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Self-reported sleep difficulty during the menopausal transition: results from a prospective cohort study

Sarah E. Tom, PhD[1], **Diana Kuh, PhD**[2], **Jack M. Guralnik, MD, PhD**[3], and **Gita Mishra, PhD**[2]

[1] Group Health Research Institute, Seattle, WA

[2] Medical Research Council Unit for Lifelong Health and Ageing, London, United Kingdom

[3]Laboratory of Epidemiology, Demography, and Biometry, National Institute on Aging, Bethesda, MD

Abstract

Objective—To examine the relationship between menopausal transition status and self-reported sleep difficulty.

Methods—Using data on women participating in the Medical Research Council National Survey of Health and Development who have been followed up from birth in March 1946 (n = 962), relationships between menopausal transition status and self-reported sleep difficulty were assessed annually between ages 48 – 54.

Results—Menopausal transition status was related to severe self-reported sleep difficulty. Odds of reporting severe self-reported sleep difficulty were increased approximately 2 to 3.5 fold (95% CI ranges from (1.08, 3.27) – (1.99, 6.04)) for most menopausal transition statuses, compared to women who remained premenopausal. After adjustment for current psychological, vasomotor, and somatic symptoms and waking frequently at night to use the toilet, only women with hysterectomy remained at an increased risk for moderate sleep difficulty.

Conclusions—The modest relationship between menopausal transition status and moderate sleep difficulty may be related to greater variation in individual definitions of moderate difficulty. Attention to the level of sleep difficulty in this group of women will assist in the decision to address current health symptoms versus sleep itself. Women without prior health problems may experience severe self-reported sleeping difficulty during the menopausal transition and require tailored care from health professionals.

Keywords

Menopause; Hysterectomy; Sleep; Longitudinal; Menopausal symptoms

INTRODUCTION

Sleep difficulty is a common problem for women during midlife. Approximately 40% of women between ages 40 and 64 in the United Kingdom,[1] Australia,[2] and the United

Address correspondence to: Sarah E. Tom, PhD, Group Health Research Institute 1730 Minor Ave, Suite 1600, Seattle WA 98101-1448. Tel.: 206-287-2205, Fax: 206-287-2871, tom.s@ghc.org .

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States[3,4] report difficulty with sleep. Understanding the nature of this symptom is complicated by the dynamic features of both sleep disturbance and of potential correlates of sleep. It is not clear whether midlife is a period of increased onset of new sleep problems, or whether most problems during these years reflect an exacerbation of existing symptoms.[5] Midlife is a period of the convergence of multiple risk factors concerning menopause, overall health, and stress that may influence sleep.

Evidence concerning the relationship between the menopausal transition and sleep has been mixed. The menopausal transition, as indicated through hormonal levels[6 - 9] or characteristics of menstruation,[3,8] has been shown to be related to sleep disturbance. However, some studies have not identified this relationship between characteristics of menstruation and sleep disturbance.[9-11] Other concurrent factors that may be chronic or acute may also play a role in sleep. For example, psychological distress and life stress[3,6,7,9,12,13] have been shown consistently to be related to poor sleep during the menopausal transition. From a management perspective, it is important to understand whether sleep difficulty during midlife is related to the menopausal transition, these other risk factors[14] or other age-related changes.

Evaluation of these complexities of sleep at midlife requires longitudinal data that begins earlier in adulthood and includes multiple risk factors. Most studies evaluating self-reported sleep during the menopausal transition have been cross- sectional[4, 15] or with a limited sample size.[6,10] One central consequence of these study characteristics is the limited ability to distinguish age and menopause effects. Two recent large, longitudinal American studies[8,9] have not been subject to these drawbacks, but no similar analysis has been carried out among a British sample. Previous studies have not included risk factors for sleep difficulty from earlier in life, which could indicate longitudinal patterns in propensities for sleep disturbance and related health characteristics prior to menopause. The Medical Research Council National Survey of Health and Development (NSHD) provides the opportunity to consider risk factors from earlier adult life and from the present to study sleep during the menopausal transition. Analysis of this cohort has shown that psychological and physical health symptoms at age 43 were related to duration of poor sleep during the menopausal transition,[16] suggesting the importance of examining sleep longitudinally. Longitudinal analysis of the cohort is required to validate previous cross-sectional analysis that showed an increase is trouble sleeping during the menopausal transition.[17]

Using longitudinal and repeat data from a nationally representative British cohort study, the purpose of this study is to examine the relationship between the menopausal transition and self-reported sleep difficulty. In order isolate the associations between menopausal transition status and sleep from other concurrent and longitudinal risk factors, the study also accounts for age, current somatic, vasomotor and psychological symptoms and prior measures of socioeconomic status, physical and mental health, health behaviors, and history of trouble sleeping.

