Original Contribution

A Systematic Evaluation of Factors Associated With Nocturia—The Population-based FINNO Study

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In a case-control study with prevalence sampling, the authors explored the correlates for nocturia and their population-level impact. In 2003–2004, questionnaires were mailed to 6,000 subjects (aged 18–79 years) randomly identified from the Finnish Population Register (62.4% participated; 53.7% were female). Questionnaires contained items on medical conditions, medications, lifestyle, sociodemographic and reproductive factors, urinary symptoms, and snoring. Nocturia was defined as ≥2 voids/night. In age-adjusted analyses, factors associated with nocturia were entered into a multivariate model. Backward elimination was used to select variables for the final model, with adjustment for confounding. Although numerous correlates were identified, none affected ≥50% of nocturia cases of both sexes. The factors with the greatest impact at the population level were (urinary) urgency (attributable number/1,000 subjects (AN) = 24), benign prostatic hyperplasia (AN = 19), and snoring (AN = 16) for men and overweight and obesity (AN = 40), urgency (AN = 24), and snoring (AN = 17) for women. Moreover, correlates included prostate cancer and antidepressant use for men, coronary artery disease and diabetes for women, and restless legs syndrome and obesity for both sexes. Although several correlates were identified, none accounted for a substantial proportion of the population burden, highlighting the multifactorial etiology of nocturia.

coronary artery disease; diabetes mellitus; life style; obesity; prostatic hyperplasia; prostatic neoplasms; sleep disorders; urinary bladder, overactive

Abbreviations: BPH, benign prostatic hyperplasia; FINNO, Finnish National Nocturia and Overactive Bladder.

Nocturia (waking at night to urinate) is a common cause of awakenings and may lead to sleep maintenance insomnia (1–3). Nocturia can be bothersome (4) and is associated with impaired mental and somatic health (5), impaired quality of life (4), and even increased mortality (6).

The etiology of nocturia is inadequately understood. Nocturia is frequently attributed to aging or childbirth in women and to benign prostatic hyperplasia (BPH) in men. Other related conditions include overactive bladder syndrome; nocturnal polyuria; obstructive sleep apnea; awakening for other reasons such as anxiety; primary sleep disorders; and use of diuretics, caffeine, or alcohol (7–9). Bedtime fluid intake correlates poorly with nocturia episodes (10).

Nocturia persists frequently following simple prostatectomy (11). In one study, 38% of men reported ≥2 voids/night 3 years after transurethral resection of the prostate (12). Several pharmacologic approaches have yielded limited nocturia reductions or significant side effects (7, 13–25).

To our knowledge, no earlier study comprehensively covered the possible associations of medical conditions; medications; lifestyle; and anthropometric, reproductive, and sociodemographic factors with nocturia. We explored correlates for nocturia and assessed their population-level impact in a large population-based study.

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MATERIALS AND METHODS

Finnish National Nocturia and Overactive Bladder (FINNO) Study

In 2003–2004, questionnaires were mailed to 6,000 subjects aged 18–79 years randomly identified from the Population Register Centre. Age stratification was used with oversampling of younger age groups to ensure precise estimates even in age groups experiencing lower nocturia frequency (3, 26). More information on the FINNO Study (including characterization of nonrespondents) has been published previously (3, 26, 27).

Outcome

Nocturia cases were defined as subjects reporting 2 or more voids/night because this frequency involves clinically significant bother (4). All subjects without nocturia were considered controls in unconditional logistic regression analyses. Self-reported nocturia frequency was determined by using a previously described algorithm (27) combining responses to the Danish Prostatic Symptom Score (28) and the American Urological Association Symptom Index (29) (Web Table 1; this information is described in the first of 4 supplementary tables, each referred to as ''Web table'' in the text and posted on the *Journal*'s website (http://aje. oupjournals.org/)).

Correlate assessment

Self-reported information on physician-diagnosed conditions, prescribed medication, specific symptoms, and lifestyle factors was obtained by using questions modified from surveys conducted by the National Public Health Institute (30). Comorbidity indicators were formulated for 36 conditions deemed common or previously hypothesized as determinants of lower urinary tract symptoms (Web Tables 1 and 2). Medication use was classified into 27 groups by using the Anatomical Therapeutic Chemical Classification (31) (Web Tables 1 and 3). Lifestyle factors included body mass index, smoking, and alcohol and coffee consumption (Web Tables 1 and 4). The Danish Prostatic Symptom Score questions were used to evaluate (urinary) urgency and stress urinary incontinence (28) and the Basic Nordic Sleep Questionnaire to evaluate snoring (32) (Web Tables 1 and 4). These symptoms have been specifically shown to be risk factors for nocturia (26, 33, 34).

