

A Longitudinal Study of Bidirectional Relationships between Sleep Disorder and Frequency of Nocturia: Results from the Iwaki Health Promotion Project

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Keywords

Nocturia · Sleep disorder · Longitudinal analysis · Lower urinary tract symptoms

Abstract

Introduction: The causal relationship between sleep disorder and frequency of nocturia remains unclear. **Methods:** We longitudinally evaluated sleep disorder and frequency of nocturia in 547 community-dwelling adults between baseline and 5-year follow-up. We included participants ≥ 50 years old who have no sleep disorder (the Pittsburgh Sleep Quality Index [PSQI] ≥ 5) nor nocturia (≥ 1). For 5 years, we evaluated the temporal changes in sleep disorder and nocturia and the bidirectional relationships between sleep disorder and nocturia. **Results:** Of the 547 participants, we included 268 adults with a median age of 61 years in this study. Median PSQI and nocturia were significantly increased for 5 years from 2 to 3 and from 1 to 2, respectively. New onset of sleep disorder (PSQI > 5) and nocturia > 1 was observed in 42

(16%) and 137 (51%) participants, respectively. The cross-lagged panel analysis showed that the path coefficient from PSQI to nocturia ($\beta = 0.22, p = 0.031$) was significantly higher than that from nocturia to PSQI ($\beta = 0.02, p = 0.941$). **Conclusions:** Our longitudinal study showed the effect of sleep disorder on nocturia was significant, although nocturia may not significantly worsen sleep disorder in community-dwelling adults.

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Introduction

The presence of lower urinary tract symptoms (LUTS) remarkably reduces health status and quality of life in men and women [1–5]. Nocturia (nocturnal urination) is one of the more bothersome symptoms than daytime LUTS in older individuals [6–9]. Also, nocturia and sleep disorder have a close relationship due to frequent nocturnal awakening [10–13]. Both nocturia and poor sleep quality are related to unfavorable outcomes such as heart

disease, diabetes, depression, falls, accidents, impaired cognition, and poor quality of life [14–18]. However, it is difficult to define the association of nocturia with sleep disorder because of the complex relationship [19]. Our previous study showed that sleep disorder may have a greater influence on the health-related quality of life than nocturia [20]. Also, a recent longitudinal study suggested the negative influence of sleep problems on nocturia [21]. Accordingly, we hypothesized that the effect of sleep disorder on nocturia may be stronger than that of nocturia on sleep disorder. In this longitudinal study, we aimed to investigate the natural history and causal relationship between sleep disorder and nocturia in community-dwelling adults for 5 years.

Materials and Methods

Design and Ethics Statement

The study was conducted following the ethical standards of the Declaration of Helsinki. This study was approved by the Ethics Committee of Hiroasaki University School of Medicine. All subjects provided written informed consent before participating in the study. This observational study was registered at the UMIN-CTR (UMIN000039744).

Patient Selection, Data Collection, and Evaluation

The Iwaki Health Promotion Project was a comprehensive study clarifying the etiology of lifestyle-related diseases to promote health and extend the lifespan of residents of the city of Hiroasaki (Iwaki district) in the northern part of Japan including 4,105 participants [22–24]. Of those, we longitudinally evaluated sleep disorder and frequency of nocturia in 547 adults in the Iwaki Health Promotion Project with baseline and 5-year follow-up between 2009 and 2017. Information on the disease history of cardiovascular disease (CVD) and type 2 diabetes mellitus (DM) was obtained via questionnaire. Diabetic patients were defined as those with a history of type 2 DM or those who met the relevant diagnostic criteria and required glycemic control. CVD was defined as a positive history of cardiac surgery, myocardial infarction, angina, stroke, or taking any cardiotoxic agents. Sleep disorder and frequency of nocturia were measured using the Japanese version of the Pittsburgh Sleep Quality Index (PSQI) [20] and the International Prostate Symptom Score (IPSS). The PSQI is a widely used tool to measure the quality and pattern of sleep in older adults. The total scores provide an assessment of overall sleep quality (range 0–21), and sleep disorder was defined as a PSQI > 5.

