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REVIEW

Molecular and Clinical Perspectives on the Regulation of Sleep and Uric Acid Metabolism

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Abstract: Uric acid, the end product of purine metabolism, is closely associated with metabolic disorders, including gout and metabolic syndrome. Emerging evidence highlights a bidirectional relationship between uric acid metabolism and sleep regulation. Elevated uric acid levels can adversely affect sleep quality via oxidative stress and neuroinflammatory pathways, while sleep deprivation may promote uric acid synthesis and impair its excretion. This reciprocal interaction may form a vicious cycle, potentially accelerating the onset and progression of various metabolic diseases. This review summarizes recent clinical and experimental findings, focusing on the molecular mechanisms underlying the bidirectional regulation between uric acid metabolism and sleep. The implications of this relationship in the pathophysiology of metabolic disorders are discussed. Understanding this interplay underscores the importance of targeting uric acid levels and sleep quality as integrated strategies for managing metabolic diseases. These insights provide a foundation for the development of novel therapeutic interventions designed to enhance clinical outcomes in metabolic syndrome.

Keywords: uric acid metabolism, sleep, bidirectional regulation, metabolic disease

Introduction

Uric acid, the end product of purine metabolism, plays diverse physiological roles and is eliminated primarily by the kidneys.[1] Its synthesis and clearance are governed by diet, renal function, and genetic factors, underscoring the importance of maintaining uric acid homeostasis. As a potent antioxidant, uric acid scavenges reactive oxygen species, mitigating oxidative stress-induced cellular damage.[2] In the central nervous system, it provides neuroprotection against oxidative injury, potentially reducing risks of neurodegenerative diseases such as Alzheimer's and Parkinson's.[3,4] Similarly, in the cardiovascular system, uric acid helps preserve endothelial integrity by counteracting oxidative insults and modulating vasomotor function, which may reduce the risk of hypertension and atherosclerosis.[2,5,6] Additionally, uric acid modulates inflammatory responses and immune cell activity, supporting immune homeostasis.[7,8] Both hyperuricemia and hypouricemia pose health risks: elevated levels are linked to gout, nephrolithiasis, and increased cardiovascular disease, while low levels impair antioxidant defenses and neuroprotection, heightening oxidative damage susceptibility.[9–12] Therefore, the balance of uric acid metabolism is vital not only for normal physiological functions but also for the prevention and management of various diseases.

Sleep is a fundamental restorative process, and its architecture is essential for metabolic homeostasis. Alterations in sleep structure, especially the balance between non-rapid eye movement (NREM) and rapid eye movement (REM) sleep are closely linked to metabolic health.[13] Within NREM sleep, slow-wave activity (N3 stage) directly influences insulin sensitivity, energy expenditure, and lipid metabolism.[14] Moreover, the circadian fluctuations in circulating uric acid levels synchronize with increased antioxidant demands during NREM sleep, implying an adaptive regulatory role for uric acid across the sleep-wake cycle.[15,16] Unhealthy lifestyle factors, dysregulation of uric acid metabolism, and sleep disturbances form a bidirectional loop —sleep deprivation, mental disorder, or poor sleep quality can precipitate hyperuricemia and gout flares, while elevated uric acid promotes oxidative stress and inflammation, further disrupting sleep architecture.[17–20] This pathological feedback loop not only impairs metabolic homeostasis but also elevates risks of diabetes, hypertension, and cardiometabolic disorders.

Given the rhythmicity of uric acid levels in synchrony with sleep-wake cycles and their shared roles in energy balance, redox regulation, and immune modulation, elucidating the bidirectional mechanisms between uric acid

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metabolism and sleep is of substantial clinical importance. Sleep disturbances can alter biomarkers of metabolic diseases, including uric acid and inflammatory markers, exacerbating insulin resistance and cardiovascular risks through interconnected pathways of oxidative stress and circadian dysregulation. A more profound understanding could inform strategies for the early diagnosis, prevention, and management of hyperuricemia, sleep disorders, and related metabolic conditions. This review synthesizes existing evidence on the interaction between uric acid and sleep, delineates key molecular pathways, and assesses clinical implications. Despite recent advancements, significant gaps remain in longitudinal studies and mechanistic details, positioning this review as a foundational synthesis aimed at bridging these gaps and guiding future research toward more targeted therapeutic interventions.

