Received: 13 October 2023 | Accepted: 8 December 2023

DOI: 10.1002/pros.24656

REVIEW ARTICLE

The Prostate WILEY

Link between circadian rhythm and benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS)

Dana Cavanaugh BSN, RN[1,2] | Alfonso Urbanucci PhD[3,4] | Nihal E. Mohamed PhD[1,2] | Ashutosh K. Tewari MBBS[1,2] | Mariana Figueiro PhD[2,5] | Natasha Kyprianou MBBS, PhD[1,2,6]

[1]Department of Urology, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[2]Tisch Cancer Institute at Mount Sinai, New York, New York, USA

[3]Prostate Cancer Research Center, Faculty of Medicine and Health Technology and FiCanMid, Tampere University, Tampere, Finland

[4]Department of Tumor Biology, Institute for Cancer Research, Oslo University Hospital, Oslo, Norway

[5]Department of Population Health Science and Policy, Light and Health Research Center, Mount Sinai Health, New York, New York, USA

[6]Department of Oncological Sciences, Icahn School of Medicine at Mount Sinai, New York, New York, USA

Correspondence

Natasha Kyprianou, MBBS, PhD and Mariana Figueiro, PhD, Tisch Cancer Institute at Mount Sinai, 1425 Madison Ave, New York, NY 10029, USA.
Email: Natasha.kyprianou@mountsinai.org and Mariana.Figueiro@mountsinai.org

Funding information

Tampere Institute for Advanced Study, Grant/Award Number: NIH/NIOSH R01OH01668; Pfizer, Grant/Award Number: (#76180091); The National Institute of Nursing Research, Grant/Award Number: 1R21 NR016518-01A1; Finnish Cancer Foundation; Norwegian Cancer Society, Grant/Award Number: (#198016-2018); Academy of Finland, Grant/Award Numbers: (#349314), NCI/NIH R01 CA232574-01A1

Abstract

Background: Benign prostatic hyperplasia (BPH) is the most common urologic disease in aging males, affecting 50% of men over 50 and up to 80% of men over 80 years old. Its negative impact on health-related quality of life implores further investigation into its risk factors and strategies for effective management. Although the exact molecular mechanisms underlying pathophysiological onset of BPH are poorly defined, the current hypothesized contributors to BPH and lower urinary tract symptoms (LUTS) include aging, inflammation, metabolic syndrome, and hormonal changes. These processes are indirectly influenced by circadian rhythm disruption. In this article, we review the recent evidence on the potential association of light changes/circadian rhythm disruption and the onset of BPH and impact on treatment.

Methods: A narrative literature review was conducted using PubMed and Google Scholar to identify supporting evidence. The articles referenced ranged from 1975 to 2023.

Results: A clear relationship between BPH/LUTS and circadian rhythm disruption is yet to be established. However, common mediators influence both diseases, including proinflammatory states, metabolic syndrome, and hormonal regulation that can be asserted to circadian disruption. Some studies have identified a possible relationship between general LUTS and sleep disturbance, but little research has been done on the medical management of these diseases and how circadian rhythm disruption further affects treatment outcomes.

Conclusions: There is evidence to implicate a relationship between BPH/LUTS and circadian rhythm disruptions. However, there is scarce literature on potential specific link in medical management of the disease and treatment outcomes with circadian rhythm disruption. Further study is warranted to provide BPH patients with insights into circadian rhythm directed appropriate interventions.

KEYWORDS

benign prostate growth, benign prostatic hyperplasia, circadian rhythm disruption, light, lower urinary tract symptoms, racial disparities, risk factors, therapeutic management

1 | INTRODUCTION

1.1 | Background

Benign prostatic hyperplasia (BPH) is a condition that affects the aging male population, with onset of symptoms occurring around age 50. This urologic disease affects over 200 million men worldwide, and in the United States, accounts for about 23 million clinic visits and 1.2 million emergency department (ED) visits.[1] By the age 80, over 80% of men are diagnosed with BPH,[2] deeming it the most common urologic disease in men.[3] BPH is characterized as an enlargement of the prostate gland due to the proliferation of prostatic stromal and epithelial cells in the transitional zone.[4] The enlargement of the gland restricts urine flow through the prostatic urethra, causing lower urinary tract symptoms (LUTS).[4] These symptoms include frequent urination, incomplete bladder emptying, increased urgency, difficulty starting a stream, and nocturia. Of those individuals reporting symptoms of LUTS, 30%–48% experience moderate-to-severe symptoms.[5] Although not life-threatening, these symptoms can significantly impair individuals' health-related quality of life (HRQoL) and may lead to complications such as urinary tract infections, urinary retention, and bladder stones.[6]

The current treatment options for BPH range from pharmacological intervention to surgery, depending on the size of the prostate, patient's age and overall health, and severity of symptoms. Patients are commonly prescribed α-1 adrenoceptor antagonists (including tamsulosin, alfuzosin, doxazosin, terazosin), that function to relax the smooth muscle of the bladder neck and prostate.[4] Smooth muscle relaxation reduces prostatic tone, thereby decreasing urinary obstruction and allowing for urine flow.[7] Within 1–2 weeks of starting treatment with α-1 adrenergic antagonists, obstructive and irritative LUTS from BPH have been demonstrated to improve.[7] α-1 adrenergic antagonists not only work on the prostatic and bladder smooth muscle, but also cause vasodilation of the systemic vasculature, resulting in a lowering of blood pressure.[8] Because of this vasodilation, α-1 antagonists can have adverse effects of syncope, dizziness, and headache. To avoid complications from these adverse effects, such as falls, it is recommended that patients should take α-1 antagonists at night to prevent orthostatic hypotension.[8,9] BPH is also medically managed using 5-α reductase inhibitors, such as finasteride. Normal and abnormal prostate growth is stimulated by dihydrotestosterone (DHT), a potent androgen formed from testosterone by the enzyme 5-α reductase[10,11] consequential to binding/activating the androgen receptor (AR) signaling. 5-α reductase inhibitors target the conversation of testosterone to DHT, significantly lowering both circulating and intraprostatic levels of the active androgen, thus reducing the size of the prostate gland.[12]

The pathogenesis of BPH is driven by deregulation of tissue homeostasis mediated by chronic inflammation, aging, hormonal changes, and metabolic syndrome, defined as a group of risk factors specific for cardiovascular disease.[13–16] There is growing evidence that expansion of inflammatory states, regulation of hormones, such as antidiuretic hormone (ADH) and testosterone, and disease progression can be regulated by the circadian clock.[17,18]

