Nocturia as a Risk Factor for All-Cause and Cardiovascular Disease Mortality

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Abstract

This study aimed to evaluate the relationship between nocturia and mortality risk using the National Health and Nutrition Examination Survey database 2005–2010, given that only few studies have investigated nocturia or its association with mortality using this database. Data were obtained from the database, and nocturia was defined based on the symptom questionnaire. We categorized patients into two groups: mild nocturia (2–3 voids/night) and moderate-to-severe nocturia (≥4 voids/night). Mortality data were obtained by linking the primary database to death certificate data found in the National Death Index with mortality follow-up up to December 31, 2015. Multiple Cox proportional hazard regression analyses were performed with adjustment for confounding variables at the baseline survey. We included 9,892 adults (4,758 men, 5,134 women) in this study. Nocturia occurred in 3,314 individuals (33.5%). In the multiple Cox regression analysis (results presented as hazard ratio, 95% confidence interval), nocturia was significantly associated with all-cause (1.21, 1.08–1.35, p=0.001) and cardiovascular disease (1.45, 1.13–1.85, p=0.003) mortality. Both mild and moderate-to-severe nocturia were significantly associated with all-cause (1.14, 1.02–1.28, p=0.021 and 1.62, 1.34–1.98, p<0.001, respectively) and cardiovascular disease (1.43, 1.11–1.84, p=0.006 and 1.58, 1.01–2.45, p=0.043, respectively) mortality. Nocturia was significantly associated with mortality in men and women after adjustments for major confounding factors. Moreover, the mortality risk increased with increasing nocturia severity.

Introduction

Nocturia was defined by the International Continence Society (ICS) in 2002 as a complaint of waking at night for one or more times to void\(^1\), but this definition was updated in 2018 by ICS as waking at night to pass urine during the main sleep period.\(^2\) Nocturia is a highly prevalent and bothersome lower urinary tract symptom among older adults and the general population.\(^3\) About 30 years ago, the prevalence of nocturia was about 25% in women and 20% in men,\(^4\) but recently, with the increasing older population, this prevalence has increased to 34.9% in women and 30.5% in men.\(^5\) Some reports suggest that the prevalence reaches 60% in men and women above 70 years old.\(^6,7\)

Nocturia has been associated with many comorbidities including cardiovascular diseases (such as coronary heart disease, hypertension, and heart failure), and endocrine disorders (such as diabetes mellitus and central diabetes insipidus).\(^4,5,8\) It has also been associated with chronic illnesses, such as chronic respiratory disease, neurological disease, and malignancy.\(^9\) Considering its associations with these many chronic comorbid conditions, several studies have reported a relationship between nocturia and mortality.\(^3,4,9\) However, despite the increase in nocturia and comorbidities in older people, this relationship cannot be completely explained in terms of older age, and related evidence is limited in the literature. To optimally assess the effect of nocturia on mortality while minimizing the risk of bias, fluctuations in nocturia and follow-up after the initial evaluation should be considered, and a validated nocturia assessment and reliable registration of all deaths during follow-up should be used.\(^9\)
The National Health and Nutrition Examination Survey (NHANES), a nationally representative population-based sample of the United States, was conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention (CDC). To date, only a few studies have investigated nocturia or its association with mortality using NHANES data. Only one study reported an association between nocturia and mortality risk using NHANES III 1988–1994, but the data used were about 30 years old. Therefore, we investigated the relationship between nocturia and mortality risk in the United States between 2005 and 2010 using recent NHANES data.

**Patients And Methods**

**Study design**

NHANES is a biannual national representative survey to evaluate the health and nutritional status of populations in the United States by the CDC. It is a cross-sectional study that samples participants who undergo health and nutrition questionnaire-based surveys, physical examinations, and laboratory tests. The National Center for Health Statistics’ Research Ethics Review Board approved the NHANES protocol (Protocol #2005-06), and each participant provided written consent. This study was carried out in accordance with the relevant guidelines and regulations and the recommendations of the Declaration of Helsinki. Household surveys included demographic and socioeconomic data as well as health and nutritional status information. Anthropometric measures and laboratory tests were conducted using standardized protocols. We obtained baseline data, including nocturia questionnaire information, anthropometric data, and laboratory data using three cycles of NHANES from 2005 to 2010. We linked the mortality information to baseline data from NHANES 2005 to 2010. The mortality information of NHANES was obtained from public-use linked mortality files at the National Center for Health Statistics, which was based on the probabilistic match between NHANES and National Death Index death certificate records up to December 31, 2015.

