

Association of Nocturia and Mortality: Results From the Third National Health and Nutrition Examination Survey

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Purpose: Nocturia, a common problem in men and women, has been associated with chronic illnesses such as heart disease and hypertension. Using data from the Third National Health and Nutrition Examination Survey we investigated the association of nocturia with subsequent mortality risk.

Materials and Methods: NHANES III is a national probability survey of the United States between 1988 and 1994. Mortality data were obtained by linkage of NHANES III to the National Death Index. Cox proportional hazards regression models were used to assess the association between nocturia and all cause mortality, controlling for potential confounders in a sample of 15,988 men and women 20 years old or older.

Results: The prevalence of nocturia, defined as 2 or more voiding episodes nightly, was 15.5% in men and 20.9% in women. Multivariate analyses showed a statistically significant trend of increased mortality risk with increased number of voiding episodes in men and women. The magnitude of the nocturia and mortality association was greater in those younger than 65 years with attenuated associations in the 65 years old or older age group.

Conclusions: Nocturia is a strong predictor of mortality, more so in younger men and women than in the elderly, with a dose-response pattern in increased mortality risk with increasing number of voiding episodes nightly. Potential underlying mechanisms of the observed association of nocturia and increased mortality risk include sleep disruption and subsequent development of related comorbid conditions.

Key Words: nocturia, mortality

NOCTURIA is 1 of the most commonly reported urological symptoms in men and women. Data from NHANES III show an increasing prevalence of nocturia with age, with a prevalence rate of less than 10% for men younger than 40 years increasing to more than 40% for men in their 70s.¹ Similar results have been reported for men and women in other epidemiological studies.²⁻⁴ In a recent survey in the United States nocturnal awakenings were reported by approximately 25%

of women and 20% of men, with nocturia as the most frequent cause reported by both genders.⁵ The resulting sleep loss is associated with daytime fatigue and subsequent reduced quality of life.^{2,6} Furthermore, sleep loss has been shown to alter carbohydrate metabolism and endocrine function.⁷ As might be expected in those who may be ambulating to the bathroom in the dark, nocturia has been associated with a significantly increased risk of falls and hip frac-

Abbreviations and Acronyms

NHANES III = Third National Health and Nutrition Examination Survey
CVD = cardiovascular disease
BMI = body mass index

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tures in elderly men and women.^{5,8–10} In addition, there is increasing evidence of the association of nocturia with chronic conditions such as heart disease, diabetes and depression.^{3,11,12}

Two international studies have reported a link between nocturia severity and mortality risk but to our knowledge no similar studies from the United States have been published.^{8,10} Additionally, both studies have been restricted to older adults only. Using data from the NHANES III we investigated the association of nocturia with subsequent mortality risk.

METHODS

The NHANES III is a national probability survey of the United States civilian, noninstitutionalized population. The survey was conducted between 1988 and 1994 by the National Center for Health Statistics of the Centers for Disease Control and Prevention. A complex, multistage, stratified cluster sampling design was used to obtain a representative sample of the United States population. A detailed description of the survey methods and data collection procedures has been published elsewhere.¹³

The NHANES III survey was conducted in households, with questionnaires administered to families, adults and children. Household surveys included demographic, socioeconomic and health history questions. Standardized medical examinations were completed at mobile medical centers with blood pressure and anthropometric measurements including height, weight and waist circumference. All survey instruments were available in Spanish and English. Nocturia was assessed by the question, “how many times a night do you usually get up to urinate (pass water)?” with responses recorded as 0, 1, 2 and 3 or more times. Nocturia was included in the analysis as collected and also dichotomized as 2 or more times vs 0 or once.

Mortality data were obtained by linkage of the NHANES III to death certificate data found in the National Death Index with mortality followup through December 31, 2000. Mortality information is based on the probabilistic match between NHANES III survey and National Death Index death certificate records based on the criteria of Social Security number, first name, middle initial, last name, month of birth, day of birth, year of birth, gender, father's surname, state of birth, race, state of residence, state of birth and marital status. Survey records eligible for linkage had at least 1 of the combinations of identifying data elements including 1) Social Security number, gender, full date of birth present, 2) last name, first initial, month of birth, year of birth present or 3) last name, first initial, Social Security number present. Details of the linkage methodology can be found in the NHANES III Linked Mortality File Methodology Report.¹⁴ All participants 17 years or older at the time of survey were eligible for mortality followup.