Circadian rhythms are oscillations of biological processes that repeat themselves at about every 24 h.[19] These rhythms are regulated by an internal "biological clock" that is located in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus.[20] The master biological clock generates and regulates biological and behavioral processes such as sleep/wake cycle, core body temperature, metabolism, and hormonal regulation.[21] Peripheral systems, organs, and cells also exhibit circadian rhythms driven by peripheral oscillators, which are controlled by the master biological clock.[22] The circadian cellular protein machinery is under the control of an intense chain of transcriptional and translational feedback loops which rely on divergent interactions of key transcription factors during the "day phase" versus, others in the "night phase."[23] This circadian clock transcriptional-translational feedback loop dictates the 24 h cycle. During the day phase, transcription factors CLOCK and BMAL1 heterodimerize to induce the transcription of target genes *Period* and *Cryptochrome*, which are translated into proteins PER and CRY. PER and CRY form complexes that accumulate in the nucleus into the late evening. During the night phase, PER and CRY proteins dimerize and act as negative regulators by repressing CLOCK/BMAL1 transcription of *Period* and *Cryptochrome*, creating a negative feedback loop. Once the PER:CRY complexes' are degraded due to relatively short half-lives, the CLOCK:BMAL1 complex is no longer inhibited, marking the start of the next cycle the following morning.[24] The master clock in the SCN therefore works in concert to synchronize these peripheral oscillators on a cellular level.[22] Such internal synchronization is critically important in regulating cell cycle, DNA repair, apoptosis, and immune modulation at the cellular level.[25] The master biological clock is influenced by environmental factors, most notably the exposure to light–dark patterns reaching the back of the eye.[26] There is a direct neural track from the retina to the SCN that transmits environmental light signals to the master biological clock.[27] Entrainment is the term used to describe when environmental cues and human physiological processes are in sync. Individuals experiencing chronic fluctuations in their light–dark exposures, such as shift workers, those experiencing chronic jet lag, and those with noise/light pollution, can be at risk for desynchronization of oscillations and cellular processes.[28] Evidence demonstrates that circadian rhythm disruption can cause a vast range of complications, such as metabolic disorders, cancer, and cardiovascular disease.[29–31]

1.2 | Rationale and knowledge gap

The literature is scarce when it comes to reporting the relationship between circadian rhythm disruption and the pathogenesis of BPH/LUTS. Given that some primary treatments of BPH, such as α-1 antagonists, have a time component to their administration, it is important to assess how circadian disruption affects the management of these diseases.

1.3 | Objective

In this review, we focus on the relationship between circadian rhythm disruption and the progression and management of BPH/LUTS. We present this article in accordance with the narrative review reporting checklist.

2 | METHODS

The literature was reviewed using PubMed and Google Scholar. Articles were identified from 1975 to 2023. Key phrases searched were descriptive of BPH mediators, circadian rhythm mediators, BPH/LUTS and circadian rhythm relationship/association, BPH management, and effects of circadian rhythm disruption on medical management. Journal articles as well as web-based guidelines were included.

3 | DISCUSSION

3.1 | Circadian rhythm disruption in human disease: Epidemiological insights

BPH and circadian rhythm disruption are independently prevalent conditions that have significant healthcare burdens and impairments to HRQoL. HRQoL is a multidimensional construct that describes individuals perceived physical, mental, and social health. A causative relationship between BPH and circadian rhythm disruption has not yet formatively been explored. Doing so can provide insight into how to provide high quality care for these patients and best practices for medical management.

Various factors can disrupt circadian rhythms, including shift work, chronic jet lag, exposure to electric light at night, and environmental noise pollution.[32–35] It is estimated that about 25% of the US populations are rotating shift workers, which amounts to between 26 and 38 million US adults.[36] A 2021 meta-analysis of the prevalence of shift work disorder (SWD) conducted by Pallesen et al. found that among shift workers, 26.5% suffered from SWD.[37] SWD is defined by the American Sleep Disorders Association as insomnia/excessive sleepiness resulting in reduction in sleep time caused by the misalignment between the timing of the master biological clock and sleep time, with symptoms lasting for at least 3 months.[38] Sleep disturbances from SWD are associated with significant clinical distress and impairment of social, occupational, and overall level of functioning.[39] There is a significant body of evidence in the literature detailing the consequences of shift work on physiological and psychological disease. Shift work is associated with increased incidence of myocardial infarction and ischemic stroke,[40] metabolic syndrome,[41] cancer,[42] gastrointestinal disorders,[43] and reproductive complications, including reduced conception rates and increased miscarriage rates.[44] Additionally, shift workers are at an increased risk of mental health disorders, including depression, anxiety, suicidal ideation, and impaired cognitive function, as a result of poor sleep quality and duration.[45,46]

Studies have found that jet lag caused from international flights crossing multiple time zones, and chronic jet lag, such as those of flight crews, often manifest symptoms of disturbed sleep, dysmorphic mood, and gastrointestinal disorders.[47] Circadian rhythm disruption is also seen in those experiencing environment noise pollution and night-time light pollution. Nocturnal noise pollution, such as from transportation, can disrupt sleep quality and sleep architecture, causing a greater risk of cardiovascular and metabolic pathologies perhaps due to the release of stress hormones, particularly cortisol.[48] Noise pollution is associated with the dysregulation of the master biological clock, affecting peripheral clock mechanisms.[49] Nocturnal light may also impact sleep and lead to circadian rhythm disruption; significantly it was reported that over 80% of humans and 99% of those living in the United States and Europe are exposed to some kind of light at night.[50] Light at night can come from TVs, computer screens, smartphones, and e-readers, as well as environmental factors like living in an urban setting.[47] Exposure to light at night, depending on the amount of light and duration of exposure, can lead to circadian and sleep disruption.[47]

3.2 | Impact of circadian rhythm disruption on the prostate health

The association between circadian rhythm disruption and prostatic health has been best explored in prostate cancer. There is a wealth of evidence to suggest that circadian rhythm disruption can influence tumorigenesis[51] through the downregulation of tumor suppressive genes,[52] disruption of the immune system,[53] and decreased release of melatonin which has antitumor properties.[54] Certain circadian machinery has been demonstrated to be associated with prostate cancer treatment resistance. Prostate cancer cells treated with long-term exposure to enzalutamide, an AR-targeting monotherapy, revealed massive epigenomic reprogramming in response to treatment toward elements that induce pro-survival signaling. These elements were notably found to be enriched for the circadian clock core regulator ARNTL. Posttreatment ARNTL levels were associated with patients' clinical outcomes, and ARNTL knockout strongly decreased prostate cancer cell growth. Thus, at the molecular level, an intense reprogramming of the chromatin structure and activation of the central circadian clock regulator ARNTL transcription factor can mechanistically drive tumor plasticity in advanced therapeutically resistant prostate cancer.[55] This study also suggests that AR signaling and its therapeutic targeting can, per se, modulate the circadian rhythm of not only prostate cells, but, potentially influence all tissues under endocrine control that express the AR and maintain an intact androgen signaling dynamic. Regarding other prostatic diseases, there has been limited work so far to evaluate circadian rhythm disruption on BPH development and therapeutic response to medications (5-α reductase inhibitors and/or α-1 adrenergic antagonists).