METHODS

Study Population

The NSHD is a social-class stratified, random sample of singleton births in England, Scotland, and Wales during one week in March 1946. Data has been collected on the 2547 women and 2815 men in the cohort over 20 times since birth. Women study members responded to annual postal questionnaires between ages 47-54. The analysis uses data collected on trouble sleeping; vasomotor, somatic, and psychological symptoms, waking at night to use the toilet, and life stress from ages 48-54. Menopausal transition status from ages 48 – 54 years required information on menopausal status from ages 47 – 54 years, since

the assessment of menopausal transition status at age x requires menopausal status at age x and age x – 1. The analysis period is from ages 48 – 54 years, and measurement of a variable at each age is referred to as "annual" below. Trained nurses collected information on sociodemographic characteristics, history of sleep trouble, physical and psychological health, and health behavior at home visits at ages 26, 43, and 53 years. Among the 1778 eligible women study members, 1572 participated in at least one wave between ages 47-54. Ethical approval for this study was given by the North Thames Multicentre Research Committee.

Outcome: Annual self-reported sleep difficulty

Women were asked whether they experienced trouble sleeping in the previous 12 months and, if so, how much this symptom bothered them. Women who reported being bothered by trouble sleeping a lot (the 'severe' group) or a little (the 'moderate' group) were compared with those who reported no trouble or had not been bothered (the 'none' group).

Definition of annual menopausal transition status

Menopausal status was based on self-reported menstrual bleeding. Status categories utilized were postmenopausal (no reported menstrual bleeding in the past 12 months), perimenopausal (bleeding in the past 12 months but not 3 months or decreased regularity compared to the previous year), premenopausal (bleeding in the past 3 months and with the same or increased regularity as in the past year), hysterectomy, and initiation of hormone therapy (HT) prior to the final menstrual period. Transition categories between consecutive years were defined as the following: pre-pre (remained premenopausal), pre-peri (became perimenopausal), pre/peri-post (from premenopausal or perimenopausal to postmenopausal), peri,-peri (remained perimenopausal), post-post (remained postmenopausal), pre/peri-HT (initiation of HT while premenopausal or perimenopausal), HT-HT (used HT for at least one year), pre/peri/hyst-hyst (women who were premenopausal or perimenopausal and then had hysterectomy with or without bilateral oophorectomy or who had hysterectomy with or without bilateral oophorectomy for at least one year and were not using HT).

Potential confounding or mediating variables

The following groups of potential confounders/mediators were included in the analyses because they were hypothesized to be associated with trouble sleeping and/or with aspects of women's health at midlife: age,[1] vasomotor symptoms,[7,18,19] night time awakening to use the toilet,[19] history of trouble sleeping,[20] life stress,[21] adult socio-demographic factors,[18] physical health and somatic symptoms,[4, 11, 18, 22, 23] psychological symptoms,[3,4,7] and health behavior.[4, 8, 18]

Annual vasomotor and somatic symptoms and night time awakening to use the toilet

Vasomotor symptoms were represented by a binary indicator for whether the respondent was bothered at all by either night sweats or hot flushes.[17] Somatic symptoms were measured as a cumulative score (range 0 – 24) based on eight symptoms such as headache, pain, and dizziness, as described elsewhere.[17] The score was categorized into approximate quarters for analysis. The variable "waking at night to use the toilet" referred to whether the respondent woke up on average at least twice a night. These three variables were assessed annually.

Annual psychological symptoms and life stress

Women were asked about symptoms of anxiety or depression, irritability, tearfulness, feelings of panic, or forgetfulness in the previous 12 months. The grouping of these psychological symptoms was based on a previous factor analysis on 20 symptoms at age

47.[17] Responses were coded as: *have not had this symptom* (0), *have had this symptom but it didn't bother me* (1), *have had this symptom and it bothered me a little* (2), *have had this symptom and it bothered me a lot* (3). At each age, scores for psychological symptoms responses across these five symptoms (range 0-15) were summed. Individual sums of scores were categorized into quarters based on the distribution of the average scores over all available waves. Work stress and family stress refer to the number of difficulties the study member experienced in each category and have been described elsewhere.[24] These two scales were utilized separately in the analysis.