**Definition of nocturia and Covariates**

Nocturia was defined based on the symptom questionnaire. We categorized the participants into two groups based on the frequency of nocturia into mild (2–3 voids/night) and moderate-to-severe (≥4 voids/night) nocturia. Covariates in this analysis included age, sex, race/ethnicity, smoking status, alcohol consumption, sleep duration, body mass index (BMI), sleep duration, and metabolic disorders at baseline survey such as dyslipidemia, hypertension, diabetes mellitus, and cardiovascular disease. Hypertension was defined as follows: average value of three recorded systolic blood pressures >140 mmHg, average diastolic blood pressure >90 mmHg, or hypertension treatment. We used glucose concentration and hemoglobin A1c (HbA1c) to define diabetes mellitus as follows: fasting blood glucose >126 mg/dL, random blood glucose >200 mg/dL, HbA1c >6.5%, or diabetes mellitus treatment. We defined dyslipidemia as fasting total cholesterol >240 mg/dL or dyslipidemia treatment.

**Statistical analysis**
Continuous variables are presented as means ± SD with p-values according to nocturia using the t-test. Categorical variables are presented as numbers (%) with p-values using the chi-square test. We estimated hazard ratios (HR) using multiple Cox proportional hazard regression analyses to investigate the effect of nocturia on all-cause mortality and cardiovascular disease mortality. Moreover, considering the heterogeneity of the confounding variables according to nocturia, we conducted subgroup analysis with propensity score matching data (1:1 matching) using R version 3.1.0 (The R Foundation for Statistical Computing, Vienna, Austria). We defined that P-value less than 0.05 was statistically significant in this study. Statistical analysis was performed using SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

Results

The study included 9,892 adults (4,758 men, 5,134 women) (Figure 1). Nocturia occurred in 3,314 individuals (33.5% of total; 31.7% of men; 35.1% of women). The participants’ clinical characteristics obtained from NHANES 2005–2010 are presented in Table 1. Nocturia was more common in older individuals, women, smokers, and those with higher BMI and metabolic diseases such as hypertension, diabetes, and hyperlipidemia. In addition, the prevalence of cardiovascular disease was significantly higher in those with nocturia at the baseline survey. In the follow-up data up to 2015, adults with nocturia showed a significantly higher incidence of all-cause and cardiovascular disease mortality than those without nocturia (Table 1).
Table 1
Participants’ clinical characteristics obtained from the National Health and Nutrition Examination Survey dataset between 2005 and 2010

| Characteristics                | With nocturia | Before propensity score matching | After propensity score matching |
|-------------------------------|--------------|----------------------------------|--------------------------------|
|                               | (N=3314)     | p-value                          | p-value                        |
|                               | (N=6578)     |                                  |                                |
| Age                           | 59.8 ± 16.0  | 51.1 ± 16.4 < 0.001              | 59.6 ± 15.0 0.655              |
| Sex (female)                  | 1804 (54.4%) | 3330 (50.6%) < 0.001             | 1804 (54.4%) 1.000             |
| Race/ethnicities              |              | < 0.001                          | < 0.001                        |
| Hispanics                      | 832 (25.1%)  | 1486 (22.6%)                    | 685 (20.7%)                    |
| Non-Hispanic Whites           | 1588 (47.9%) | 3730 (56.7%)                    | 1931 (58.3%)                   |
| Non-Hispanic Blacks           | 793 (23.9%)  | 1092 (16.6%)                    | 588 (17.7%)                    |
| Other races                   | 101 (3.0%)   | 270 (4.1%)                      | 110 (3.3%)                     |
| Smoking (≥100 cigarettes in life) | 1699 (51.3%) | 3013 (45.8%) < 0.001            | 1701 (51.3%) 0.980            |
| Alcohol consumption (≥12 drinks in one year) | 2150 (64.9%) | 4839 (73.6%) < 0.001            | 1133 (34.2%) 0.439            |
| Sleep duration, hours         | 6.8 ± 1.6    | 6.9 ± 1.3 0.001                 | 6.8 ± 1.4 0.231                |
| Body mass index, kg/m²        | 30.7 ± 7.0   | 29.1 ± 6.6  < 0.001             | 30.4 ± 7.0 0.070               |
| Systolic blood pressure, mmHg | 128.4 ± 20.5 | 123.3 ± 17.4 < 0.001           | 128.4 ± 18.9 0.919            |
| Diastolic blood pressure, mmHg | 68.9 ± 13.9  | 70.3 ± 12.4 < 0.001            | 69.4 ± 13.5 0.168             |
| Fasting glucose, mg/dL        | 116.2 ± 44.0 | 108.3 ± 34.0 < 0.001           | 115.6 ± 40.4 0.727            |
| Hemoglobin A1c, %             | 6.0 ± 1.3    | 5.7 ± 1.0  < 0.001             | 5.9 ± 1.1 0.017                |