The pathogenesis of BPH is characterized by a multilayered complexity, with diverse cellular processes (apoptosis, epithelial-to-mesenchymal transition, inflammation) contributing to its development and severity of symptoms. It has been suggested that chronic prostatic inflammation causes increased severity of BPH/LUTS.[2] Being in a proinflammatory state may cause chronic tissue damage of the prostate, and with repeated subsequent wound healing, the prostate tissue proliferates and becomes enlarged. Disruption to circadian rhythms has been found to elevate inflammatory response to lipopolysaccharides, increasing the pathogenicity of inflammatory markers[56] and thus upregulating immune response. Inflammatory cells and immune response in the gut microbiome also exhibit circadian rhythms. Circadian disturbances in rats are associated with an increased upregulation of proinflammatory cytokines *IL-1A*, *IL-17RA*, and *Stat3* expression in the colon mucosa, leading to both acute and delayed colitis-associated inflammation.[57,58] Clinical studies have shown that night-shift workers with circadian rhythm disorders have significantly elevated inflammatory markers,[59] implicating an effect of circadian rhythm disorders on BPH/LUTS through proinflammatory states (Figure 1).

A potential association between development and progression of BPH/LUTS with metabolic syndrome[60] has also been postulated. Metabolic syndrome is characterized as a risk cluster including central obesity, hypertension, hyperglycemia, and hyperlipemia.[61] The evidence suggests that metabolic syndrome increases the risk of more severe LUTS symptoms, such as nocturia, in men with BPH.[62] Circadian rhythm disruption can also impact metabolic syndrome clinical outcomes. Adipose tissue, similar to prostate tissue, has peripheral clock genes that regulate adipokines involved in glucose and lipid metabolism.[63] Studies show that simulation of jet lag increases body weight and glucose intolerance in comparison to the normal 12 h of light and dark.[63,64] One may also consider that since circadian rhythm disruption is associated with the metabolic syndrome, and metabolic syndrome is a risk factor of BPH progression, circadian rhythm disruption may be indirectly associated with the BPH symptom severity. A recent study by Xiong et al.,[65] evaluated the "Circadian Syndrome" (CircS), proposed by Zimmet et al. in 2019 as a reclustering of metabolic syndrome to underline the vital impact circadian rhythm disruption has on the components of metabolic syndrome.[66] This investigative team proposed that since circadian rhythms play such a defining role in metabolic processes, metabolic syndrome should be expanded and reclassified as CircS with the addition of sleep disturbances, depression, steatohepatitis, and cognitive dysfunction.[66] By redefining the cluster as CircS, Zimmet et al. suggest that CircS is a more comprehensive research criterion. Over 4 years, Xiong et al. compared the incidence of BPH in those experiencing CircS to metabolic syndrome. Participants were classified as having CircS if they had ≥4 components (depression, reduced sleep duration, abdominal obesity, hypertension, hyperglycemia, high triglycerides, and low HDL cholesterol), whereas they were classified as having MetS if they had ≥3 components. It was found that individuals with CircS have a

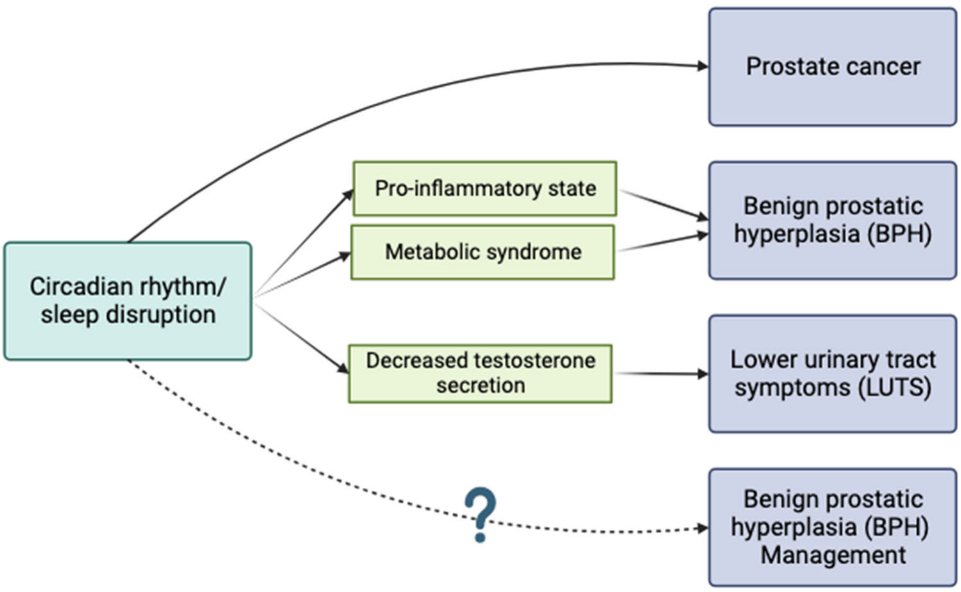

FIGURE 1 Schema summarizing the relationships between circadian rhythm/sleep disruption and prostatic diseases through shared mediators. There is an established correlation between cellular circadian rhythm disruption and prostate cancer, represented by the solid arrow. Relationships with between circadian rhythm disruption and prostatic disorders through shared mediators is represented by faded arrows. Circadian rhythm disruption leads to proinflammatory states, potentially influencing BPH. Circadian rhythm disruption is also indirectly associated (via metabolic syndrome) with BPH. Sleep disruption leads to decreased testosterone secretion, that ultimately impact LUTS. The relationship between circadian rhythm disruption and BPH treatment management strategies, including medication administration, have not yet been determined, and is represented by the dashed arrow. BPH, benign prostatic hyperplasia; LUTS, lower urinary tract symptoms. [Color figure can be viewed at wileyonlinelibrary.com]

3.62% higher risk of BPH/LUTS than those with MetS. The addition of reduced sleep duration and depression to the MetS risk cluster, which underlines circadian rhythm disruption, had a higher predictive power than MetS alone. This points to CircS, with the additional inclusion of sleep disturbances and depression, as a better predictor of BPH incidence and prevalence than MetS.

