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SCIENTIFIC INVESTIGATIONS

Nocturia, Insomnia Symptoms and Mortality among Older Men: The Health, Aging and Body Composition Study

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Study Objectives: To examine the association between nocturia (walking up from sleep for urination) and mortality risk among community dwelling older men.
Methods: This is a secondary data analysis using data obtained from the Health Aging Body Composition (Health ABC) study. Frequency of nocturia was determined at baseline using a questionnaire.
Results: A total of 1,478 older men, mean (SD) age 73.8 (2.9) years, were included in the analysis. During a follow up period of 9.9 years, a total of 760 deaths were reported. Mortality rate was significantly higher for participants with 3 or more nocturia episodes per night, in comparison to those with 0–1 episodes (HR [CI] : 1.21 [1.00–1.47], p = 0.055), even after controlling for baseline characteristics which included demographic variables, body mass index, lower urinary tract symptoms, use of loop diuretics, insomnia symptoms, feeling excessively sleepy during the day/daytime naps, sleep duration, and use of sleep medications. However, the association between ≥ 3 nocturia episodes per night and mortality risk was no longer statistically significant once prevalent diabetes mellitus and cardiovascular disease were included in the model (HR [CI]: 1.18 [0.97- 1.44], p = 0.100).
Conclusions: Nocturia is associated with mortality independent of insomnia symptoms and sleep duration. The relationship is explained in part by prevalent cardiovascular disease and diabetes mellitus. The results underscore the impact of these medical conditions on the association between 3 or more nocturia episodes and increased mortality risk among older men.
Keywords: nocturia, insomnia symptoms, mortality
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INTRODUCTION

Nocturia, commonly known as one of the lower urinary tract symptoms (LUTS), is also a common sleep related complaint among older adults,[1–5] with two or more nocturia episodes per night reported by over 30% of the elderly.[6–9] Multiple factors contribute to the high prevalence of nocturia among older men. Age related changes in the genitourinary system such as decreased bladder capacity and benign prostatic hypertrophy increase the risk of frequent urination.[6,7,10–13] Other factors implicated in the pathogenesis of nocturia include polyuria and/or nocturnal polyuria which could be due to uncontrolled diabetes mellitus, vasopressin deficiency, fluid redistribution in supine position associated with edematous states such as congestive heart failure, low albumin, chronic kidney disease, as well as primary sleep disorders such as obstructive sleep apnea and hypopnea.[14–18] In some cases, individuals may report the need to urinate as the reason for their waking up from sleep, even if they wake up for reasons unrelated to bladder pathology.[3]

As previously suggested,[19] the cause of nocturia among older men is most probably multifactorial, and this could explain the previously reported associations between frequent nocturia episodes and higher disease burden.[20,21] Additionally, previous studies have reported significant association between frequent nocturia episodes and higher mortality risk among older adults with cardiovascular disease and diabetes mellitus.[22,23] Furthermore, nocturia has been reported to predict mortality risk among older adults even after controlling for diabetes mellitus and cardiovascular disease.[24,25] One of the mechanisms that is forwarded to explain the association between nocturia and higher mortality risk is sleep disturbance caused by nocturia episodes.[25] However, we are not aware of any published

BRIEF SUMMARY
Current Knowledge/Study Rationale: Nocturia is a common complaint among older adults and associated with sleep related complaints, as well as higher morbidity burden and mortality rate. In this study, we examine if the association between nocturia and mortality is independent of insomnia symptoms, prevalent diabetes mellitus and cardiovascular morbidity.
Study Impact: Results of the study indicate that the association between 3 or more nocturia episodes and mortality is independent of insomnia symptoms and this association may be partly explained by prevalent diabetes mellitus and cardiovascular morbidity. These findings underscore the importance of these morbidities on the association between frequent nocturia episodes and higher mortality rate.

studies that examined if the association between nocturia and mortality risk is independent of sleep disturbance. The first objective of the current study is to examine whether nocturia predicts higher mortality risk independent of sleep related factors such as insomnia symptoms, sleep duration, and use of sleep medications.

Two of the common causes of nocturia, cardiovascular disease and diabetes mellitus, are also leading causes of death among older adults,[26] suggesting that these medical conditions could explain the association between nocturia frequency and mortality risk. However, two previous studies have reported significant associations between nocturia and higher mortality risk even after controlling for cardiovascular disease and diabetes mellitus, although these studies have several limitations. For example, in one of the studies, participants were mostly white older men and women living in Sweden,[24] and whether findings from this study would be applicable to older men of other racial groups may be debatable. In both of these studies,[24,25] prevalent cardiovascular disease and diabetes mellitus were determined based on single questions for each of these conditions, and these questions may not capture the full spectrum of these medical conditions. The second objective of the current study is to examine whether the association between nocturia frequency and mortality is independent of cardiovascular disease and diabetes mellitus, using well-characterized data derived from a biracial sample of older men.

