stage. Latencies to SWS and REM were calculated from the sleep onset to the first occurrence of the respective sleep stage. An awakening was determined as entering a wake stage from sleep. The criteria of the American Sleep Disorders Association were used to score arousals [18]. Arousal index (ARI) was the sum of awakenings per hour and arousals per hour.

Apnea–hypopnea index (AHI) was scored manually. Apnea was defined as at least 90% reduction in airflow (amplitude of the nasal flow signal) for at least 10 seconds, and hypopneas were defined as a minimum reduction of 30% in airflow for at least 10 seconds accompanied by a 4% desaturation before the event. After manually removing the possible artifacts, the mean and minimum SaO_2 levels, percentage of SaO_2 below 90%, and the arterial oxyhemoglobin desaturation events of 4% units or more per hour (ODI_4) were calculated using the Embla/Somnologica system.

Statistical analyses

The dependent *t*-test for paired samples was used to compare within-patient changes for continuous variables (PSG variables, age, BMI, and BDI total score), and the McNemar–Bowker test was used to compare changes in categorical variables (marital status, night sweats, and hot flashes). To further analyze the difference between the baseline and follow-up, we used Cohens' *d* for effect size that indicates the standardized difference between the means of baseline and follow-up. An ordinary least squares regression was fitted for the change of each PSG variable with a change in S-FSH concentration (continuous) and a change in time (10 years, constant) as covariates. This allowed the simultaneous study of the effect of menopausal change and aging on the change in the PSG variables. The regression model yields unstandardized B coefficients, which signify the change in PSG variable when S-FSH concentration increases by 1 IU/L or when time is increased by 10 years. The results were reported with 95% confidence interval (CI). The regression analysis was repeated by including changes in BMI, night sweats, hot flashes, and BDI total score as covariates in the regression model. In addition, post hoc analyses of a regression model including AHI in relation to SWS or sleep latency were performed. The *p*-values <.05 were considered statistically significant, and all *p*-values were two-sided. The statistical analysis was performed using Python software with Pandas 0.25.1, Scipy 1.3.1, and Statsmodels 0.10.1 libraries.

Results

The characteristics of the study sample are reported in Table 1. During the 10-year follow-up, BMI and the frequency of hot flashes increased. At baseline three women and at the 10-year follow-up two women had BDI score > 12. Compared with the baseline, follow-up sleep architecture had changed: S1 sleep, SWS, as well as the frequency of awakenings and arousals increased, whereas S2 sleep and sleep latency to S2 sleep decreased. AHI and ODI_4 increased (Table 2).

In the regression analysis, change in S-FSH concentration was associated with the sleep latency and latency to S2: when S-FSH level increased by 1 IU/L, sleep latency increased by 0.49 minutes and sleep latency to S2 sleep increased by 0.45 minutes. Thus, counted from the mean increase of S-FSH level of 63.1 IU/L in a 10-year follow-up, the increases were 30.91 and 28.40 minutes, respectively. Aging by 10 years was associated with a decrease of 12.4% in S2 sleep, an increase of 8.5% in SWS, as well as a reduction of 40.5 minutes in sleep latency and of 43.4 minutes in sleep latency to S2 sleep and an increase of 12.4 events/hour in ARI. In addition, AHI increased by 19.1 events/hour, ODI4 by 8.8 events/hour, and REM-AHI increased by 33.4 events/hour in association with aging by 10 years. (Table 3, and Supplementary Table S1 for detailed adjusted results, Figures 2 and 3)

After adjustment with BMI, night sweats, hot flashes, and BDI, an increase of 1 unit in S-FSH concentration was associated with an increase of 0.45 minutes (95% CI: 0.07 to 0.83) in sleep latency.

