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Nocturia is associated with an increased risk of coronary heart disease and death

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Abstract

- To determine whether nocturia is associated with the development of diabetes mellitus, hypertension, coronary heart disease (CHD) and occurrence of death.
- We studied data obtained from a retrospective cohort of randomly selected men, aged 40–79 years in 1990, from Olmsted County, MN, USA.
- Nocturia was defined as waking to urinate 2 times per night.
- Men were followed every 2 years through repeated questionnaires and community medical records to assess development of diabetes mellitus and hypertension, and occurrence of death. CHD was ascertained through ongoing surveillance of heart disease in Olmsted County.
- Cox proportional hazard models were used to estimate associations between baseline nocturia and each of the outcomes.
- A total of 2447 men were followed for a median of 17.1 years (25th and 75th percentiles: 15.0, 17.4 years).
- Nocturia was not significantly associated with the later development of diabetes mellitus or hypertension in this study.
- Younger men (<60 years of age) with moderate nocturia were more likely to develop CHD later in life than younger men without nocturia (hazard ratio [HR]: 1.68; 95% confidence interval [CI]: 1.13, 2.49). This association was no longer significant when adjusted for age, body mass index (BMI) and urological medications (HR: 1.36; 95% CI: 0.87, 2.22).
- Older men (≥60 years of age) with moderate nocturia were more likely to die than older men without moderate nocturia, even after adjusting for age, BMI, urological medications and CHD (HR: 1.48; 95% CI: 1.15, 1.91).

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CONFLICT OF INTEREST

Steven Jacobson is an employee of Kaiser Permanente and Cynthia Girman is an employee of a shareholder in Merck.

- Nocturia may be a marker for increased risk of CHD in younger men, and death in older men.

Keywords

nocturia; diabetes mellitus; cardiovascular disease; hypertension; cohort

INTRODUCTION

Nocturia (awakening at night 1 times to void) is a common clinical complaint, and the prevalence of this condition increases dramatically with aging.[1–5] An increasing number of awakening events is associated with poorer quality sleep[6] and increasing disturbance in perceived quality of life, [7–9] particularly in those who have difficulty returning to sleep. [10] Additionally, nocturia has been associated with increased mortality, [11, 12] possibly because nocturia is associated with a number of systemic illnesses including cardiac disease [7, 12], type II diabetes, sleep apnoea, hypertension, depression [1, 13] and end-stage renal disease.[14] Most previous studies, however, have assessed associations between nocturia and systemic illnesses only at a single point in time. This makes it difficult to determine if nocturia is an early manifestation of these illnesses, or a complication resulting from these conditions. If nocturia is an early marker for specific chronic diseases, men who suffer from nocturia could be targeted for therapies to treat these conditions at an early stage.

To address this question, we examined associations between nocturia and later development of hypertension, diabetes mellitus, coronary heart disease (CHD), or death among men participating in a retrospective cohort study in Olmsted County, MN, USA.

MATERIALS AND METHODS

Study subjects

Details of the Natural History of Prostatism: the Olmsted County Study have been published previously.[15] Briefly, a random sample of men from Olmsted County, MN, USA, aged 40–79 years in 1990, was identified using the resources of the Rochester Epidemiology Project.[16, 17] Those with a previous history of prostate cancer, prostatectomy, or other urological conditions (bladder cancer, bladder disorders or surgery, and urethral disorders or surgery) were excluded. Of the 3874 eligible men, 2115 (55%) agreed to participate and completed a detailed questionnaire including questions similar to those of the AUA symptom index (AUASI). Specifically, the response categories in our questionnaire are worded as, ‘I do not have the symptom’, ‘rarely’, ‘a few times’, ‘fairly often’, ‘usually’, ‘almost always’ and ‘always’. For the present study, the top two categories were collapsed into a single category to match the highest AUASI category of ‘almost always’.[18] The cohort has been followed every two years thereafter (up until 2007) using questionnaires similar to the initial examination. To replace men who either died or dropped out of the study during the follow-up period, additional men were randomly sampled from the community and were invited to participate during the first 4 years of follow-up ($n=332$). Since that time the study has been maintained as a closed cohort.