Covariates in the analysis included age, race/ethnicity, marital status, education (years), BMI, waist circumference, smoking, self-reported CVD, diabetes and hypertension. Medications used in the last month were collected in NHANES III through participant self-report, with recording of container information by the interviewer when possible.

We created 6 categorical variables for prescription medications using National Drug Code therapeutic class codes to indicate use of medications in the classes of 1) lower urinary tract relaxants or stimulants, 2) α -agonists or α -blockers, 3) diuretics, 4) antilipemics, 5) antidepressants, and 6) nondiuretic antihypertensives, calcium channel blockers, β -blockers and angiotensin-converting enzyme inhibitors.

National estimates of prevalence and association measures were calculated with participant data weighted to account for survey design, nonresponse and the probabil-

Table 1. Characteristics of the analysis sample

	No. Men (%)	No. Women (%)
Nocturia episodes:		
0	3,076 (52.4)	3,216 (45.5)
1	2,487 (33.1)	2,938 (32.6)
2	1,118 (9.8)	1,388 (13.2)
3+	774 (5.7)	991 (7.7)
Nocturia 2 or more times	1,892 (15.5)	2,379 (20.9)
Deaths	1,473 (11.1)	1,238 (10.2)
Age:		
20–39	1,499 (22.4)	1,753 (21.2)
30–39	1,378 (24.5)	1,760 (23.0)
40–49	1,154 (19.6)	1,287 (18.1)
50–59	802 (12.5)	934 (12.3)
60–69	1,131 (11.2)	1,115 (12.0)
70–79	841 (2.6)	942 (9.0)
80–90	650 (2.6)	742 (4.4)
Race/ethnicity:*		
NonHispanic white	3,249 (46.1)	3,777 (44.2)
NonHispanic black	2,058 (29.2)	2,550 (36.2)
Mexican-American	2,148 (30.5)	2,206 (25.9)
Marital status:		
Married	5,175 (71.3)	4,591 (61.4)
Widowed	411 (2.6)	1,464 (11.9)
Divorced/separated	602 (8.11)	1,186 (13.3)
Never married	1,267 (18.0)	1,292 (13.5)
Education (yrs):		
0–8	1,965 (10.6)	1,902 (10.3)
9–11	1,250 (13.6)	1,423 (13.1)
12	2,066 (31.6)	2,852 (37.2)
13+	2,174 (44.2)	2,356 (39.4)
BMI (kg/m ²):		
Less than 25	2,953 (40.0)	3,421 (49.6)
25–29	2,989 (40.3)	2,590 (26.0)
30+	1,513 (19.7)	2,522 (24.4)
Smoking:		
Never	2,609 (35.5)	5,188 (52.8)
Former	2,561 (32.5)	1,486 (21.0)
Current	2,285 (32.0)	1,859 (26.6)
Comorbid conditions:		
CVD	775 (6.8)	648 (5.2)
Diabetes	557 (5.1)	812 (6.2)
Hypertension	1,938 (23.0)	2,613 (26.1)
Medication use:		
Lower urinary tract relaxant or stimulant	13 (0.1)	13 (0.2)
α -Agonists or α -blockers	1,094 (11.6)	1,447 (14.2)
Diuretics	558 (4.8)	955 (9.3)
Antilipemics	139 (2.2)	197 (2.5)
Antidepressants	129 (1.9)	308 (3.8)
Nondiuretic antihypertensives, calcium channel blockers, β -blockers + angiotensin-converting enzyme inhibitors	126 (1.2)	148 (1.2)

* Unweighted percent.

ity of selection into the sample. Cox proportional hazards regression models were used to assess the association between nocturia and mortality, and to control for the effect of potential confounders and effect modifiers.¹⁵ Kaplan-Meier survival curves were used to graphically represent survival curves. The assumption of proportionality was assessed graphically (log-log survival curves) and by testing the interaction of included covariates with time.

A total of 16,923 participants 20 years old or older had mortality followup data available. Of this group 935 (5.5%) had missing data on 1 or more covariates and were excluded from the analysis. Analyses were conducted on a final sample of 15,988 men and women, 20 years old or older, with complete data on all covariates included in the analysis. All statistics were generated using SUDAAN® 10.0 and SAS®.

RESULTS

Characteristics of the analysis sample are presented in table 1. A total of 7,455 men and 8,533 women included in the analysis contributed 134,777 person-years of followup (median followup 8.8 years). There were 2,711 deaths observed during followup. The overall prevalence of nocturia, defined as 2 or more episodes of urination at night, was 15.5% in men and 20.9% in women. The prevalence of nocturia increased rapidly with age in men and women with similar age specific prevalence rates (fig. 1).