Methodology

This narrative review explores the interplay between uric acid metabolism and sleep, emphasizing the bidirectional molecular mechanisms that regulate both processes. A structured search of PubMed, Web of Science, and Embase was conducted using MeSH terms and free-text keywords: ("Uric acid" OR "Uric acid metabolism" OR "Hyperuricemia") AND ("sleep" OR "sleep architecture" OR "sleep quality" OR "REM sleep" OR "NREM sleep" OR "deep sleep" OR "sleep disturbance"). No date restriction was applied; studies in English involving human subjects or animal models were eligible. After deduplication, titles and abstracts were independently screened by two reviewers for relevance to the review topic. Potentially relevant articles underwent full-text evaluation to confirm reports of molecular mechanisms or clinical correlations between uric acid metabolism and sleep. The exclusion criteria included the absence of relevant mechanisms, ineligible study designs, or unobtainable full texts. The selection process is illustrated in Figure 1. Study characteristics, stratified by level of evidence, are summarized in Table 1; Risk-of-bias ratings (good, fair, or poor) are presented in Table 2. Findings are synthesized narratively with critical appraisal. The paper adheres to the SANRA guidelines for narrative reviews.[21,22]

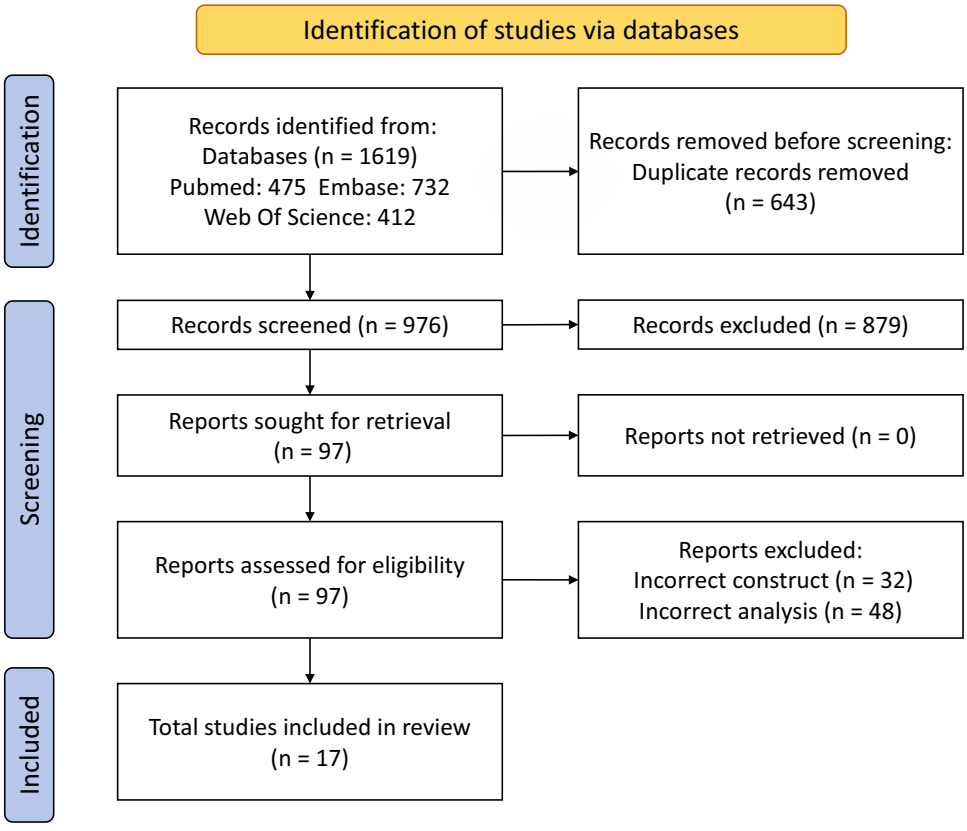

Figure 1 PRISMA flowchart of search results at each step of the review. Notes: The figure was prepared using the PRISMA 2020 flow-diagram template (https://prisma-statement.org) and adapted from Page MJ, McKenzie JE, Bossuyt PM et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71. doi:10.1136/bmj.n71. Creative Commons.[130]