Ascertainment of nocturia

Nocturia was measured by a previously validated questionnaire that contains questions similar to those of the AUASI.[19, 20] Specifically, nocturia was defined by the response to the question, ‘Over the last month, how many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?’ Nocturia was considered present if the patient answered with 2 times per night.

Ascertainment of outcomes

Presence of diabetes mellitus and hypertension was ascertained by self-report of a doctor's or physician's diagnosis of diabetes mellitus or high blood pressure, or by report of anti-hyperglycaemic or anti-hypertensive medication use. Presence of CHD was ascertained through ongoing surveillance of heart disease in the Olmsted County community (RO1 HL 059205; Principal Investigator: V Roger).[21, 22] CHD was defined as sudden cardiac death, myocardial infarction and angiographically diagnosed coronary disease.[22–24] Death was ascertained through multiple sources, including death certificates filed in Olmsted County, autopsy reports, obituary notices and electronic death certificate data obtained from the state of Minnesota.

Statistical analysis

Separate analyses were conducted for each outcome, and men with diabetes mellitus, hypertension or CHD before baseline were excluded from the analyses involving those outcomes. Follow-up was from the start of the study until the first occurrence of the outcome being analysed or the last follow-up. Participants who reported nocturia before the development of the outcome in the analysis were considered exposed. Cox proportional hazard models were used to estimate the associations between baseline nocturia and each of the outcomes, and are presented as hazard ratios (HRs) and their associated 95% CIs. Proportional hazards assumptions were assessed using Schoenfeld residuals. Multivariable models were used to adjust for potential confounders including age, body mass index (BMI), and medical therapies for LUTS and overactive bladder (OAB). Individuals with a BMI ≥ 30 kg/m² were classified as obese. Models assessing the association between baseline nocturia and death were also adjusted for presence of CHD.

RESULTS

Overall, 2447 men participated in the present study, and their median age at baseline was 52 years (Table 1). In addition, 18% of the men reported having nocturia at baseline (Table 1). Men were followed for a median of 17.1 years (25th and 75th percentiles: 15.0, 17.4 years). During this time, 6.5% developed diabetes mellitus, 32.0% developed hypertension, 15.9% developed CHD and 19.0% died (Table 1).

In univariate models, baseline nocturia was significantly associated with later development of CHD and death, but these associations were attenuated after adjusting for baseline age, BMI and use of α -blockers, 5 α -reductase inhibitors or OAB medications (Table 2). As nocturia was strongly associated with increasing age, we stratified the analyses in Table 2 by age group (Table 3). There was an association between moderate nocturia (≥ 2 times per night) with development of CHD in younger men (HR: 1.68, 95% CI: 1.13, 2.49; Table 3). This was slightly attenuated and no longer significant when adjusting for age, BMI and urological medications (adjusted HR: 1.36, 95% CI: 0.87, 2.22). This association was not observed among older men (HR: 0.92; 95% CI: 0.65, 1.31). Conversely, after adjustment for age, BMI and urological medications, there was a significant increased risk of death for older men with moderate nocturia (HR: 1.48, 95% CI: 1.15, 1.91; Table 3). The increased risk was not statistically significant in younger men (HR: 1.31, 95% CI: 0.73, 2.35).

DISCUSSION

In the present study, nocturia was not associated with later development of either diabetes mellitus or hypertension; however, we found that younger men (<60 years of age) with moderate nocturia were more likely to later develop CHD later in life than younger men

without nocturia. Additionally, older men (> 60 years of age) with moderate nocturia were more likely to die compared with older men without moderate nocturia.

Nocturia was not significantly associated with the later development of diabetes mellitus in the present study. Nocturia is highly associated with a current diagnosis of diabetes mellitus [8], but it is known to resolve with successful management of diabetes-associated osmotic diuresis. Although nocturia is a common symptom of new onset diabetes mellitus, our results suggest that moderate nocturia is not a marker for the subsequent development of diabetes mellitus. Instead, nocturia that is associated with diabetes is probably a secondary phenomenon, resulting from physiological changes that follow the development of diabetes mellitus. In support of this theory, hyperinsulinaemia has been associated with increased sympathetic nervous system activity, which may contribute to increased nocturia.[25] Diabetes also causes cystopathy, [26, 27] and these bladder changes may contribute to the development of nocturia in patients with diabetes.