Inclusion and Exclusion Criteria

The inclusion criteria were participants (1) aged 50 years or older, (2) who do not have sleep disorder (PSQI ≤ 5), and (3) with frequency of nocturia 0 or 1 time per night (nocturia ≤ 1) at baseline. The exclusion criteria were insufficient report of questionnaire for comorbidity, PSQI, and IPSS at baseline and 5-year follow-up.

Outcomes

We compared PSQI and frequency of nocturia between baseline and 5-year follow-up and evaluated the rate of new onset of sleep disorder (PSQI > 5) or frequency of nocturia greater than 1 time per night (nocturia > 1). The bidirectional association between nocturia and sleep disorder was assessed using a cross-lagged panel analysis to evaluate the effect of baseline PSQI on nocturia at 5-year follow-up and the effect of baseline nocturia on PSQI at 5-year follow-up.

Statistical Analysis

Statistical analysis was performed with GraphPad Prism ver. 7.00 (GraphPad Software, San Diego, CA, USA), Microsoft Excel (Microsoft Corporation, Redmond, WA, USA), BellCurve for Excel (Social Survey Research Information Co., Ltd., Tokyo, Japan), and IBM SPSS Amos 26 (Stats Guild Inc., Chiba, Japan). Categorical variables were compared using Fisher's exact test or the χ^2 test. Quantitative variables were expressed as median and interquartile range (IQR). The differences between groups were compared using the Student's *t* test for normally distributed data or the Mann-Whitney U test for non-normally distributed data. The difference among the 3 groups was compared using one-way ANOVA. A multivariable analysis was performed to identify whether baseline sleep disorder is an independent risk factor for nocturia in men or women including age, DM, and CVD. The bidirectionality association between sleep disorder and frequency of nocturia was evaluated using a cross-lagged panel analysis adjusted for age and sex. This analysis estimated standardized coefficients between 2 related variables over time and evaluated the strength of the temporal relationship [25]. Goodness of fit of the panel was evaluated by a comparative fit index (CFI ≥ 0.90), the Tucker-Lewis index (TLI ≥ 0.90), root mean square error of approximation (RMSEA ≤ 0.08), and standardized root mean square residual (SRMR ≤ 0.08) [25]. A standardized regression coefficient of a cross-lagged panel analysis was defined by the β value. Differences were considered statistically significant at $p < 0.05$.

Results

Baseline Characteristics

The background of participants is presented in Table 1. Of the 547 participants, we excluded 279 patients who were younger than 50 years ($n = 160$), had PSQI > 5 ($n = 44$) or nocturia > 1 ($n = 65$), or had insufficient report of questionnaires ($n = 10$) (Fig. 1a). Finally, 268 (92 men and 176 women) with a median age of 61 (IQR 56–65) years were included in this study. The median PSQI and frequency of nocturia at baseline were 2 (IQR 1–3) and 1 (IQR 0–1), respectively. The number of participants who started any medication for LUTS was 7 (2.6%) in this cohort.

Outcomes

The median PSQI and nocturia were significantly increased for 5 years from 2 to 3 (Fig. 1b: $p < 0.001$) and