HDL, high-density lipoprotein

Data are expressed as means ± standard deviation or number (%).
In the multiple Cox regression analysis, nocturia was significantly associated with all-cause mortality (HR: 1.21, 95%CI: 1.08–1.35, p=0.001) and cardiovascular disease mortality (HR 1.45, 95%CI: 1.13–1.85, p=0.003). Mild and moderate-to-severe nocturia were both significantly associated with all-cause mortality (HR 1.14, 95%CI: 1.02–1.28, p=0.021; HR 1.62, 95%CI: 1.34–1.98, p<0.001, respectively) and cardiovascular disease mortality (HR 1.43, 95%CI: 1.11–1.84, p=0.006; HR 1.58, 95%CI: 1.01–2.45, p=0.043, respectively) (Table 2). Considering the heterogeneity of the participants with nocturia, additional analysis was performed using 1:1 propensity score matching; heterogeneity remained between the nocturia and non-nocturia groups regarding a few confounding factors after propensity score matching. With propensity score matching, nocturia was still significantly associated with all-cause mortality (HR 1.25, 95%CI: 1.10–1.41, p<0.001) and cardiovascular disease mortality (HR 1.58, 95%CI: 1.2–2.07, p=0.001). Moreover, mild and moderate-to-severe nocturia were still significantly associated with all-cause mortality (HR 1.18, 95%CI: 1.04–1.34, p=0.012; HR 1.69, 95%CI: 1.37–2.09, p<0.001,

| Characteristics                              | With nocturia (N=3314) | Before propensity score matching | After propensity score matching |
|---------------------------------------------|------------------------|----------------------------------|--------------------------------|
|                                            |                        | Without nocturia (N=6578)       |                                |
|                                            |                        | p-value                          |                                |
|                                            |                        | Without nocturia (N=3314)       | p-value                        |
| Total cholesterol, mg/dL                    | 200.1 ± 46.9           | 202.8 ± 43.1                     | 0.007                          |
|                                            |                        | 200.7 ± 43.5                     | 0.631                          |
| Triglycerides, mg/dL                        | 155.6 ± 146.6          | 139.7 ± 111.9                     | < 0.001                         |
|                                            |                        | 143.7 ± 99.9                     | 0.007                          |
| HDL-cholesterol, mg/dL                      | 53.4 ± 16.9            | 53.4 ± 16.4                      | 0.967                          |
|                                            |                        | 52.7 ± 16.2                      | 0.089                          |
| Diabetes mellitus                           | 1051 (31.7%)           | 1142 (17.4%)                     | < 0.001                         |
|                                            |                        | 979 (29.5%)                      | 0.058                          |
| Hypertension                                | 2305 (69.6%)           | 3156 (48.0%)                     | < 0.001                         |
|                                            |                        | 2301 (69.4%)                     | 0.936                          |
| Dyslipidemia                                | 2188 (66.0%)           | 3641 (55.4%)                     | < 0.001                         |
|                                            |                        | 2186 (66.0%)                     | 0.979                          |
| Cardiovascular disease at baseline survey   | 639 (19.3%)            | 590 (9.0%)                       | < 0.001                         |
|                                            |                        | 558 (16.8%)                      | 0.011                          |
| Death                                       | 604 (18.2%)            | 571 (8.7%)                       | < 0.001                         |
|                                            |                        | 466 (14.1%)                      | < 0.001                         |
| Cardiovascular disease death                | 141 (4.3%)             | 100 (1.5%)                       | < 0.001                         |
|                                            |                        | 84 (2.5%)                        | < 0.001                         |

