

Prostatic Diseases and Male Voiding Dysfunction

Shift Workers With Shift Work Disorder Have Worse Lower Urinary Tract Symptoms



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OBJECTIVE	To examine the association between shift work or shift work disorder (SWD) and lower urinary tract symptoms (LUTS). Nonstandard shift workers are defined as those working shifts outside of a normal 7 AM-6 PM work day.
METHODS	Men presenting to a single andrology clinic between July 2014 and June 2017 completed questionnaires that included questions about work schedules, shift work status, SWD[1][1], personal well-being via the Patient Health Questionnaire-9, and LUTS (International Prostate Symptom Score [IPSS]). Men who had previously undergone prostate surgery were excluded. Shift work and SWD on IPSS was assessed via multivariate linear regression.
RESULTS	Of the 2571 men who completed all questionnaires, 619 (24.1%) reported working nonstandard shifts in the past month. Of these, 196 (31.7%) had high risk of SWD as determined by a questionnaire. When controlling for age, medications, surgical intervention for benign prostatic hyperplasia, comorbidities, and testosterone (T) levels, nonstandard shift work overall was not associated with worse LUTS ($P = .82$). However, nonstandard shift workers at high risk for SWD had IPSS scores that were clinically significantly higher (3.74 points \pm 0.57 standard error) than nonstandard shift workers without SWD ($P < .0001$).
CONCLUSION	Nonstandard shift workers at high risk for SWD have worse LUTS than those without SWD. However, no association between nonstandard shift work and LUTS was found. UROLOGY 128: 66–70, 2019. © 2019 Elsevier Inc.

Lower urinary tract symptoms (LUTS) include incomplete emptying of the bladder, nocturia, weakness of urinary stream, and urinary urgency and frequency, and are present in up to 97% of men above age 65.¹ LUTS in men are often due to benign prostatic hyperplasia (BPH) with certain risk factors including socioeconomic status, obesity, smoking, and other comorbid conditions associated with more severe symptoms.²

One potential risk factor or exacerbating factor for LUTS is poor sleep. More severe LUTS, in particular nocturia, disrupt sleep and lead to worse sleep³ and quality of life (QoL).⁴ Treatment of LUTS results in better sleep⁵; however, the relationship between LUTS and sleep quality has been incompletely elucidated. Araujo et al tested the theory of a bidirectional relationship between poor sleep quality and LUTS and found that both poor sleep quality and sleep restriction have a positive association with LUTS on 5-year follow-up.⁶

Sleep quality and circadian rhythms can be impacted by abnormal sleep schedules. Shift workers comprise more than 15% of the current US workforce and are at increased risk for disruption of sleep quality via shift work disorder (SWD). SWD is a circadian rhythm disorder, present in 10% of shift workers, defined by the Diagnostic and Statistical Manual (DSM-5) and the International Classification of Sleep Disorders third edition as insomnia or excessive sleepiness, accompanied by a reduction of total sleep time due to work schedule, with symptoms present and associated with shift work for at least 3

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months that cause significant distress or impairment in mental, physical, social, or other areas of functioning, and must exclude another current sleep disorder.⁷⁻⁹ Physiologically, shift workers with SWD have shorter sleep duration, shorter sleep latency during night time hours, hyper-reactivity to novel stimuli, and reduced brain response to auditory stimuli compared to shift workers without SWD.¹⁰

Scovell et al recently examined 228 nonstandard shift workers and observed that those who reported difficulties falling asleep also reported more severe LUTS than those with no difficulties falling asleep, suggesting that men with SWD have an increased risk for worse LUTS.¹¹ Here we examine a large cohort of nonstandard shift workers and try to determine if an association between LUTS severity in men at high and low risk for SWD exists.