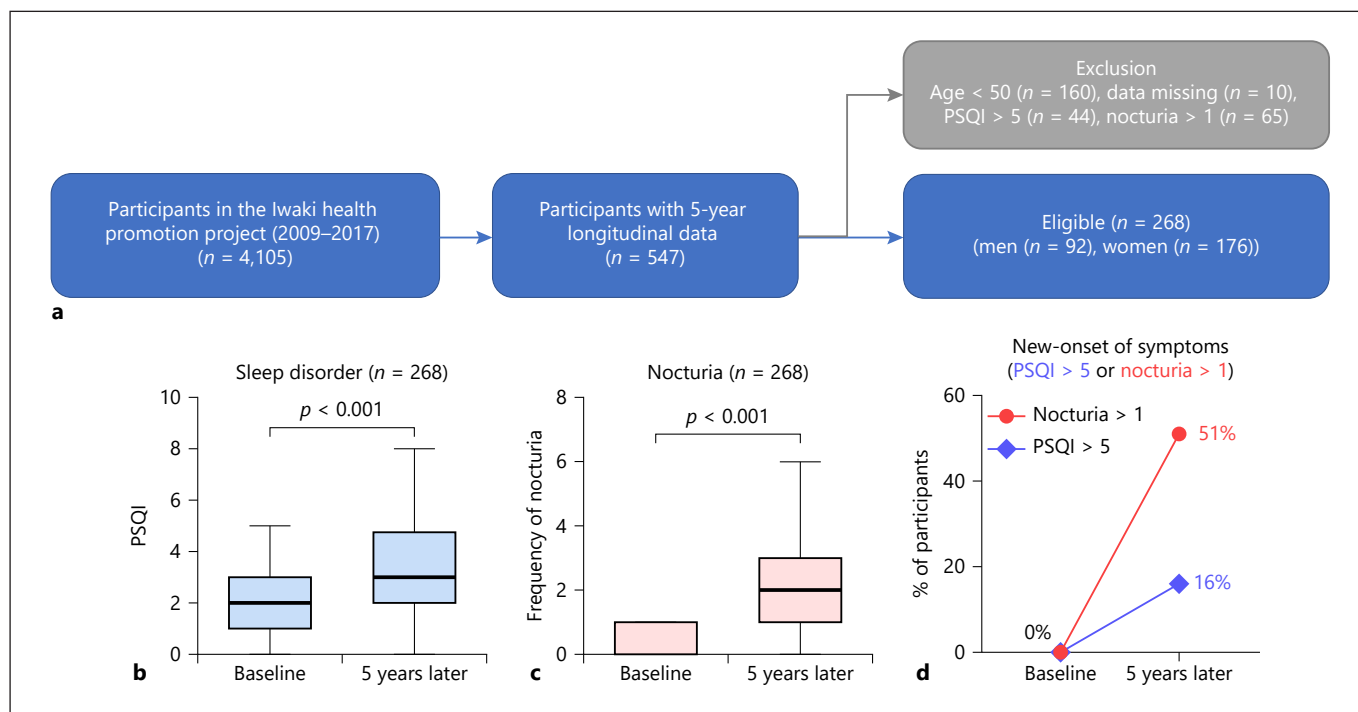


Fig. 1. Patient selection and the association between sleep disorder and nocturia for 5-year follow-up. **a** We selected 268 individuals from the 4,105 participants in the Iwaki Health Promotion Project (2009–2017). We compared sleep disorder (**b**) and frequency of nocturia (**c**) at baseline and at 5-year follow-up. The rate of new onsets of sleep disorder (PSQI > 5) and nocturia >1 was evaluated (**d**). PSQI, Pittsburgh Sleep Quality Index.

Table 1. Background of participants

	All	Study group
Number of participants, <i>n</i>	547	268
Age, median (IQR), years	57 (47–64)	61 (56–65)
Male, <i>n</i> (%)	208 (38)	92 (34)
DM, <i>n</i> (%)	49 (9)	29 (11)
CVD, <i>n</i> (%)	40 (7)	21 (8)
Smoking, <i>n</i> (%)	180 (33)	69 (26)
BMI, mean (IQR), kg/m ²	23 (21–25)	23 (21–25)

IQR, interquartile range; CVD, cardiovascular disease; DM, diabetes mellitus.

from 1 to 2 (Fig. 1c: $p < 0.001$), respectively. New onset of sleep disorder (PSQI > 5) and nocturia >1 was observed in 42 (16%) and 137 (51%) participants, respectively (Fig. 1d; Table 2). A similar trend was observed in both men and women. The PSQI and nocturia were significantly increased for 5 years in men (Fig. 2a–c) and wom-

en (Fig. 2d–f). However, multivariable logistic regression showed that baseline sleep disorder was an independent risk factor for nocturia in men, but it was not the case in women (Table 3).

