BEHAVIORAL SLEEP MEDICINE, 1(2), 69–80

Effects of Menopausal Status on Sleep in Midlife Women

Katherine M. Sharkey
Biological Rhythms Research Laboratory
Rush-Presbyterian–St. Luke's Medical Center, Chicago, IL

Helen M. Bearpark[1]

Christine Acebo
Sleep and Chronobiology Research Laboratory
Department of Psychiatry and Human Behavior
E. P. Bradley Hospital/Brown University, Providence, RI

Richard P. Millman
Sleep Disorders Center
Department of Medicine
Rhode Island Hospital/Brown University, Providence, RI

Anita Cavallo
Department of Pediatrics
Children's Hospital Medical Center
University of Cincinnati College of Medicine, Cincinnati, OH

Mary A. Carskadon
Sleep and Chronobiology Research Laboratory
Department of Psychiatry and Human Behavior
E. P. Bradley Hospital/Brown University, Providence, RI

Disturbed sleep is a common complaint of midlife women often attributed to menopause, though few studies have examined direct effects of menopausal status on

Requests for reprints should be sent to Mary A. Carskadon, Sleep and Chronobiology Research Laboratory, Department of Psychiatry and Human Behavior, E. P. Bradley Hospital/Brown University, 1011 Veterans Memorial Parkway, Providence, RI 02915. E-mail: mary_carskadon@brown.edu

[1]Deceased.

sleep. Our objective was to assess this issue in healthy midlife women. We examined sleep polysomnographically on 2 consecutive nights in 25 women (ages 45 – 56 yrs) without sleep complaints (13 pre-menopausal; 12 post-menopausal). Groups differed in Stage 1 % (lower in post-menopausal) and slow wave sleep latency (shorter in post-menopausal). Subjective sleep reports did not differ. Age correlated negatively with Stage 1 % and positively with Stage 4 %. These results indicate that menopausal status plays a minimal role in sleep quality and sleep stage distribution in healthy midlife women without sleep complaints.

Most population surveys describe sleep problems as more common in women than men (e.g., Bixler, Kales, Jacoby, Soldatos, & Vela-Bueno, 1984; Bliwise, King, Harris, & Haskell, 1992; Ford & Kamerow, 1989; Karacan, Thornby, & Williams, 1983; Lugaresi, Cirignotta, Zucconi, Mondini, Lenzi, & Coccagna, 1983; Welstein, Dement, Redington, Guilleminault, & Mitler, 1983). In addition, complaints of poor sleep are more prevalent in midlife women than in younger women (e.g., Lugaresi et al., 1983), and disturbed sleep is a common complaint in peri-menopausal women (Anderson, Hamburger, Lin, & Rebar, 1987; Owens & Matthews, 1998). Fewer studies have examined laboratory-recorded sleep in women of this age group. A notable exception is a study by Shaver, Giblen, and Paulsen (1991) that examined sleep polysomnographically in eighty-two women aged 40 to 59 years, thus providing some of the first normative sleep data for middle-aged women.

Sleep disturbances reported by women in midlife may be derived from a number of sources including the hormonal changes of menopause. Declining estrogen levels in the years prior to menopause have been associated with disturbed sleep in midlife women (Hollander, Freeman, Sammel, Berlin, Grisso, & Battistini, 2001). Estrogen replacement therapy in menopausal women has been shown to improve sleep architecture (Schiff, Regestein, Tulchinsky, & Ryan, 1979; Thompson & Oswald, 1977) and subjective ratings of sleep quality (Asplund & Aberg, 1995; Wiklund, Berg, Hammar, Karlberg, Lindgren, & Sandlin, 1992). It is unclear, however, whether the estrogen administered in these studies affected sleep per se or whether it ameliorated other menopausal symptoms that interfere with sleep. For example, one study of hormone replacement therapy in postmenopausal women found no change in objectively measured sleep parameters, although other menopausal symptoms (i.e., hot flashes, sweating, vaginal dryness) were alleviated (Purdie, Empson, Crichton, & Macdonald, 1995). Furthermore, a study of the long-term effects of hormone replacement therapy on sleep demonstrated more disturbed sleep in postmenopausal women who took hormone replacements than in women who were not taking hormones (Moe, Larsen, Vitiello, & Prinz, 1997). Other proposed explanations for disturbed sleep in midlife women include the presence of occult sleep disorders (Clark, Flowers, Boots, & Shettar, 1995), psychological distress (Krystal, Edinger, Wohlgemuth, & Marsh, 1998; Stone & Perlstein, 1994), and behaviorally-conditioned insomnia linked to physiological sleep disturbances (Krystal et al., 1998).