HDL, high-density lipoprotein

Data are expressed as means ± standard deviation or number (%).
respectively) and cardiovascular disease mortality (HR 1.52, 95%CI: 1.15–2.02, p=0.004; HR 1.94, 95%CI: 1.23–3.08, p=0.005, respectively) (Table 2).

| Table 2 | The association between nocturia and mortality |
|---------|-----------------------------------------------|
|         | Full data                                      | Propensity score matching data |
|         | HR (95% CI) | P-value | HR (95% CI) | P-value |
| All-cause mortality | | | | |
| Nocturia (≥2times) | 1.21 (1.08-1.35) | 0.001 | 1.25 (1.10-1.41) | <0.001 |
| Mild nocturia (2-3 times) | 1.14 (1.02-1.28) | 0.021 | 1.18 (1.04-1.34) | 0.012 |
| Moderate to severe nocturia (≥4 times) | 1.62 (1.34-1.96) | <0.001 | 1.69 (1.37-2.09) | <0.001 |
| Cardiovascular disease -mortality | | | | |
| Nocturia (≥2times) | 1.45 (1.13-1.85) | 0.003 | 1.58 (1.20-2.07) | 0.001 |
| Mild nocturia (2-3 times) | 1.43 (1.11-1.84) | 0.006 | 1.52 (1.15-2.02) | 0.004 |
| Moderate to severe nocturia (≥4 times) | 1.58 (1.01-2.45) | 0.043 | 1.94 (1.23-3.08) | 0.005 |

HR, hazard ratio; CI, confidence interval

Multiple Cox regression model adjusted for age, sex, race, body mass index, smoking status, alcohol consumption, sleep duration, dyslipidemia, hypertension, diabetes mellitus and cardiovascular disease at baseline survey.

In the subgroup analyses according to sex and cardiovascular disease status at the baseline survey, significant results were also found (Table 3). Nocturia was significantly associated with all-cause mortality in men (HR 1.24, 95%CI: 1.07–1.43, p=0.004) and women (HR 1.19, 95%CI: 1.00–1.40, p=0.045). Considering the presence of cardiovascular disease at baseline, nocturia was significantly associated with all-cause mortality in both men and women without cardiovascular disease, but this association was absent in both sexes with cardiovascular disease. Nocturia was significantly associated with cardiovascular disease mortality (HR 1.70, 95%CI: 1.24–2.32, p=0.001) only in men, regardless of the presence of cardiovascular disease at baseline (Table 3).
### Table 3
Association between nocturia (≥2 times) and mortality stratified by sex and cardiovascular disease status at baseline survey

|                        | All-cause mortality | Cardiovascular disease mortality |
|------------------------|---------------------|---------------------------------|
|                        | HR (95% CI)         | P-value                         | HR (95% CI)         | P-value                         |
| Overall                |                     |                                 |                    |
| Men                    | 1.24 (1.07-1.43)    | 0.004                           | 1.70 (1.24-2.32)   | 0.001                           |
| Women                  | 1.19 (1.00-1.40)    | 0.045                           | 1.17 (0.78-1.74)   | 0.449                           |
| Without cardiovascular disease at baseline survey |                     |                                 |                    |
| Men                    | 1.32 (1.09-1.60)    | 0.005                           | 1.58 (1.00-2.49)   | 0.049                           |
| Women                  | 1.24 (1.01-1.52)    | 0.041                           | 1.09 (0.63-1.91)   | 0.753                           |
| With cardiovascular disease at baseline survey |                     |                                 |                    |
| Men                    | 1.12 (0.90-1.40)    | 0.311                           | 1.82 (1.17-2.82)   | 0.008                           |
| Women                  | 1.08 (0.81-1.43)    | 0.601                           | 1.29 (0.72-2.29)   | 0.393                           |

HR, hazard ratio; CI, confidence interval

Multiple Cox regression model adjusted for age, race, body mass index, smoking status, alcohol consumption, sleep duration, dyslipidemia, hypertension, and diabetes mellitus