Additional studies have evaluated the association between circadian rhythm disruption and specific LUTS, such as nocturia and nocturnal polyuria (NP) mediated through circadian-driven hormonal processes. Water homeostasis and micturition follow a circadian pattern. The kidney and bladder are two genitourinary organs whose function is dictated by their own peripheral circadian clocks which can be affected by master circadian clock disruption.[67,68] Significantly, fluid intake, urine production, urine storage, and diuresis follow distinct circadian rhythms, with urination occurring less frequently at night.[69] This process follows a diurnal pattern controlled by the master circadian clock in the SCN. Based on this knowledge, it has been hypothesized that the release of ADH, which controls diuresis, follows a circadian pattern. ADH is normally released at night to decrease diuresis,[70] a process that can be impaired by circadian disruption, contributing to nocturia.[71,72] One must also consider however that LUTS, such as nocturia and NP, may occur independently of a BPH diagnosis. Circadian rhythm disruption may affect nocturia and NP without mechanisms specific to BPH.

Additional evidence suggests an relationship between LUTS/BPH and sleep disturbance, without directly implicating circadian rhythm disruption.[73–75] However, frequent night urination is significantly associated with reduced time and quality of sleep, thus, leading to chronic day-time tiredness and circadian rhythm disruption.[76] Reduced sleep quality and time can also cause hormonal abnormalities, including low testosterone, increased stress hormone levels such as cortisol, and lower thyroid levels which in turn could be associated with increased circadian rhythm disruption.[77,78] Furthermore, Araujo et al. found that poor sleep quality increased the risk of obstructive and irritative LUTS, and sleep restriction increased the risk of irritative LUTS by twofold. This study however did not evaluate specifically a diagnosis of BPH, but rather only general LUTS.[73] Another study tracked shift workers and found a correlation between impaired sleep quality and more significant LUTS.[74] These disruptions in sleep and increased incidence of LUTS could be related to androgen secretion.[75] Testosterone secretion is associated with sleep/wake cycles in a diurnal rhythm, in which serum concentration increases during sleep and decreases during wakefulness[79] (Figure 1). The regulation of testosterone therefore is critically influenced by sleep disruption: serum testosterone levels inappropriately fall during nighttime awakening.[80] It should be noted that this study found that the amount of sleep was more significant to testosterone regulation than the timing (night vs. day) of sleep, suggesting that sleep restriction decreases serum testosterone concentration.[80] Significantly enough, BPH has been shown to be modulated by decreased testosterone levels.[81,82] This indicates a potential relationship between BPH/LUTS progression and sleep disturbance mediated through decreased testosterone levels from reduced sleep.

3.3 | Racial disparities and circadian rhythm association in BPH/LUTS

In the United States, the Prostate Cancer Prevention Trial reported a 41% increased incidence risk of Black and Hispanic men having BPH/LUTS compared to that of White men.[1,83] Furthermore, the risk of progressing from mild to moderate/severe BPH were 68% higher than White men.[83] In the Flint Men's Health Study of African American men, although 37% had moderate-to-severe LUTS impairment, only 8.2% were diagnosed with BPH before the study and 3% reported being medically treated for BPH.[84] The significant difference in the proportion of Black men who had LUTS and who were diagnosed and treated with BPH suggests that many Black men are being underdiagnosed and untreated. Among White men, the decision to receive medical care for LUTS is in function of symptom severity, but this relationship in Black men has not been determined.[85] Racial disparities in BPH evaluation and management may arise from a myriad of socioeconomic determinants of health (SDOH) related factors, including socioeconomic status, access to healthcare, and bias and discrimination in healthcare settings. Barriers to quality healthcare, as a result of economic burden and difficulty paying healthcare costs, were associated with worsening LUTS.[86] In a retrospective study on men presenting to the ED with acute urinary retention, Black and Hispanic men were more likely to present at ED than any other group, implicating that these patients may be untreated/undertreated for BPH in the outpatient setting[87] and rather reach healthcare for acute episodes. In fact, when controlling for economic factors, Black men were less likely to report a previous BPH diagnosis.[88] The California Medicaid program indicated that Black men with BPH, who were receiving the same insurance benefits, were 15.4% less likely to be medically treated during their first year of diagnosis than White patients.[89] This highlights additional underpinnings beyond socioeconomic status in racial disparity in BPH diagnosis and management. Furthermore, cultural differences in BPH/LUTS symptom reporting and symptom attribution may lead to under-reporting of symptoms experienced, less help-seeking behaviors, and delayed clinical care thus contributing to existing racial disparities in BPH.[90–92]

Diverse risk factors and comorbidities contribute to the development of BPH, including metabolic syndrome and cardiovascular disease, via hormonal changes, heterogeneity of prostate cell−cell subtypes and inflammatory signaling pathways. These risk factors, potentially mediated by SDOH, disproportionately affect historically marginalized populations in the United States.[93,94]

Black men may be at higher risk for experiencing circadian rhythm disruption due to various factors such as night shift work, environmental conditions (i.e., noise pollution, light at night exposure), socioeconomic status, and chronic comorbidities (i.e., diabetes, obesity, chronic stress, cardiovascular disease). Black and Hispanic individuals are overrepresented in night shift work: compared to White individuals, as they are twice as likely to work night shifts.[95,96] Racial disparities also exist in environmental conditions due to residential segregation, in which ethnic communities were only granted loans to live in less desirable and more hazardous areas.[97] Defined as "redlined" neighborhoods, these areas are closer to industrial plants, highways, and factories, and suffer from over-crowding.[98] Such conditions significantly increase noise pollution and light at night exposure,[99] and can contribute to circadian rhythm disruption. Furthermore, comorbidities that influence circadian rhythm disruption, such as metabolic syndrome, inflammatory states, and obesity, disproportionally affect racially diverse populations.[100]

In summary, disruption of circadian rhythm is a potential risk factor of BPH incidence among Black men, but further studies are needed to dissect the relationship between racial disparities in BPH evaluation and management and the factors involved in circadian rhythm disruption.