Table 1 Summary of Key Characteristics of Included Studies

Study and Date of Publication	Types of Disorders	Sample	Age (Years)	Sample Size	Evaluation Basis	Results	Research Methods
Yu et al (2022)[16]	Sleep Disorder	Adults	>18	34025	Questionnaire investigation, Blood biochemistry analysis	Sleep duration inversely correlates with hyperuricemia, suggesting longer sleep may protect against elevated uric acid.	Prospective Longitudinal Study
Shen et al (2019)[4]	pRBD	Adults	>18	12923	Questionnaire surveys, Blood biochemistry analysis, PSG	Higher serum urate is associated with lower pRBD risk, implying urate may modulate prodromal Parkinsonian pathology.	Prospective cohort study
Yang et al (2023)[6]	OSAS	Adults	>18	5584	Questionnaire surveys, Blood biochemistry analysis	Serum uric acid exhibits a U-shaped, nonlinear relationship with all-cause mortality.	Prospective cohort study
Dai et al (2025)[10]	Sleep Disorder	Adults	≥20	5837	Questionnaire surveys, Blood biochemistry analysis	In hyperuricemia subjects, sleep duration shows a U-shaped association with mortality, whereas self-reported sleep disturbances do not.	Prospective cohort study
Zou et al (2022)[19]	Sleep Disorder	Adults	37-73	386439	Questionnaire surveys, Blood biochemistry analysis	Short sleep causally increases hyperuricemia risk in women but has minimal effect in men.	Cross-sectional study (combined with Mendelian Randomization)
Zhang et al (2023)[23]	Sleep Rhythm Disorders	Adults	18-50	730	Questionnaire surveys, Blood biochemistry analysis	Frequent night shifts and heavy workload impair nurses' sleep and elevate metabolic risk factors.	Retrospective cohort study
Zhao et al (2017)[11]	Chronic Insomnia	Adults	≥18	600	Questionnaire surveys, Blood biochemistry analysis	Low serum uric acid is linked to both the occurrence and severity of chronic insomnia.	Case-control study
Hirotsu et al (2013)[24]	OSAS	Adults	20-80	1042	Questionnaire investigation, PSG, Blood biochemistry analysis	Higher uric acid levels are strongly associated with OSAS severity.	Cross-sectional Study
Oh JS et al (2014)[25]	Sleep Rhythm Disorders	Adults	>18	1029	Questionnaire surveys, Blood biochemistry analysis	Among male steelworkers, shift work significantly increases hyperuricemia prevalence compared to day work.	Cross-sectional Study
Li et al (2018)[26]	iRBD	Adults	50-91	87	Questionnaire surveys, Blood biochemistry analysis, PSG, CT/MRI	iRBD patients with lower uric acid demonstrate greater cognitive impairment, reflecting urate's antioxidant and neuroprotective roles.	Cross-sectional Study
Chou et al (2020)[15]	Sleep Disorder	Adults	≥18	4555	Questionnaire investigation, Blood biochemistry analysis	Poor sleep quality associates with lower uric acid, while short sleep duration associates with higher uric acid.	Cross-sectional study
Wang et al (2021)[27]	Daytime Drowsiness	Adults	30-79	22038	Questionnaire investigation, Blood biochemistry analysis	Longer daytime naps—but not nocturnal sleep—independently predict hyperuricemia risk in a Chinese population.	Cross-sectional Study

(*Continued*)

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Table 1 (Continued).