METHODS

Study Population

De-identified data for the current analysis are obtained from the Health Aging and Body Composition (Health ABC) study. Details about recruitment in Health ABC study have been described previously.[27] In short, this is a prospective cohort study in which 3,075 (1,584 females and 1,491 males) community dwelling older adults between the age of 70 to 79 years and living in areas surrounding Pittsburgh, PA, and Memphis, TN, were recruited between March 1997 and July 1998. Because information on nocturia was not collected from women in the Health ABC study, the current analysis was performed based on data obtained from male participants (n = 1,491).

Nocturia Frequency

The International Prostate Symptoms Score (I-PSS) questionnaire, administered at baseline, includes the following question: "During the past 30 days, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?" Response choices to the nocturia question included "0," "1," "2," "3," "4," and "5 or more." In the current analysis, study participants were categorized into 3 groups based on self-reported nocturia frequency "0 to 1," "2," or "3 or more" times per night. Lower urinary tract symptom score was derived from participant's response to the I-PSS questionnaire after excluding response to the nocturia question. Of a total of 1,491 male participants, data on nocturia was available for 1,478 participants (99%) (13 participants, 10 white and 3 black, did not complete the I-PSS questionnaire).

Sleep Assessment

Insomnia symptoms were determined based on responses to the following questions. How often do you experience the following: (1) "trouble falling asleep," (2) "waking up from sleep with difficulty going back to sleep," (3) "waking up too early in the morning and be unable to go back to sleep," and (4) "feeling not rested during the day no matter how many hour of sleep you had." Responses to these questions included "Never," "Rarely," "Sometimes," "Often," and "Almost Always"; participants who responded "Often" or "Almost Always" to any one of the questions were considered to have significant insomnia symptoms. Based on this definition, 3 categories were created, including: (1) participants with none of these insomnia symptoms; (2) participants with difficulty falling asleep, staying asleep, or waking up too early in the morning, but no symptoms related to feeling not rested during the day; and (3) participants who reported insomnia symptoms as above and feeling not rested during the day. In addition, daytime sleep-wake related complaints were assessed based on response to the following 2 questions: (1) "How often do you feel excessively (overly) sleepy during the day (excessively sleepy)?" and response to this question included "never," "rarely," "sometimes," "often," and always"; (2) "During a usual week, how many times do you nap for 5 minutes or more (daytime nap)?" and responses were recorded as the number of naps per week. For the purpose of this analysis, "excessively sleepy" and "daytime nap" were combined (sleepiness/napping) and 2 categories were created as follows: (1): Excessively sleepy (never, rarely, sometimes) or naps (0 or 1–7 per week); and (2): Excessively sleepy (often, always) or naps (> 7 per week).

Self-reported sleep duration was assessed using the following question "How many hours of sleep do you usually get at night?" Participants responded with duration of sleep in hours. Use of sleep medication was determined based on the question "Do you take sleeping pills or other medication to help you sleep" with the following responses: "Never," "Rarely," "Sometimes," "Often," or "Almost Always."

Follow-up

After initial clinic visit for baseline evaluation, participants were requested to return to clinic at 12 months for follow-up assessment. In addition, telephone interview assessments were done 6 months after baseline and yearly clinic-visit assessments. Study participants or individuals who were identified as proxy were contacted (if the participant could not be reached) during these follow-up visits and telephone interviews. Deaths were identified during 6-month telephone interviews, during scheduling for annual clinic visits, or by review of obituaries. Once death of a participant was reported, "Decedent Proxy Interview" of a designated proxy or next of kin was conducted by study personnel, and death certificates and relevant medical records were obtained for adjudication of cause of death.[28] Deaths included in this analysis were ascertained through March 2011. Vital status (alive or died) was available for 1,424 participants (96%), and participants for whom information on vital status was not available were assumed to be alive. Documented date of last contact was taken as the censor date for those who were alive and those on whom vital status information was not available.

Baseline Characteristics

Baseline variables of interest included demographic variables as well as clinical variables that have been previously associated with nocturia and/or sleep disturbance. These included body mass index (BMI), smoking status, alcohol consumption, lower urinary tract symptoms, history of cardiovascular disease, and diabetes mellitus. Weight and height were measured at baseline and BMI was calculated based on the standard formula (weight in kilograms divided by height in meters squared). Prevalent cardiovascular disease at baseline was determined based on the following criteria: (1) History of coronary artery bypass graft surgery, or (2) history of carotid endarterectomy, or (3) self-reported history of myocardial infarction and use of anti-angina medication, or (4) major Q-wave abnormality on baseline electrocardiogram, or (5) history of congestive heart failure. Prevalent diabetes mellitus (DM) was determined based on self-reported history or use of medication for DM or fasting blood sugar of > 126 mg/dL at baseline. Responses to the following 2 questions were used to determine history of falls. "During the past 12 months, have you fallen and landed on the ground?" and "How many times have you fallen in the last 12 months?" History of fracture was derived from response to the following question: "Has a doctor ever told you that you broke or fractured a bone after the age of 45?"