3.4 | Circadian rhythm disruption and medical management of BPH

α-1 adrenoceptor antagonists are the first-life treatment prescribed to alleviate LUTS. Due to the side effect of orthostatic hypotension, it is recommended that patients take this medication at night. However, this brings into question what the proper medication management is for patients who are awake at night due to their work or lifestyle, and thus experiencing circadian rhythm disruption. Furthermore, circadian rhythms may play a role in the metabolic processing of medications and the consequential impact on the severity of side effects. This could lead to medical noncompliance, which regarding medications like 5-α reductase inhibitors, could accelerate BPH symptomatic progression. The impact of circadian rhythm disruption on effective administration of BPH medications represents a critically understudied area.

4 | CONCLUSIONS

In the United States alone, at least 800,000 and possibly as many as three million individuals are impacted by circadian rhythm disruption.[101] If shift work and jet lag are included in this definition, this statistic includes several millions of people,[101] affecting medical personnel, pilots, law enforcement, security, firefighters, machine operators, and those who live in noise and light polluted areas. BPH and LUTS cause significant impairment to individuals' quality of life and increases individual and societal health burdens. Understanding the correlation between those with BPH and circadian rhythm disruption can influence management strategies, such as timing of medications and light therapy. A potential functional association between the circadian rhythm disruption with clinical progression of BPH, warrants an insightful investigation of the molecular mechanisms governing development and management of BPH in the context of circadian rhythm changes impacting the prostate and bladder microenvironment dynamics.

Moving forward, retrospective investigation of the consequences of circadian rhythm disruption on the medical management of patients with BPH can be pursued by examining clinical trials. Alternatively future designing controlled prospective trials aiming at dissecting differential timing in drug administration and management of clinical outcomes in patient cohorts with different levels of disruption of their circadian rhythms.

ACKNOWLEDGMENTS

The authors wish to thank Dr. Steven Kaplan, Mount Sinai Urology for useful discussions. This work was supported by NCI/NIH R01 CA232574-01A1 (N. K.); Academy of Finland (#349314), the Norwegian Cancer Society (#198016-2018), and the Finnish Cancer Foundation and the Tampere Institute for Advanced Study (A. U.); The National Institute of Nursing Research 1R21 NR016518-01A1, and Pfizer Grant (#76180091) (NM); Grant #R01OH01668/NIH/NIOSH (MGF).

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available in PubMed at https://pubmed.ncbi.nlm.nih.gov/. These data were derived from the following resources available in the public domain:- PubMed, https://pubmed.ncbi.nlm.nih.gov/- Google Scholar, https://scholar.google.com/.

ORCID

Dana Cavanaugh http://orcid.org/0000-0002-8636-503X
Natasha Kyprianou http://orcid.org/0000-0002-9382-9664

REFERENCES

1. Ayangbesan A, Kavoussi N. Racial disparities in diagnosis and management of benign prostatic hyperplasia: a review. *Curr Urol Rep*. 2022;23(11):297-302. doi:10.1007/s11934-022-01118-5
2. De Nunzio C, Presicce F, Tubaro A. Inflammatory mediators in the development and progression of benign prostatic hyperplasia. *Nat Rev Urol*. 2016;13(10):613-626. doi:10.1038/nrurol.2016.168
3. Awedew AF, Han H, Abbasi B, et al.The global, regional, and national burden of benign prostatic hyperplasia in 204 countries and territories from 2000 to 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet Healthy Longevity*. 2022;3(11):e754-e776. doi:10.1016/S2666-7568(22)00213-6
4. Roehrborn CG. Pathology of benign prostatic hyperplasia. *Int J Impotence Res*. 2008;20(suppl 3):S11-S18. doi:10.1038/ijir.2008.55
5. Russo GI, Urzì D, Cimino S. Chapter 1—epidemiology of LUTS and BPH. In: Morgia G, Russo GI, eds. *Lower Urinary Tract Symptoms and Benign Prostatic Hyperplasia*. Academic Press; 2018:1-14.
6. McVary KT, Roehrborn CG, Avins AL, et al. Update on AUA guideline on the management of benign prostatic hyperplasia. *J Urol*. 2011;185(5):1793-1803. doi:10.1016/j.juro.2011.01.074
7. Kirby RS, Roehrborn C, Boyle P, et al. Efficacy and tolerability of doxazosin and finasteride, alone or in combination, in treatment of symptomatic benign prostatic hyperplasia: the Prospective European Doxazosin and Combination Therapy (PREDICT) trial. *Urology*. 2003;61(1):119-126. doi:10.1016/s0090-4295(02)02114-3
8. Nachawati D, Patel JB. *Alpha Blockers*. StatPearls; 2023.