Study and Date of Publication	Types of Disorders	Sample	Age (Years)	Sample Size	Evaluation Basis	Results	Research Methods
Yu et al (2021)[20]	Sleep Disorder	Adults	≥18	8289	Questionnaire surveys, Blood biochemistry analysis	Short sleep raises hyperuricemia risk irrespective of cardiometabolic status, especially in those without hypertension, diabetes, or obesity.	Cross-sectional Study
Hasíkova´ et al (2021)[28]	iRBD	Adults	≥50	85	Questionnaire surveys, Blood biochemistry analysis, PSG, DAT-SPECT	iRBD patients exhibit elevated serum allantoin and allantoin/urate ratios, indicating increased systemic oxidative stress.	Cross-sectional Study
Zhou et al (2023)[12]	Sleep Disorders in Parkinson's Patients	Adults	50-75	233	Questionnaire surveys, Blood biochemistry analysis, PSG	In Parkinson's disease, low serum uric acid correlates with poor sleep quality, suggesting its utility as a sleep disorder biomarker.	Cross-sectional Study
Sunadome et al (2023)[29]	SDB	Adults	34-80	7895	Questionnaire surveys, Blood biochemistry analysis, Pulse oximeters, Actiwatch Spectrum Plus	In women, serum uric acid ≥5 mg/dL doubles MS-SDB risk and is linked to higher diabetes prevalence.	Cross-sectional Study
Park et al (2025)[30]	OSAS	Adults	≥40	11728	Questionnaire surveys, Blood biochemistry analysis	High OSAS risk independently associates with hyperuricemia.	Cross-sectional Study

Physiological Pathways of Uric Acid Metabolism

Uric Acid Synthesis and Elimination

Uric acid primarily arises from the catabolism of purine nucleotides. During cellular processes, the breakdown of DNA and RNA produces hypoxanthine and xanthine, which are further oxidized by xanthine oxidase (XO) to generate uric acid.[31] The activity of XO is regulated by hypoxia-inducible factor-1α (HIF-1α), with hypoxic conditions significantly upregulating XO activity, thereby increasing uric acid production.[32,33] Following synthesis mainly in the liver, uric acid circulates in the bloodstream and is excreted by the kidneys through a coordinated process involving glomerular filtration, tubular secretion, and reabsorption, maintaining a dynamic balance between production and excretion.[2,34] Under physiological conditions, uric acid serves as a potent antioxidant, protecting neural, cardiovascular, and renal tissues from oxidative stress.[35–37] However, when uric acid production exceeds renal clearance, hyperuricemia develops, increasing the risk of gout, metabolic syndrome, and other chronic conditions.

Dysregulation of Uric Acid Metabolism and Circadian Rhythms

The primary abnormality in uric acid metabolism is hyperuricemia, which results from increased synthesis, decreased renal clearance, or a combination of both. Beyond its central role in gout, hyperuricemia has been implicated in the pathogenesis of metabolic syndrome, type 2 diabetes mellitus, and cardiovascular diseases.[38] Mechanistically, elevated serum uric acid induces oxidative stress, activates inflammatory pathways, and disrupts lipid metabolism, all of which contribute to insulin resistance, impaired glycemic regulation, and lipid accumulation—factors that collectively increase the risk of diabetes and cardiovascular diseases.[29,39] In the kidneys, urate crystal deposition can lead to nephrolithiasis and tubular injury, creating a cycle of uric acid retention and progressive renal impairment.[40] In the central nervous system, physiological levels of uric acid protect neurons by scavenging reactive oxygen species (ROS) and inhibiting lipid peroxidation.[41–44] However, when uric acid is supersaturated, it can compromise the blood-brain barrier by