The cross-lagged panel analysis showed that baseline PSQI was significantly associated with the follow-up frequency of nocturia after 5 years ($p = 0.031$). Conversely, baseline frequency of nocturia was not significantly associated with the follow-up PSQI after 5 years ($p = 0.941$). The path coefficient from PSQI to nocturia ($\beta = 0.22$) was approximately 10-fold higher than that from nocturia to PSQI ($\beta = 0.02$) (Fig. 3a). Goodness of fit of this model was acceptable with CFI = 1.00, TLI = 1.13, RMSEA = 0.01, and SRMR = 0.08. There was no significant difference in the PSQI at baseline between baseline nocturia 0 and 1 ($p = 0.741$) and in the PSQI at the 5-year follow-up between baseline nocturia 0 and 1 ($p = 0.413$) (Fig. 3b). Conversely, a significant difference was observed in the frequency of nocturia at 5-year follow-up among baseline PSQI 0–1, 2–3, and 4–5 ($p = 0.036$), while there was no significant difference in the frequency of nocturia at baseline PSQI ($p = 0.354$) (Fig. 3c).

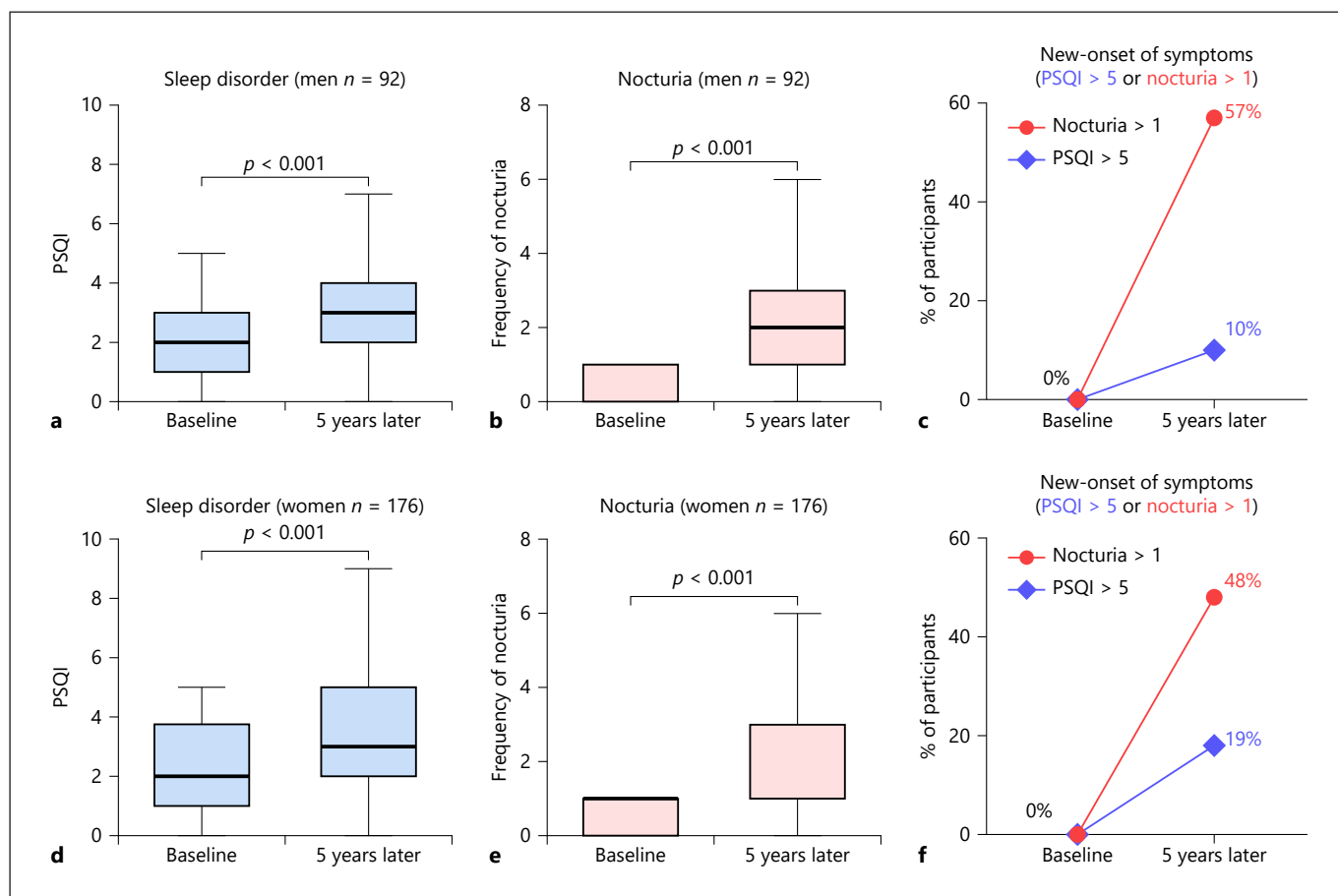


Fig. 2. Association between sleep disorder and nocturia for 5-year follow-up in men or women. We compared sleep disorder (**a, d**), frequency of nocturia (**b, e**), and the rate of new onsets of sleep disorder (PSQI > 5) and nocturia > 1 (**c, f**) at baseline and at 5-year follow-up in men or women. PSQI, Pittsburgh Sleep Quality Index.