9. Mansbart F, Kienberger G, Sönnichsen A, Mann E. Efficacy and safety of adrenergic alpha-1 receptor antagonists in older adults: a systematic review and meta-analysis supporting the development of recommendations to reduce potentially inappropriate prescribing. *BMC Geriatr*. 2022;22(1):771. doi:10.1186/s12877-022-03415-7
10. Salisbury BH, Tadi P. *5 Alpha Reductase Inhibitors*. StatPearls; 2023.
11. Barkin J. Benign prostatic hyperplasia and lower urinary tract symptoms: evidence and approaches for best case management. *Can J Urol*. 2011;18(suppl):14-19.
12. Kim EH, Brockman JA, Andriole GL. The use of 5-alpha reductase inhibitors in the treatment of benign prostatic hyperplasia. *Asian J Urol*. 2018;5(1):28-32. doi:10.1016/j.ajur.2017.11.005
13. Lee KL, Peehl DM. Molecular and cellular pathogenesis of benign prostatic hyperplasia. *J Urol*. 2004;172(5 Pt 1):1784-1791. doi:10.1097/01.ju.0000133655.71782.14
14. Ho CKM, Habib FK. Estrogen and androgen signaling in the pathogenesis of BPH. *Nat Rev Urol*. 2011;8(1):29-41. doi:10.1038/nrurol.2010.207
15. Fibbi B, Penna G, Morelli A, Adorini L, Maggi M. Chronic inflammation in the pathogenesis of benign prostatic hyperplasia. *Int J Androl*. 2010;33(3):475-488. doi:10.1111/j.1365-2605.2009.00972.x
16. He Q, Wang Z, Liu G, Daneshgari F, MacLennan GT, Gupta S. Metabolic syndrome, inflammation and lower urinary tract symptoms: possible translational links. *Prostate Cancer Prostatic Dis*. 2016;19(1):7-13. doi:10.1038/pcan.2015.43
17. Wittert G. The relationship between sleep disorders and testosterone. *Curr Op Endocrinol, Diabetes Obesity*. 2014;21(3):239-243. doi:10.1097/MED.0000000000000069
18. Bishehsari F, Voigt RM, Keshavarzian A. Circadian rhythms and the gut microbiota: from the metabolic syndrome to cancer. *Nat Rev Endocrinol*. 2020;16(12):731-739. doi:10.1038/s41574-020-00427-4
19. Zee PC, Attarian H, Videnovic A. Circadian rhythm abnormalities. *CONTINUUM: Lifelong Learn Neurol*. 2013;19(1 Sleep Disorders):132-147. doi:10.1212/01.CON.0000427209.21177.aa
20. Hofstra WA, de Weerd AW. How to assess circadian rhythm in humans: a review of literature. *Epilep Behavior: E&B*. 2008;13(3):438-444. doi:10.1016/j.yebeh.2008.06.002
21. Vitaterna MH, Takahashi JS, Turek FW. Overview of circadian rhythms. *Alcohol Research Health*. 2001;25(2):85-93.
22. Yamazaki S, Numano R, Abe M, et al. Resetting central and peripheral circadian oscillators in transgenic rats. *Science*. 2000;288(5466):682-685. doi:10.1126/science.288.5466.682
23. Takahashi JS, Hong HK, Ko CH, McDearmon EL. The genetics of mammalian circadian order and disorder: implications for physiology and disease. *Nat Rev Genet*. 2008;9(10):764-775. doi:10.1038/nrg2430
24. Takahashi JS. Transcriptional architecture of the mammalian circadian clock. *Nat Rev Genet*. 2017;18(3):164-179. doi:10.1038/nrg.2016.150
25. James SM, Honn KA, Gaddameedhi S, Van Dongen HPA. Shift work: disrupted circadian rhythms and sleep-implications for health and well-being. *Curr Sleep Med Rep*. 2017;3(2):104-112. doi:10.1007/s40675-017-0071-6
26. Czeisler CA. The effect of light on the human circadian pacemaker. *Ciba Found Symp*. 1995;183:254-290.; Discussion 290-302. doi:10.1002/9780470514597.ch14
27. Brown GM. Chronopharmacological actions of the pineal gland. *Drug Metabol Drug Interact*. 1990;8(3-4):189-201.
28. Chakrabarti S, Michor F. Circadian clock effects on cellular proliferation: insights from theory and experiments. *Curr Opin Cell Biol*. 2020;67:17-26. doi:10.1016/j.ceb.2020.07.003
29. Potter GDM, Skene DJ, Arendt J, Cade JE, Grant PJ, Hardie LJ. Circadian rhythm and sleep disruption: causes, metabolic consequences, and countermeasures. *Endocr Rev*. 2016;37(6):584-608. doi:10.1210/er.2016-1083
30. Savvidis C, Koutsilieris M. Circadian rhythm disruption in cancer biology. *Mol Med*. 2012;18(1):1249-1260. doi:10.2119/molmed.2012.00077
31. Thosar SS, Butler MP, Shea SA. Role of the circadian system in cardiovascular disease. *J Clin Invest*. 2018;128(6):2157-2167. doi:10.1172/JCI80590
32. Daiber A, Frenis K, Kuntic M, et al. Redox regulatory changes of circadian rhythm by the environmental risk factors traffic noise and air pollution. *Antioxid Redox Sig*. 2022;37(10-12):679-703. doi:10.1089/ars.2021.0272
33. Comperatore CA, Krueger GP. Circadian rhythm desynchronosis, jet lag, shift lag, and coping strategies. *Occup Med Apr*. 1990;5(2):323-341.
34. Gander P, Mulrine HM, van den Berg MJ, et al. Does the circadian clock drift when pilots fly multiple transpacific flights with 1- to 2-day layovers? *Chronobiol Int*. 2016;33(8):982-994. doi:10.1080/07420528.2016.1189430
35. Lunn RM, Blask DE, Coogan AN, et al. Health consequences of electric lighting practices in the modern world: a report on the National Toxicology Program's workshop on shift work at night, artificial light at night, and circadian disruption. *Sci Total Environ*. 2017;607-608:1073-1084. doi:10.1016/j.scitotenv.2017.07.056
36. Kryger MH, Roth T, Dement WC. *Principles and Practice of Sleep Medicine E-Book*. Elsevier Health Sciences; 2010.
37. Pallesen S, Bjorvatn B, Waage S, Harris A, Sagoe D. Prevalence of shift work disorder: a systematic review and meta-analysis. *Front Psychol*. 2021;12:638252. doi:10.3389/fpsyg.2021.638252
38. American Academy of Sleep Medicine. International classification of sleep disorders—third edition (ICSD-3). AASM Resour Libr2014. 2313.
39. Wright Jr. KP, Bogan RK, Wyatt JK. Shift work and the assessment and management of shift work disorder (SWD). *Sleep Med Rev*. 2013;17(1):41-54. doi:10.1016/j.smrv.2012.02.002
40. Vyas MV, Garg AX, Iansavichus AV, et al. Shift work and vascular events: systematic review and meta-analysis. *BMJ*. 2012;345:e4800. doi:10.1136/bmj.e4800
41. Wang F, Zhang L, Zhang Y, et al. Meta-analysis on night shift work and risk of metabolic syndrome. *Obesity Rev*. 2014;15(9):709-720. doi:10.1111/obr.12194
42. Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan Collaborative Cohort Study. *Am J Epidemiol*. 2006;164(6):549-555. doi:10.1093/aje/kwj232
43. Knutsson A, Bøggild H. Gastrointestinal disorders among shift workers. *Scand J Work Environ Health*. 2010;36(2):85-95.
44. Mahoney MM. Shift work, jet lag, and female reproduction. *Int J Endocrinol*. 2010;2010:1-9. doi:10.1155/2010/813764
45. Drake CL, Roehrs T, Richardson G, Walsh JK, Roth T. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. *Sleep*. 2004;27(8):1453-1462. doi:10.1093/sleep/27.8.1453
46. Brown JP, Martin D, Nagaria Z, Verceles AC, Jobe SL, Wickwire EM. Mental health consequences of shift work: an updated review. *Curr Psychiatry Rep*. 2020;22(2):7. doi:10.1007/s11920-020-1131-z
47. Walker 2nd WH, Walton JC, DeVries AC, Nelson RJ. Circadian rhythm disruption and mental health. *Transl Psychiatry*. 2020;10(1):28. doi:10.1038/s41398-020-0694-0
48. Halperin D. Environmental noise and sleep disturbances: a threat to health? *Sleep Sci*. 2014;7(4):209-212. doi:10.1016/j.slsci.2014.11.003