Socio-demographic factors at ages 26, 43, and 53 years

Educational level by age 26 was categorized as no qualifications, up to ordinary secondary qualifications ('O'-levels usually attained at 16 years, and their training equivalents) advanced secondary qualifications ('A'-levels, usually attained at 18 years, or degree level and their equivalents). Marital status at age 43 was classified as married or not married. Number of children at age 53 was categorized as no children, one, two, three, and four or more children.

Health and history of trouble sleeping at age 43 years

The Psychiatric Symptom Frequency Scale (PSF Scale) was used to assess symptoms relating to anxiety and depression.[25] The scale measures the frequency of symptoms in the past year according to 25 questions. The PSF Scale score was categorized into approximate quarters for analysis. Respondents indicated physical health conditions for which they had seen medical professionals in the past year from a list of 27 conditions including heart disease, diabetes, and severe headaches or migraine. The number of prescriptions used for the same list of conditions was also enumerated, as an indicator of severity of health conditions. History of trouble sleeping status indicated whether the respondent reported ever experiencing trouble sleeping or trouble getting off to sleep or waking up and not being able to get back to sleep for a spell of a minimum of up to four months, once or twice a week, or three to ten times a month. This variable is included in the analysis to examine if women's experiences of sleep difficulty during the menopausal transition are independent of a propensity for sleep disturbance.

Health behaviors at age 43 years

Exercise status was categorized as inactive, participated in vigorous activities once a week or less, or participated in vigorous activities more than once a week.[26] Cigarette smoking status was dichotomized as ever smoker or non-smoker. Body mass index (weight in kilograms/height in meters^2) was categorized as < 20 – 24.9, 25-29.9, and 30 or greater. Alcohol consumption referred to an average of 0 drinks/day (abstainers), 0.1-1.0 drinks/day (very light drinkers), 1.1-2.0 drinks/day (light drinkers), 2.1-4.0 drinks/day (moderate drinkers), and >4.1 drinks/day (heavy drinkers), and the last two groups were combined due to small number of respondents in each category.[27]

Statistical analysis

Analyses compare women in two separate groupings: women with severe trouble sleeping versus women with no trouble sleeping, and separately, women with moderate trouble sleeping versus women with no trouble sleeping. Women who reported moderate difficulty in some years and severe difficulty in other years were assigned to the comparison appropriate to the given year. For example, a woman who reported severe sleep difficulty at age 49 and moderate sleep difficulty at age 50 would be analyzed in the comparison 'severe versus none' at age 49 and in the other comparison 'moderate versus none' at age 50. Because a woman contributed to both models in a given year if she reported no sleep

difficulty but only a single model if she reported moderate or severe sleep difficulty, the sample size for each model across years was than the full analysis sample size (n = 962). Generalized estimating equations (GEEs) were utilized to examine relationships between menopausal transition status and sleep difficulty. This method accounts for the correlation of repeated outcome measures from the same study participants. The first stage of analysis examined the age-adjusted relationships between each risk factor and trouble sleeping for each outcome grouping (e.g. moderate versus none and severe versus none). In this stage, a separate age-adjusted model was run per exposure variable, and a model including only age was also run. Variables for menopausal transition status, psychological, somatic, and vasomotor symptoms; waking to use the toilet at night; and work-related and family-related stress were all treated as time-dependent covariates in the GEEs. To test the statistical significance of age-adjusted relationships for menopausal transition status, a test of heterogeneity was utilized. For all other categorical variables, a linear test of trend was carried out, and a Wald test was performed for binary variables. Variables that were associated with severe or moderate trouble sleeping at the 0.05 level (for at least one category for categorical variables) were further retained in the respective analyses.

In the second stage of analysis, a series of three GEEs for each outcome grouping were then performed that included variables in hypothesized order of importance. Immediate/concurrent variables were hypothesized to have the most relevant impact and were therefore included in the first adjustment. Then the models adjusted for life stress and variables from age 43. The primary influence of these variables was hypothesized to operate through current symptoms. The order of inclusion of specific variables was the following: first, age; second, current vasomotor, somatic, and psychological symptoms and waking up at night to use the toilet; and third, life stress and socio-demographic characteristics, history of trouble sleeping, physical and mental health status at age 43, and health behaviors at age 43. The GEEs were performed in Stata Version 10 using the command “xtgee.” The link was set to logit, and the correlation to exchangeable. The sample size for longitudinal data analysis was 962 women who had information on all variables that were not time-dependent and information on all annually assessed covariates for at least one year.