METHODS

Participants

Men presenting to a single academic men's health clinic between July 2014 and June 2017 completed an IRB-approved, in-office, internet-based survey. Participants were considered nonstandard shift workers if work began before 7 AM or after 2 PM, if they worked regularly outside the 7 AM-6 PM workday, or if they regularly rotated between standard and nonstandard shifts. Nonstandard shift work status was verified by cross-referencing reported average starting and ending shift times and whether men had consistent or rotating shifts. Testosterone (T) levels were assessed. Medical history, surgical history, and current medications were obtained via patient history, survey questions, and electronic medical records. Survey respondents were not selected based on presenting symptoms, age, or race. Men who had previously undergone prostate surgery were excluded.

Surveys

Survey data were collected electronically (www.surveymonkey.com) with only data from completed questionnaires included. The survey included questions about work schedules, a validated questionnaire to screen for SWD that divided men working nonstandard shifts into high and low risk for SWD,¹² the validated International Prostate Symptom Score (IPSS) questionnaire to assess the presence and severity of LUTS, and the patient health questionnaire-9 (PHQ-9) to assess for depressive symptoms. If entries were submitted by the same participant at multiple visits, the first entry was included and others were excluded. Additional variables including testosterone use in the last 2 weeks, BPH medication use, sleep medication use, comorbidities (via the Charlson Comorbidity Index (CCI)), and age were also collected in the survey.

Hormone Analysis

All testosterone samples were analyzed in the Laboratory for Male Reproductive Research and Testing at Baylor College of Medicine on a single Beckman Coulter Access2 assay system (Beckman Coulter, Brea, CA) using enzyme-linked immunoassay.

Statistical Analysis

Multiple linear regression was performed to assess the association of shift work and SWD on LUTS as assessed by IPSS. IPSS was also analyzed via subscores for voiding and storage dysfunction. SWD is a multifaceted diagnosis with 3 main elements: (1) circadian rhythm disruption, (2) sleep disturbance, and (3) associated distress. To determine which of these factors most prominently impacts LUTS, we analyzed additional survey questions about shift schedule, sleep quality, and personal well-being (Tables 2-4). Additional variables including testosterone (T) level, testosterone use in the last 2 weeks, BPH medications use, sleep medications use, comorbidities (via the CCI), and age were controlled for using linear regression. STATA version 14.2IC for Mac (STATA Corp, College Station, TX) was used for all statistical analyses, with $P < .05$ considered statistically significant.

Table 1. Cohort demographics

	Standard Daytime Workers n = 1952	Shift Workers, No Shift Work Disorder n = 423	Shift Workers + Shift Work Disorder n = 196
IPSS			
Voiding subscore (median (IQR))	1 (0-5)	1 (0-3)	2 (0-7)
Storage subscore (median (IQR))	3 (1-5)	2 (1-5)	4 (2-7)
Total IPSS score (median (IQR))	5 (2-10)	4 (2-8)	6 (3-14)
Age (years) (median (IQR))	44.5 (36.3-57.7)	38.6 (32.8-46.9)	38.4 (32.7-45.4)
CCI			
0 n (%)	1619 (83%)	374 (88%)	185 (94%)
1 n (%)	111 (6%)	16 (4%)	5 (2.5%)
2 n (%)	165 (8%)	23 (6%)	5 (2.5%)
>2 n (%)	57 (3%)	10 (2%)	1 (1%)
T2DM (n (%))	94 (5%)	15 (4%)	2 (1%)
T use in past 2 weeks (n (%))	860 (44%)	187 (44%)	72 (37%)
BPH medication use (n (%))	443 (28%)	124 (29%)	35 (18%)
Sleep medication use (n (%))	124 (6%)	50 (12%)	15 (8%)
Serum T level (ng/dL) (median (IQR))	452 (269-891)	505 (283-1004)	403 (245-909)

T2DM, type 2 diabetes mellitus.