Similarly to diabetes mellitus, we did not find an association between nocturia and later development of hypertension. Nocturia and hypertension have been correlated with each other in previous studies, possibly because the use of diuretics for the treatment of hypertension, cardiac failure or peripheral oedema is highly correlated with nocturia.[8] Nocturia may, therefore, be attributable to treatment of hypertension, rather than a marker for the subsequent development of hypertension. It was not possible, however, to directly assess the relationship between use of hypertensive medications and development of nocturia in the present study.

By contrast to hypertension and diabetes mellitus, the present data suggest that young men (<60 years of age) with nocturia may be at an increased risk of later developing CHD. After adjustments for baseline age, BMI and urological medications, these results were not statistically significant, but were suggestive of an increased risk. It is possible that the younger men with moderate nocturia at baseline may have a disordered cardiovascular system homeostasis. This directly contradicts the conclusions of Weiss et al. [28] who concluded that nocturia in a pre-selected younger population of patients with OAB is probably more related to a decreased nocturnal bladder capacity as measured by nocturnal bladder capacity indices.[29] Because the prevalence of BPH-associated outlet obstruction causing nocturia is lower in this age group, cardiovascular factors leading to nocturia may play a larger role than genitourinary ones in the patient <60 years old. In particular, the association between nocturia and CHD was attenuated after adjusting for BMI. As high BMI is an important risk factor for CHD, our data lend support to the hypothesis that cardiovascular factors may play a role in the development of nocturia, and, as such, nocturia may be an early marker for CHD in younger men. This risk was not seen in men > 60 years of age, suggesting that age and nocturia associated with lower urinary tract dysfunction might play a larger role in this symptomatology. Patient evaluation should include bladder diaries to determine the underlying pathophysiology of moderate nocturia. If confirmed as nocturia polyuria, evaluation for undiagnosed cardiac disease may be appropriate.

We found that older men (> 60 years of age) with moderate nocturia were at an increased risk of death, and this increased risk remained, even after adjusting for CHD, hypertension and diabetes mellitus. These results are similar to those of previous studies. In a multivariate analysis, Swedish male pensioners with nocturia > 3 times per night had a 1.9 times higher death rate compared with matched cohorts during a follow-up of 54 months.[11] Additionally, Kupelian *et al.* [30] found that nocturia was significantly associated with an increased risk of death in both men and women, and the risk increased with increasing number of nocturia episodes per night. Several studies have recently found associations between nocturia and hip fractures in elderly populations, [31, 32] [33] and it is possible that

nocturia among these older men led to hip fracture, and subsequently death. Unfortunately, we do not have data available to determine the risk of hip fractures in this population.

Additionally, obstructive sleep apnoea (OSA) has a potential mediating role in the association between nocturia and long-term health outcomes.[34–37] OSA is related to adverse long-term health outcomes, and may also cause night waking, which could then be followed by micturition. OSA is therefore a potential confounder of the association between nocturia and adverse outcomes. Polysomnographic information was not available in this cohort of men; however, based on a sleep questionnaire during follow-up, relatively few men were considered to be heavy snorers and only 6% reported daily sleep disordered breathing.[38] Therefore, it seems less likely that OSA is a strong confounder in this cohort. Additionally, previous studies suggest that OSA causes adverse outcomes via the development of hypertension. In the present cohort, we did not see an association between nocturia and development of hypertension, and associations between nocturia and death in older men remained significant even after adjustment for hypertension.

Potential limitations of the present study include the lack of either frequency volume charts or bladder diaries among study participants, making it impossible to distinguish nocturnal polyuria from increased nocturnal frequency.[39] In addition, we were unable to determine the specific underlying causes of the nocturia among the study participants. There was also a relatively small number of men with diabetes mellitus in this population, resulting in limited power to detect small associations with nocturia. Using a combined CHD outcome (consisting of angioplasty, CABG, incident myocardial infarction, positive angio, and sudden cardiac death) also has limitations, as it is possible for nocturia to be a marker of some, but not all of these conditions. If this is the case, our HRs are underestimates of the true associations between nocturia and subgroups of CHD; however, we had limited power to analyse associations between nocturia and the individual CHD outcomes, particularly in the age-specific subgroup analyses. The present study suggests that nocturia is a sign of later development of CHD, therefore, associations with specific types of CHD will need to be assessed in future studies.