Table 1. Characteristics of the sample at baseline and at the 10-year follow-up expressed as means (*SD*) or percentages

	Baseline (*N* = 57)	10-year follow-up (*N* = 57)	Difference	*P*
Age, y	46.0 (0.9)	56.7 (0.9)	10.7 (0.7)	<.001
S-FSH, IU/L	7.8 (4.0)	70.9 (25.8)	63.1 (6.1)	<.001
BMI, kg/m^2	2.7 (5.6)	29.4 (6.8)	2.7 (2.3)	<.001
Domestic partnership status, %				
Yes	74.1	74.1	0	
No	25.7	25.8	0.1	
Education, %				
Lower	18.9			
Higher	81.0			
Night sweats, %				.103
Almost daily	1.7	12.5	10.8	
Once a week	8.9	23.2	14.3	
Once a month	14.2	7.1	–7.1	
Seldom or never	75.0	57.1	–17.9	
Hot flashes, %				.017
Almost daily	0	13.8	13.8	
Once a week	3.4	15.5	12.1	
Once a month	6.9	10.3	3.4	
Seldom or never	89.7	60.3	–29.4	
BDI total score	5.4 (5.7)	4.7 (3.4)	–0.7 (5.0)	.287

SD, standard deviation; S-FSH, serum follicle stimulating hormone concentration; IU/L, international units per liter; kg/m^2, kilograms per square meter; BMI, body mass index; BDI, Beck Depression Inventory.

Table 2. PSG results at baseline and at the 10-year follow-up, expressed as means (*SD*)

PSG	Baseline (*N* = 57)	10-year follow-up (*N* = 57)	Mean difference	*P*	*d*
TST, min	360.2 (74.2)	349.2 (57.6)	–11.0 (90.4)	.363	–0.16
Sleep efficiency, %	78.6 (16.2)	77.5 (12.4)	–1.1 (19.0)	.671	–0.07
Sleep latency, min	34.1 (25.4)	24.5 (25.9)	–9.7 (36.7)	.051	–0.37
Sleep latency to S2, min	40.5 (30.6)	25.9 (25.9)	–14.5 (40.6)	.009	–0.51
Sleep latency to SWS, min	35.8 (44.3	21.9 (22.5)	–14.7 (49.9)	.034	–0.39
Sleep latency to REM, min	146.0 (72.2)	130.4 (69.4)	–15.7 (84.8)	.172	–0.22
S1, %	8.4 (6.4)	11.2 (7.7)	2.8 (9.1)	.022	0.40
S2, %	55.2 (10.3)	44.5 (7.4)	–10.7 (12.9)	<.001	–1.18
SWS, %	17.9 (11.8)	26.1 (7.4)	8.2 (11.2)	<.001	0.82
REM, %	18.5 (7.1)	18.2 (5.7)	–0.3 (6.8)	.729	–0.05
Sleep stage transitions/h	20.2 (7.1)	18.15 (5.3)	–2.1 (9.2)	.097	–0.33
Transitions from SWS to wake	0.1 (0.3)	0.1 (0.2)	0.0 (0.4)	1	0.00
WASO, min	65.0 (58.7)	77.2 (46.2)	12.1 (66.7)	.174	0.23
Awakenings/h	2.8 (2.3)	4.0 (2.1)	1.2 (2.7)	.002	0.53
Arousals/h	4.8 (3.7)	11.7 (9.1)	6.8 (8.7)	<.001	0.97
ARI/h	7.6 (4.7)	15.5 (10.7)	7.9 (10.4)	<.001	0.94
AHI/h	4.1 (5.0)	14.6 (19.7)	10.5 (18.4)	<.001	0.73
Hypopnea/h	3.4 (4.5)	8.0 (9.8)	4.6 (8.9)	<.001	0.59
REM-AHI/h	9.2 (9.8)	28.9 (32.1)	17.8 (25.9)	<.001	0.82
Mean SaO_2, %	94.5 (4.5)	94.9 (1.8)	0.3 (4.5)	.609	0.10
Minimum SaO_2, %	84.0 (11.1)	87.2 (5.0)	3.0 (11.6)	.058	0.36
Sat < 90 %	2.1 (11.1)	2.9 (8.1)	0.9 (13.1)	.608	0.09
ODI_4, h	4.1 (6.4)	9.7 (13.4)	5.6 (9.9)	<.001	0.53

SD, standard deviation; d, Cohens' d for effect size; min, minutes; TST, total sleep time; S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow wave sleep; h, hour; WASO, wake after sleep onset; REM, rapid eye movement sleep; ARI, arousal index; AHI, apnea–hypopnea index; SaO_2, oxygen saturation; Min SaO_2, minimum oxygen saturation; ODI_4, episodes of arterial oxyhemoglobin desaturation of 4% units or more per hour.