RESULTS

To describe the study sample, Table 1 displays some of the key characteristics at age 51 years, the sample mean age at menopause. The percentage of women with moderate or severe trouble sleeping increased from 37.6% at age 48 years to 48.2% at age 54 years. Table 2 displays age-adjusted odds ratios for risk factors and the separate outcomes of moderate sleep trouble and severe sleep trouble. Increasing age was a risk factor for both outcomes. In the age-adjusted models, vasomotor symptoms, somatic symptoms, waking to use the toilet at night, psychological symptoms, work-related stress, family-related stress, symptoms of depression and anxiety, number of physical conditions, history of trouble sleeping, and use of prescription medication were related both to moderate and severe trouble sleeping. Ever smoking was also related to severe trouble sleeping. Further multivariate analyses adjusted for these covariates.

The following menopausal transition groups had increased odds of moderate self-reported sleep difficulty, compared to women who remained premenopausal (pre-pre), even after adjusting for age: remaining perimenopausal (peri-peri), transition from premenopausal or perimenopausal to postmenopausal (pre/peri-post), initiation of HT prior to postmenopause (pre/peri-HT), and hysterectomy (pre/peri/hyst-hyst) (Table 3, model 1). After adjusting for current symptoms in the vasomotor, somatic, and psychological domains and waking at night to use the toilet, only women with hysterectomy (pre/peri/hyst-hyst) remained at increased risk for moderate self-reported sleep difficulty (Table 3, model 2). The

relationship between hysterectomy (pre/peri/hyst-hyst) and increased odds of experiencing moderate self-reported trouble sleeping persisted with adjustments for life stress, parity, physical and psychological and history of sleep status at age 43, and use of prescription medications at age 43 (Table 3, Model 3).

All menopausal transition groups had increased odds of self-reported severe sleep difficulty, compared to women who remained premenopausal (pre-pre), even after adjusting for age (Table 4, Model 1). With adjustments for current symptoms in the vasomotor, somatic, and psychological domains and waking at night to use the toilet, women who transitioned from premenopause to perimenopause (pre-peri) no longer had increased odds of severe self-reported sleep difficulty, compared to women who remained premenopausal (pre-pre). The strength of association between menopausal transition status and sleep difficulty was attenuated but was still statistically significant for women who remained perimenopausal (peri-peri), became postmenopausal (pre/peri-post), or who initiated HT (pre/peri-HT) (Table 4, Model 2). The stability of these estimates persisted with the additional adjustments for life stress, health characteristics, use of prescription medication and smoking status at age 43 for women who remained postmenopausal (post-post), continued using HT (HT-HT), or had hysterectomy (pre/peri/hyst-hyst) (Table 4, Model 3). There was a slight increase in the odds ratios for women who remained perimenopausal (peri-peri) and transitioned to postmenopause (pre/peri-post), initiated use of HT (pre/peri-HT).

DISCUSSION

In a birth cohort study that prospectively captured the menopausal transition from age 48 – 54 years, menopausal transition status was more strongly related to severe sleep difficulty than to moderate sleep difficulty. Adjusting for risk factors in earlier adulthood strengthened the relationships between menopausal transition status and severe self-reported sleep difficulty, indicating that some women with severe sleep difficulties during the menopausal transition have not previously experienced poorer physical and psychological health than their peers. Women who had a hysterectomy, transitioned to postmenopause, or who had initiated HT in the previous year had particularly high odds of severe self-reported sleep difficulty in the fully-adjusted model. The relationship between menopausal transition status and moderate sleep difficulty was attenuated with the inclusion of current symptoms.