Few studies have examined the direct effects of menopause on sleep. In a cross-sectional polysomnographic study of women at different menopausal stages, Shaver, Giblen, Lentz, and Lee (1988) found few differences among pre-, peri-, and post-menopausal women; they concluded that sleep efficiency might be affected by menopausal status, particularly in relation to episodes of vasomotor instability ("hot flashes"). The latter finding is supported by another polysomnographic study demonstrating significantly lower sleep efficiency and more frequent arousals and sleep stage transitions in post-menopausal women with hot flashes versus those reporting no hot flashes (Woodward & Freedman, 1994).

We have reported previously the effects of nocturnal nasal occlusion in a sample of women aged 45 to 56 years who differed in menopausal status, were not taking hormone replacement, and were all self-identified good sleepers (Carskadon, Bearpark, Sharkey, Millman, Rosenberg, Cavello, et al., 1997). Here we report on sleep data collected during the two baseline nights (Night 1 and Night 2) in the same group of normal female participants. Our objective was to assess possible effects of menopausal status on sleep in this group of midlife women.

METHOD

Participants

Women aged 45 to 55 years were recruited by newspaper advertisements and flyers. Exclusion criteria were: surgical menopause, current use of hormone replacement treatment, pregnancy, use of medication affecting the central nervous or respiratory systems, current or recent (within one year) smoking, high caffeine intake (i.e., unable to reduce consumption to ≤ 2 cups of caffeinated beverage per day during the study), having full dentures or undergoing orthodontic treatment requiring braces, presence of a major physical illness, self-report of sleeping < 7 hours per night, or report of sleep disorders or major sleep problems. Women who reported snoring were not excluded; however, participants with an apnea/hypopnea index ≥ 10 on Night 1 were excluded ($n = 1$). We attempted to include only women who were clearly either pre- or post-menopausal. Potential volunteers who reported fluctuations in menstrual cycle length were considered peri-menopausal and excluded. Thirty-one women fulfilled the above criteria and were enrolled in the study.

Menopausal Status

Each participant provided a menstrual history regarding frequency and regularity of menstrual periods, length of time since last menstrual period, and occurrence of hot flashes. In addition, all participants still menstruating kept a menstrual cycle

diary for at least two cycles. We attempted to schedule pre-menopausal women for study during the follicular phase of their menstrual cycles (days 1–14, beginning at the onset of menses).

Serum concentrations of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) were assessed for all participants using a fluoroimmunoassay (Delfia Pharmacia, Turku, Finland) by Smith-Kline Beecham Laboratories. Fifteen participants were categorized as pre-menopausal, based on regular menses, an FSH to LH ratio < 1, and FSH and LH concentrations in the normal menstruating female range. Twelve participants were post-menopausal, as evidenced by the absence of menses for at least 11 months, an FSH to LH ratio > 1, and FSH and LH concentrations in the menopausal range. In addition, in spite of our prospective exclusion criteria, four women were classified as peri-menopausal based on intermediate FSH and LH levels, FSH to LH ratios > 1, and irregular menses. Thirteen of the pre-menopausal women were studied in the follicular phase of their menstrual cycles and two were studied in the late luteal phase. Data from the four peri-menopausal participants and two pre-menopausal participants who were studied during the late luteal phase of their menstrual cycles were excluded from the present analyses.

Thus, data are presented here for 25 of 31 women who were studied in the laboratory (Table 1). Participants ranged in age from 45.1 to 56.0 years ($M = 49.8 \pm 3.8$ years). Twenty-one participants completed the Beck Depression Inventory (BDI; Beck, Ward, Mendelson, Mock, & Erbaugh, 1961). There were no differences in the BDI scores among menopausal groups, $F(1, 19) = 1.1$, p = ns; and none of the participants scored in the depressive range of 17 or above. Twenty-four participants were Caucasian; one was African American. The study was approved by the

TABLE 1
Demographic Variables

	Premenopausal (n = 13)		*Post Menopausal (n = 12)*	
Variables	*M ± SD*	*Range*	*M ± SD*	*Range*
Age (years)[a]	46.9 ± 1.9	45.1–51.2	52.8 ± 2.7	46.6–56
Height (inches)	64 ± 3	60–70	64 ± 3	58–69
Weight (pounds)	159 ± 39	114–224	160 ± 39	105–250
Body Mass Index (kg/m^2)	27.3 ± 6.2	20–38.3	27.7 ± 8.3	18.6–48.9
FSH (mIU/ml)	7.1 ± 3.7	3.1–13.7	65.3 ± 28.9	25.2–129.8
LH (mIU/ml)	6 ± 1.9	3.6–10.1	38.7 ± 13.1	23–70.8
Beck Depression Inventory score	5.1 ± 4.4	0–15	2.9 ± 5	0–16

Note. FSH = follicle-stimulating hormone; LH = luteinizing hormone.