Aging by 10 years resulted in a reduction of 46.8 minutes (95% CI: –77.2 to –16.4) in sleep latency, increase of 12.8% (95% CI: 2.32 to 23.3) in SWS, and a decrease of 50.6 minutes (95% CI: –85.3 to –15.9) in latency to S2 sleep. There was no association between S-FSH level or aging and awakenings, arousals, AHI, and ODI_4 nor REM-AHI after controlling for the confounding factors (Table 3).

Post hoc regression analyses showed no association of AHI neither with SWS nor sleep latency.

Discussion

Sleep is an important determinant of mood, cognitive function, and quality of life. Menopause is a physiologic period of hormonal transition challenging sleep quality. We repeated polygraphic sleep studies and S-FSH measurements at 10-year interval both before and after menopausal transition. Compared with the baseline, sleep polarized on one hand with more S1 sleep, arousals, awakenings, sleep apnea, and hypoxia events but on the other

Table 3. The results of linear regression analyses, expressing the effects of time and FSH on sleep variables

PSG	Effect of time				Effect of FSH			
	B	95% CI	P	Adj. P	B	95% CI	P	Adj. P
TST, min	15.7	−47.2 to 78.5	.620	.266	−0.42	−1.34 to 0.50	.362	.257
Sleep efficiency, %	6.0	−7.2 to 19.1	.368	.231	−0.11	−0.30 to 0.08	.252	.254
Sleep latency, min	−40.5	−64.6 to −16.5	.001	.003	0.49	0.14 to 0.84	.007	.021
Sleep latency to S2, min	−43.4	−70.6 to −16.2	.002	.005	0.46	0.19 to 0.86	.025	.061
Sleep latency to SWS, min	6.2	−29.2 to 41.7	.726	.586	−0.33	−0.84 to 0.19	.205	.124
Sleep latency to REM, min	−3.5	−63.0 to 56.0	.907	.901	−0.19	−1.06 to 0.68	.658	.698
S1, %	6.1	−0.2 to 12.3	.058	.402	−0.05	−0.14 to 0.04	.270	.537
S2, %	−12.4	−21.4 to −3.4	.008	.023	0.03	−0.11 to 0.16	.690	.663
SWS, %	8.5	0.7 to 16.3	.034	.018	0.00	−0.12 to 0.11	.933	.705
REM, %	−2.2	−7.0 to 2.6	.359	.533	0.03	−0.04 to 0.10	.395	.549
Sleep stage transitions/h	0.6	−5.8 to 7.0	.850	.635	−0.04	−0.14 to 0.05	.371	.239
Transitions from SWS to wake	−0.1	−0.3 to 0.2	.494	.587	0.00	−0.002 to 0.005	.459	.579
WASO, min	14.5	−32.2 to 61.3	.536	.807	−0.04	−0.72 to 0.65	.912	.959
Awakenings/h	1.3	−0.6 to 3.2	.178	.784	0.00	−0.03 to 0.03	.905	.708
Arousals/h	11.6	5.6 to 17.5	.000	.051	−0.07	−0.16 to 0.01	.091	.423
ARI/h	12.4	5.2 to 19.6	.001	.124	−0.07	−0.18 to 0.03	.180	.651
AHI/h	19.1	6.4 to 31.8	.004	.741	−0.14	−0.32 to 0.05	.148	.908
Hypopnea/h	10.1	4.0 to 16.1	.002	.346	−0.09	−0.18 to 0.001	.053	.528
REM-AHI / h	33.4	15.8 to 51.0	.000	.147	−0.25	−0.50 to 0.01	.060	.389
Mean SaO_2, %	−0.4	−3.6 to 2.7	.779	.787	0.01	−0.03 to 0.06	.607	.403
Minimum SaO_2, %	4.7	−3.4 to 12.8	.248	.212	−0.03	−0.15 to 0.09	.642	.899
Sat < 90 %	7.7	−1.3 to 16.7	.091	.093	−0.11	−0.24 to 0.02	.105	.124
ODI_4/h	8.8	1.9 to 15.7	.014	.412	−0.05	−0.15 to 0.05	.320	.814

The results are presented as both unadjusted and adjusted with BMI, night sweats, hot flashes, and BDI total score (*p*-values only) and expressed as coefficient B. The effect of time, aging of 10 years; the effect of FSH, 1 unit (IU/L) increase in S-FSH concentration.
BMI, body mass index; BDI, Beck Depression Inventory; S-FSH, serum follicle stimulating hormone; 95% CI, 95% confidence interval; min, minutes; TST, total sleep time; S1, stage 1 sleep; S2, stage 2 sleep; SWS, slow wave sleep; REM, rapid eye movement sleep; WASO, wake after sleep onset; ARI, arousal index; AHI, apnea-hypopnea index; SaO_2, oxygen saturation; Min SaO_2, minimum oxygen saturation; ODI_4, episodes of arterial oxyhemoglobin desaturation of 4% units or more per hour; IU/L, international units per liter.