Table 2. Changes in IPSS score based on shift work schedule

IPSS Total	Independent Variable		
	Coeff.	Std Error	P value
Hours per day working shifts	-0.02	0.05	.65
Days per week working shifts	0.16	0.10	.12
Duration of working shifts			
<1 month	-	-	-
1-6 months	-1.24	1.55	.42
7-12 months	-0.37	1.55	.81
1-5 years	0.23	1.28	.86
>5 years	-0.13	1.21	.92
Type of shift			
Regular, during the day	-	-	-
Regular, during the evening	0.48	1.16	.68
Regular, during the nighttime	-0.47	1.23	.70
Rotating	0.22	0.49	.65

Table 3. Changes in IPSS score based on sleep quality

IPSS Total	Independent Variable		
	Coeff.	Std Error	P Value
Overall sleep quantity			
Sufficient	-	-	-
Slightly insufficient	1.17	0.56	<.001
Somewhat insufficient	1.61	0.58	.01
Very insufficient	2.70	0.80	<.001
Feeling sleepy at work			
No problem	-	-	-
Minor problem	0.71	0.59	.22
Considerable problem	1.55	0.72	.03
Serious problem	1.97	1.14	.08
Falling asleep			
No problem	-	-	-
Minor problem	2.05	0.48	<.001
Considerable problem	0.76	0.73	.30
Serious problem	3.23	1.14	.01
Staying asleep			
No problem	-	-	-
Minor problem	1.70	0.47	<.001
Considerable problem	1.87	0.71	.01
Serious problem	3.84	1.08	<.001
Waking too early and being unable to fall back asleep			
No problem	-	-	-
Minor problem	1.62	0.49	<.001
Considerable problem	2.11	0.71	<.001
Serious problem	3.08	1.12	<.001
Quality of sleep			
Satisfactory	-	-	-
Slightly unsatisfactory	2.20	0.50	<.001
Somewhat unsatisfactory	2.23	0.62	<.001
Very unsatisfactory	2.72	0.89	<.001
Sleep typically obtained during the			
Night-time	-	-	-
Day-time	-1.48	1.18	.21
Mix of day-time and night-time	0.99	0.54	.07

P<0.05 is bolded

RESULTS

Of the 2571 men who completed the questionnaires, 619 (24.1%) reported working nonstandard shifts in the past month.

Of these, 196 (31.7%) had a high risk of SWD (Table 1). The uncontrolled population of nonstandard shift workers with high risk of SWD was observed to have worse LUTS compared to nonstandard shift workers at low risk for SWD, despite being a population that is slightly younger and with fewer comorbidities.

When variables were controlled, nonstandard shift work was not associated with worse LUTS as nonstandard shift work only increased IPSS by 0.04 ± 0.26 standard error ($P = .82$). However, nonstandard shift workers at high risk for SWD had IPSS scores that were statistically and clinically significant as IPSS scores were 3.74 points ± 0.57 standard error higher than nonstandard shift workers without SWD ($P < .0001$). The IPSS consists of 7 questions that can be grouped into subscores for voiding symptoms and storage symptoms. When sub scores were grouped in this fashion, SWD was significantly associated with worse LUTS in both voiding (increase of 2.21 ± 0.31 points) and storage (increase of 1.48 ± 0.24 points) sub scores of IPSS ($P < .0001$ for both sub scores).

In the linear regression model, age, as expected, was a significant independent predictor of LUTS severity ($P < .00001$) with each year increase in age correlating with a 0.11 to 0.12-point increase in IPSS score for the SWD and shift work regression model, respectively.

When a model controlling for age, CCI, T use in the last 2 weeks, and T level was used, our analysis found that duration of shift per day, days of shift work per week, duration of working shifts, type of shifts, and time when sleep was obtained did not impact LUTS ($P > .05$).

When assessing sleep factors, significantly worse LUTS were correlated with worse sleep quality and increased difficulty staying asleep ($P < .05$). Increased difficulty falling asleep and waking up too early and being unable to fall back asleep were associated with clinically worse LUTS ($P < .05$). When describing overall quality of sleep, any quality of sleep less than "Satisfactory" was significantly associated with worse LUTS ($P < .0001$). Finally, men who described a moderate or highly likely chance of dozing off while driving were also at increased risk of worse LUTS ($P < .02$). Based on these results, sleep quality as perceived by the respondent appears to play a large role in the relationship between SWD and LUTS.