In addition, the present study was retrospective, power was somewhat limited, particularly for the subgroup analyses, and the possibility that our diabetes mellitus and hypertension results were false-negatives, can not be excluded. Finally, the present study population was Caucasian and predominantly upper middle class, and results may not be generalizable to populations with dissimilar characteristics.

In conclusion, nocturia does not appear to be a marker for later development of hypertension or diabetes mellitus, but may be a marker for increased risk of CHD in younger men, and death in older men.

Abbreviations

CHD	coronary heart disease
HR	hazard ratio
BMI	body mass index
OAB	overactive bladder
AUASI	AUA symptom index
OSA	obstructive sleep apnoea

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Table 1

Characteristics of the study population

Characteristic	N=2447
Median (25 th , 75 th percentile) baseline age, years	51.88 (44.82, 62.77)
Median (25 th , 75 th percentile) baseline BMI, kg/m ²	27.97 (25.56, 30.78)
Baseline age, years	
40–49, <i>n</i> (%)	1086 (44.38)
50–59, <i>n</i> (%)	619 (25.30)
60–69, <i>n</i> (%)	463 (18.92)
70+, <i>n</i> (%)	279 (11.40)
Baseline nocturia [*] , <i>n</i> (%)	440 (17.98)
Baseline night-time urination frequency	
Unknown, <i>n</i> (%)	18 (0.74)
0 times per night, <i>n</i> (%)	934 (38.17)
1 time per night, <i>n</i> (%)	1055 (43.11)
2 times per night, <i>n</i> (%)	247 (10.09)
3 times per night, <i>n</i> (%)	193 (7.89)
Outcomes	
Diabetes mellitus [†] , <i>n</i> (%)	151 (6.53)
Hypertension [†] , <i>n</i> (%)	577 (32.04)
CHD [†] , <i>n</i> (%)	359 (15.86)
Death, <i>n</i> (%)	465 (19.00)

^{*}
(>1 time per night)

[†] Those with events of interest at or before baseline were removed. Diabetes mellitus denominator: *n*=2313; hypertension denominator: *n*=1801; CHD denominator: *n*=2264.

TABLE 2

Association between nocturia (>1 time per night) and adverse outcomes

Outcome	Unadjusted	Age-adjusted	Multivariable-adjusted*
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Diabetes mellitus	1.12 (0.74, 1.72)	1.11 (0.72, 1.70)	0.97 (0.61, 1.54)
Hypertension	1.16 (0.93, 1.45)	0.98 (0.78, 1.23)	0.86 (0.68, 1.10)
CHD	1.58 (1.24, 2.03)	1.13 (0.87, 1.45)	1.03 (0.78, 1.36)
Death	2.22 (1.82, 2.71)	1.14 (0.93, 1.40)	1.22 (0.96, 1.54)

* Adjusted for baseline age, BMI, and use of α -blockers, 5 α -reductase inhibitors, and/or OAB medications; death adjusted for baseline age, BMI, use of α -blockers, 5 α -reductase inhibitors and/or OAB medications, and CHD.

TABLE 3

Association between nocturia (>1 time per night) and adverse outcomes stratified by age group

Age group	Outcome	Unadjusted	Adjusted*
		HR (95% CI)	HR (95% CI)
40–59 years	Diabetes mellitus	1.26 (0.75, 2.11)	1.06 (0.61, 1.85)
	Hypertension	1.19 (0.89, 1.59)	1.05 (0.77, 1.43)
	CHD	1.68 (1.13, 2.49)	1.36 (0.87, 2.12)
	Death	1.32 (0.79, 2.21)	1.31 (0.73, 2.35)
60 years	Diabetes mellitus	0.85 (0.40, 1.81)	0.74 (0.32, 1.74)
	Hypertension	0.81 (0.57, 1.16)	0.74 (0.51, 1.07)
	CHD	0.95 (0.69, 1.31)	0.92 (0.65, 1.31)
	Death	1.37 (1.10, 1.70)	1.48 (1.15, 1.91)

* Adjusted for baseline age, BMI, and use of α -blockers, 5 α -reductase inhibitors, and/or OAB medications; death adjusted for baseline age, BMI, use of α -blockers, 5 α -reductase inhibitors and/or OAB medications, and CHD.