Previous studies have not evaluated moderate and severe sleep difficulty separately. Differences in methodology used in previous studies may explain why certain findings support our results for moderate sleep difficulty, while other findings support our results for severe sleep difficulty. Some longitudinal[9, 11] studies have shown no relationship between menopausal transition status and sleep. These studies have used a continuous index outcome, which may mask differences in severe and moderate sleep problems. If women do not experience symptom levels evenly over the possible range of sleep problems, results may reflect relationships between menopausal status and the common level of sleep difficulty. Approximately 72% of women reporting any type of sleep difficulty in the NSHD at age 51 had moderate sleep difficulty. If this distribution of sleep difficulty was similar in other studies, then it is possible that those results are weighted towards those with moderate sleep difficulty and away from severe sleep difficulty. One study does show a low level of sleep symptoms as compared to other measured symptoms, such as hot flashes.[11] Although these two studies failed to find an association between menopausal status and sleep, they did both detect strong associations between menopausal status and other symptoms potentially related to sleep, such as vasomotor and depressive symptoms.[9, 11] These results suggest that menopausal status may have an indirect relation to sleep through other symptoms during the menopausal transition. A cross-sectional study that measured nine outcomes of sleep found menopausal transition status to be related only to difficulty initiating sleep and sleep

fragmentation. These are two aspects of sleep particularly likely to be affected by night sweats,[15] and these results support a role for other symptoms in the relationship between menopausal status and sleep disturbance.

Other cross-sectional studies that used a binary outcome variable have demonstrated a relationship between menopausal status and sleep difficulty.[3,17] These findings support the severe sleep results of this study and may reflect a select group of women more likely to experience severe sleep problems. The grouping together of moderate and severe sleep difficulty in the binary outcome measure could have the same effect of weighing the results towards moderate sleep difficulty as the abovementioned studies. However, because both of these studies were cross-sectional examinations performed early during more comprehensive longitudinal studies, women who had transitioned to postmenopause may not be representative of their peers' later experiences. For example, the cross-sectional study of the NSHD analyzed data from when the study members were aged 47 years.[17] As the mean age at menopause is age 51 years in the cohort, it is possible that women with early menopause had a worse symptom profile that their peers who transitioned later. For example, early age at menopause is linked to increased mortality.[28, 29] Likewise in the second cross-sectional study, nearly two-thirds of women were under age 50.[3] Women under age 50 years who were at most menopausal statuses other than premenopause reported a higher prevalence of sleep difficulty than their counterparts aged 50 years and over. These two cross-sectional studies may have represented a group of women with more severe sleep difficulty.

One leading hypothesis concerning the mechanism underlying the increase in sleep difficulty over the menopausal transition relates to changing hormonal levels. Few studies have tested this relationship with self-reported sleep difficulty. Recent longitudinal evidence has shown that lower inhibin B levels and higher FSH levels are associated with poor sleep quality.[9] Decreases in estradiol have been associated with trouble falling asleep and sleep fragmentation, and also increases in FSH with sleep fragmentation.[8] However, another analysis found no relationships between levels of follicle-stimulating hormone, estrone, or testosterone and trouble sleeping.[30] In the case of women who had hysterectomy, there is emerging evidence for a complementary hypothesis to the sudden decrease in hormones as the cause of sleep disturbance. Increased sleep difficulty among women with hysterectomy may be related to an underlying worse profile of health prior to menopause or worse health after hysterectomy, as compared to women with natural menopause.[31, 34]

This study is limited in its ability to measure health and characterize sleep. Some measures of health and health behaviors, such as exercise and physical health conditions, were assessed only at age 43 years, and not annually from ages 48 – 54 years when the outcomes were measured. While we adjusted for annual measures of risk factors such as somatic, vasomotor, and psychological symptoms, it is possible this was not an adequate conceptualization of health. The extent to which these risk factors and sleep may be considered as separate versus parts of a single syndrome is not clear.[35] The survey question about self-reported sleep difficulty refers to the past year. Women may not accurately recall experiences over the past year, or their responses may be influenced by more recent experiences. These problems may also apply to the other symptoms assessed annually in a similar fashion. The survey question about the overall quality of sleep does not allow for analysis of specific characteristics of sleep trouble, such as difficulty initiating sleep or waking early.[8,9] The NSHD did not assess objective measures of sleep that are commonly measured with actigraphy or polysomnography, such as sleep disruptions or sleep disordered breathing. Subjective and objective measures of sleep may not reflect the same processes and may be related to different risk factors. [6,19] As with any subjective measurement, there will be differences in individuals' valuation of severity. If there is less misclassification with severe sleep difficulty, heterogeneity between moderate and no sleep disturbance may relate

to the weak results for the moderate group. However, self-assessed report remains an important dimension of health, as one's own perception of health may prompt the decision to seek medical help.[21]

Several unique characteristics of this analysis contribute to the value of this study. The incorporation of risk factors from earlier adult life accounts for health characteristics and propensity for sleep difficulty that existed prior to the menopausal transition. The menopausal transition status used included women who initiated HT prior to the final menstrual period, thus including a broader population than some other studies.[9] Because women in the study are of the same age, relationships with sleep difficulty cannot be attributed to age distribution or cohort differences.

