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Original Article

Factors associated with poor sleep during menopause: results from the Midlife Women's Health Study

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ABSTRACT

Background: Poor sleep is one of the most common problems reported during menopause, and is known to vary throughout the menopause transition. The objective of this study was to describe the dynamics of poor sleep among participants of the Midlife Women's Health Study and to identify risk factors associated with poor sleep during the menopausal transition.
Methods: Annual responses to surveys that included questions about the frequency of sleep disturbances and insomnia were analyzed to determine the likelihood of persistent poor sleep throughout the menopausal transition and the correlation of responses to the different sleep-related questions, including frequency of restless sleep during the first year of the study. Responses to questions about a large number of potential risk factors were used to identify risk factors for poor sleep.
Results: Poor sleep in premenopause was not predictive of poor sleep in perimenopause, and poor sleep in perimenopause was not predictive of poor sleep in postmenopause. Frequencies of each of the measures of poor sleep were highly correlated. For all sleep outcomes, high frequency of depression was related to a high frequency of poor sleep. Vasomotor symptoms were also significantly related with a higher frequency of all poor sleep outcomes. A history of smoking was also associated with higher frequencies of insomnia and sleep disturbances.
Conclusions: The risk factors identified for poor sleep, depression and vasomotor symptoms, were consistently associated with poor sleep throughout the menopausal transition. The likelihood of these risk factors changed from premenopause, through perimenopause, and into postmenopause, however, which could explain changes in sleep difficulties across the menopausal transition. Treatment of these risk factors should be considered when addressing sleep difficulties in menopausal women.

1. Introduction

One of the most common problems reported during menopause is poor sleep, with one-third to half of all women aged 40–64 reporting sleep problems [1]. Sleep problems seem to peak in late perimenopause and continue into postmenopause [2], with the odds of reporting severe sleep difficulty increased 2–3.5 fold during the menopausal transition [3,4]. While it is possible that these problems are due to aging [5,6], their clear variation across menopause stages [7] even when controlling for age [8] indicates that menopause itself plays a role in disrupting women's sleep [9,10]. This may be due to direct physical impacts (changes in the hypothalamic-pituitary-ovarian hormones) or be related to emotional or behavioral responses to menopause (ie, stress or behavior changes) [9] or both [11]. However, other studies have found that the best predictor of poor sleep during menopause is poor sleep prior to menopause [12].

Although many studies have examined the role of different risk factors for poor sleep, reports have shown variable results due to heterogeneity in study design [9] and the fact that sleep is a complex outcome with many different functions (such as sleep efficiency [8], sleep architecture [5], sleep duration [13], night awakenings [14], circadian robustness [15], and polysomnography [15,16]), each of which can be affected by different risk factors [17]. Adding to the problems in determining the role of risk factors is the fact that many risk factor effects are likely bidirectional [9]; for

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instance, poor sleep is known to increase depression, anxiety, and stress, which in turn increase rates of poor sleep [2,8,9,17,18].

Poor sleep includes insomnia, restless sleep, and sleep disturbances; the frequency of each of these outcomes was self-reported during the Midlife Women's Health Study. The objective of this study was to describe the dynamics of poor sleep among participants of the Midlife Women's Health Study and to identify risk factors associated with poor sleep during the menopausal transition.

2. Methods

2.1. Data collection

The Midlife Women's Health Study was a cohort study of hot flashes among women 45–54 years of age conducted starting in 2006 among residents of Baltimore and its surrounding counties. All participants gave written informed consent according to procedures approved by the University of Illinois and Johns Hopkins University Institutional Review Boards. The study design for the parent study is described in detail elsewhere [19]. Briefly, women were recruited by mail, and were included if they were in the target age range, had intact ovaries and uteri, and were pre- or perimenopausal. Exclusion criteria consisted of pregnancy, a history of cancer, exogenous female hormone or herbal/plant substance, and no menstrual periods within the past year.