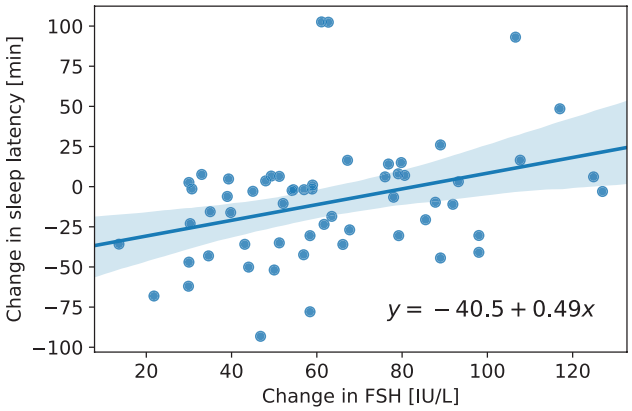

Figure 2. Scatter plot visualization of the relationship between the change in FSH (IU/L) and sleep latency (min). The regression line is given by ordinary least squares linear regression. The regression coefficients, their 95% CIs, and their *p*-values are given in Table 3.

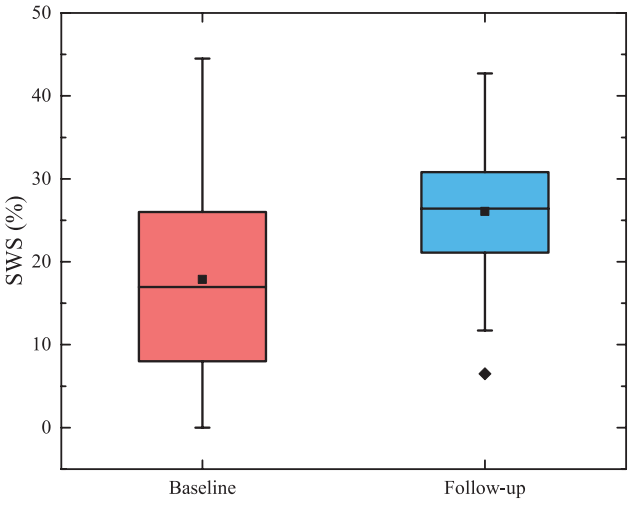

Figure 3. Blox pot visualization of the percentage of SWS at baseline and 10-year follow-up, $p < .001$. Pink color, baseline cohort; blue color, follow-up cohort; diamond, outlier; small squares, means.

hand with more SWS and shorter sleep latency. An unexpected finding was that the S-FSH level and the time factor had opposite effects on sleep latencies. According to multiple linear regression analysis, sleep latencies increased with increasing S-FSH level, whereas they decreased with 10 years of time. Our results demonstrate that the observed changes in sleep architecture across menopause are a composite of several factors, including increasing age and S-FSH level, which not only always essentially need to have additive but can also have opposing effects.

Our study design allowed us to separately study the effects of menopause and aging on sleep. Contrary to our expectations, aging by 10 years through the menopausal period did not worsen sleep architecture, but instead we found a reduction in sleep latency and an increase in the proportion of deep sleep, while no effect was observed in TST. These results are mainly in line with previous studies on middle-aged women

[2, 8, 10], though conflicting with the findings of studies on sleep and aging in general [5, 19]. We used S-FSH concentration as a marker for reproductive aging. Changes in gonadotropins, such as S-FSH, typically precede changes in those indices of menopause based on defining menstrual bleeding regularity, which makes increased S-FSH level a rather good marker of menopause. Although S-FSH level increased during follow-up and sleep latency decreased with aging, higher S-FSH level was associated with longer latencies. The difference between baseline and 10-year follow-up groups showed a modest difference in sleep latency and sleep latency to S2. However, our multiple regression analysis (multiple of independent variables) revealed that the effect of time was indeed greater. The relationship between the S-FSH level and sleep latency was positive and the S-FSH level increased in the groups. Therefore, the time has a greater effect on decreased sleep latency, which was revealed by multiple regression analysis also accounting the prolonging effect of S-FSH level on sleep latency, compared with the calculated difference of the means between the groups.