The association of nocturia and mortality is presented in table 2. Unadjusted analyses show statistically significant dose-response associations of large magnitude between nocturia and mortality in men and women. Because the primary confounder and modifier of the association between nocturia and

mortality was age, analyses were repeated stratifying by age grouped in 3 categories of younger than 50, 50 to 64, and 65 years old or older. Kaplan-Meier survival curves stratified by the 3 age groups show that within each age group men and women with 2 or more voiding episodes nightly had worse survival than participants reporting no voiding episodes (fig. 2). Survival was worse with an increasing number of voiding episodes nightly. These results were consistent within gender and age groups.

Multivariate analyses were conducted by first adjusting for sociodemographic factors, BMI and smoking. A second model adjusted for comorbid conditions such as cardiovascular disease, diabetes, hypertension and prescription medication use in addition to variables included in the first model. The association of nocturia and mortality was attenuated on multivariate analyses but remained statistically significant (table 2). The association was stronger in younger men (younger than 50 years) and women (50 to 64 years old), and was attenuated but statistically significant in the 65 years old or older age group. A significant trend in increased risk of mortality was consistently observed with increasing number of voiding episodes, especially in younger or middle-aged men and women. These results also indicate that the association between nocturia and mortality is only partially explained by comorbid CVD, diabetes and hypertension.

To investigate the role of comorbidity and obesity analyses were further stratified by CVD, diabetes and obesity status (table 3). Due to small numbers in