Finally, we assessed factors that may be associated with individual distress. Impaired physical and mental function was associated with clinically and statistically worse LUTS ($P < .04$). When assessing for depressive symptoms, increase in PHQ-9 and PHQ-2 scores were associated with worse LUTS ($P < .0001$). When PHQ-9 is categorically described based on score cut-offs for severity of depression, men with clinical depression had significantly and clinically worse LUTS ($P < .01$). These results suggest that associated personal distress, 1 factor of SWD, is significantly associated with worse LUTS.

DISCUSSION

The results of this study add to the emerging literature on the bidirectional relationship between sleep disturbance and LUTS. While the link between nocturia and sleep disturbances that impact both sleep quality and overall QoL is well defined,^{3,5,13-15} how sleep disturbances affect urinary function more globally is incompletely understood. Recent investigation has focused on how sleep apnea and disordered breathing during sleep impact LUTS. Parthasarathy et al found that after adjusting for

Table 4. Changes in IPSS score based on personal wellbeing

IPSS Total	Independent Variable		
	Coeff.	Std Error	P Value
Physical and mental functioning			
Normal	-	-	-
Slightly decreased	1.37	0.54	.01
Somewhat decreased	1.70	0.82	.04
Very decreased	3.56	1.36	.01
Sense of wellbeing			
Normal	-	-	-
Slightly decreased	0.96	0.61	.12
Somewhat decreased	2.33	0.99	.02
Very decreased	0.82	1.64	.62
PHQ2	0.72	0.18	<.001
PHQ9 (continuous)	0.32	0.05	<.001
PHQ9 (categorical)			
PHQ9: no symptoms (0-4)	-	-	-
PHQ9: minimal symptoms (5-9)	2.42	0.52	<.001
PHQ9: MDD, mild (10-14)	2.94	0.78	<.001
PHQ9: MDD, moderate (15-19)	3.84	1.19	<.001
PHQ9: MDD, severe (>20)	3.90	1.55	.01

P<0.05 is bolded

age, body mass index (BMI), diuretic use, diabetes mellitus, and alpha-blocker use, nocturia was independently associated with sleep disordered breathing (measured as Apnea Hypopnea index >15 per hour; odds ratio 1.3; 95% confidence interval, 1.2-1.5).¹⁶ Nocturia was also associated with adverse objective alterations of sleep and self-reported excessive daytime sleepiness (*P* <.05).¹⁶ A different study has observed that 70.6% of patients complaining of nocturia had sleep disordered breathing, which improved when continuous positive airway pressure was used in subjects resistant to conventional therapy.¹⁷ Rai et al examined 618 male veterans and found that nocturia and other voiding symptoms such as frequency were predictors of a positive Berlin score, which is used to screen for sleep apnea.¹⁸ Park et al found that nocturia episodes significantly decreased from 1.7 ± 1.1 to 0.8 ± 1.2 (*P* = .002) per night in 66 men treated surgically for sleep apnea. Additionally, 3 separate scores including the IPSS score, overactive bladder symptom score, and QoL score showed significant improvement in symptoms after surgical intervention on 3 month follow-up.¹⁹

While these results are encouraging in patients with sleep disturbance due to sleep apnea or disordered breathing during sleep, there are other sleep disorders, including circadian rhythm disorders, that may also negatively impact LUTS. In this study, men at high risk for SWD demonstrated IPSS scores 3.74 points higher than men at low risk for SWD. Based on the results showing the impact of age on LUTS in this cohort, the presence of SWD adds ~30 years of age impact on IPSS score. A 3.1 point difference in IPSS is considered clinically significant and perceptible.²⁰ Previous studies show persons with SWD sleep 5.5 hours per night on average versus 6.4 hours per night for nonstandard shift workers without SWD.⁸

Besides SWD, shift workers are at increased risk for metabolic dysfunction, increased BMI, and cognitive impairment, along with other comorbidities.^{7,21,22} These adverse associations with shift work have yet to be directly related to SWD. It is possible that the disruption of circadian rhythms that occurs with SWD and not shift work itself is responsible for these changes. This distinction may be important for determining which shift workers may be at highest risk for poor outcomes, as not every shift worker has SWD.