[a]Indicates significant differences between menopausal groups. Normal ranges of hormone concentrations in menstruating women are FSH: 0.6–13.3 mIU/ml; LH: 0.5–71.8 mIU/ml. Normal values in menopausal women are FSH: 31–134 mIU/ml; LH: 15–64 mIU/ml.

E. P. Bradley Hospital Institutional Review Board; all participants gave informed consent and were paid for their participation.

Polysomnography

Two consecutive nights of polysomnography were performed with bedtimes adjusted to provide approximately 8 hr in bed on each study night. Recordings began between 22.00 and 23.00 hr. The following parameters were measured: EEG (from C3/A2 or C4/A1 and O1/A2 or O2/A1), right and left EOG, submental EMG, nasal and oral airflow by thermistors or thermocouples, and respiratory effort using strain gauges taped to the chest and abdomen. Oxygen saturation ($Sa0_2$) was measured with an Ohmeda Biox 3740 or Biox III pulse oximeter using a finger probe, and EKG was recorded from a modified lead II position. Leg movements were recorded in 23 participants, in 21 from EMG activity of the anterior tibialis muscles using standard electrode placements (Coleman, 1982), and in 2 from electronic activity monitors attached to the ankles (Pro-Tech Services, Inc., Woodinville, WA). All recordings were made on Grass Instruments polygraphs at a paper speed of 10 mm/s. Sleep was scored visually in 30-sec epochs using standard criteria (Rechtschaffen & Kales, 1968) by 2 trained scorers who maintained an inter-scorer reliability > 85%. An apnea was scored when airflow fell below 20% of the preceding steady state respiration amplitude for at least 10 sec during sleep. Hypopneas were scored when the airflow signal dropped to between 20% and 50% of the preceding steady state amplitude for at least 10 sec and was accompanied either by an arousal or a ≥ 4% drop in oxygen saturation. Periodic leg movements were scored according to the criteria of Coleman: duration of 0.5 to 4 sec, amplitude ≥ 50% of waking ankle dorsiflexion calibration, occurring in a series of at least four consecutive movements separated by > 4 sec but < 90 sec, and not occurring at the termination of a respiratory event.

The following variables were assessed: Total Recording Time (TRT) = time in minutes from lights out to lights on; Sleep Period Time (SPT) = minutes from sleep onset to the last epoch of sleep including all intervening wakefulness; Total Sleep Time (TST) = minutes of sleep recorded during TRT; Sleep Efficiency % =TST/TRT × 100; Sleep Latency = time in minutes from lights out to the first of three consecutive epochs of any stage of sleep; Latency to continuous sleep = time in minutes from lights out to the first of 20 consecutive epochs of continuous sleep (including Stage 1); minutes and percentages (of TST) of Sleep Stages: 1, 2, 3, 4, SWS (Stage 3 + Stage 4), and REM; Latency to slow wave sleep (SWS) from sleep onset to the first epoch of SWS, including intervening wakefulness; REM Latency from sleep onset to the first epoch of REM sleep, including intervening wakefulness; % Wake after sleep onset (% WASO) = number of minutes of wakefulness/SPT × 100; Wake Index = number of awakenings ≥ 15 sec × 60/TST; Transient Arousal Index = number of transient arousals ≥ 3

sec <15 sec × 60/TST; Apnea-Hypopnea Index (AHI) = number of apneas + number of hypopneas × 60/TST; Periodic leg movements Index (PLM Index) = number of Periodic Leg Movements × 60/TST. The Somnibus spreadsheet program was used to calculate summary sleep variable statistics (Behavioral Cybernetics, Cambridge, MA).

Subjectively-Reported Sleep and Mood

Participants completed a morning questionnaire immediately after waking to estimate sleep latency, number of awakenings, and total sleep time. They also reported any hot flashes during the night and rated their sleep as adequate or inadequate.