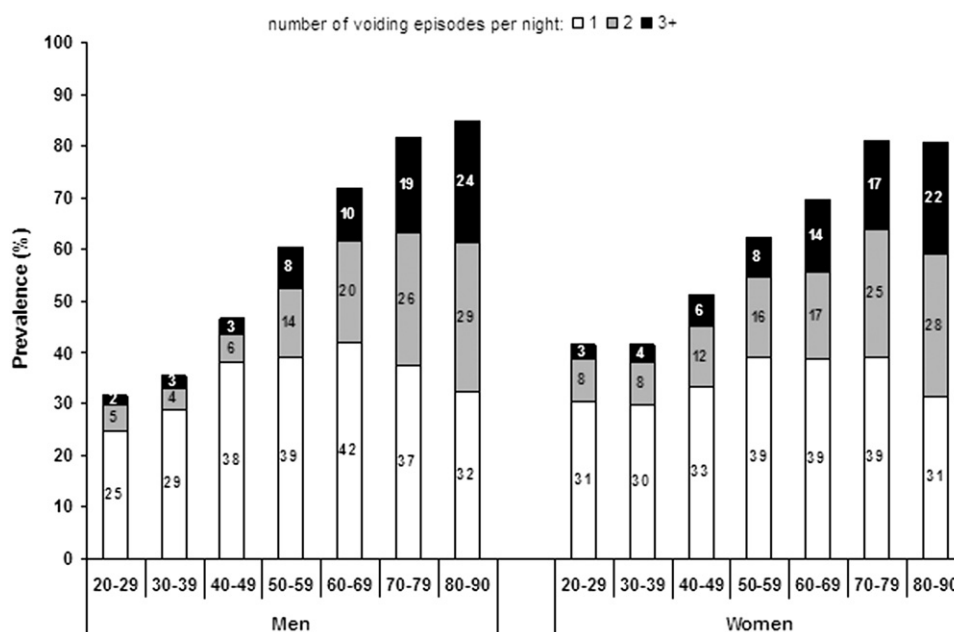


Figure 1. Prevalence of nocturia by gender and age

Table 2. Association of nocturia and mortality by gender and age

No. Nocturia Episodes	Men HR (95% CI)*	Women HR (95% CI)*
Age 20–49:		
0	1.00	1.00
1	1.40 (0.86, 2.29)	1.32 (0.53, 3.27)
2	2.55 (1.12, 5.83)	1.19 (0.53, 2.69)
3+	3.94 (1.80, 8.64)	1.38 (0.66, 2.89)
Trend test p value	0.002	0.366
2 or More vs less than 2 p Value	2.56 (1.32, 4.94) 0.006	1.10 (0.66, 1.86) 0.705
Age 50–64:		
0	1.00	1.00
1	0.81 (0.49, 1.32)	1.13 (0.67, 1.91)
2	1.16 (0.66, 2.05)	2.25 (1.46, 3.46)
3+	1.85 (0.97, 3.53)	1.87 (0.89, 3.90)
Trend test p value	0.087	0.011
2 or More vs less than 2 p Value	1.60 (1.06, 2.41) 0.026	1.94 (1.27, 2.96) 0.003
Age 65–90:		
0	1.00	1.00
1	1.07 (0.84, 1.37)	0.84 (0.64, 1.11)
2	1.38 (1.04, 1.84)	1.04 (0.85, 1.28)
3+	1.45 (1.06, 1.98)	1.12 (0.85, 1.48)
Trend test p value	0.005	0.137
2 or More vs less than 2 p Value	1.35 (1.11, 1.63) 0.003	1.19 (1.04, 1.37) 0.012
Overall:		
0	1.00	1.00
1	1.13 (0.91, 1.39)	0.99 (0.77, 1.27)
2	1.54 (1.18, 2.00)	1.28 (1.04, 1.57)
3+	1.70 (1.32, 2.20)	1.34 (1.02, 1.76)
Trend test p value	<0.001	0.003
2 or More vs less than 2 p Value	1.49 (1.25, 1.78) <0.001	1.32 (1.14, 1.51) <0.001

* Adjusted for age, BMI, marital status, education, smoking, CVD, diabetes, hypertension and medication use (diuretics, antihypertensive drugs, lipid lowering drugs, antidepressants).

some cells age groups were collapsed as 20 to 65 years old and 65 years or older, with nocturia defined as 2 or more voiding episodes nightly vs less than 2 voiding episodes. Results again indicated a stronger relationship of nocturia and mortality in men and women younger than 65 years. This association was observed primarily in those reporting no CVD or diabetes. When stratifying based on obesity, defined as BMI 30 kg/m² or greater, or waist circumference greater than 102 cm, the magnitude of the association was similar in the obese and nonobese group in men while a slightly stronger association was observed in obese vs nonobese women.

DISCUSSION

This study demonstrates the public health importance of nocturia, which has increasing prevalence in aging men and women with rates in excess of 40% in those older than 70 years. These data indicate that nocturia is a predictor of mortality even after

accounting for potential confounders. In addition, a dose-response pattern was observed with increased mortality risk with increasing number of voiding episodes nightly. The magnitude of the association between nocturia and mortality risk was greater in younger men (younger than 50 years) and middle-aged women (50 to 64 years old).

The results of the present analysis of the prevalence of nocturia among men and women in NHANES III are consistent with previous reports from population based epidemiological studies.^{2,16} To our knowledge the prevalence rates for women are the first to be reported from a nationally representative sample in the United States, confirming the high prevalence of nocturia in women and the comparability of prevalence rates across age groups in men and women. Prevalence increases with age in men and women with a more rapid increase observed in men. The consistent epidemiological finding that nocturia is of similar prevalence in men and women casts serious doubt on a major role of prostatism or prostatic enlargement as causal factors in nocturia at the level of the population. Kidney function, sleep disruption and other age related but not gender specific mechanisms should be considered.

Few studies have reported on the association of nocturia and mortality, and these have been restricted to older men and women. Asplund et al conducted a study of nocturia and mortality in a sample of 6,143 members of the Swedish Pensioner's Association (mean age 73 years).⁸ In a followup period of 54 months men reporting 3 or more nocturnal voiding episodes had a mortality rate 1.9 (1.4–2.6) times higher than the whole group of men, while for women the difference was 1.3 (0.9, 2.0) times higher. Bursztyn et al reported on differences in survival during a 12-year period in 456 subjects who were 70 years old, with nocturia defined as 2 or more voiding episodes nightly.¹⁰ Multivariate analyses showed no overall association with a hazard ratio of 0.89 (95% CI 0.55, 1.43). However, a significant interaction was observed with coronary heart disease with an HR of 2.16 (95% CI 1.01, 4.61) suggesting that nocturia was a predictor of mortality in older patients with coronary heart disease. Overall the results of the present study are consistent with these previous reports. In contrast to the results of Asplund et al, an association of nocturia and mortality was observed for men and women.⁸ In addition, the increased risk of nocturia was observed primarily in those with no history of CVD or diabetes rather than only in those with CVD as reported by Bursztyn et al.¹⁰

The reported association of nocturia with chronic illnesses (CVD, diabetes, hypertension),^{3,17} in addition to an increased risk of falls and fractures,⁹ suggests that the association of nocturia and mortality may involve multiple underlying pathways.

