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## Investigating the associations between nocturia and sleep disorders in perimenopausal women

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### Abstract

**Purpose**—To determine the associations between nocturia and sleep disorders in perimenopausal women.

**Material and Methods**—100 women with nocturia were compared to 200 women without nocturia. The presence of obstructive sleep apnea, insomnia, anxiety and menopausal stage were assessed using validated questionnaires. Comorbidities associated with nocturia were determined by bivariable analysis and multivariable logistic regression.

**Results**—Independent associations for nocturia were anxiety (OR 2.11, 95%CI 1.08,4.13), African American race (OR 2.00, 95%CI 1.06,3.85), obstructive sleep apnea (OR 1.73, 95%CI 1.18,2.53) and insomnia (OR 1.11, 95%CI 1.05,1.12).

**Conclusion**—Nocturia is associated with sleep disorders in perimenopausal women.

### Keywords

nocturia; sleep disorders; menopause

### Introduction

Nocturia can have a significant impact on a woman's health and quality of life.<sup>1</sup> Furthermore, the prevalence of nocturia increases with advancing age.<sup>2</sup> Lower urinary tract symptoms such as urinary incontinence, urinary urgency and frequency have also been shown to be associated with both advancing age and menopause in women.<sup>3-4</sup> Known risk factors for nocturia include diabetes, cardiovascular disease and obstructive sleep apnea. There have been many studies<sup>5-7</sup> that have investigated the relationship between nocturia and sleep disorders. Most of these have focused on elderly subjects that included both men and women.

Menopause may also be associated with sleep disorders due to its relationship with hot flashes and anxiety at this stage in life. However, there are very few studies<sup>2</sup> that have investigated the relationship between nocturia and sleep disorders in women during the menopausal

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transition. Furthermore, these studies have not accounted for the contribution of hot flashes, anxiety or menopausal stage and its role in the development of sleep disorders during the late reproductive years. The aim of this study was to determine the association between nocturia and sleep disorders in a group of perimenopausal women.

## Material and Methods

This investigation was conducted as a nested cross-sectional analysis at period 11 of a total of 15 planned annual assessments in the parent study the Penn Ovarian Aging Study. The Penn Ovarian Study is a prospective longitudinal cohort study of women who were randomly identified in their late reproductive years. The main objective of the project was to evaluate the relationship between changes in reproductive hormone levels and various symptoms associated with the menopausal transition. The cohort was recruited from Philadelphia County from 1996-1997 by random digit dialing. Women were eligible if they had normal menstrual cycles (22-35 days), between the ages 35-47, an intact uterus and at least one ovary. Women were excluded if there was a history of alcohol or drug abuse, current use of hormonal medication or oral contraception and any medical problem that could compromise ovarian function. The Institutional Review Board at the University of Pennsylvania approved this study.

At each assessment blood specimens, anthropometric measures, and extensive questionnaires were obtained. Repeat blood samples one month apart were collected in order to ensure reliable point estimates of hormone measurements. Estradiol levels were determined from blood samples taken within the first six days of the menstrual cycle by radioimmunoassay using Coat-A-Count commercial kits (Diagnostic Products, Los Angeles, CA). The intra- and inter-assay coefficients of variation were consistently less than 5% for all estradiol assays.

Trained research interviewers conducted the interviews and collected the data. A standardized question ascertaining nocturic frequency was added to the self-report questionnaires given to the 311 eligible study participants at Period 11. The study participants were asked: 'During the night, how many times do you have to get up to urinate, on average?' The response options ranged from 0-4, with '0' representing no episodes of voiding at night to a maximum of '4 or more' episodes. This question has been used in prior validated instruments used to ascertain a woman's lower urinary tract symptoms.<sup>8-9</sup> For the purpose of this study we defined nocturia as  $\geq 2$  episodes of nighttime voiding.<sup>5,10</sup>

The definitions of menopausal stage were determined based on the Stages of Reproductive Aging Workshop consensus statement on a staging system for reproductive aging women.<sup>11-12</sup> Early perimenopausal transition was defined as a change in cycle length of 7 or more days in either direction for one or two menstrual cycles compared with the participant's personal baseline at enrollment in the cohort. Late perimenopausal transition was defined as 3-11 months of amenorrhea during the study. Menopause was defined as 12 or months of amenorrhea with no hysterectomy.