With the exception of the alcohol consumption question (response rate: men, 86%; women, 76%), data on potential correlates were highly available (men, 97%–100%; women, 95%–100%). Alcohol consumption was not associated with nocturia.

Potential confounders

Age, sociodemographic factors (marital status, education, employment, urbanization) (3), and female reproductive/gynecologic factors (parity, postpartum period, menopausal status, hormone therapy, hysterectomy, stress urinary incontinence surgery) (27) were treated as potential confounders.

Data on urbanization, parity, and delivery date(s) were obtained from the population register. Information on each potential confounder was available for at least 99% of subjects.

Statistical analysis

Logistic regression was used for the analyses stratified by sex, with nocturia as the outcome. All potential correlates and confounders associated ($P < 0.10$) with nocturia in the age-adjusted analyses (basic analysis population) were entered into the multivariate model (Web Figure 1, also posted on the *Journal*'s website (http://aje.oupjournals.org/)). In these analyses, potential correlates and confounders numbered 16 and 2 for men and 18 and 6 for women, respectively. Backward elimination techniques were used to select variables for the final model, with likelihood ratio tests used to determine significance ($P < 0.05$). Finally, cofactors that were not actual confounders (they did not change any estimate by $\geq 10\%$) were eliminated. Confirmed confounders were age for men, menopausal status for women, and employment for both sexes. The final analysis included subjects with information on nocturia, correlates, and confounders (Web Figure 1). For the correlates identified, age-standardized sensitivity, positive predictive value, attributable fraction in the exposed, population attributable fraction, and attributable number were calculated (35).

RESULTS

Of the 6,000 subjects approached, 3,727 (62.4%) participated; 23 were unavailable, and 130 were excluded because of pregnancy, puerperium, or urinary tract infection (Web Figure 1). (The response rate was approximately 32% after the first round, 50% after the second round, and 62.4% after the final, third round.) Of the 3,597 subjects included, 98% provided nocturia information (basic analysis population). The 3,307 subjects (92%) who responded to all nocturia, correlate, and confounder questions formed the final analysis population. Prevalence of nocturia was 12.5% (95% confidence interval: 10.7, 14.3) among men and 12.9% (95% confidence interval: 11.0, 14.9) among women (age standardized to match Finland's age structure (36)). Excluding subjects with missing information on any correlate or confounder (final analysis population) did not change these estimates. For more detail, refer to Table 1 and to Web Tables 2–4. Correlates for nocturia included (urinary) urgency, snoring, restless legs syndrome, and obesity for both sexes; BPH, antidepressant use, and prostate cancer for men; and overweight, diabetes, and coronary artery disease for women (Table 1).

At the population level (Table 2), urgency and snoring (both sexes), BPH (men only), and overweight/obesity (women only) accounted for the largest proportion of nocturia. At the individual level, the strongest correlate for both sexes was urgency, although odds ratio differences between correlates were mainly statistically nonsignificant (Table 1).

No correlate affected 50% or more of men with nocturia (Figure 1): BPH, urgency, and snoring had the highest sensitivity for nocturia (31%–49%). Of the women with nocturia, 71% were overweight or obese; other correlates were reported by 50% or more of women with nocturia (Figure 2).

Table 1. Prevalences (%) and Odds Ratios of Correlates for Nocturia in Multivariate Analyses[a] in the Population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004