### Discussion

Our study using data from NHANES 2005–2010 reported that 33.5% of the participants (men, 31.7%; women, 35.1%) had nocturia (≥2 voids/night). A previous study from NHANES III 1988–1994 showed that the prevalence of nocturia (≥2 voids/night) was 15.5% in men and 20.9% in women, and our results showed that the prevalence of nocturia has increased over the last two decades in the United States. This increase may be due to the rapidly aging population. A study of NHANES 2005–2016 reported that more than 80% of those ≥60 years old experienced nocturia ≥1 void/night, while approximately 50% of these experienced nocturia ≥2 voids/night. The elderly population of the United States will be 88.5 million (20% of the total population) by 2050, with nocturia more likely to develop in the future.

The ICS defines nocturia as voiding that occurs during the main sleep period. However, some physicians do not consider 1 void during sleep hours to be clinically significant. This may be because some studies have reported that <2 voids/night is not bothersome and that ≥2 voids/night can compromise the quality of life. In this study, we defined nocturia as ≥2 voids during sleep at night. We also categorized mild nocturia as 2–3 voids during sleep at night and moderate-to-severe nocturia as ≥4 voids during sleep at
night. Based on this definition and categorization, we showed that nocturia is a dose-dependent predictor of mortality, where mortality risk increased as the episodes of nocturia increased. The results of the present study are consistent with those reported in these previous studies.\textsuperscript{3, 4, 9, 15}

Our results are also consistent with previous reports from a United States population-based study. In NHANES III 1988–1994, nocturia (≥2 voids/night) was associated with poorer survival compared with 0–1 voids in men and women.\textsuperscript{4} This association was particularly notable in subjects below 65 years old, with attenuated associations in those ≥65 years old. The current study did not analyze according to age group, but there may be a difference in the age proportion of our population compared to that of the previous study.

Two recent studies\textsuperscript{3, 9} have investigated the association between nocturia and mortality, and a systematic review and meta-analysis including 11 observational studies has revealed an association between nocturia and mortality.\textsuperscript{9} In this analysis, although nocturia was defined as 2 or 3 voids on separate occasions, nocturia was shown to be associated with increased mortality risk (risk ratio 1.27, 95%CI: 1.16–1.40). In a longitudinal, general population cohort study of 9,762 Japanese men and women, subjects with nocturia were at greater risk of death than those without nocturia in a dose-dependent manner (HR 1.46 for 1 time, 95%CI: 1.02–2.09; HR 1.85 for 2 times, 95%CI: 1.23–2.77; and HR 2.06 for ≥3 times, 95%CI: 1.28–3.32) during the 5-year observation period.\textsuperscript{3}

Multiple pathways are considered to underlie the relationship between nocturia and mortality.\textsuperscript{3} Sleep loss can negatively affect health by decreasing immune function and increasing the risk of cardiovascular disease, obesity, and type 2 diabetes mellitus.\textsuperscript{5, 16} These comorbidities could lead to death, suggesting that chronic illnesses are associated with nocturia and mortality. More specifically, sleep disturbance due to nocturia could increase cardiovascular disease mortality by inhibiting physiological nighttime blood pressure drop and increasing sympathetic activity.\textsuperscript{17} Moreover, fractures and other injuries may result from falls associated with severe nocturia and daytime fatigue and could impair performance status and cause frailty, which could lead to death.\textsuperscript{9, 18} The reported association of nocturia with falls and fractures, in addition to an increased risk of chronic illnesses (such as cardiovascular disease, hypertension, and diabetes), suggests that the association of nocturia and mortality may involve multiple pathways.\textsuperscript{4}