Data Analysis

Data were analyzed using SPSS for Windows (Ver. 6.0). The effect of menopausal group and differences between the two study nights were examined by multiple analysis of variance (MANOVA). Pearson correlations were used to assess a possible relationship of age to sleep parameters. A probability value of 0.05 was considered statistically significant. Mean data are presented ± standard deviation.

RESULTS

Menopausal Status and Polysomnographic Sleep Parameters

Our primary question concerned whether menopausal status per se in this age-constrained group of women had a substantial effect on sleep. Only two sleep variables showed statistically significant main effects of menopausal group: Stage 1 sleep percentage, $F(1, 23) = 12.5$, $p = .002$; and Latency to Slow Wave Sleep, $F(1, 23) = 5.93$, $p = .02$. Post hoc comparisons revealed that pre-menopausal women had higher Stage 1 sleep percentage and longer latency to SWS than post-menopausal women (see Table 2).

Age

Although age range was constrained in selection of these participants, mean age differed significantly between menopausal groups, $F(1, 23) = 41.8$, $p < .001$. Women in the post-menopausal group were older ($M = 52.8 \pm 2.7$) than women in the pre-menopausal group ($M = 46.9 \pm 1.9$). Age per se correlated significantly with two sleep parameters: percentage of Stage 4 sleep on both recording nights (Night 1: $r = .50$, $p = .01$; Night 2: $r = .49$, $p = .014$) and percentage Stage 1 sleep on

TABLE 2
Sleep Parameters Categorized by Menopausal Group

	Premenopausal (n = 13)		*Post Menopausal (n = 12)*	
Variables	*Night 1*	*Night 2*	*Night 1*	*Night 2*
Total recording time (minutes)	474 ± 10	475 ± 3	476 ± 7	475 ± 6
Total sleep time (minutes)	395 ± 47	411 ± 42	399 ± 45	410 ± 42
Sleep efficiency (%)	88 ± 9	89 ± 9	88 ± 8	88 ± 9
Sleep latency (minutes)	22 ± 11	15 ± 13	22 ± 18	10 ± 6
Latency to CS (minutes)	52 ± 53	28 ± 25	31 ± 26	15 ± 15
Stage 1 (%)[a]	11.9 ± 4.5	12.1 ± 3.6	8.5 ± 3.4	6.9 ± 3.1
Stage 2 (%)	59.1 ± 7.5	56.8 ± 5.4	58.5 ± 8.3	57.1 ± 9
Stage 3 (%)	10.2 ± 6.3	10.7 ± 5	12.6 ± 5.8	12.2 ± 5.2
Stage 4 (%)	2.3 ± 3.6	2.3 ± 3.7	5 ± 4	4.7 ± 5
SWS (%)	12.5 ± 8.6	13 ± 7	17.7 ± 8.7	16.9 ± 8.6
REM (%)	16.5 ± 4.1	18 ± 5.1	15.3 ± 3.3	19 ± 4.2
Latency to SWS (minutes)[a]	54 ± 50	27 ± 15	20 ± 16	17 ± 11
REM latency (minutes)	153 ± 72	107 ± 50	135 ± 84	88 ± 30
Percentage of WASO	14.1 ± 12.6	11.9 ± 10	15 ± 10.5	14.3 ± 13.1
Wake index (events/hr)	4.2 ± 2.1	3.1 ± 1.1	3.2 ± 1.3	2.7 ± 1.2
Transient arousal index(events/hr)	18.3 ± 9.6	16.8 ± 9.6	19.7 ± 14.9	19.9 ± 14.1
Apnea-hypopnea index (events/hr)	0.8 ± 1.3	1.1 ± 1.9	0.6 ± 0.7	1.6 ± 1.7
Periodic leg movement index	1.2 ± 2.7	0.8 ± 1.6	1 ± 1.2	0.7 ± 1.9

Note. CS = continuous sleep; SWS = slow wave sleep; REM = rapid eye movement sleep; WASO = wake after sleep onset.

[a]Indicates significant differences between menopausal groups. One premenopausal participant had a periodic leg movement index (PLM) of 53.6 on Night 1 and 46.2 on Night 2. Her PLM indexes are not included in the means listed in the table; her data were included in the remaining analyses.

Night 2 ($r = -.52$, $p = .008$). These correlations parallel the findings above—Stage 1 sleep percent was lower and Stage 4 sleep percent was higher in older (and post-menopausal) women.