Information on the following medical conditions was collected using validated and reliable, self-administered questionnaires: obstructive sleep apnea, insomnia and anxiety. The Multivariable Apnea Risk Assessment Index<sup>13</sup> (MAP Index) measured the severity of obstructive sleep apnea symptoms.<sup>13</sup> An insomnia score was assigned based on the Women's Health Initiative (WHI) insomnia rating scale.<sup>14</sup> Anxiety was assessed using the Zung Anxiety Index.<sup>15</sup> Established score ranges for the Zung Anxiety Index include: normal anxiety (20-35), moderate anxiety (36-47) and high anxiety (48-60).

The presence of hot flashes in the past month was queried in interview and the severity was categorized as mild, moderate and severe. Any smoking or alcohol use over the last 12 months was recorded. Demographic data included the level of education (greater or less than a high

school diploma), parity, current employment, income level and marital status. Information regarding the presence of diabetes, hypertension, diuretic use and current treatment for a urinary tract infection was also collected.

A bivariable analysis was performed to assess the association between nocturia and the two sleep disorders (obstructive sleep apnea and insomnia). Bivariable analysis was also performed to determine the association between nocturia and other covariates that are known confounding factors in the relationship between nocturia and sleep disorders. The MAP Index, insomnia scale, parity and estradiol levels were treated as continuous variables. Because of the skewed distribution of estradiol, the hormone values were transformed on the log scale. Remaining variables were either categorized (menopausal stage, hot flashes severity, body mass index (BMI), income level, anxiety and age) or dichotomized (nocturia, presence of hot flashes, alcohol or tobacco use, depression, marital status, employment status, education, diabetes, hypertension, diuretic use and current treatment for urinary tract infection).

To adjust for the influence of the various covariates on the association of nocturia with sleep disorders, a multivariable logistic regression model was developed utilizing a backward elimination strategy to identify independent associations for nocturia. Covariates were included in the model if the variable was associated with the outcome with a P-value  $\leq$  0.20 and if the inclusion of the confounder influenced other associations of interest by 15% or more.<sup>16</sup> All analyses were conducted using STATA 9.2 (Stata Corp., College Station, TX). A two-sided P value of  $<$  0.05 was considered statistically significant.

The prevalence of sleep disorders has been reported to be 37%.<sup>17</sup> At an alpha of 0.05 and a beta of 0.20, we determined that we would need 99 women in the nocturia group and 200 women in the no nocturia group to detect an odds ratio of 2.0 or greater for sleep disorders between the two groups.

## Results

Of the 311 participants at Period 11 in the parent study, data was available on 300 women. 100 women were identified with nocturia and compared to 200 women without nocturia. Forty seven percent women were African American and 53% were Caucasian. The mean age, parity and estradiol levels were similar between the two groups. Demographic information, comorbidities characteristics, and bivariable unadjusted associations are presented in Table I.

Significant unadjusted associations identified for nocturia were obstructive sleep apnea (MAP Index), insomnia, worsening anxiety, BMI, low income, smoking and African American race. Women with a BMI  $>$ 35 had significantly increased odds of nocturia when compared to women with BMI in the normal range (BMI 18-24). A test of trend demonstrated that more women are affected by nocturia with increasing BMI ( $p <$  0.001). Similarly, we observed that a greater number of women reported nocturia with increasing age but the trend did not reach significant levels ( $p =$  0.16). Women in the late perimenopausal stage had increased odds of nocturia in comparison to those in the early perimenopausal stage. Women in menopause did not have increased odds of nocturia versus those in the early perimenopausal stage. We did not find any association between estradiol levels and nocturia. However, the presence of moderate to severe hot flashes was significantly associated with nocturia. We also found that the presence of hot flashes corresponded with worsening anxiety (test for trend,  $p$ -value = 0.001). Women with diabetes, hypertension, and a history of current diuretic use or treatment for a urinary tract infection did not have increased odds of nocturia.