Table 2. Difference of PSQI and frequency of nocturia ($n = 268$)

	Baseline	5-Year follow-up
PSQI, median (IQR)	2 (1–3)	3 (2–5)
% of PSQI > 5	0 (0%)	42 (16%)
Nocturia, median (IQR)	1 (0–1)	2 (1–3)
% of nocturia > 1	0 (0%)	137 (51%)

PSQI, Pittsburgh Sleep Quality Index; IQR, interquartile range.

Discussion

This longitudinal study demonstrated that sleep disorder and frequency of nocturia were significantly increased over 5 years in community-dwelling adults. Median PSQI

and frequency of nocturia increased by 1 point and 1 time per night, respectively. The new onset of nocturia > 1 (51%) was higher than that of sleep disorder (PSQI > 5, 16%) over 5 years. The cross-lagged panel analysis showed that the path coefficient from PSQI to nocturia was significantly stronger (approximately 10-fold) than that from nocturia to PSQI. A similar finding was observed in participants who had PSQI > 5 or nocturia > 1 at baseline. These observations suggested sleep disorder may have a meaningful effect on nocturia worsening in community-dwelling adults. However, the longitudinal effect of baseline sleep quality on nocturia was not significant in the subanalysis of women. As the pathogenesis of nocturia in aging individuals is different between both sexes, further large studies are necessary to address this issue.

Sleep disorder is an important consideration in the management of nocturia in the older population [13, 17,