	Prevalence[b]	95% CI	OR	95% CI
Men				
Urinary urgency	7.5	6.1, 9.0	7.39	4.46, 12.23
Prostate cancer	1.2	0.7, 1.8	5.45	1.74, 17.08
Antidepressant use	2.5	1.7, 3.3	3.16	1.29, 7.73
Restless legs syndrome	3.0	2.1, 4.0	2.91	1.30, 6.52
Benign prostatic hyperplasia	7.8	6.3, 9.3	2.18	1.31, 3.65
Obesity[c]	13.2	11.2, 15.1	2.07	1.17, 3.67
Snoring	35.1	31.9, 38.2	1.49	1.00, 2.22
Women				
Urinary urgency	9.9	8.2, 11.6	4.92	3.15, 7.67
Coronary artery disease	4.5	3.1, 5.8	3.13	1.48, 6.64
Restless legs syndrome	3.6	2.5, 4.8	2.86	1.41, 5.83
Diabetes	4.7	3.4, 5.9	2.68	1.38, 5.20
Obesity[c]	13.3	11.4, 15.3	2.18	1.30, 3.66
Overweight[c]	32.3	29.2, 35.4	1.90	1.25, 2.88
Snoring	18.4	16.1, 20.7	1.76	1.17, 2.64

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Also adjusted for identified confounders (age and employment for men; employment and menopausal status for women).

[b] Age standardization using the age structure of Finland (36).

[c] Normal-weight (body mass index < 25 kg/m^2) subjects were considered the reference (37).

A majority of men with prostate cancer or urgency reported nocturia, yielding positive predictive values of 74% and 59%, respectively. Half of the men with BPH, and a minority of men with other correlates, reported nocturia (Figure 1). Among women, no correlates were associated with a 50% or greater probability of nocturia (Figure 2).

Generally, questionnaire mailing round did not affect correlate prevalence. However, 4 exceptions emerged (age adjusted). First-round responders reported more nocturia and urgency than responders in subsequent rounds (P for trend = 0.01 for both nocturia and urgency; sexes combined). Moreover, first-round male responders reported more antidepressant use (P for trend = 0.04), and first-round female responders were slightly less obese than those in subsequent rounds (P for trend = 0.05). However, the odds ratio estimates for these factors were similar for each round, suggesting absence of systematic error.

DISCUSSION

In this large, population-based study, numerous factors associated with nocturia were identified. However, no single correlate accounted for more than half of the cases of nocturia, highlighting its multifactorial etiology. At the population

Table 2. Fraction of Nocturia Attributable to Identified Correlates in the Population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004[a]

	Attributable Fraction in the Exposed, %[b,c]	Population Attributable Fraction, %[c,d]	Attributable No./1,000 Subjects[c,e]
Men			
Urinary urgency	77.2	24.0	24
Benign prostatic hyperplasia	69.1	13.1	19
Snoring	30.3	14.4	16
Obesity[f]	29.1	5.9	6
Antidepressant use	65.6	4.3	6
Restless legs syndrome	53.1	4.7	4
Prostate cancer	65.8	3.9	3
Women			
Overweight/obesity[f]	51.5	35.4	40
Urinary urgency	71.0	21.3	24
Snoring	46.8	16.4	17
Diabetes	63.3	8.6	9
Restless legs syndrome	63.4	7.4	7
Coronary artery disease	44.9	7.4	4

[a] Age standardization using the age structure of Finland (36).

[b] Attributable fraction in the exposed refers to the proportion by which prevalence of the condition (nocturia) among exposed persons (with the correlate) would be reduced if the exposure (correlate) were eliminated (35).

[c] Regarding formulae of attributable fractions and attributable number, it is assumed that causes other than the one under investigation have similar effects on the exposed and unexposed groups (35).

[d] Population attributable fraction refers to the proportion by which prevalence of the condition (nocturia) in the entire population would be reduced if the exposure (correlate) were eliminated (35).

[e] Attributable number refers to the number of prevalent cases of the condition (nocturia) attributable to the exposure (correlate) (35).

[f] Body mass index (BMI) was classified as a dichotomous variable when calculating attributable fractions because of the dichotomous nature of these measures. Hence, the reference groups were not obese (BMI < 30 kg/m^2) for men and normal weight (BMI < 25 kg/m^2) for women because overweight (BMI 25–30 kg/m^2) was associated with nocturia in women only.

level, urgency, BPH, and snoring for men and overweight/obesity, urgency, and snoring for women accounted for the largest proportion of nocturia.

Our FINNO Study population is representative of Finnish adults in terms of sociodemographic, anthropometric, and female reproductive factors (3, 27, 37). The frequencies of comorbidities, medications, and lifestyle factors were similar to those in large-scale population surveys conducted by the National Public Health Institute (38–40).