The results of multivariable logistic regression are presented in Table II. After adjusting for confounding factors, significant associations for nocturia on multivariable analysis were

obstructive sleep apnea, insomnia, African American race, anxiety, BMI>35 and household income less than \$15,000. Age was not significantly associated with nocturia in the final model.

## Discussion

Prior studies that have investigated the relationship between nocturia and sleep disorders have focused on an older population that included both men and women.<sup>5-7</sup> In the present study, we have specifically investigated the relationship between nocturia and sleep disorders in perimenopausal women. This group is unique because they have several potential risk factors for nocturia including hot flashes, anxiety and menopausal stage. Furthermore, using a MEDLINE search of 'nocturia' and 'insomnia,' we were unable to identify any prior study that has examined this relationship.

The most important finding of our study was that nocturia was significantly associated with obstructive sleep apnea, insomnia, and anxiety in perimenopausal women. In agreement with other studies<sup>10</sup>, we found that significant associations for nocturia in this population were obesity and African American race. We believe that our findings are valid because we used validated instruments to measure nocturia, sleep disorders and other covariates. The MAP Index, WHI insomnia scale and Zung anxiety Index have been appropriately tested and have shown to have a high positive predictive value for the diagnosis of obstructive sleep apnea, insomnia and anxiety respectively.

Two studies have previously reported on the relationship between nocturia and some indirect measures of insomnia.<sup>1-2</sup> Lin et al. reported that 11.9% of women who reported 2 or more episodes of nocturia also reported sleep disruption or daytime somnolence.<sup>2</sup> We utilized a validated and reliable instrument (WHI Insomnia scale) designed specifically to measure insomnia. In our study, we found insomnia to be independently associated with nocturia in women undergoing the menopausal transition. The underlying mechanism by which insomnia results in nocturia is unclear but maybe due to the disruption in circadian sleep cycle. One prior study has shown these disruptions may result in alteration of regulatory hormones such as cortisol, leptin, and melatonin that affect metabolic and physiologic functions.<sup>18</sup> These changes can promote a nocturnal eating/drinking syndrome<sup>19</sup> where >50% of an individual's daily caloric intake occurs. Increases in fluid intake have been linked to micturition frequency and could be the cause of increased nighttime voiding. Further studies are required to determine if insomnia is associated with increased nighttime fluid intake.

The association of nocturia with obstructive sleep apnea has been reported earlier but has not been thoroughly investigated in a population of women undergoing the menopausal transition. One prior study has examined the association of sleep disorders in women during the late reproductive years. Asplund et al.<sup>6</sup> reported an association between poor sleep and nocturia; however, validated instruments to assess sleep patterns were not used and the precise type of sleep disorder was not identified. We found obstructive sleep apnea, as assessed by the MAP Index, was significantly associated with nocturia in perimenopausal women. Although subjects did not undergo overnight laboratory polysomnography, the gold standard study for identification of obstructive sleep apnea, the MAP Index has been shown to be an accurate tool for identifying subjects with obstructive apnea symptoms with a positive predictive value of 80%.<sup>13</sup> These findings are clinically important. A woman presenting with symptoms of nocturia would benefit from an evaluation by a sleep specialist for insomnia or obstructive sleep apnea.

There are several possible etiologies for nocturia in women with obstructive apnea symptoms. Increased levels of atrial natriuretic peptide, a hormone with diuretic effects, have been recorded in individuals with obstructive sleep apnea.<sup>7</sup> These increased levels of atrial natriuretic peptide

are likely to be the result of the wide fluctuations in intrathoracic pressure that occur during apneic events, leading to hemodynamic changes in the atria<sup>7</sup> that mistakenly signal the presence of fluid overload. Similarly, increased intra-abdominal pressure generated during apneic events may be transmitted to the bladder increasing detrusor pressure on cystometrograms.<sup>20</sup> The relationship between the increased detrusor pressure during an apneic episode and nocturia needs further investigation.