49. Patrick DM, Harrison DG. Nocturnal noise knocks NOS by Nox: mechanisms underlying cardiovascular dysfunction in response to noise pollution. *Eur Heart J*. 2018;39(38):3540-3542. doi:10.1093/eurheartj/ehy431
50. Falchi F, Cinzano P, Duriscoe D, et al. The new world atlas of artificial night sky brightness. *Sci Adv*. 2016;2(6):e1600377. doi:10.1126/sciadv.1600377
51. Zhu WZ, He QY, Feng DC, Wei Q, Yang L. Circadian rhythm in prostate cancer: time to take notice of the clock. *Asian J Androl*. 2023;25(2):184-191. doi:10.4103/aja202255
52. Cao Q, Gery S, Dashti A, et al. A role for the clock gene per1 in prostate cancer. *Cancer Res*. 2009;69(19):7619-7625. doi:10.1158/0008-5472.CAN-08-4199
53. Hadadi E, Acloque H. Role of circadian rhythm disorders on EMT and tumour-immune interactions in endocrine-related cancers. *Endocr Relat Cancer*. 2021;28(2):R67-R80. doi:10.1530/ERC-20-0390
54. Jung-Hynes B, Huang W, Reiter RJ, Ahmad N. Melatonin resynchronizes dysregulated circadian rhythm circuitry in human prostate cancer cells. *J Pineal Res*. 2010;49(1):no. doi:10.1111/j.1600-079X.2010.00767.x
55. Linder S, Hoogstraat M, Stelloo S, et al. Drug-induced epigenomic plasticity reprograms circadian rhythm regulation to drive prostate cancer toward androgen independence. *Cancer Discovery*. 2022;12(9):2074-2097. doi:10.1158/2159-8290.CD-21-0576
56. Adams KL, Castanon-Cervantes O, Evans JA, Davidson AJ. Environmental circadian disruption elevates the IL-6 response to lipopolysaccharide in blood. *J Biol Rhythms*. 2013;28(4):272-277. doi:10.1177/0748730413494561
57. Gombert M, Carrasco-Luna J, Pin-Arboledas G, Codoñer-Franch P. The connection of circadian rhythm to inflammatory bowel disease. *Transl Res*. 2019;206:107-118. doi:10.1016/j.trsl.2018.12.001
58. Polidarová L, Houdek P, Sumová A. Chronic disruptions of circadian sleep regulation induce specific proinflammatory responses in the rat colon. *Chronobiol Int*. 2017;34(9):1273-1287. doi:10.1080/07420528.2017.1361436
59. Puttonen S, Viitasalo K, Härmä M. Effect of shiftwork on systemic markers of inflammation. *Chronobiol Int*. 2011;28(6):528-535. doi:10.3109/07420528.2011.580869
60. Vignozzi L, Gacci M, Maggi M. Lower urinary tract symptoms, benign prostatic hyperplasia and metabolic syndrome. *Nat Rev Urol*. 2016;13(2):108-119. doi:10.1038/nrurol.2015.301
61. Alberti KG, Eckel RH, Grundy SM, et al. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. *Circulation*. 2009;120(16):1640-1645. doi:10.1161/CIRCULATIONAHA.109.192644
62. De Nunzio C, Brassetti A, Proietti F, Deroma M, Esperto F, Tubaro A. Metabolic syndrome and smoking are associated with an increased risk of nocturia in male patients with benign prostatic enlargement. *Prostate Cancer Prostatic Dis*. 2018;21(2):287-292. doi:10.1038/s41391-017-0003-z
63. Hernández-García J, Navas-Carrillo D, Orenes-Piñero E. Alterations of circadian rhythms and their impact on obesity, metabolic syndrome and cardiovascular diseases. *Crit Rev Food Sci Nutr*. 2020;60(6):1038-1047. doi:10.1080/10408398.2018.1556579
64. Figueiro MG, Radetsky L, Plitnick B, Rea MS. Glucose tolerance in mice exposed to light-dark stimulus patterns mirroring dayshift and rotating shift schedules. *Sci Rep*. 2017;7:40661. doi:10.1038/srep40661
65. Xiong Y, Zhang F, Wu C, et al. The circadian syndrome predicts lower urinary tract symptoms suggestive of benign prostatic hyperplasia better than metabolic syndrome in aging males: a 4-year follow-up study. *Front Med*. 2021;8:715830. doi:10.3389/fmed.2021.715830
66. Zimmet P, Alberti KGMM, Stern N, et al. The circadian syndrome: is the metabolic syndrome and much more. *J Intern Med*. 2019;286(2):181-191. doi:10.1111/joim.12924
67. Kim JW, Moon YT, Kim KD. Nocturia: the circadian voiding disorder. *Investig Clin Urol*. 2016;57(3):165-173. doi:10.4111/icu.2016.57.3.165
68. Firsov D, Bonny O. Circadian rhythms and the kidney. *Nature Rev Nephrol*. 2018;14(10):626-635. doi:10.1038/s41581-018-0048-9
69. Negoro H, Kanematsu A, Yoshimura K, Ogawa O. Chronobiology of micturition: putative role of the circadian clock. *J Urol*. 2013;190(3):843-849. doi:10.1016/j.juro.2013.02.024
70. Klerman EB. Clinical aspects of human circadian rhythms. *J Biol Rhythms*. 2005;20(4):375-386. doi:10.1177/0748730405278353
71. Birder LA, Van Kerrebroeck PEV. Pathophysiological mechanisms of nocturia and nocturnal polyuria: the contribution of cellular function, the urinary bladder urothelium, and circadian rhythm. *Urology*. 2019;133S:14-23. doi:10.1016/j.urology.2019.07.020
72. George CPL, Messerli FH, Genest J, et al. Diurnal variation of plasma vasopressin in man. *J Clin Endocrinol Metabolism*. 1975;41(2):332-338. doi:10.1210/jcem-41-2-332
73. Araujo AB, Yaggi HK, Yang M, McVary KT, Fang SC, Bliwise DL. Sleep related problems and urological symptoms: testing the hypothesis of bidirectionality in a longitudinal, population based study. *J Urol*. 2014;191(1):100-106. doi:10.1016/j.juro.2013.07.011
74. Scovell JM, Pastuszak AW, Slawin J, Badal J, Link RE, Lipshultz LI. Impaired sleep quality is associated with more significant lower urinary tract symptoms in male shift workers. *Urology*. 2017;99:197-202. doi:10.1016/j.urology.2016.05.076
75. Li Y, Zhou X, Qiu S, et al. Association of sleep quality with lower urinary tract symptoms/benign prostatic hyperplasia among men in China: a cross-sectional study. *Front Aging Neurosci*. 2022;14:938407. doi:10.3389/fnagi.2022.938407
76. Cakir OO, McVary KT. LUTS and sleep disorders: emerging risk factor. *Curr Urol Rep*. 2012;13(6):407-412. doi:10.1007/s11934-012-0281-x
77. Helfand BT, McVary KT, Meleth S, et al. The relationship between lower urinary tract symptom severity and sleep disturbance in the CAMUS trial. *J Urol*. 2011;185(6):2223-2228. doi:10.1016/j.juro.2011.02.012
78. Przydacz M, Skalski M, Sobanski J, et al. Association between lower urinary tract symptoms and sleep quality of patients with depression. *Medicina*. 2021;57(4):394. doi:10.3390/medicina57040394
79. Copinschi G, Caufriez A. Sleep and hormonal changes in aging. *Endocrinol Metab Clin North Am*. 2013;42(2):371-389. doi:10.1016/j.ecl.2013.02.009
80. Axelsson J, Ingre M, Åkerstedt T, Holmbäck U. Effects of acutely displaced sleep on testosterone. *J Clin Endocrinol Metabolism*. 2005;90(8):4530-4535. doi:10.1210/jc.2005-0520
81. Mearini L, Costantini E, Zucchi A, et al. Testosterone levels in benign prostatic hypertrophy and prostate cancer. *Urol Int*. 2008;80(2):134-140. doi:10.1159/000112602
82. Rastrelli G, Vignozzi L, Corona G, Maggi M. Testosterone and benign prostatic hyperplasia. *Sexual Med Rev*. 2019;7(2):259-271. doi:10.1016/j.sxmr.2018.10.006
83. Kristal AR, Arnold KB, Schenk JM, et al. Race/ethnicity, obesity, health related behaviors and the risk of symptomatic benign prostatic hyperplasia: results from the prostate cancer prevention trial. *J Urol*. 2007;177(4):1395-1400.; Quiz 1591. doi:10.1016/j.juro.2006.11.065