Concordant with earlier reports (26, 41–44), urinary urgency was strongly associated with nocturia in both sexes, yet only 1 in 3 with nocturia reported urgency. Among men,
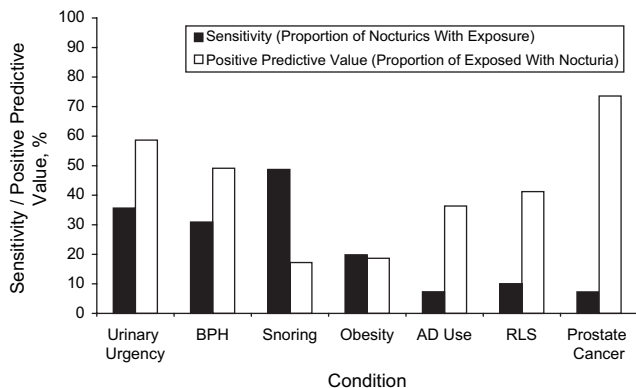
Figure 1. Sensitivity and positive predictive value for correlates of nocturia among men (in order: the correlate with the greatest impact at the population level is given first) in the population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004. AD, antidepressant; BPH, benign prostatic hyperplasia; RLS, restless legs syndrome. Body mass index (BMI) was classified as a dichotomous variable when calculating sensitivity and positive predictive value because of the dichotomous nature of these measures. Hence, the reference groups were not obese (BMI < 30 kg/m²) for men and normal weight (BMI < 25 kg/m²) for women because overweight (BMI 25–30 kg/m²) was associated with nocturia in women only.
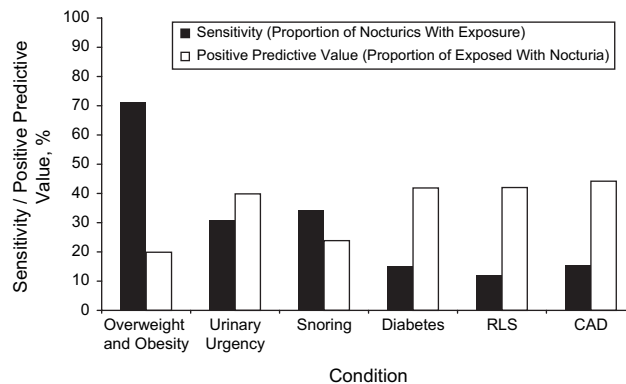
Figure 2. Sensitivity and positive predictive value for correlates of nocturia among women (in order: the correlate with the greatest impact at the population level is given first) in the population-based Finnish National Nocturia and Overactive Bladder Study, Finland, 2003–2004. CAD, coronary artery disease; RLS, restless legs syndrome. Body mass index (BMI) was classified as a dichotomous variable when calculating sensitivity and positive predictive value because of the dichotomous nature of these measures. Hence, the reference groups were not obese (BMI < 30 kg/m²) for men and normal weight (BMI < 25 kg/m²) for women because overweight (BMI 25–30 kg/m²) was associated with nocturia in women only.

BPH had the second highest population impact, but only a third with nocturia reported BPH. Lower urinary tract symptoms suggestive of benign prostatic obstruction constitute a well-recognized risk factor for nocturia (45). However, the impact of BPH may be overestimated. In Japanese studies, nocturia was the lower urinary tract symptom least related to prostatic obstruction, and treatment to relieve obstruction had less of an effect on nocturia than on other symptoms (15, 46). In a lower urinary tract symptoms/BPH study, patients receiving doxazosin experienced very modest reductions in nocturia, whereas finasteride had no effect (23). In the current study, prostate cancer was associated with nocturia. More than 70% of men with prostate cancer reported at least 2 voids/night, yet only 7% of men with nocturia reported prostate cancer.

Concurring with earlier findings (37, 47–49), nocturia was associated with *obesity* in both sexes and, among women, also with *overweight*. Indeed, overweight/obesity had the greatest population impact among women.

Snoring had a strong population impact because of its high prevalence, yet the strength of association was relatively weak (odds ratio = 1.5–1.8). Snoring has been associated with nocturia (34). The severity of obstructive sleep apnea predicted nocturia frequency, and continuous positive airway pressure treatment decreased nocturia (50). In a home sleep study, the prevalence of obstructive sleep apnea was double among urogynecology patients with nocturia compared with those without (51). In our study, reported obstructive sleep apnea was not associated with nocturia after adjustment, which may be due to correlation with snoring (three-quarters of subjects with obstructive sleep apnea reported snoring, and snoring was 10 times more prevalent than obstructive sleep apnea).