CONCLUSIONS

Menopausal transition status was related to trouble sleeping, as indicated through self-report. The relationship between menopausal transition status and sleep difficulty was weaker for moderate sleep difficulty than for severe sleep difficulty. Treatment of psychological, vasomotor, and somatic symptoms may contribute to improved sleep during the menopausal transition for those with moderate sleep symptoms. However, because of possible differences in interpretations regarding what level of sleep difficulty constitutes moderate difficulty, further information is needed to determine whether treatment of these symptoms or another strategy is most appropriate. Women may require additional attention from health professionals for sleep problems around the time of transition to postmenopause or hysterectomy. For women who report severe sleep difficulty, the relationships remained with adjustment by potential mediators and confounders, suggesting that the relationship is not due to longer-term trends in health or from other concurrent correlates of sleep. Some women experienced severe sleep problems for the first time during the menopausal transition and continued to have difficulty in postmenopause. Therefore, the menopausal transition may present an important public health opportunity for women to learn management of severe sleep disturbance. As the women in the NSHD continue to age, it will be possible to examine if there are relationships between sleep difficulty during the menopausal transition and this symptom in later postmenopause as well as other health outcomes.

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Summary
Sleep disturbance is common during the menopausal transition. Severity of sleep disturbance should inform management strategies.

Table 1

Limited Study Sample Characteristics at Age 51 Years (N = 669)[1,2]

Characteristic	Percent of sample at age 51 years
Menopausal Transition Status	
pre-pre	12.71
pre-peri	7.17
peri-peri	15.10
pre/peri-post	6.73
post-post	17.64
pre/peri-HT	2.84
HT-HT	18.09
pre/peri/hyst-hyst	19.73
Symptoms	
vasomotor symptoms	
No	41.85
Yes	58.15
somatic symptoms (0 - 21)	
0 - 2	26.76
3-6	22.12
5 -7	22.87
≥ 8	28.25
psychological symptoms (0 - 15)	
0-1	30.19
2-3	12.71
4-5	27.06
≥ 6	30.04
Life events	
Family-related (number)	
0	56.50
1	21.67
2	10.01
3	5.98
4	5.83
Education at Age 26 Years	
None	31.54
Lower secondary level qualifications	36.32
Advanced secondary	24.81
Degree level or equivalent	7.32
Psychiatric Symptom Frequency Score	

Characteristic	Percent of sample at age 51 years
at Age 43 Years (0 - 90)	
0 - 4	22.27
5 - 9	27.20
10 - 16	24.66
≥ 17	25.86
Number of Physical Conditions at Age 43 Years (0 - 9)	
0	46.34
1	31.99
≥ 2	21.67
History of Trouble Sleeping at Age 43 Years	
No	83.11
Yes	16.89

[1] Unless otherwise indicated, the variable was measured annually between ages 48 – 54 years

[2] This table only shows some of the key characteristics used in multivariate analysis to provide a description of the study population.

Table 2

Age adjusted odds ratios for sample characteristics and moderate or severe self-reported sleep difficulty, age 48 – 54[1]