84. Wei JT, Schottenfeld D, Cooper K, et al. The natural history of lower urinary tract symptoms in Black American men: relationships with aging, prostate size, flow rate and bothersomeness. *J Urol*. 2001;165(5):1521-1525.
85. Roberts RO, Chute CG, Rhodes T, et al. Natural history of prostatism: worry and embarrassment from urinary symptoms and health care-seeking behavior. *Urology*. 1994;43(5):621-628. doi:10.1016/0090-4295(94)90174-0
86. Hall SA, Link CL, Hu JC, Eggers PW, McKinlay JB. Drug treatment of urological symptoms: estimating the magnitude of unmet need in a community-based sample. *BJU Int*. 2009;104(11):1680-1688. doi:10.1111/j.1464-410X.2009.08686.x
87. Patel PM, Sweigert SE, Nelson M, et al. Disparities in benign prostatic hyperplasia progression: predictors of presentation to the emergency department in urinary retention. *J Urol*. 2020;204(2):332-336. doi:10.1097/JU.0000000000000787
88. Fowke JH, Murff HJ, Signorello LB, Lund L, Blot WJ. Race and socioeconomic status are independently associated with benign prostatic hyperplasia. *J Urol*. 2008;180:2091-2096. doi:10.1016/j.juro.2008.07.059
89. Gill H. Racial disparities in the treatment of benign prostatic hyperplasia. *Med Surg Urol*. 2015;4:157. doi:10.4172/2168-9857.1000157
90. Hoke GP, McWilliams GW. Epidemiology of benign prostatic hyperplasia and comorbidities in racial and ethnic minority populations. *Am J Med*. 2008;121(8 suppl 2):S3-S10. doi:10.1016/j.amjmed.2008.05.021
91. Joseph MA. Risk factors for lower urinary tract symptoms in a population-based sample of African-American men. *Am J Epidemiol*. 2003;157(10):906-914. doi:10.1093/aje/kwg051
92. Johnson TV, Abbasi A, Ehrlich SS, et al. Patient misunderstanding of the individual questions of the American Urological Association symptom score. *J Urol*. 2008;179(6):2291-2295.; Discussion 2294-2295. doi:10.1016/j.juro.2008.01.140
93. Wong MD, Shapiro MF, Boscardin WJ, Ettner SL. Contribution of major diseases to disparities in mortality. *N Engl J Med*. 2002;347(20):1585-1592. doi:10.1056/NEJMsa012979
94. Skelly AH. Type 2 diabetes mellitus. *Nurs Clin North Am*. 2006;41(4):531-547. doi:10.1016/j.cnur.2006.07.011
95. Stamatakis KA, Kaplan GA, Roberts RE. Short sleep duration across income, education, and race/ethnic groups: population prevalence and growing disparities during 34 years of follow-up. *Ann Epidemiol*. 2007;17(12):948-955. doi:10.1016/j.annepidem.2007.07.096
96. Ertel KA, Berkman LF, Buxton OM. Socioeconomic status, occupational characteristics, and sleep duration in African/Caribbean immigrants and US White health care workers. *Sleep*. 2011;34(4):509-518. doi:10.1093/sleep/34.4.509
97. Huang SJ, Sehgal NJ. Association of historic redlining and present-day health in Baltimore. *PLoS One*. 2022;17(1):e0261028. doi:10.1371/journal.pone.0261028
98. Johnson DA, Lisabeth L, Hickson D, et al. The social patterning of sleep in African Americans: associations of socioeconomic position and neighborhood characteristics with sleep in the Jackson Heart Study. *Sleep*. 2016;39(9):1749-1759. doi:10.5665/sleep.6106
99. Seltenrich N. Inequality of noise exposures: a portrait of the United States. *Environ Health Perspect*. 2017;125(9):094003. doi:10.1289/EHP2471
100. Ghosh-Dastidar B, Cohen D, Hunter G, et al. Distance to store, food prices, and obesity in urban food deserts. *Am J Prev Med*. 2014;47(5):587-595. doi:10.1016/j.amepre.2014.07.005
101. Duffy JF, Abbott SM, Burgess HJ, et al. Workshop report. Circadian rhythm sleep-wake disorders: gaps and opportunities. *Sleep*. 2021;44(5):1. doi:10.1093/sleep/zsaa281

How to cite this article: Cavanaugh D, Urbanucci A, Mohamed NE, Tewari AK, Figueiro M, Kyprianou N. Link between circadian rhythm and benign prostatic hyperplasia (BPH)/lower urinary tract symptoms (LUTS). *The Prostate*. 2024;84:417-425. doi:10.1002/pros.24656