Statistical Analysis

Baseline Characteristics

Demographic and clinical characteristics of participants by frequency of nocturia status were determined using one-way analysis of variance and χ^2 test statistics for continuous and categorical variables, respectively. Linear trend across nocturia groups was determined using a modified Wilcoxon rank test available in Stata statistical software.[29]

Mortality

Time interval between last date of contact or date of death and date of first clinic visit (time 0) was utilized to calculate participant follow-up time. Kaplan-Meier survival curves were used to plot pattern of survival time by frequency of nocturia. Cox proportional hazards (PH) and Cox time dependent covariate models were used to evaluate the association between nocturia frequency and mortality.

Demographic and baseline clinical characteristics were considered for inclusion in the Cox PH model if they had previously been associated with nocturia and/or mortality, or if they were deemed biologically relevant. These covariates were: age, race, study site, education level, marital status, baseline BMI, smoking status, use of alcoholic drinks, I-PSS score (excluding nocturia), use of loop diuretics, insomnia symptoms, sleep duration, use of sleep medications, daytime sleepiness/nap behavior, prevalent cardiovascular disease, and prevalent diabetes mellitus.

To determine whether these variables should be included in the model, Kaplan-Meier survival curve for each of the categorical covariates and Cox-regression model for each of the continuous variables were run separately with mortality as the outcome of interest. Variables that were associated with mortality at p value ≤ 0.05 were included in the final Cox regression model. Interaction terms that include nocturia frequency and age, race, study site, insomnia complaints, use of sleep aids, and body mass index were also included in the model.

A total of 4 Cox-regression models were created, including: Model 1 unadjusted model; model 2 which included model 1 and demographic and lifestyle related variables; model 3 which included variables in model 2 and BMI, lower urinary tract symptoms, use of loop diuretics, insomnia symptoms, sleepiness/napping, sleep duration, and use of sleep medication; and model 4 which include variables in model 3 and prevalent diabetes mellitus and cardiovascular disease. Because there was no significant relationship between nocturia episodes and history of falls/fractures, they were not included in the regression model. In order to exclude the possible effect of use of sleep medications on the association between nocturia status and risk of mortality, Cox regression analysis was repeated after excluding participants who reported use of sleep aids. A two-sided p value < 0.05 was used to indicate statistical significance. Analyses were performed using Stata version 13 software.

RESULTS

Nocturia Frequency

A total of 1,478 participants responded to the nocturia question and are included in the analysis. Nocturia episodes per night were reported as 0, 1, 2, and 3 or more by 12%, 39%, 26%, and 23% of participants, respectively. **Table 1** and **Table 2** show selected demographic and clinical characteristics of study participants by nocturia frequency. Three or more and two episodes of nocturia were more prevalent among black participants than white participants (26% vs. 20% for ≥ 3 nocturia episodes and 28% vs. 26% for 2 nocturia episodes, respectively, p = 0.005). However, after stratification by educational status, significant difference in nocturia frequency between black and white study participants was observed only among participants with less than 12 years of education (29% vs. 15% for ≥ 3 nocturia episodes, and 28% vs. 24% for 2 nocturia episodes [p = 0.015], respectively). As expected, the prevalence of cardiovascular disease and diabetes mellitus were higher among participants with higher nocturia frequency. At baseline, a total of 271 participants (19%) reported one or more falls, with 185 participants (13%) reporting a single fall, while 86 participants (6%) reported two or more falls; and there was no significant association between nocturia frequency and falls. A total of 238 participants (16%) reported fracture (any bone), while 11 participants (< 1%) reported hip fracture during the previous 12 months; and there was no significant association between nocturia episodes and history of fracture.

Table 3 shows the distribution of sleep related complaints among study participants by nocturia status. As shown, the proportion of participants who reported insomnia symptoms was higher among those with increased frequency of nocturia episodes. Overall, 19%, 25%, and 33% of participants with 0–1, 2, and ≥ 3 nocturia episodes, respectively, reported one

Table 1—Selected demographic and lifestyle characteristics of study participants by nocturia frequency at baseline.

	Nocturia				Statistics
	0–1 EPN (n = 758)	2 EPN (n = 390)	≥ 3 EPN (n = 330)	Total (n = 1,478)	p value
Age in years, mean (SD)	73.6 (2.9)	73.8 (2.8)	74.2 (2.8)	73.8 (2.9)	0.010 ‡
Race					
Black (%)	254 (66)	151 (61)	144 (56)	549	0.005 *
White (%)	504 (34)	239 (39)	186 (43)	929	
Site					
Memphis (%)	381 (50)	211 (54)	157 (48)	749	0.207 *
Pittsburgh (%)	377 (50)	179 (46)	173 (52)	729	
Marital status					0.367 *
Currently married (%)	527 (74)	273 (74)	221 (70)	1,021	
Currently not married (%)	187 (26)	98 (26)	96 (30)	381	
Education					0.172 *
Less than high school (%)	193 (25)	109 (28)	103 (31)	405	
High school complete (%)	194 (26)	92 (24)	88 (27)	374	
Post high school (%)	371 (49)	88 (48)	137 (42)	696	
Smoking status					0.245 *
Never (%)	220 (29)	126 (32)	93 (28)	439	
Current smoker (%)	93 (12)	38 (10)	29 (9)	160	
Former smoker (%)	443 (59)	225 (58)	208 (63)	876	
Drinking status					0.339 *
No (%)	307 (41)	164 (42)	156 (48)	627	
≤ 1 per day (%)	359 (48)	180 (47)	136 (41)	675	
> 1 per day (%)	87 (11)	42 (11)	37 (11)	166	

EPN, Episodes per night. *χ^2 p value. Bonferroni test: ‡Nocturia 0–1 vs. Nocturia ≥ 3 = 0.008.