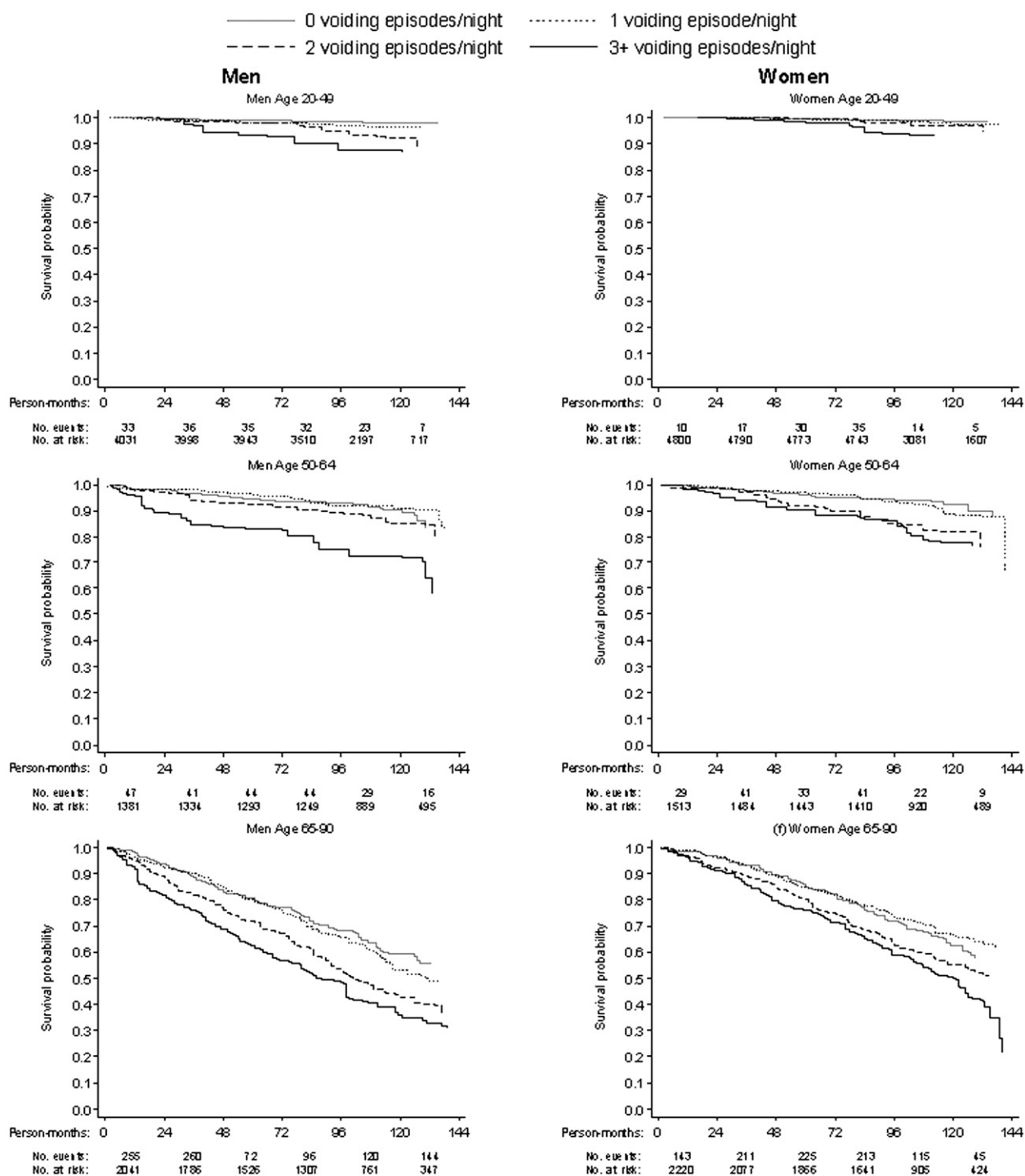


Figure 2. Survival probability by nocturia (number of voiding episodes per night) stratified by gender and age

Although in our analyses we adjusted for prevalent chronic comorbid conditions at baseline, data on subsequent incident CVD or diabetes were not available. An additional limitation is the lack of data on other potential confounders associated with nocturia such as overactive bladder syndrome, restless legs syndrome, obstructive sleep apnea, benign prostatic hyperplasia or venous insufficiency/peripheral edema.¹⁸