In our study, nocturia was significantly associated with anxiety as well as hot flashes on bivariable analysis. However, on multivariable analysis, the relationship between nocturia and hot flashes disappeared. After controlling for confounding factors, the association anxiety and nocturia remained significant. This finding is not surprising because anxiety can cause sleep disturbance<sup>21</sup> which may in turn result in women with greater opportunities to void at night.

Very few studies have examined the relationship between nocturia and menopausal stage. Lin et al.<sup>5</sup> did investigate nocturia in perimenopausal women but they arbitrarily assigned the stages of menopause based on age. We defined the stages of menopause based on detailed menstrual diaries completed prospectively by study participants. The menstrual stages were based on the Stages of Reproductive Aging Workshop consensus statement that outlined the optimal transition points during a woman's late reproductive years. These stages have been validated by the changes in reproductive hormones.<sup>12</sup> On bivariable analysis, we initially did see an association between late perimenopausal stage and nocturia; however, that association disappeared on multivariable analysis. To definitively answer this question, a longitudinal study exploring the relationship between menopausal stage and nocturia is required.

We found that African American women in the menopausal transition were significantly more likely to report nocturia than Caucasian women. This association persisted even after controlling for confounding factors. Our finding is in agreement with that of FitzGerald et al.<sup>10</sup> who also reported a similar increase in the odds of nocturia in women with African American race. These findings could be attributed to the structural differences in the pelvic floor and the bladder neck identified between Caucasian and African American women<sup>22-24</sup> or to unidentified factors that make these populations different.

Some limitations of our study should be considered. Nocturia was self-reported and the possibility of recall bias exists; however, this bias is likely to be non-differential between groups and would bias the results toward the null. The use of a standardized question to determine nocturia further reduces the likelihood of misclassification. Another limitation of our study is that we did not use the current International Continence Society definition of nocturia.<sup>25</sup> Prior studies have shown that there may be an increase in episodes of nocturnal micturition that is associated with aging.<sup>2,26</sup> Similar to FitzGerald et al.,<sup>10</sup> we utilized a more conservative definition ( $\geq 2$  episodes of night-time voids) in an attempt to identify a subset of women with 'pathologic nocturia'.<sup>5</sup> Finally, a cross-sectional design allows us to only identify associations between nocturia and various risk factors. To determine causality, a longitudinal study design would be required.

## Conclusion

It appears that significant associations for nocturia are obstructive sleep apnea, insomnia, anxiety and obesity. Clinicians should be aware of these associations, as these disorders are treatable conditions.

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**Table I**

Bivariable associations of nocturia with selected variables

	Nocturia N=100(%)	No Nocturia N=200(%)	Unadjusted OR (95% CI)	P-value
Age (y)				0.08
40-44	6 (6)	28 (14)	Reference	Reference
45-49	46 (46)	87 (44)	1.07(0.18-6.20)	0.94
50-54	46 (46)	46 (37)	2.64(0.56-12.5)	0.22
55-59	2 (2)	10 (5)	3.06(.64-14.6)	0.16
BMI				0.001
<25	15 (15)	47 (24)	Reference	Reference
25-29	19 (19)	66 (33)	0.90(0.42-1.95)	0.79
30-34	16 (16)	39 (19)	1.28 (0.56-2.92)	0.55
>35	50 (50)	48 (24)	3.26(1.61-6.59)	0.001
Race				
Caucasian	34 (34)	124 (62)	Reference	Reference
African American	66 (66)	76 (38)	3.16(1.92-5.23)	<0.001
Hot flashes				
No	30 (30)	87 (44)		
Yes	70 (70)	113 (56)	1.80(1.08-2.99)	0.025
Hot flashes severity				0.001
None	30 (30)	87 (44)	Reference	Reference
Mild	19 (19)	57 (28)	0.97(0.50-1.88)	0.92
Moderate	33 (33)	46 (24)	2.08(1.13-3.83)	0.019
Severe	18 (18)	10 (5)	5.22(2.17-12.5)	<0.001
Smoking				
No	59 (59)	144 (73)		
Yes	41 (41)	54 (27)	1.85(1.17-3.07)	0.017
Marital status				
No	46 (46)	86 (40)		
Yes	54 (54)	120 (60)	0.78(0.48-1.27)	0.32
Employed				
No	25 (25)	29 (14)		
Yes	75 (75)	171 (86)	0.51(0.28-0.93)	0.027
Hypertension				
No	76 (76)	142 (71)		
Yes	24 (24)	58 (29)	0.77(0.45-1.34)	0.36
Diabetes				
No	94 (94)	185 (92)		
Yes	6 (6)	15 (8)	0.79(0.31-2.04)	0.63
Diuretic use				
No	90 (90)	189 (94)		
Yes	10 (10)	11 (6)	1.91(0.80-4.56)	0.15