Table 2—Selected clinical characteristics of study participants by nocturia frequency at baseline.

	Nocturia				Statistics
	0–1 EPN (n = 758)	2 EPN (n = 390)	≥ 3 EPN (n = 330)	Total (n = 1,478)	p value
Body mass index, (kg/m^2), mean (SD)	26.7 (3.7)	27.2 (4.1)	27.8 (4.3)	27.1 (4.0)	< 0.001 ‡
I-PSS score, mean (SD) (excluding nocturia)	3.3 (3.4)	4.8 (3.9) †	6.0 (4.5)	4.3 (3.9)	< 0.001
History of falls					
None (%)	623 (82)	315 (81)	263 (80)	1,201	0.627 †
One fall (%)	87 (12)	54 (14)	44 (13)	185	
Two or more falls (%)	45 (6)	19 (5)	22 (7)	86	
History of fracture					
No fracture after age 45 years (%)	644 (85)	320 (82)	271(82)	1,235	0.238 *
Fracture after age 45 years (%)	113 (15)	68 (18)	57 (17)	238	
Use of loop diuretic medications					
No (%)	676 (89)	338 (87)	285 (87)	1,299	0.418 *
Yes (%)	82 (11)	49 (13)	44 (13)	175	
Diabetes mellitus					
No (%)	614 (81)	303 (78)	242 (73)	1,159	0.017 *
Yes (%)	144 (19)	87 (22)	88 (27)	319	0.004 †
Cardiovascular Disease					
No (%)	588 (78)	277 (72)	226 (69)	1,091	0.010 *
Yes (%)	170 (22)	110 (28)	103 (31)	383	0.001 †

EPN, episodes per night; I-PSS, International Prostate Specific Symptoms. *χ^2 p value. †p value for trend. Bonferroni test: ‡Nocturia 0–1 vs. Nocturia ≥ 3 < 0.001.

or more insomnia symptoms ($p < 0.001$). Participants with ≥ 3 nocturia episodes were also more likely to report feeling excessively sleepy during the day often or always ($p < 0.001$), and taking more than 7 naps per week ($p = 0.005$). There was no statistically significant relationship between nocturia symptoms and sleep duration.

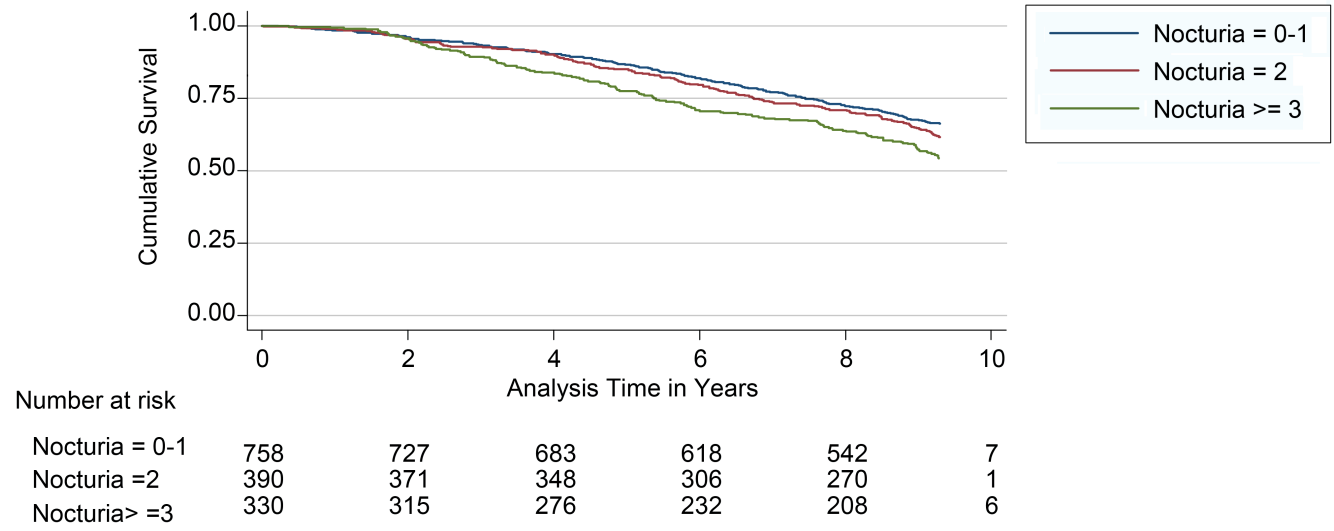
A total of 760 of 1,478 participants (51%) died during the study period. Mortality rates were higher for participants who reported ≥ 3 nocturia episodes, compared with those who reported 2 and 0–1 nocturia episodes per night (83 per 1,000 PY, 63 per 1,000 PY, and 59 per 1,000 PY respectively). Cardiovascular diseases and diabetes mellitus accounted for 37% and 1%

Table 3—Baseline sleep characteristics of study participants by nocturia frequency.