	Moderate versus None (95% CI)[2]	P value[4]	Severe versus None (95% CI)[3]	P value[4]
Age (per year increase)	1.07 (1.04, 1.10)	< 0.01	1.08 (1.04, 1.12)	< 0.01
Symptoms				
vasomotor symptoms				
No	1.00	< 0.01	1.00	< 0.01
Yes	1.64 (1.44, 1.88)		2.12 (1.76, 2.55)	
somatic symptoms (0 - 21)				
0 - 2	1.00	< 0.01	1.00	< 0.01
3 - 4	1.52 (1.25, 1.84)		2.08 (1.43, 3.01)	
5 - 7	2.51 (2.06, 3.06)		4.91 (3.39, 7.12)	
≥ 8	3.98 (3.21, 4.94)		11.03 (7.50, 16.21)	
waking to use the toilet at night				
No	1.00	< 0.01	1.00	< 0.01
Yes	1.55 (1.29, 1.85)		2.07 (1.66, 2.57)	
psychological symptoms (0 - 15)				
0-1	1.00	< 0.01	1.00	< 0.01
2-3	2.05 (1.52, 2.77)		2.43 (1.44, 4.11)	
4-5	2.69 (1.99, 3.54)		3.78 (2.27, 6.32)	
≥ 6	2.99 (2.22, 4.04)		6.48 (3.96, 10.60)	
Life events				
Work-related (number)				
0	1.00	< 0.01	1.00	< 0.01
1	1.27 (1.11, 1.47)		1.61 (1.33, 1.95)	
2	1.62 (1.32, 1.99)		2.09 (1.61, 2.70)	
3	2.16 (1.68, 2.76)		3.93 (2.97, 5.20)	
Family-related (number)				
0	1.00	< 0.01	1.00	< 0.01
1	1.33 (1.15, 1.54)		1.45 (1.19, 1.77)	
2	1.68 (1.38, 2.03)		2.21 (1.72, 2.83)	
3	1.87 (1.45, 2.40)		2.41 (1.77, 3.27)	
4	2.94 (2.20, 3.93)		3.65 (2.63, 5.06)	
Education at Age 26 Years				
None	1.00	0.07	1.00	0.83
Lower secondary level qualifications	0.98 (0.77, 1.25)		0.79 (0.56, 1.11)	
Advanced secondary	1.30 (1.00, 1.69)		1.04 (0.72, 1.51)	
Degree level or equivalent	1.20 (0.79, 1.81)		0.80 (0.43, 1.50)	
Marital Status at Age 43 Years				
Not married	1.00	0.21	1.00	0.76

	Moderate versus None (95% CI)[2]	P value[4]	Severe versus None (95% CI)[3]	P value[4]
Married	1.18 (0.91, 1.54)		0.94 (0.66, 1.35)	
Number of Children at Age 53 Years				
0	0.62 (0.45, 0.86)	0.06	0.68 (0.43, 1.10)	0.26
1	0.93 (0.68, 1.28)		1.09 (0.70, 1.70)	
2	1.00		1.00	
3	0.87 (0.67, 1.12)		1.01 (0.70, 1.45)	
≥ 4	1.05 (0.72, 1.55)		1.04 (0.60. 1.80)	
Psychiatric Symptom Frequency Score at Age 43 Years (0 - 90)				
0 - 4	1.00	< 0.01	1.00	< 0.01
5 - 9	2.05 (1.52, 2.77)		2.43 (1.44, 4.11)	
10 - 16	2.69 (1.99, 3.64)		3.78 (2.27, 6.32)	
≥ 17	2.99 (2.22, 4.04)		6.48 (3.96, 10.60)	
Number of Physical Conditions at Age 43 Years (0 - 9)				
0	1.00	< 0.01	1.00	< 0.01
1	1.37 (1.09, 1.72)		1.62 (1.15, 2.27)	
≥ 2	1.63 (1.27, 2.10)		2.43 (1.70, 3.46)	
History of Trouble Sleeping at Age 43 Years				
No	1.00	< 0.01	1.00	< 0.01
Yes	2.31 (1.79, 3.00)		4.06 (2.96, 5.57)	
Use of Prescription Medication at Age 43 Years (0 - 7)				
0	1.00	< 0.01	1.00	< 0.01
1	1.50 (1.20, 1.88)		1.90 (1.38, 2.62)	
≥ 2	1.31 (0.98, 1.75)		2.23 (1.51, 3.28)	
Exercise at Age 43 Years				
Inactive	1.00	0.37	1.00	0.12
Vigorous < 1x/week	1.11 (0.87, 1.42)		0.91 (0.64, 1.30)	
Vigorous > 1x/week	1.10 (0.86, 1.41)		0.74 (0.51, 1.08)	
Ever Smoked at Age 43 Years				
No	1.00	0.20	1.00	0.04
Yes	1.14 (0.93, 1.39)		1.35 (1.02, 1.80)	
Alcohol Consumption in Drinks/day at Age 43 Years				
0	1.00	0.77	1.00	0.6
0.1 - 1.0	1.07 (0.85, 1.34)		0.87 (0.62, 1.2)	
1.1 - 2.0	0.83 (0.61, 1.13)		0.84 (0.54, 1.30)	
≥ 2.1	1.09 (0.75, 1.57)		0.96 (0.57, 1.62)	
Body Mass Index at Age 43 Years				
<18.5	1.00	0.97	1.00	0.04
18.5-24.9	1.35 (0.89, 2.03)		1.27 (0.69, 2.34)	