The finding that in men and women younger than 65 years the association between nocturia and mortality is of greater magnitude for those without comorbid conditions supports the hypothesis that nocturia is a marker of impending morbidity (eg CVD or diabetes) and subsequent mortality risk (table 3). An adverse effect of chronic sleep loss on metabolic and endocrine function has been reported previ-

Table 3. Nocturia and mortality association stratified by comorbid conditions and obesity by gender and age

	HR (95% CI)*							
	No CVD	CVD	No Diabetes	Diabetes	BMI Less Than 30 kg/m ²	BMI 30 kg/m ² or Greater	Waist Circumference Less Than 102 cm†	Waist Circumference 102 cm or Greater†
Men:								
Age 20–64	2.08 (1.43, 3.01)	1.59 (0.68, 3.72)	2.00 (1.41, 2.84)	2.04 (0.88, 4.71)	2.12 (1.38, 3.27)	2.35 (1.22, 4.55)	1.85 (1.16, 2.96)	2.64 (1.44, 4.84)
Age 65–90	1.42 (1.12, 1.79)	1.11 (0.83, 1.50)	1.44 (1.18, 1.76)	1.04 (0.63, 1.73)	1.44 (1.16, 1.79)	0.97 (0.63, 1.50)	1.47 (1.15, 1.86)	1.43 (1.00, 2.04)
Overall	1.63 (1.31, 2.02)	1.20 (0.90, 1.61)	1.58 (1.32, 1.91)	1.34 (0.91, 1.97)	1.58 (1.28, 1.96)	1.55 (1.00, 2.40)	1.56 (1.23, 1.98)	1.74 (1.28, 2.36)
Women:								
Age 20–64	1.88 (1.30, 2.70)	0.95 (0.44, 2.02)	1.86 (1.35, 2.55)	1.45 (0.64, 3.29)	1.66 (1.07, 2.58)	2.36 (1.35, 4.15)	1.73 (1.14, 2.64)	1.88 (1.09, 3.25)
Age 65–90	1.16 (0.98, 1.38)	1.44 (0.96, 2.15)	1.35 (1.13, 1.60)	1.01 (0.70, 1.47)	1.27 (1.06, 1.51)	1.67 (1.10, 2.55)	1.19 (0.97, 1.45)	1.68 (1.1, 2.57)
Overall	1.37 (1.16, 1.62)	1.46 (0.97, 2.19)	1.50 (1.26, 1.77)	1.19 (0.79, 1.77)	1.33 (1.12, 1.58)	2.12 (1.48, 3.05)	1.31 (1.07, 1.59)	1.91 (1.29, 2.82)

* Hazard ratios adjusted for age, marital status, education and smoking. BMI included in models stratified by CVD or diabetes.

† Subgroup of 6,966 men and 7,862 women with waist circumference measurement.

ously,⁷ and reduction in sleep duration and sleep quality has been associated with an increased risk of obesity and type 2 diabetes.^{19,20}

The observed association between nocturia and mortality even in younger men and women in whom rates of prevalent CVD or diabetes are lowest is consistent with the hypothesis that sleep disruption may be 1 mechanism linking nocturia and increased mortality risk. As the prevalence of comorbid conditions is higher in older (older than 65 years) men and women, it is not surprising that the attenuation in the nocturia and mortality association was more pronounced than in the younger age group. As chronic conditions are already present in older men and women, nocturia may be a direct marker of increased mortality risk. Although some of the mortality in adults with nocturia may be linked to those nocturnal events (such as falls and fractures) related to nighttime voiding itself, it is likely that increased nocturic frequency is a marker for other comorbidities and risk factors such as frailty in older Americans. Based on our results it is possible that nocturic frequency might be used by clinicians as a marker or clinical indicator for assessment of overall health and mortality risk, and may present a window

of opportunity for intervention in men and women who otherwise may not be considered at increased risk. Importantly it remains to be proven that interventions for this disorder will reduce morbidity or subsequent mortality risk.

CONCLUSIONS

Data from the NHANES III, a nationally representative sample, indicate that nocturia is a predictor of mortality in men and women after accounting for major confounding factors. The magnitude of the association was greater in men and women younger than 65 years and in those without a comorbid condition at baseline. A dose-response pattern of increased mortality risk with increasing number of nocturnal voiding episodes was observed. Further investigations are needed to determine the underlying mechanisms of the observed association between nocturia and increased mortality risk. Nocturia may be a clinically useful marker of overall health and mortality risk in younger and older adults.

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