Previous meta-analysis uniformly showed age-related decreases in TST and sleep efficiency accompanied by increases in WASO and sleep latency [5, 19]. However, the decline in SWS is ambiguous according to the latest data [19]. In our previous study with a 6-year follow-up, we could reproduce the deteriorative effects of aging on TST, sleep efficiency, and WASO [9]. In contrast, our present study showed decreased sleep latency accompanied by increased SWS as an effect of aging and no effect on TST, sleep efficiency, or WASO. Potentially, sleep deteriorates with aging close to menopause but is restored to some extent later on. Longitudinal studies with PSG parameters are missing, but our results are somewhat comparable to a longitudinal study by Matthews et al. [10] with actigraphy measures of 300 middle-aged women at a baseline, a 3-year, and a 12-year follow-up (mean ages 52–64 years). They were also unable to show the expected adverse sleep effects in middle-aged women across the study period of 12 years. In contrast, they witnessed increased sleep duration and decreased WASO, whereas the effect on sleep latency varied between the three assessments, and longer latencies seemed to be associated with the late postmenopausal phase. The observed increase in SWS in our study has also been shown in two cross-sectional studies on women [2, 8]. In those studies, the women were allocated in terms of menopausal status rather than age, and analysis was adjusted for age, but premenopausal women were clearly younger (mean ages 41.6 and 34.6 years, respectively) than the postmenopausal women (mean ages 55.2 and 59.5 years, respectively).

The longitudinal setting of our study allowed us to better distinguish between the effects of menopausal hormonal changes and aging on sleep. Most of the findings appeared to be associated with aging but menopause seemed to interfere with the previously established age-related decline in sleep architecture. According to our study, the increase in SWS was not associated with increasing S-FSH level, though our previous study with a shorter follow-up time was suggesting this to be the case [9]. One can hypothesize that the remarkable increase in S-FSH level at the time of menopause is more important rather than typically reached steady state later in postmenopause. This is in accordance with a previous study showing that a more rapid increase in S-FSH level during the previous 7 years was positively associated with SWS and TST in middle-aged women (mean age at sleep study 52 years) [15].

In our study, the effects of the hormonal changes even during the postmenopausal era were demonstrated by the increase in the frequency of hot flashes at the follow-up. This might have reflected in the increase in arousals at the time of the follow-up. When controlling for vasomotor symptoms, the increase in arousals diminished to a trend. However, the arousals were not associated with S-FSH level. In contrast, our previous study showed increased sleep fragmentation, in terms of a higher frequency of awakenings and transitions from SWS to wake, at the 6-year follow-up, even when adjusted with vasomotor symptoms but only as an effect of aging not S-FSH level [9]. The significance of vasomotor symptoms, especially self-reported ones, on objectively measured sleep fragmentation is equivocal and possibly dependent on various types of measurements and the time of the measurement [20]. Some researchers have found no relationship [12, 21], whereas others have reported lower sleep efficiency, higher WASO, and longer sleep latency [22], as well as a higher frequency of awakenings [23, 24].

The loss of significance in the frequency of arousals might also be contributing to controlling for BMI. Higher BMI is linked to higher AHI, which in turn results in more fragmented sleep. Previous studies show that the prevalence of sleep-disordered breathing (SDB) increases during the menopausal transition [20, 21, 25, 26]. In female sleep apnea, hypopneas and prolonged partial upper airway obstruction predominate [20, 27]. In the present study, the AHI consisted mainly of hypopneas. However, we did not find any association between S-FSH level and SDB in the present or in our previous 6-year follow-up study. In addition, the association between aging and AHI, REM-AHI, or ODI_4 in the present study and AHI in our previous study lost significance after controlling for BMI and other confounding factors. Sleep disturbances and especially short sleep duration can have metabolic effects and higher odds of obesity [28]. BMI increased during our 10 years of follow-up and one could argue that the observed increase in SWS and decrease in sleep latency could also be due to sleep deprivation that might be induced by increasing AHI. We did some additional post hoc analysis on the possible effect of AHI on SWS and sleep latency but found no association. In addition, our study showed no difference in TST or in the proportions of the other sleep stages, arguing against a substantial interference of sleep deprivation.