Participants had a baseline clinic visit, which included height and weight measurements to calculate body mass index (BMI) and the completion of a detailed 26-page baseline survey. Among the survey questions were the items “Please indicate how frequently you experienced sleep disturbances during the past year”, “Please indicate how frequently you experienced insomnia during the past year”, each on a five-point Likert scale (never, less than once per month, one to four times per month, two to four times per week, or more than five times per week); these questions resemble those of the MIDUS study, which have been validated [20]. Participants were also asked in the baseline survey to complete the statement “During the past week my sleep was restless” with a four-point Likert scale (rarely, some of the time, moderately, or most of the time). Such self-reporting of perceived sleep quality [9], although not necessarily correlating with actual sleep efficiency [1], has been found to be clinically relevant [21].

Participants were asked to complete a follow-up questionnaire during an annual clinic visit after the baseline visit. This questionnaire repeated previous questions about insomnia and sleep disturbances in the previous year, as well as most other questions from the initial survey (excluding questions for which the answers would not change). Clinic visits were repeated weekly over four weeks, for a total of four visits in each year. Blood samples were collected at each scheduled clinic visit and stored until measurement of hormone levels as described below.

Menopausal status was defined as follows: premenopausal women were those who experienced their last menstrual period within the past three months and reported 11 or more periods within the past year; perimenopausal women were those who experienced: their last menstrual period within the past year, but not within the past three months; their last menstrual period within the past three months and experienced 10 or fewer periods within the past year. Postmenopausal women were those women who had not experienced a menstrual period within the past year. Follow-up was discontinued for women if they reported hormone therapy, an oophorectomy, or a cancer diagnosis. At the four year visit, follow-up was discontinued for women who were determined to be postmenopausal. Recruitment and follow-up were completed in late June 2015, with women followed for one to seven years, based on time of enrollment and menopause status at year four.

Serum extracted from the collected blood samples was used to measure estradiol levels in each sample using commercially available, previously validated enzyme-linked immunosorbent assay (ELISA) kits (DRG, Springfield, New Jersey, USA) [22–25]. The minimum detection limits and intra-assay coefficients of variation were seven pg/ml and 3.3 ± 0.17%, respectively. The average inter-assay coefficient of variation for all assays was less than five. For estradiol concentrations among all women enrolled in the study, the number of values below the limit of detection during year one were: visit one, n = 7; visit two, n = 3; visit three, n = 13; visit four, n = 6. In the case of values lower than the detection limits for the assay, we used the limit of detection as the hormone value. Each sample was measured in duplicate within the same assay. Totals from the four samples in each year were averaged to account for variability in day of menstrual cycle, as participants were not expected to be able to schedule initial clinic visits on a particular day of their menstrual cycle due to the unpredictability of cycles during the menopausal transition. Estradiol levels were log-transformed to meet normality assumptions.

2.2. Dynamics of sleep outcomes

To determine the persistence of poor sleep through the menopausal transition, we calculated the probability of insomnia or sleep disturbances persisting from premenopause to perimenopause (pre-peri analysis) and the probability of insomnia or sleep disturbances persisting from perimenopause to postmenopause (peri-post analysis). Participants were assigned a menopause status for each year of the study. Women who transitioned from premenopause to perimenopause during the study were included in the pre-peri analysis, and women who transitioned from perimenopause to postmenopause during the study were included in the peri-post analysis. For each woman-stage combination, the worst responses for each sleep outcome (the most frequent occurrences of insomnia and sleep disturbances) were determined. The probability of insomnia or sleep disturbances persisting between stages was calculated using a proportional odds logistic regression model, where the outcome variable was the Likert value at the later stage and the predictor variable was the Likert value at the earlier stage. The predictor variable was considered as a linear variable, a categorical variable, or an ordinal variable. All models were fit with the *polr* function in the MASS package [26] in R 3.4.1 [27].

2.3. Interactions among sleep outcomes

To determine the degree of correspondence among the three sleep outcomes (insomnia, sleep disturbances, and restless sleep) at the baseline clinic visit, Kendall's tau was calculated for each two-way comparison using the Kendall package [28] in R 3.4.1 [27].

2.4. Risk factors for poor sleep

To determine the risk factors for poor sleep outcomes, ordinal logistic regression models were fit to each of the three outcomes. For sleep disturbance and insomnia, all years of data were included by using random effects for repeated measures within women by year of study; for restless sleep, only the first year of data was included and the analysis was cross-sectional in nature. First, univariable models were fit for the variables menopause status, age, race, BMI, income level, health status, hot flashes,