In the present study, there was a significantly higher prevalence of cardiovascular disease and cardiovascular disease mortality in those with nocturia. Particularly, compared with all-cause mortality, cardiovascular disease mortality showed a higher HR. Our results indicate that nocturia severity was associated with an increased risk of all-cause mortality (HR, mild vs. moderate-severe nocturia, 1.14 vs. 1.62 with no propensity score matching, 1.18 vs. 1.69 after propensity score matching). Interestingly, the dose-dependent relationships were even more prominent in cardiovascular disease mortality (HR 1.43 vs. 1.58 with no propensity score matching, 1.52 vs. 1.94 after propensity score matching). Therefore, our findings indicate that the risk of cardiovascular disease and all-cause mortality increased as the episodes of nocturia increased.
In a previous report of 70-year-old adults, subjects with nocturia had a greater risk of cardiovascular disease than those without nocturia (HR 2.16, 95%CI: 1.01–4.61) suggesting that nocturia is a predictor of mortality in older patients with cardiovascular disease. Several studies have shown that cardiovascular disease is associated with nocturia in both clinical and community-based populations. In the Boston Area Community Health study, cardiovascular disease was independently correlated with nocturia (odds ratio [OR] 1.37, 95%CI: 1.01-1.87), and in the Finnish National Nocturia and Overactive Bladder study, cardiovascular disease was associated with nocturia in women (OR 3.13, 95%CI: 1.48–6.64).

In our sub analysis, nocturia in men and women without cardiovascular disease at the baseline survey was associated with the risk of all-cause mortality. However, nocturia was associated with the risk of cardiovascular disease mortality only in men, regardless of the presence of cardiovascular disease at baseline. These results suggest that nocturia is a risk factor for all-cause mortality in men and women when the effect on cardiovascular disease is excluded. However, cardiovascular disease mortality was associated with nocturia in men, suggesting sex differences in cardiovascular disease.

This study had several potential limitations. First, the lack of information on the voiding diary of participants made it difficult to determine the underlying pathophysiology of nocturia in detail. Second, we excluded many participants due to missing data and conducted our research as a cross-sectional study, resulting in limited power. Several studies have found a relationship between nocturia and hip fractures in older people, and nocturia among these older populations is likely to cause hip fractures and death. However, we did not have data to determine the association between nocturia and the risk of hip fractures and subsequent mortality risk in this population. Therefore, prospective studies are needed to identify the causal relationship between nocturia and mortality.

The main strengths of our study were the use of a nationally representative large population-based sample of men and women and the high response rate, which enables us to accurately determine the association between nocturia and mortality. Another strength of our study was that all-cause mortality and cardiovascular disease mortality were analyzed separately, and the investigation of mortality risk according to the severity of nocturia was conducted. Thus, it was possible to investigate in detail whether the cause of death was cardiovascular disease and if the positive association between nocturia and mortality risk increased with increased nocturia severity. Finally, through full data and 1:1 propensity score matching analysis for confounding variables, a more accurate analysis could be made regarding the causal relationship between nocturia and mortality.

Conclusion

Our population-based study demonstrated that mortality was significantly associated with mild and moderate-to-severe nocturia in men and women after adjusting for major confounding factors. Our study also showed that cardiovascular disease mortality was associated with nocturia in a dose-dependent manner. To our knowledge, this study is one of the most recent and largest investigations of the
relationship between nocturia and mortality using a nationally representative population-based cohort of 
the United States. Our study provides strong support for the previously established relationship between
nocturia and mortality. Moreover, our results should help clarify the mechanisms of nocturia and the
relationship between nocturia and mortality risk.

Declarations

Author contributions:

Conceptualization: Sung Tae Cho, Shinje Moon. Data curation: Shinje Moon. Formal analysis: Shinje
Moon. Investigation: Shinje Moon. Methodology: Shinje Moon, Sung Tae Cho. Resources: Shinje Moon,
Hye Soo Chung, Yoon Jung Kim, Jae Myung Yu, Il In Park. Software: Shinje Moon. Supervision: Hye Soo
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Validation: Sung Tae Cho. Project administration: Sung Tae Cho. Visualization: Shinje Moon. Writing -
original draft: Shinje Moon, Sung Tae Cho. Writing - review & editing: Shinje Moon, Sung Tae Cho.
Approval of nal manuscript: all authors.

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A total of **31,034 participants** were recruited from NHANES 2005-2010

21,142 participants were excluded
- **13,902 participants** younger than 20 years old
- **2,309 participants** without data on nocturia or mortality
- **4,931 participants** without anthropometric or laboratory data

**9,892 participants** were included in the final analysis

Figures

**Figure 1.**

Flowchart for participant selection. NHANES, National Health and Nutrition Examination Survey.