The relatively low sample size could be viewed as a limitation of our study. After 10 years, our study cohort was reduced from the initial 116 participants to 57 due to loss in follow-up, data technical reasons, or use of MHT. However, to our knowledge, this is still the largest cohort of its kind so far, in which the same individuals are followed-up over transition of biologically confirmed menopausal status controlled for MHT. There are several issues that reduce the concern regarding our relatively small sample size. First, the large variability of measured parameters that increase the need for large sample sizes in cross-sectional studies can be reduced by pair-wise analyses, where the participants serve as their own controls. This is what we did and is a particular strength of our study. Second, the sample size must also be viewed in light of careful initial case selection, which decreased the sample size for the benefit of increased homogeneity of the study population, resulting in less variability from confounding factors. Third, the reasons for initially healthy participants not completing the 10-year follow-up investigations were not health-related. Therefore, the participants who were included in the 10-year follow-up were considered to represent

well the initial cohort. Finally, a too low sample size particularly increases the risk for type II error, which means that the study may be insufficiently powered to show differences in parameters, in which a significant difference could have turned up with more participants included. Significant differences observed in a relatively small but unbiased population are unlikely to lose their significance with increasing sample size. Therefore, we conclude that our sample size, even if relatively small, represented a decent balance between data credibility and study economics. We acknowledge the need for repeating our early findings in a larger study population, particularly to verify our somewhat controversial unexpected findings.

Other limitations of our study include lack of evaluation of self-reported sleep quality, objective measures of vasomotor symptoms, and characterization of chronotype (morningness vs eveningness). Either a possible impact of the so-called first night effect could not have been excluded because we did not have any adaptation nights [29, 30]. However, the protocol was the same both at the baseline and at the 10-year follow-up. Finally, we did not consider the possible sleep effects of additional common stressors in middle-aged women (marital problems, work demands, and empty nest syndrome) that affect at least self-reported sleep quality [31]. Significant study strengths are the longitudinal design with the long follow-up time, repeated PSG assessments, as well as repeated S-FSH measurements. PSG is the gold standard for measuring sleep architecture, and S-FSH is a reliable marker of reproductive aging. These assessments in a longitudinal setting with a 10-year follow-up allowed us to estimate the effects of both menopausal hormonal changes and aging on sleep architecture for the first time in a comparable setting.

In summary, the sleep architecture of middle-aged women does not seem to worsen over a 10-year time span from premenopause to postmenopause. The longitudinal setting of the study gives a unique view to sleep architecture alterations across menopause. Contrary to the initial hypothesis, SWS increases and sleep latency shortens, while TST remains unchanged. Furthermore, these changes are independently age-related and not associated with alterations in S-FSH concentrations. Menopausal transition seems to counteract the physiological age-related sleep deterioration, which challenges our understanding of the physiologic mechanisms behind the well-established increase in sleep complaints across menopause. We hope that our partially controversial and unexpected results could be repeated in future larger study populations.

Supplementary Material

Supplementary material is available at *SLEEP* online.