The mechanism by which SWD negatively impacts LUTS appears to be more related to impaired sleep and personal distress rather than pure shift work. Sleep quality and shift work have been tightly linked to metabolic syndrome²¹ which has been associated with prostatic inflammation and higher IPSS scores.²³ While the relationship between LUTS and metabolic syndrome was not evaluated in the present study, an increase in LUTS severity due to inflammation secondary to metabolic syndrome seems unlikely, given the significant symptoms in men at high risk for SWD when comorbidities were relatively few, controlled for, and not shown to be an independent risk factor for worse LUTS.

In a feed-forward manner, SWD may also result in more bothersome LUTS, which may result in increased sleep disturbances. Vaughan et al examined 55 men, finding that men with more difficulty falling asleep reported higher bother than men with a similar number of episodes of nocturia, suggesting that sleep issues directly impact LUTS.²⁴ The psychological impact of poor sleep quality resulting from abnormal circadian rhythms may also contribute to LUTS severity. Nurses working night-shifts report lower job satisfaction and more physical and psychiatric symptoms compared to daytime-shift nurses.²⁵ Additionally, Scovell et al reported on the psychological effect of nonstandard shift work as nonstandard male shift workers with a decreased sense of well-being reported or reduced cognitive function reported more severe LUTS when compared to men who did not report these concerns.¹¹ Physiologic stress may also impact LUTS severity. Ullrich et al followed 83 men with BPH and found that under stressful conditions, greater increase in cortisol level compared to baseline was associated with greater bother (*P* <.05) and BPH Impact Index (*P* <.001) scores.²⁶ Yet, there remains a dearth of research that demonstrates a direct mechanistic connection between low quality sleep and LUTS. At present, the understanding is limited and may involve multifactorial linkages between both physiological and psychological factors.

This study has several important limitations. It is retrospective and relies on subjective symptoms scores. Additionally, BMI data were not collected, and T levels were not strictly determined using morning blood draws nor adjusted for shift schedules. However, as we and a recent meta-analysis demonstrate that exogenous testosterone administration does not worsen LUTS, we believe that the timing of blood draws for testosterone level determination will not significantly impact our results.²⁷ Men

who participated in this study were unselected and questionnaires were given to all presenting men. Additionally, sleep apnea was not assessed.

The strengths of the study include a large sample size and the ability to control for age, comorbidity, BPH medication use, BPH surgery, and hormone levels. The availability of control groups that include both standard daytime shift workers and nonstandard shift workers with low risk for SWD further allows us to support our conclusions.

Further work is needed to assess whether interventions designed to treat SWD have significant impact on LUTS. A 2010 study by Soda et al²⁸ found that lifestyle modifications including (1) restriction of fluid intake, (2) refraining from excessive time in bed, (3) moderate daily exercise, and (4) keeping warm in bed could significantly decrease nocturnal voids and urine volume.²⁸ Initial work in this area identified a variant in the melatonin receptor (MTNR1A) in a Finnish population of shift workers that may be associated with job-related exhaustion and may reduce melatonin signaling in the brain.²⁹ LUTS that are exacerbated by or due to SWD may also be ameliorated with schedule changes, lifestyle/sleep hygiene measures, and pharmacologic interventions such as melatonin. Lastly, an improved understanding of risk factors for SWD among nonstandard shift workers is highly desirable.^{7,8}

CONCLUSION

Male nonstandard shift workers at high risk for SWD have worse LUTS than their counterparts who are at low risk for SWD. This is true when factors such as age, CCI, and hormone levels are controlled for. However, no association between nonstandard shift work in general and LUTS was found. These results suggest that poor sleep, resulting in a diagnosable circadian rhythm disorder, rather than shift work itself, contributes to worse LUTS.

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