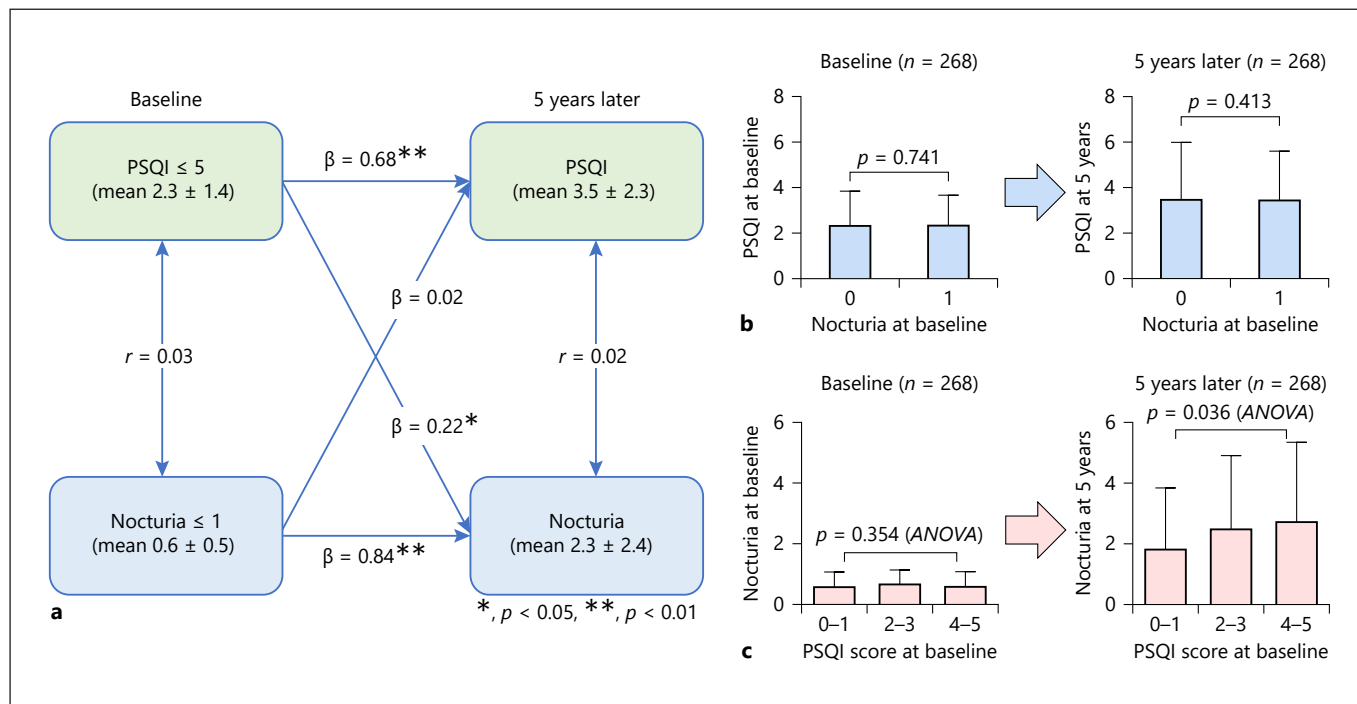


Fig. 3. Cross-lagged panel analysis for the causal relationship between sleep disorder and frequency of nocturia. The bidirectional association between nocturia and sleep disorder was assessed using a cross-lagged panel analysis to evaluate the effect of baseline PSQI on nocturia at 5-year follow-up (a), the effect of baseline nocturia on PSQI at 5-year follow-up (b), and the effect of baseline PSQI on frequency of nocturia at 5-year follow-up (c). PSQI, Pittsburgh Sleep Quality Index.

Table 3. Multivariable logistic regression analysis for the longitudinal effect of baseline PSQI on nocturia for 5 years in men (n = 92) and women (n = 176)

Men	Risk factors	p value	OR	95% CI
Age	50–82 years	0.975	1.00	0.94–1.07
Diabetes	Positive	0.212	2.28	0.63–8.31
CVD	Positive	0.940	0.95	0.26–3.52
Baseline PSQI	0–5 points	0.011	1.58	1.11–2.25
Baseline nocturia	0–1 times	0.157	2.02	0.76–5.38
Women	Risk factors	p value	OR	95% CI
Age	50–81 years	0.150	1.03	0.99–1.08
Diabetes	Positive	0.146	2.50	0.73–8.59
CVD	Positive	0.666	0.71	0.15–3.30
Baseline PSQI	0–5 points	0.676	1.05	0.84–1.30
Baseline nocturia	0–1 times	0.088	1.74	0.92–3.30

PSQI, Pittsburgh Sleep Quality Index; CVD, cardiovascular disease.

26]. Several cross-sectional studies also suggested the positive association between sleep disorder and frequency of nocturia [27, 28]. However, only a few longitudinal studies have evaluated the influence of sleep problems on nocturia [21, 25, 29]. Branche et al. [29] reported a longitudinal study including 2,258 men (median age 62, IQR 58–67 years) who were evaluated by the 6 items of the Medical Outcomes Study Sleep Scale (MOS-Sleep) and IPSS for 4 years as a part of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) study. They found that worse sleep scores among men with LUTS were significantly associated with the progression of LUTS (hazard ratio: 1.06, 95% confidential interval: 1.01–1.12, p = 0.029) and worse sleep scores among asymptomatic men were suggestively associated with the progression of LUTS (hazard ratio: 1.41, 95% confidential interval: 0.92–2.17, p = 0.12). Their observation supports our findings that sleep problems may be a key factor for preceding LUTS including nocturia. Fukunaga et al. [21] reported a longitudinal study including 5,297 men (median age 62, IQR 50–74 years) who were evaluated by IPSS and sleep disorder. Their study suggested that sleep disturbance was significantly associ-

ated with worsening LUTS [21]. However, these studies report an association between sleep disorder and frequency of nocturia but not bidirectional relationships between sleep disorder and frequency of nocturia. Therefore, our study demonstrated the bidirectional association between them using a cross-lagged panel analysis.