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References

1. Leger D, *et al*. Prevalence of insomnia in a survey of 12,778 adults in France. *J Sleep Res*. 2000;**9**:35–42.
2. Young T, *et al*. Objective and subjective sleep quality in premenopausal, perimenopausal, and postmenopausal women in the Wisconsin Sleep Cohort Study. *Sleep*. 2003;**26**:667–672.
3. Kravitz HM, *et al*. Sleep difficulty in women at midlife: a community survey of sleep and the menopausal transition. *Menopause*. 2003;**10**:19–28.
4. Kravitz HM, *et al*. Sleep disturbance during the menopausal transition in a multi-ethnic community sample of women. *Sleep*. 2008;**31**:979–990.
5. Ohayon MM, *et al*. Meta-analysis of quantitative sleep parameters from childhood to old age in healthy individuals: developing normative sleep values across the human lifespan. *Sleep*. 2004;**27**:1255–1273.
6. Shaver J, *et al*. Sleep patterns and stability in perimenopausal women. *Sleep*. 1988;**11**:556–561.
7. Kalleinen N, *et al*. Sleep and the menopause – do postmenopausal women experience worse sleep than premenopausal women? *Menopause Int*. 2008;**14**:97–104.
8. Hachul H, *et al*. The effect of menopause on objective sleep parameters: data from an epidemiologic study in São Paulo, Brazil. *Maturitas*. 2015;**80**:170–178.
9. Lampio L, *et al*. Sleep during menopausal transition: a 6-year follow-up. *Sleep*. 2017;**40(7)**. doi:10.1093/sleep/zsx090
10. Matthews KA, *et al*. Does midlife aging impact women's sleep duration, continuity, and timing? A longitudinal analysis from the Study of Women's Health Across the Nation. *Sleep*. 2020;**43(4)**. doi:10.1093/sleep/zsz259
11. Kravitz HM, *et al*. Relationship of day-to-day reproductive hormone levels to sleep in midlife women. *Arch Intern Med*. 2005;**165**:2370–2376.
12. Polo-Kantola P, *et al*. Climacteric symptoms and sleep quality. *Obstet Gynecol*. 1999;**94**:219–224.
13. Antonijevic IA, *et al*. On the role of menopause for sleep-endocrine alterations associated with major depression. *Psychoneuroendocrinology*. 2003;**28**:401–418.
14. de Zambotti M, *et al*. Interaction between reproductive hormones and physiological sleep in women. *J Clin Endocrinol Metab*. 2015;**100**:1426–1433.
15. Sowers MF, *et al*. Sex steroid hormone profiles are related to sleep measures from polysomnography and the Pittsburgh Sleep Quality Index. *Sleep*. 2008;**31**:1339–1349.
16. Beck AT, *et al*. An inventory for measuring depression. *Arch Gen Psychiatry*. 1961;**4**:561–571.
17. Rechtschaffen A, *et al*. *A Manual of Standardized Terminology, Techniques and Scoring Systems for Sleep Stages of Human Subjects*. Los Angeles, CA: Brain Information Service/Brain Research Institute, UCLA; 1968.
18. The Atlas Task Force: Bonnet M, *et al*. ASDA report. EEG arousals: scoring rules and examples. *Sleep*. 1992;**15**:173–184.
19. Boulos MI, *et al*. Normal polysomnography parameters in healthy adults: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;**7**:533–543.
20. Polo-Kantola P. Sleep problems in midlife and beyond. *Maturitas*. 2011;**68**:224–232.

21. Young T, *et al*. Menopausal status and sleep-disordered breathing in the Wisconsin Sleep Cohort Study. *Am J Respir Crit Care Med*. 2003;**167**:1181–1185.
22. Thurston RC, *et al*. Are vasomotor symptoms associated with sleep characteristics among symptomatic midlife women? Comparisons of self-report and objective measures. *Menopause*. 2012;**19**:742–748.
23. Erlik Y, *et al*. Association of waking episodes with menopausal hot flushes. *JAMA*. 1981;**245**:1741–1744.
24. Freedman RR, *et al*. Effects of REM sleep and ambient temperature on hot flash-induced sleep disturbance. *Menopause*. 2006;**13**:576–583.
25. Anttalainen U, *et al*. Impact of menopause on the manifestation and severity of sleep-disordered breathing. *Acta Obstet Gynecol Scand*. 2006;**85**:1381–1388.
26. Lindberg E, *et al*. Role of menopause and hormone replacement therapy in sleep-disordered breathing. *Sleep Med Rev*. 2020;**49**:101225.
27. Anttalainen U, *et al*. Gender differences in age and BMI distributions in partial upper airway obstruction during sleep. *Respir Physiol Neurobiol*. 2007;**159**:219–226.
28. Wu Y, *et al*. Sleep duration and obesity among adults: a meta-analysis of prospective studies. *Sleep Med*. 2014;**15**:1456–1462.
29. Agnew HW Jr, *et al*. The first night effect: an EEG study of sleep. *Psychophysiology*. 1966;**2**:263–266.
30. Virtanen I, *et al*. First-night effect on sleep in different female reproductive states. *Behav Sleep Med*. 2018;**16**:437–447.
31. Lampio L, *et al*. Predictors of sleep disturbance in menopausal transition. *Maturitas*. 2016;**94**:137–142.