To our knowledge, no association has been reported between nocturia and restless legs syndrome. Increased nocturia among patients with restless legs syndrome may reflect sleep disturbance (52). Moreover, such patients use more medications (particularly antidepressants) than controls do (53). Nocturia has previously been linked to (untreated) depression (54, 55) and use of selective serotonin-reuptake inhibitors (54). In our study, only for men was nocturia associated with antidepressant use; depression itself was not associated with nocturia.

Diabetes and coronary artery disease were associated with nocturia in the age-adjusted analyses for both sexes but for only women in multivariate analysis. An association between diabetes and nocturia has been reported sometimes (43, 47, 49, 50, 56–60), but not always (10, 42, 45). In the BACH Survey (47), nocturia was associated with increasing body mass index, diabetes, and cardiac disease, whereas among Danes aged 60–80 years (49), increasing body mass index, diabetes, urinary incontinence, and recurrent cystitis were associated with 2 voids/night. In both surveys (47, 49), sex was used as a covariate, but results were not reported by gender. Some earlier reports (47, 59, 61), but not all (42, 43, 45, 49, 58), found cardiac/coronary disease a correlate for nocturia.

Coffee or alcohol consumption (10, 33, 41, 43, 49, 62, 63) and smoking (33, 49, 61, 63) have been shown elsewhere not to be associated with nocturia. Our findings were the same.

Differences in our results from previous findings may be explained by differences in study procedures and samples (64). Several factors explored here were not assessed in earlier studies (10, 41–43, 45–47, 49–51, 55, 56, 58, 59, 61–63). In addition, several previous studies were not population based (41, 43, 46, 50, 51, 59, 61). The association of numerous factors with nocturia in age-adjusted analyses,

partly differing by gender, highlights the importance of appropriate analysis, including controlling for confounders. Given the multiple possible determinants (7–10, 34, 41–43, 45–51, 54, 56–63), we assessed numerous candidates. Because of inconsistencies in the literature, using existing evidence to choose the potential confounders was not justified. Hence, because of the exploratory nature of this analysis, we used stepwise methods for model building (65).

By our methodology, we avoided selection bias due to treatment seeking (reflecting both severity and health care service use). Our study's strengths include 1) a representative sample of both sexes and all adult ages, 2) a high participation rate and completeness of questionnaire responses, 3) a large number of relevant factors, 4) systematic control for confounding, and 5) assessment of nocturia and related symptoms with validated instruments. Furthermore, determinant prevalences were largely similar by response round, indicating absence of selection bias; any trend in the risk estimates by response round was also lacking.

This study has some limitations. First, the validity of self-report has not been established for all characteristics we considered. Second, alcohol consumption reporting was incomplete, yet nocturia prevalence did not vary by alcohol consumption among those reporting this information. In addition, reported alcohol consumption was comparable with the national statistics (66). Third, we had no information on physical activity, although physical activity has not previously been related to nocturia (41). Finally, these results from the Finnish population may not be directly generalizable to other ethnicities because impact measures generally are context specific. There may be ethnic differences in the prevalence of nocturia. Socioeconomic status attenuated, but did not entirely remove, the effect of race/ethnicity on nocturia (67).

Nocturia has been classified as a symptom caused by 1) nocturnal polyuria, 2) low nocturnal bladder capacity, 3) diminished global bladder capacity, 4) a combination of nocturnal polyuria and low bladder capacity, 5) global polyuria, and/or 6) sleep disorders (7). We found several risk factors that may well cause these pathways and, finally, nocturia. However, the pathways are probably complex, and there may also be numerous other underlying causes for the associations, such as autonomic nervous system hyperactivity and/or metabolic syndrome (68, 69). At the population level, urgency, BPH, and snoring for men and overweight and obesity, urgency, and snoring for women explained the largest proportion of nocturia, whereas obesity, antidepressant use, and prostate cancer in men; diabetes and coronary artery disease in women; and restless legs syndrome in both sexes had less of an impact. Even though numerous correlates for nocturia were identified, none was associated with nocturia in more than half of the affected subjects of both sexes, highlighting the multifactorial etiology.

ACKNOWLEDGMENTS

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