	Nocturia				Statistics
	0–1 EPN (n = 758)	2 EPN (n = 390)	≥ 3 EPN (n = 330)	Total (n = 1,478)	p value
No insomnia symptoms	612 (81%)	290 (75(%)	218 (67%)	1,120	
DFA or DSA without feeling unrested	108 (15%)	76 (20%)	77 (24%)	261	< 0.001 *
Feeling unrested during the day	33 (4%)	20 (5%)	29 (9%)	82	< 0.001 †
Sleep Duration					
6 to 8 hours (%)	611 (81)	306 (80)	253 (80)	1,170	
< 6 hours (%)	93 (12)	40 (10)	36 (11)	269	0.215 *
> 8 hours (%)	48 (7)	39 (10)	27 (9)	114	
Use sleep medication					
Never / Rarely (%)	701 (92)	352 (90)	292 (91)	1,352	
Sometimes (%)	29 (4)	14 (4)	11 (3)	54	0.296 *
Often / Always (%)	27 (4)	24 (6)	19 (6)	70	
Excessive daytime sleepiness					
Never or rarely	594 (78)	278 (71)	214 (65)	1,086 (73)	
Sometimes	126 (17)	92 (24)	87 (26)	305 (21)	< 0.001 *,†
Often or always	38 (5)	20 (5)	29 (9)	87 (6)	
Number of naps					
0 naps per week (%)	232 (31)	88 (23)	74 (23)	394 (27)	0.005 *
1–7 naps per week (%)	474 (64)	277 (73)	224 (70)	975 (68)	0.003 †
> 7 naps per week (%)	39 (5)	15 (4)	22 (7)	76 (5)	

EPN, episodes per nigh; DFA, difficulty falling asleep; DSA, difficulty staying asleep. *χ^2 p value. † p for trend.

Figure 1—Kaplan-Meier survival estimates by nocturia frequency.



Log rank test p = 0.007.

of the underlying causes of death, while malignant neoplasm and dementia were reported as underlying causes of death in 30% and 8% of study participants, respectively. Of the malignant neoplasms reported as underlying causes of death, lung cancer, prostate cancer, and colon cancer accounted for 25%, 13%, and 10% of the cancers. **Figure 1** shows Kaplan Meier survival curves by nocturia frequency, and as shown participants with ≥ 3 nocturia episodes had significantly lower survival rates during follow-up.

Table 4 shows mortality hazard rates by nocturia frequency in unadjusted and adjusted Cox regression models. As shown, hazard rate was significantly elevated among participants with ≥ 3 nocturia episodes compared with those with 2 and 0–1 nocturia episodes per night, even after adjusting for potentially confounding factors which include demographic and lifestyle variables, BMI, lower urinary tract symptoms, insomnia symptoms, sleep duration, use of sleep medications and sleepy/napping (HR [CI]: 1.21 [1.00–1.47], p = 0.055). There were no significant interactions between nocturia frequency and age, race, study site, insomnia symptoms, sleep medication use, and BMI (p > 0.1).

Results of Cox regression analysis performed after including prevalent cardiovascular disease and diabetes mellitus (**Table 4**,

Table 4—Results of Cox proportional hazard models showing the association between nocturia frequency and mortality (outcome variable) in unadjusted and adjusted models.

	Hazard Ratio and Confidence Interval for Unadjusted and Adjusted Models			
Nocturia Frequency	Unadjusted Model 1 (n = 1,333)	Partially Adjusted Model 2 (n = 1,333)	Partially Adjusted Model 3 (n = 1,333)	Fully Adjusted Model 4 (n = 1,333)
0–1	1.0	1.0	1.0	1.0
2	1.07 (0.89–1.28) p = 0.475	1.07 (0.89–1.28) p = 0.498	1.07 (0.88–1.29) p = 0.500	1.04 (0.87–1.26) p = 0.630
≥ 3	1.28 (1.07–1.54) p = 0.008	1.24 (1.03–1.49) p = 0.022	1.21 (1.00–1.47) p = 0.055	1.18 (0.97–1.44) p = 1.00