	Nocturia N=100(%)	No Nocturia N=200(%)	Unadjusted OR (95% CI)	P-value
UTI				
No	99 (99)	193 (97)		
Yes	1 (1)	7 (3)	0.28(0.01-1.77)	0.20
Alcohol				
No	86 (86)	158 (79)		
Yes	14 (14)	42 (21)	0.61(0.32-1.18)	0.15
Education				
<high school	56 (56)	71 (35)	Reference	
≥high school	44 (44)	129 (65)	0.43(0.27-0.71)	0.001
Menopausal Stage				
Early transition	38 (38)	83 (41)	Reference	Reference
Late transition	29 (29)	33 (17)	1.91(1.02-3.60)	0.04
Menopausal	33 (33)	84 (42)	0.86(0.49-1.49)	0.65
Anxiety				
Normal	54 (54)	161 (81)	Reference	Reference
Moderate	40 (40)	35 (17)	3.40(1.97-5.89)	<0.001
High	6 (6)	4 (2)	4.47(1.21-16.4)	0.024
Income				
<\$15,000	20 (20)	9 (4)	8.89(3.62-21.7)	<0.001
\$15,001-30,000	18 (18)	28 (14)	2.57(1.23-5.34)	0.01
\$30,001-45,000	18 (18)	29 (15)	2.48(1.20-5.14)	0.01
\$45,001-60,000	18 (18)	29 (15)	2.48 (1.20-5.14)	0.01
>\$60,000	26 (26)	105(52)	Reference	Reference
MAP Index(apnea)	0.90±1.06	0.34 ± 0.64	2.18(1.58-3.02)	<0.001
Insomnia score	11.4±5.86	7.60 ± 5.27	1.13(1.08-1.18)	<0.001
Mean Estradiol	3.33 ± 0.84	3.34 ± 0.78	0.99(0.74-1.35)	0.97
Parity	3.43 ± 2.12	3.05 ± 2.06	1.09(0.97-1.22)	0.135

OR:Odds Ratio, CI: Confidence Interval, UTI: Urinary Tract Infection

**Table II**Adjusted associations of nocturia with selected variables<sup>†</sup>

	Adjusted OR (95% CI)	P-value
MAP Index(apnea)	1.73 (1.18 – 2.53)	0.006
Insomnia score	1.11 (1.05 - 1.17)	<0.001
Anxiety		
Normal	Reference	
Moderate	2.11 (1.08 - 4.13)	0.03
High	1.70 (.35 - 8.23)	0.50
African American	2.00 (1.06 – 3.85)	0.04
Income		
<\$15000	4.50 (1.51 – 13.4)	0.007
\$15,001-30,000	1.47 (.61 - 3.57)	0.39
\$30,001-45,000	1.55 (.64 - 3.76)	0.33
\$45,001-60,000	2.10 (.89 – 4.93)	0.08
>\$60,001	Reference	
BMI		
<25	Reference	
25-29	0.90(0.36-2.20)	0.82
30-34	1.18 (0.44-3.14)	0.75
>35	2.33(1.15-5.69)	0.04

OR:Odds Ratio, CI: Confidence Interval

<sup>†</sup> model controlled for hot flashes, hot flashes severity, hypertension, diuretic use, diabetes, urinary tract infection, smoking, marital and employment status, menopausal stage, estradiol levels, alcohol use, education level and parity