It remains unclear whether nocturia is a main cause of awakening (related to urinary urgency) or a result of awakening because of sleep disorder (unrelated to urinary urgency). The population-based FINNO study [19] suggested that more than 50% of nocturia could be attributed to a specific sleep disorder. This observation suggests that urinary urgency and sleep problem need to be analyzed separately to understand the cause and effect. Although we could not address this point, a sleep disorder might be one of the key factors to improve nocturia. Therefore, further studies are necessary to determine whether intervention of sleep problems can improve the frequency of nocturia.

Although several studies reported the association between sleep problem and nocturia, clinical implication needs careful interpretation because of the background difference in the target population in each study. A community-based study or clinical trial tends to include patients from 40 to 70 years of age [20, 25, 29, 30], while a clinical practice-based study is likely to include patients from 60 to 80 years of age [20, 31]. For example, a previous study suggested that mean frequency of nocturia and age in the patients who visited the urology department due to LUTS were 2.61 and 70.9 years, respectively [31], while those in this study were 0.62 ± 0.49 and 61.4 years, respectively. Therefore, our results do not correspond with outcomes in patients who need treatment for LUTS. To address the potential effect of sleep disorder on nocturia in symptomatic participants in this cohort, we additionally evaluated natural history of participants who had baseline nocturia >1 ($n = 78$, median age 68 years) or PSQI > 5 ($n = 76$, median age 56 years) regardless of age. Our additional analyses showed a similar association between nocturia and sleep disorder and that the percentage of participants with PSQI > 5 was significantly increased from baseline to 5-year follow-up in participants with nocturia >1 (see online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000509976: 14% vs. 29%, respectively, $p < 0.001$). Similarly, the percentage of participants with nocturia >1 was significantly increased from baseline to 5-year follow-up in participants with baseline PSQI > 5 (online suppl. Fig. 1b: 14 vs. 51%, respectively, $p < 0.001$). The increase in the rate of nocturia >1 (37%) in participants with baseline PSQI > 5

was significantly higher than that of PSQI > 5 (15%) in participants with baseline nocturia >1 (online suppl. Fig. 1c: $p < 0.001$). However, our results could not directly translate to patients with LUTS in a clinic because of background differences. Therefore, the effect of sleep disorder on nocturia in patients undergoing treatment needs further study.

Limitations include the small sample size, selection bias of age and sex, limited number of evaluations, reliance on self-reported measures, and other unmeasurable confounding factors that cannot be controlled because the Iwaki Health Promotion Project was not designed to analyze the relationship between sleep disturbance and nocturia. The small number of symptomatic participants in this study may be not suitable to analyze statistical difference. Also, we could not address the effect of obstructive sleep apnea symptoms on nocturia [32] and nocturnal polyuria [33, 34] because of the lack of information. Finally, our results may not be generalizable to other populations. Despite these limitations, our study first evaluated the natural history of sleep disorder and nocturia and emphasizes the importance of recognizing the influence of sleep problems on nocturia in community-dwelling adults.

Conclusion

This longitudinal study demonstrated that sleep disorder and frequency of nocturia significantly increased over 5 years in community-dwelling adults. The effect of sleep disorder on the frequency of nocturia may be significant, although nocturia may not significantly worsen sleep disorder.

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Statement of Ethics

The study was conducted in accordance with the ethical standards of the Declaration of Helsinki. This study was approved by the Ethics Committee of Hirosaki University School of Medicine (authorization numbers, 2014-015 and 2019-099).

All subjects provided written informed consent before participating in the study.

Conflict of Interest Statement

All authors have declared no conflicts of interests.

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Author Contributions

Sakae Konishi: data collection, project management; Shingo Hatakeyama: project development, data collection, manuscript writing, and project management; Atsushi Imai: project development, data collection, manuscript writing, and project management; Mika Kumagai: project development and data collection; Teppei Okamoto: data collection; Kazutaka Okita: data collection; Itsuto Hamano: data collection; Takuma Narita: data collection; Yuta, Kojima: data collection; Hiromichi Iwamura: data collection; Hayato Yamamoto: data collection; Tohru Yoneyama: data collection; Takahiro Yoneyama: data collection; Yasuhiro Hashimoto: data collection; and Chikara Ohyama: project management.

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