Partially adjusted model 2: Variables = age in years, site of study, race, education level, marital status, history of smoking and alcohol use. Partially adjusted model 3: Variables = those included in model 2 and body mass index (log transformed), American Urological Association symptoms score, use of loop diuretics, insomnia symptoms, short sleep duration, long sleep duration and use of sleep aids, excessively sleepy/nap behavior. Fully adjusted model 4: Variables = those included in model 3 and prevalent diabetes mellitus and cardiovascular disease Variables in the full model that showed significant association with mortality include: age: HR (CI) 1.09 (1.06–1.12), p < 0.001); Site of study (Memphis = 0): HR (CI) = 0.71 (0.61–0.84), p < 0.001; Smoking: (HR (CI) 1.75 (1.23–2.30), p < 0.001; BMI (log transformed): HR (CI) 0.14 (0.05–0.51), p = 0.003; Use of loop diuretics: HR (CI) 2.23 (1.62–3.06), p < 0.001; Prevalent diabetes mellitus: HR (CI) 1.34 (1.12–1.61), p < 0.001 Prevalent cardiovascular disease = HR (CI) 1.24 (1.105–1.46), p = 0.013; Excessively sleepy/nap behavior: HR (CI) 1.46 (1.16–1.86), p = 0.002.

Model 4) showed that there was no longer statistically significant association between three or more nocturia episodes and risk of mortality (HR [CI]: 1.18 [0.97–1.44], p = 0.100). Cox regression analysis after excluding participants who reported taking sleep medications did not change the association between nocturia status and risk of mortality. Analysis was also repeated with 2 nocturia categories (0–1 episodes and ≥ 2 episodes per night), and there was no statistically significant difference in hazard rate for mortality between the 2 groups.

Proportional-hazard (PH) assumption using Schoenfeld residuals showed global test p value of = 0.016, and PH assumption was violated for the following variables: smoking (p = 0.03), body mass index (p = 0.012), and use of loop diuretics (p = 0.004). For this reason, Cox regression analysis with time-varying covariates was performed, and this result is reported in **Table 4**, model 4.

A total of 145 participants had missing values for one or more covariates and were not included in the Cox regression model 4. Those with missing values were older (74.1 vs. 73.7 years, p = 0.007), and more participants were from Pittsburgh study site than the Memphis site (15.8% vs. 12.2%, p = 0.04). Otherwise, there were no significant differences between participants who were and were not included in the final model in other characteristics, including race, smoking and drinking status, body mass index, insomnia symptoms, sleep duration, I-PSS score, morbidity burden, physical performance score, or nocturia frequency.

DISCUSSION

Results of the current study indicate significant association between 3 or more nocturia episodes per night and increased mortality rate during follow-up among community dwelling older men. This association was statistically significant even after controlling for demographic characteristics, smoking and alcohol use history, BMI, lower urinary tract symptoms, use of loop diuretics, as well as sleep related factors which include insomnia symptoms, feeling excessively sleepy during the day/daytime naps, sleep duration and use of sleep medications. These findings suggest that the association between nocturia and higher mortality risk is independent of sleep-related factors included in this study, and to our knowledge, this is the first study to report such results. However, the association between nocturia and mortality risk was attenuated and was not statistically significant when prevalent cardiovascular disease and prevalent diabetes mellitus were included in the model, suggesting that the association between nocturia and mortality risk could be explained at least in part by these two medical conditions.

Our result is in contrast to at least two previous studies mentioned above that reported significant association between nocturia and mortality risk even after controlling for prevalent diabetes and cardiovascular disease.[24,25] Several factors can account for the different findings in the current study and those reported previously. In one of these studies, study participants included older men and women living in Sweden,[24] and in the current study participants were comprised of a biracial sample of older men. Furthermore, in both studies quoted above, prevalent cardiovascular disease and diabetes mellitus were determined based on the response to a single question for each of these medical conditions; while in the current study, multiple questions as well as objective data were used to ascertain prevalent cardiovascular disease and diabetes mellitus. Last but not least, unlike the aforementioned studies, sleep-related factors and lower urinary tract symptoms were included as covariates in the current study. We think that these factors could account for the difference in the results.

The findings in our study are also in contrast to a recent study which failed to show significant association between nocturia frequency and risk of mortality after controlling for age of participants.[30] In this recent study, the participants were

younger with a median age of 60.8 years (Q1-Q3, 56.0–66.2 years), in comparison to our study in which the median age was 74.0 years (Q1-Q3, 71.0–76 years). In addition, this recent study used frequency volume chart (FVC) to estimate nocturia frequency, whereas in our study, nocturia frequency was self-reported. In the current study, information on the number of times the person wakes up from sleep for urination during the previous 30 days is obtained using a questionnaire, while the FVC estimates number of nocturia episodes over the last few days. It has been previously reported that there is only a modest correlation between questionnaire based nocturia episodes and FVC derived nocturia frequency,[31] suggesting that these two methods may be measuring different dimensions of nocturia. Furthermore, the study that reported nocturia frequency based on FVC excluded participants with history of prostatectomy, prostate cancer, bladder cancer, neurogenic bladder, while there was no exclusion made based on these diagnoses in our study. We think that these factors could explain at least in part the differences in the results between our study and the recent study mentioned above.