Hot Flashes

Of the 23 women who completed the pre-study "hot flash questionnaire," four reported currently having hot flashes (1 pre-menopausal; 3 post-menopausal) and five others reported experiencing hot flashes in the past, but not currently (1 pre-menopausal; 4 post-menopausal). In addition, five participants reported on the morning questionnaire experiencing hot flashes during the laboratory recording nights—the four women who indicated current hot flashes on the "hot flash questionnaire" and one additional pre-menopausal woman.

Based on previous reports that the effect of menopause on sleep is related to the degree of menopausal symptoms such as hot flashes (Shaver et al., 1988; Wood-

ward & Freedman, 1994), we examined this issue by dividing our sample into two groups: women who reported hot flashes at the time of the study (n = 5, 2 pre-menopausal; 3 post-menopausal) and women who did not (n = 18). In this sample there appeared to be little impact of hot flashes. For instance, the sleep efficiencies of women with hot flashes (Night 1 = 87 ± 8 %; Night 2 = 91 ± 5 %) were similar to those of women without hot flashes (Night 1 = 88 ± 9 %; Night 2 = 89 ± 8 %; $F[1, 21] = .018$, p = ns). Other sleep parameters previously shown to be susceptible to the effects of vasomotor instability, such as arousal indexes, REM latency, and Stage 4%, did not differ between these groups.

Subjective Sleep Ratings

No subjective sleep variables from morning questionnaires differed between menopausal groups. Overall, participants' average estimates of sleep onset latency were 28 ± 19 min on Night 1 and 19 ± 15 min on Night 2, and average estimates of total sleep time were 414 ± 64 min on Night 1 and 424 ± 74 min on Night 2. Participants reported an average of 3.4 ± 2.3 awakenings on Night 1 and 3.0 ± 1.9 awakenings on Night 2. Fourteen rated their sleep as inadequate on at least one recording night; however, neither menopausal status nor the experience of hot flashes had an effect on participants' tendency to report unsatisfactory sleep.

Night 1–Night 2 Variability

In general, the participants appeared to have higher quality sleep in Night 2 compared to Night 1. Across all participants, seven variables differed significantly between Nights 1 and 2. Although neither TST nor Sleep Efficiency % differed between the two nights, latency to sleep onset, latency to 10 min of continuous sleep, and number of wakes per hr were greater on Night 1 than on Night 2. REM latency and latency to SWS also showed a first night effect: on average, REM latency was 46 min longer on Night 1 than Night 2 and SWS latency decreased by 16 min on Night 2. Sleep stage distribution also showed a first night effect. Both the percentage of REM sleep and the average number of REM bouts increased on Night 2 relative to Night 1 (see Table 3).

DISCUSSION

The goal of this study was to investigate the association between menopausal status and sleep parameters. Consistent with previous reports (Shaver et al., 1988, Clark et al., 1995), our data failed to support the hypothesis that menopause per se has a significant impact on laboratory-monitored sleep in women without sleep complaints. Overall, we found few differences between menopausal groups on

TABLE 3
Major Sleep Parameters for All Participants on Nights 1 and 2

	Night 1	*Night 2*
Variables	*M* ± *SD*	*M* ± *SD*
Total sleep time (minutes)	397 ± 45	411 ± 41
Sleep efficiency (%)	88 ± 8	89 ± 9
Sleep latency (minutes)[a]	22 ± 14	13 ± 10
Latency to continuous sleep (minutes)[a]	42 ± 43	22 ± 21
Stage 1 (%)	10.2 ± 4.3	9.6 ± 4.2
Stage 2 (%)	58.8 ± 7.7	57 ± 7.2
Stage 3 (%)	11.4 ± 6.1	11.5 ± 5
Stage 4 (%)	3.6 ± 4	3.4 ± 4.5
REM (%)[a]	15.9 ± 3.7	18.5 ± 4.6
Latency to SWS (minutes)[a]	38 ± 41	22 ± 14
REM latency (minutes)[a]	144 ± 77	98 ± 42
Percentage of WASO	14.6 ± 11.4	13.1 ± 11.4
Wake index (events/hr)[a]	3.7 ± 1.8	2.9 ± 1.2
Apnea-hypopnea index (events/hr)[a]	0.7 ± 1	1.4 ± 1.8

Note. REM = rapid eye movement; SWS = slow wave sleep; WASO = wake after sleep onset.
[a]Indicates significant differences between the two recording nights, ($n = 25$).

most sleep parameters and those showing statistically significant group differences (Stage 1 sleep percentage and latency to SWS) were in a direction not predicted by previous literature on age-related sleep changes. Furthermore, the magnitude of the Stage 1 percentage difference was small and may represent a chance finding. Inspection of individual profiles did not reveal any consistent pattern to elucidate this difference. The relatively lengthy average delay to SWS sleep on night 1 in the pre-menopausal women was driven largely by data of three women with values of 2 hr or longer. These women fell asleep rather quickly, but then had extended arousals or fragmentation before reaching SWS sleep. In any case, the data do not support a relation of menopausal status to sleep disruption.