	Moderate versus None (95% CI)[2]	P value[4]	Severe versus None (95% CI)[3]	P value[4]
25-29.9	1.35 (0.87, 2.08)		1.52 (0.80, 2.89)	
≥ 30	1.13 (0.69, 1.85)		1.82 (0.91, 2.66)	

[1] Unless otherwise indicated, the variable was measured annually between ages 48 – 54 years

[2] N = 938, observations = 4072

[3] N = 888, observations = 3125

[4] p value for test of heterogeneity for menopausal transition status, test of linear trend for all other categorical variables, and Wald test for binary variables.

Table 3

Odds Ratios (95% confidence intervals) for moderate self-reported sleep difficulty versus none by menopausal transition status, ages 48 – 54 (N = 938 ; observations = 4072)

Menopausal Status	Model 1 (95% CI)	Model 2 (95% CI)	Model 3 (95% CI)
pre-pre	1.00	1.00	1.00
pre-peri	1.21 (0.95, 1.56)	1.05 (0.80, 1.39)	1.05 (0.79, 1.40)
peri-peri	1.35 (1.06, 1.71)	1.09 (0.83, 1.42)	1.13 (0.86, 1.48)
pre/peri-post	1.48 (1.09, 2.02)	1.22 (0.86, 1.72)	1.27 (0.89, 1.81)
post-post	1.18 (0.89, 1.55)	1.12 (0.83, 1.51)	1.13 (0.83, 1.54)
pre/peri-HT	1.54 (1.10, 2.16)	1.19 (0.82, 1.73)	1.20 (0.82, 1.77)
HT-HT	0.97 (0.74, 1.29)	0.89 (0.66, 1.20)	0.88 (0.65, 1.20)
pre/peri/hyst-hyst	1.56 (1.16, 2.09)	1.43 (1.05, 1.96)	1.46 (1.06, 2.02)

Model 1: Age-adjusted

Model 2: Adjusted for age, current vasomotor, somatic, and psychological symptoms, and waking to use the toilet at night, which were all measured annually from ages 48 – 54 years.

Model 3: Adjusted for age; annual measures from ages 48 – 54 years of current vasomotor, somatic, and psychological symptoms, and waking to use the toilet at night, work and family-related stress; measures from age 43 years of depression and anxiety symptoms, physical conditions, history of trouble sleeping, and use of prescription medication

Table 4

Odds Ratios (95% confidence intervals) for severe self-reported sleep difficulty versus none by menopausal transition status, ages 48 – 54 (N = 888 ; observations = 3125)

Menopausal Status	Model 1 (95% CI)	Model 2 (95% CI)	Model 3 (95% CI)
pre-pre	1.00	1.00	1.00
pre-peri	1.60 (1.09, 2.33)	1.41 (0.85, 2.34)	1.40 (0.81, 2.43)
peri-peri	2.23 (1.55, 3.21)	1.73 (1.08, 2.77)	1.97 (1.19, 3.28)
pre/peri-post	2.84 (1.85, 4.38)	2.64 (1.51, 4.59)	2.91 (1.60, 5.28)
post-post	1.87 (1.22, 2.87)	1.89 (1.13, 3.17)	1.88 (1.08, 3.27)
pre/peri-HT	2.86 (1.81, 4.52)	2.21 (1.25, 3.91)	2.64 (1.42, 4.90)
HT-HT	1.78 (1.16, 2.72)	1.71 (1.03, 2.84)	1.69 (0.98, 2.90)
pre/peri/hyst-hyst	3.20 (2.06, 4.96)	3.42 (2.04, 5.73)	3.47 (1.99, 6.04)

Model 1: Age-adjusted

Model 2: Adjusted for age, current vasomotor, somatic, and psychological symptoms, and waking to use the toilet at night, which were all measured annually from ages 48 – 54 years.

Model 3: Adjusted for age; annual measures from ages 48 – 54 years of current vasomotor, somatic, and psychological symptoms, and waking to use the toilet at night, work and family-related stress; measures from age 43 years of depression and anxiety symptoms, physical conditions, history of trouble sleeping, use of prescription medication, and smoking.