There was significant association between nocturia frequency and insomnia symptoms with the association showing a possible dose-response relationship, and this finding is in agreement with previous reports.[4,32] However, we did not find a significant association between nocturia frequency and sleep duration, and this is in contrast to a previous study that reported longer sleep duration among participants with higher nocturia frequency.[8]

In contrast to previous studies that reported significant association between nocturia frequency and prevalent as well as incident falls,[33,34] no significant association was observed in the current study. Several factors may account for this discrepancy. One factor may be the definition of falls used in these studies. In the current study, participants were asked if they had fallen down during the last 12 months, and recalling of events that happened during the last 12 months may vary among study participants. Furthermore, the current study included older men only, while previous studies that reported association between nocturia episodes and falls included both men and women.

Similar to reports from previous studies,[8,35,36] prevalence of nocturia was significantly higher among black older men than white older men (**Table 1**); however, after stratification of participants by education status, the relationship between nocturia and race was only significant among those with lower education level (< 12 years of education). Further research would be needed to clarify whether socioeconomic related factors explain the association between race and nocturia frequency found in the current study.

Our study has several strengths. Participants are older men living independently in the community at recruitment, and their medical problems were well characterized at baseline. In addition, regular follow-up of study participants was done during the study period. However, the current study also has limitations, which should be taken in to consideration when interpreting the results. Nocturia status was determined only once at baseline, and data on whether nocturia frequency has changed over time is not known. At least one previous study has indicated that the occurrence of nocturia may fluctuate with time, although this fluctuation was more common among middle-aged adults than among older adults.[37] Another limitation may be related to insomnia categories used in the current study. Insomnia was ascertained based on self-reported symptoms and no objective sleep measures were used. It is possible that some of the participants with insomnia related complaints could have additional primary sleep disorders that could account for their symptoms.

In conclusion, results of the current study indicate that nocturia is associated with mortality independent of insomnia symptoms and sleep duration. This association may be explained by prevalent cardiovascular disease and diabetes mellitus. The results underscore the impact of these medical conditions on the association between nocturia and mortality risk among older men.

ABBREVIATIONS

BMI, body mass index
CI, confidence Interval
FVC, frequency volume chart
Health ABC study, Health Aging Body Composition study
HR, hazard ratio
I-PSS questionnaire, International Prostate Symptoms Score questionnaire
LUTS, lower urinary tract symptoms
PH, proportional hazards
Q1, first quartile
Q3, third quartile
SD, standard deviation

REFERENCES

1. Van KP, Abrams P, Chaikin D, et al. The standardization of terminology in nocturia: report from the standardization subcommittee of the International Continence Society. BJU Int 2002;90 Suppl 3:11–15.
2. Bliwise DL, Foley DJ, Vitiello MV, Ansari FP, Ancoli-Israel S, Walsh JK. Nocturia and disturbed sleep in the elderly. Sleep Med 2009;10:540–8.
3. Pressman MR, Figueroa WG, Kendrick-Mohamed J, Greenspon LW, Peterson DD. Nocturia. A rarely recognized symptom of sleep apnea and other occult sleep disorders. Arch Intern Med 1996;156:545–50.
4. Coyne KS, Zhou Z, Bhattacharyya SK, Thompson CL, Dhawan R, Versi E. The prevalence of nocturia and its effect on health-related quality of life and sleep in a community sample in the USA. BJU Int 2003;92:948–54.
5. Ancoli-Israel S, Bliwise DL, Norgaard JP. The effect of nocturia on sleep. Sleep Med Rev 2011;15:91–7.
6. Norby B, Nordling J, Mortensen S. Lower urinary tract symptoms in the danish population: a population-based study of symptom prevalence, health-care seeking behavior and prevalence of treatment in elderly males and females. Eur Urol 2005;47:817–23.
7. Irwin DE, Milsom I, Kopp Z, Abrams P, Artibani W, Herschorn S. Prevalence, severity, and symptom bother of lower urinary tract symptoms among men in the EPIC study: impact of overactive bladder. Eur Urol 2009;56:14–20.
8. Markland AD, Vaughan CP, Johnson TM, Goode PS, Redden DT, Burgio KL. Prevalence of nocturia in United States men: results from the National Health and Nutrition Examination Survey. J Urol 2011;185:998–1002.
9. Bosch JL, Weiss JP. The prevalence and causes of nocturia. J Urol 2013;189:S86–S92.