Table 2 Results of Risk-of-bias Assessment for Included Studies

Author(year)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14	Overall Assessment
Yu et al (2022)[16]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	NR	Yes	Yes	NR	Yes	Fair
Shen et al (2019)[4]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Good
Yang et al (2023)[6]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Good
Dai et al (2025)[10]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Fair
Zou et al (2022)[19]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NA	Yes	Good
Zhang et al (2023)[23]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	NR	Yes	Good
Zhao et al (2017)[11]	Yes	Yes	NR	Yes	Yes	No	No	Yes	Yes	NA	Yes	Yes	NA	Yes	Fair
Hirotsu et al (2013)[24]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Oh JS et al (2014)[25]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Li et al (2018)[26]	Yes	Yes	NR	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Chou et al (2020)[15]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Wang et al (2021)[27]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Yu et al (2021)[20]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Hasíkova et al (2021)[28]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Zhou et al (2023)[12]	Yes	Yes	NR	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Sunadome et al (2023)[29]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair
Park et al (2025)[30]	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Yes	No	Yes	Yes	NA	Yes	Fair

Notes: The items for the Risk of Bias Assessment were adapted from the Study Quality Assessment Tools developed by the National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH). Available at: https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools. Q1: Was the research question or objective in this paper clearly stated? Q2: Was the study population clearly specified and defined? Q3: Was the participation rate of eligible person at 50%? Q4: Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants? Q5: Was a sample size justification, power description, or variance and effect estimates provided? Q6: For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured? Q7: Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed? Q8: For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (eg, categories of exposure, or exposure measured as continuous variable)? Q9: Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q10: Was the exposure(s) assessed more than once over time? Q11: Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants? Q12: Were the outcome assessors blinded to the exposure status of participants? Q13: Was loss to follow-up after baseline 20% or less? Q14: Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
Abbreviations: NR, not reported; NA, not applicable.

downregulating tight junction proteins, promoting neuroinflammation, and activating astrocytes—alterations that may disrupt sleep-wake regulation.[45]

Uric acid metabolism also exhibits robust circadian variation, regulated by biological clocks. Hepatic XO activity follows a diurnal rhythm, peaking during the night, indicating an intrinsic coupling between uric acid production and the sleep-wake cycle.[46,47] Animal studies have shown that knockout of the core clock gene BMAL1 disrupts normal uric acid rhythmicity and leads to fragmented sleep, highlighting the role of circadian genes in synchronizing uric acid handling with sleep architecture.[48] Clinically, prolonged daytime napping is associated with circadian misalignment and metabolic disturbances, potentially increasing uric acid synthesis and accumulation. This pattern has also been linked to a higher prevalence of metabolic syndrome and hyperuricemia.[27] Together, these findings underscore the close relationship between uric acid homeostasis, systemic metabolic regulation, renal function, and sleep processes. The diurnal fluctuations in uric acid and its responsiveness to lifestyle factors, such as daytime napping, emphasize the importance of circadian mechanisms and behavioral interventions in the prevention and management of uric acid-related disorders.

Impact of Uric Acid Dysmetabolism on Sleep

Hyperuricemia, particularly during acute gout flares, has been consistently associated with impairments in sleep efficiency and overall sleep quality. Clinical research indicates a negative correlation between serum uric acid levels and sleep parameters, suggesting that disturbances in uric acid metabolism may directly impair sleep continuity and architecture.[24] Patients with hyperuricemia often exhibit urate crystal deposition within joints, leading to acute inflammatory arthritis episodes. These episodes are characterized by intense pain and localized inflammation, which directly disrupt sleep initiation and continuity. The specific manifestations are as follows:

Alterations in Sleep Architecture

Patients with hyperuricemia often exhibit a significant reduction in slow-wave sleep (N3 stage), likely driven by central nervous system inflammation and oxidative stress triggered by elevated uric acid levels.[49–51] The increase in pro-inflammatory cytokines amplifies neuroinflammation, disrupting the homeostatic regulation of deep sleep. Simultaneously, oxidative damage to cortical energy metabolism reduces the duration of N3 sleep and shifts the proportion towards lighter NREM and REM sleep stages. These alterations not only diminish restorative deep sleep but also increase nocturnal arousals, resulting in overall poorer sleep quality.[52]