The menopausal groups also differed significantly in age and in their hormonal profiles, and age-dependent effects were evident in this age-constrained sample of healthy, midlife women. Specifically, as noted above in the group comparisons, the older women appeared to have somewhat better sleep—as evidenced by a significant positive correlation of Stage 4 sleep percentage and negative correlation of Stage 1 percentage with age. Thus, although previous studies have indicated that the prevalence of sleep disturbance increases after menopause, perhaps related to the use of hormone replacement therapy (Moe et al., 1997; Owens & Matthews, 1998) or psychological distress (Krystal et al., 1998), the present data indicate that objective sleep quality can be relatively preserved after menopause in some women. The comparison between women with hot flashes ($n = 5$) and women

without hot flashes ($n = 18$) further indicated that these symptoms did not have a major impact on sleep, and although this was a very small sample, it adds to the main finding. An important caveat, however, is that sleep was not completely undisturbed in these women. For example, both pre- and post-menopausal women averaged nearly 20 brief arousals per hour of sleep, whereas the average transient arousal index was 5.3 ± 4.1 for a group of 24 young adult women (ages 22.4 ± 1.8 years) recorded during a similar protocol in our laboratory (Acebo, Millman, Rosenberg, Cavallo, & Carskadon, 1996).

One possible explanation for our findings is that in our sample of healthy, midlife women who were not depressed, not suffering from menopausal symptoms, and who did not report difficulties sleeping, the post-menopausal participants represent a group that has undergone "successful menopause." Certainly the early stages of menopause in these midlife women were not associated with significant additional sleep disturbances. These data should serve as a caution against the assumption that menopause per se causes sleep disturbance in midlife women, when other etiologies, i.e., undiagnosed sleep disorders (Clark et al., 1995), have not been ruled out.

An alternate explanation is that there may have been an overlap of hormonal status between our pre- and post-menopausal groups, such that some of our pre-menopausal participants were actually "somewhat menopausal," despite the fact that they were still experiencing regular menstrual cycles. Decrements in sleep quality have been associated with declining estradiol levels in women of late reproductive age (Hollander et al., 2001). The notion of hormonal overlap is supported by the fact that our sample was selected from a very narrow age range, that both groups had a few individuals who experienced hot flashes, and that both groups demonstrated sleep fragmentation during the study. We further note that the post-menopausal women in our study had not been menopausal for very long ($M = 2.9 \pm 1.7$ years), and it is possible that their sleep may not have been as well preserved had they been farther from the climacteric. Inter-individual variability was high in this small group of women, which may have obscured other group differences. On the other hand, intragroup variability was equally high within pre- and post-menopausal groups on most variables, suggesting that factors other than menopausal status may account for inter-participant differences in an age-constrained sample.

The participants in our study experienced first night effects similar to those reported in studies of other age groups (Agnew et al., 1966; Carskadon, 1982; Bliwise & Bergmann, 1987; Hirshkowitz, Moore, Hamilton, Rando, & Karacan, 1992). In our sample, sleep on laboratory Night 2 differed significantly from the first in-lab night on a number of variables, including sleep onset latency and REM latency. We did not anticipate significant first night effects for slow wave sleep variables, since such effects have not been typical in reports of others (e.g., Bliwise & Bergmann, 1992). The unusual reduction of SWS latency on Night 2—although effect size was not large—may point to important differences in sleep regulation or behavioral re-

sponse to the laboratory setting in this population. For example, the first-night impact on SWS latency might indicate a lower intensity of the homeostatic sleep promoting process (Borbely, 1982) or an increased sensitivity to environmental change as a function of increased age. These factors—rather than menopausal status—could contribute to the relatively high prevalence of disturbed sleep reported by women in midlife by increasing their susceptibility to sleep fragmentation.

ACKNOWLEDGMENTS

This work was funded by National Institutes of Health Grants HL44138 and HL44138–S1.

We especially recognize the late Helen Bearpark's efforts on this project. She was a treasured colleague and is sadly missed. We thank Clayton Bennett, Jr., Jon DiOrio, Semra Aytur, Camille Brown, Catherine Darley, and Jenifer Wicks for their assistance with data collection.

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