10. Aikawa K, Yamaguchi O, Oguro T et al. New classification for men with lower urinary tract symptoms: cluster analysis using the International Prostate Symptom Score. BJU Int 2012;110:408–12.
11. Homma Y, Yoshida M, Yamanishi T, Gotoh M. Core Lower Urinary Tract Symptom score (CLSS) questionnaire: a reliable tool in the overall assessment of lower urinary tract symptoms. Int J Urol 2008;15:816–20.
12. Kay L, Stigsby B, Brasso K, Mortensen SO, Munkgaard S. Lower urinary tract symptoms--a population survey using the Danish Prostatic Symptom Score (DAN-PSS) questionnaire. Scand J Urol Nephrol 1999;33:94–9.
13. Lee SW, Doo SW, Yang WJ, Song YS. Importance of relieving the most bothersome symptom for improving quality of life in male patients with lower urinary tract symptoms. Urology 2012;80:684–7.
14. Akiyama T, Hirayama A, Fujimoto K, Torimoto K, Yoshida K, Hirao Y. Cutoff value of urinary arginine vasopressin for nocturnal polyuria in elderly men. Urology 2007;69:98–102.
15. Natsume O. A clinical investigation of nocturnal polyuria in patients with nocturia: a diurnal variation in arginine vasopressin secretion and its relevance to mean blood pressure. J Urol 2006;176:660–4.
16. Torimoto K, Hirayama A, Samma S, Yoshida K, Fujimoto K, Hirao Y. The relationship between nocturnal polyuria and the distribution of body fluid: assessment by bioelectric impedance analysis. J Urol 2009;181:219–24.
17. Endeshaw YW, Johnson TM, Kutner MH, Ouslander JG, Bliwise DL. Sleep-disordered breathing and nocturia in older adults. J Am Geriatr Soc 2004;52:957–60.
18. Bing MH, Jennum P, Moller LA, Mortensen S, Lose G. Obstructive sleep apnea in a Danish population of men and women aged 60–80 years with nocturia. J Clin Sleep Med 2012;8:515–20.
19. Weiss JP, Blaivas JG, Stember DS, Brooks MM. Nocturia in adults: etiology and classification. Neurourol Urodyn 1998;17:467–72.
20. Bing MH, Moller LA, Jennum P, Mortensen S, Lose G. Nocturia and associated morbidity in a Danish population of men and women aged 60–80 years. BJU Int 2008;102:808–14.
21. Parthasarathy S, Fitzgerald M, Goodwin JL, Unruh M, Guerra S, Quan SF. Nocturia, sleep-disordered breathing, and cardiovascular morbidity in a community-based cohort. PLoS One 2012;7:e30969.
22. Bursztyn M, Jacob JF, Stessman J. Usefulness of nocturia as a mortality risk factor for coronary heart disease among persons born in 1920 or 1921. Am J Cardiol 2006;98:1311–15.
23. Chung MS, Chuang YC, Lee JJ, Lee WC, Chancellor MB, Liu RT. Prevalence and associated risk factors of nocturia and subsequent mortality in 1,301 patients with type 2 diabetes. Int Urol Nephrol 2014;46:1269–75.
24. Asplund R. Mortality in the elderly in relation to nocturnal micturition. BJU Int 1999;84:297–301.
25. Kupelian V, Fitzgerald MP, Kaplan SA, Norgaard JP, Chiu GR, Rosen RC. Association of nocturia and mortality: results from the Third National Health and Nutrition Examination Survey. J Urol 2011;185:571–7.
26. Johnson NB, Hayes LD, Brown K, Hoo EC, Ethier KA. CDC National Health Report: leading causes of morbidity and mortality and associated behavioral risk and protective factors--United States, 2005–2013. MMWR Surveill Summ 2014;63 Suppl 4:3–27.
27. Harris TB, Visser M, Everhart J et al. Waist circumference and sagittal diameter reflect total body fat better than visceral fat in older men and women. The Health, Aging and Body Composition Study. Ann N Y Acad Sci 2000;904:462–73.
28. Health ABC study. Health ABC Death Adjudication Protocol. 2009.
29. Cuzick J. A Wilcoxon-type test for trend. Stat Med 1985;4:87–90.
30. van Doorn B, Kok ET, Blanker MH, Westers P, Bosch JL. Mortality in older men with nocturia. A 15-year followup of the Krimpen study. J Urol 2012;187:1727–31.
31. Blanker MH, Bohnen AM, Groeneveld FP, Bernsen RM, Prins A, Ruud Bosch JL. Normal voiding patterns and determinants of increased diurnal and nocturnal voiding frequency in elderly men. J Urol 2000;164:1201–5.
32. Bing MH, Moller LA, Jennum P, Mortensen S, Skovgaard LT, Lose G. Prevalence and bother of nocturia, and causes of sleep interruption in a Danish population of men and women aged 60–80 years. BJU Int 2006;98:599–604.
33. Vaughan CP, Brown CJ, Goode PS, Burgio KL, Allman RM, Johnson TM. The association of nocturia with incident falls in an elderly community-dwelling cohort. Int J Clin Pract 2010;64:577–83.
34. Stewart RB, Moore MT, May FE, Marks RG, Hale WE. Nocturia: a risk factor for falls in the elderly. J Am Geriatr Soc 1992;40:1217–20.
35. Burgio KL, Johnson TM, Goode PS, et al. Prevalence and correlates of nocturia in community-dwelling older adults. J Am Geriatr Soc 2010;58:861–6.
36. Kupelian V, Link CL, Hall SA, McKinlay JB. Are racial/ethnic disparities in the prevalence of nocturia due to socioeconomic status? Results of the BACH survey. J Urol 2009;181:1756–63.
37. van Doorn B, Blanker MH, Kok ET, Westers P, Bosch JL. Once nocturia, always nocturia? Natural history of nocturia in older men based on frequency-volume charts: the Krimpen study. J Urol 2013;186:1956–61.

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