Neurotransmitter Modulation

Elevated serum uric acid levels exert a direct influence on central neurotransmitter systems integral to sleep-wake regulation and emotional homeostasis. Specifically, hyperuricemia may disrupt the synthesis and metabolism of key monoamines—including serotonin, norepinephrine, and dopamine—which are essential neuromodulators involved in sleep architecture, mood stabilization, and arousal states. Elevated uric acid concentrations can impair serotoninergic pathways, leading to decreased serotonergic tone and subsequent disturbances in REM sleep regulation. Simultaneously, hyperuricemia interferes with noradrenergic and dopaminergic pathways, which are critical for morning alertness, neurocognitive function, and emotional regulation.[53–56] These alterations may manifest as increased nocturnal awakenings, elevated sleep fragmentation, and morning fatigue, collectively impairing sleep's restorative quality and the stability of affective states.

Molecular Regulatory Pathways

Uric acid influences sleep regulation through multiple molecular pathways, disrupting the complex neurochemical networks that govern sleep-wake cycles (Figure 2).

Competitive Regulation

Uric acid disrupts sleep regulation by inhibiting AMP-activated protein kinase (AMPK), the principal cellular energy sensor. Under energy deficit, AMP/ADP binding to AMPK's γ-subunit induces a conformational shift that facilitates LKB1-mediated phosphorylation of the α-subunit at Thr172, thereby activating downstream cascades controlling glucose uptake, fatty-acid β-oxidation, and mitochondrial biogenesis to restore ATP homeostasis.[57] In the nervous system, AMPK not only governs neuronal bioenergetics but also directly modulates sleep-wake architecture, enhancing NREM sleep depth and restorative efficiency. Elevated uric acid impairs this mechanism via two synergistic pathways: competitive inhibition of upstream kinases (eg, LKB1) and ROS-mediated interference with Thr172 phosphorylation.[32,58] The resulting AMPK hypoactivity in hypothalamic and brainstem sleep centers diminishes neuronal energy sensing and markedly attenuates NREM slow-wave activity (δ-power). Ordinarily, active AMPK sustains neuronal ATP generation and ion-channel homeostasis to synchronize cortical slow-wave oscillations; its suppression leads to energy insufficiency, weakened slow waves, reduced sleep intensity, fragmented continuity, and impaired recovery.[59,60] Moreover, AMPK phosphorylates the core clock protein CRY1 at Ser71, promoting its recruitment by the E3 ubiquitin ligase FBXL3 for proteasomal degradation. This turnover prevents excessive nuclear accumulation of CRY1, allowing the CLOCK-BMAL1 complex to drive rhythmic transcription of clock genes. By blocking AMPK signaling, uric acid reduces CRY1 phosphorylation, impedes its clearance, and thereby amplifies CRY1-mediated repression of CLOCK-BMAL1, disrupting circadian oscillations and sleep-wake synchronization.[61] In sum, uric acid's competitive inhibition of AMPK activation undermines neuronal energy metabolism and NREM sleep quality while derailing molecular clock dynamics—mechanisms that converge to produce sleep dysfunction.

Epigenetic Regulation

Chronic exposure to elevated uric acid acts as a metabolic stressor that triggers epigenetic reprogramming of monocytes, mirroring the molecular signature of trained immunity.[62] This imprint renders monocytes hypersensitive to inflammatory stimuli and primes them for exaggerated secretion of TNF-α, IL-1β, and IL-6 upon subsequent challenge with PAMPs or Damage-associated Molecular Patterns (DAMPs).[63] Mechanistically, this involves two layers of epigenetic control:

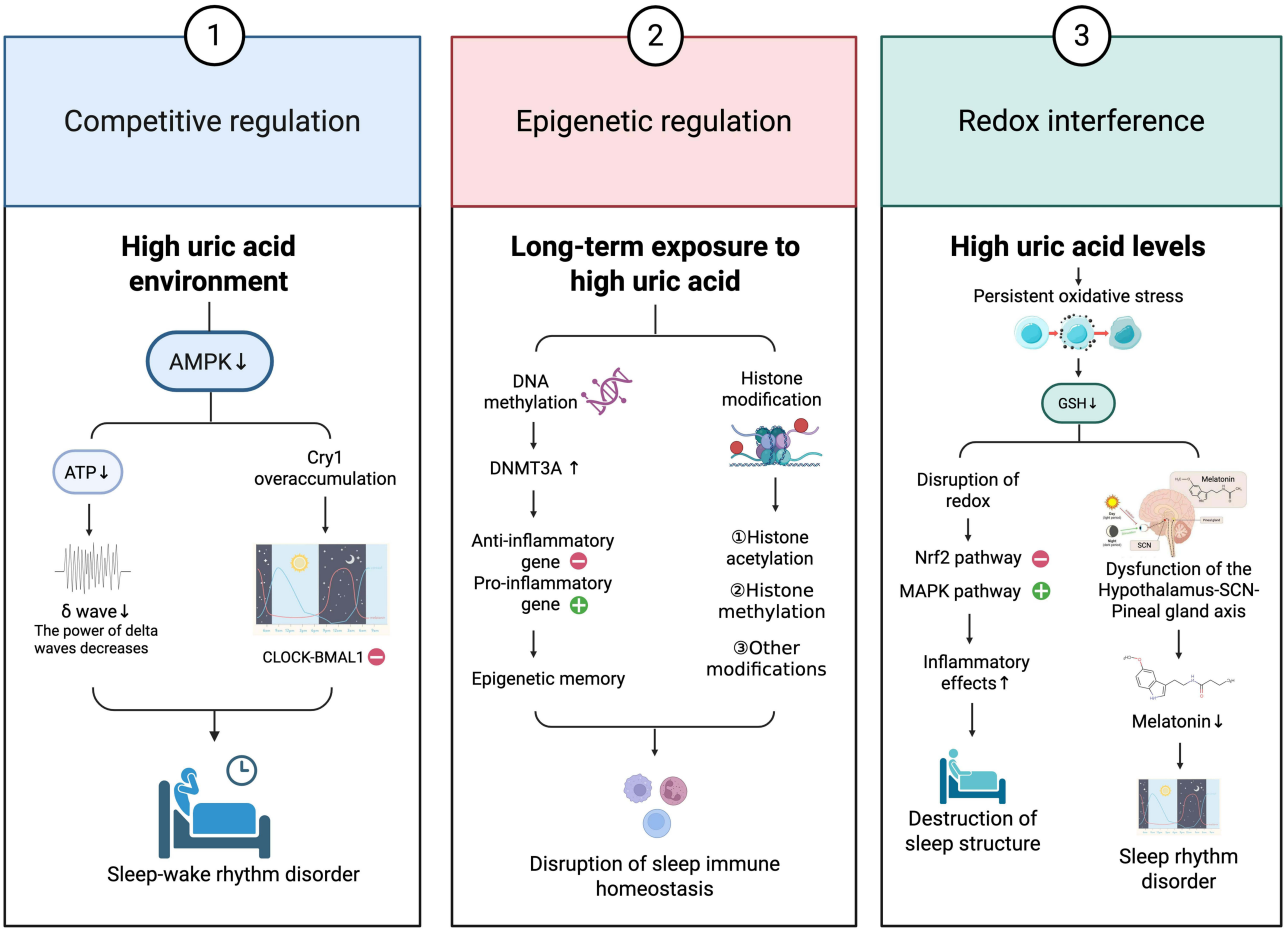

Figure 2 The molecular mechanism by which uric acid interferes with sleep regulation. Created in BioRender. Xie, Y. (2025) https://BioRender.com/woqjmyt.

1) DNA methylation: High uric acid up-regulates DNA Methyltransferase 3A (DNMT3A), increasing 5-mC density within CpG islands of anti-inflammatory promoters (NRF2, PGC-1α, FOXP3), which results in the hypermethylation and transcriptional repression of anti-inflammatory gene promoters. Concurrently, it reduces the methylation levels of pro-inflammatory genes such as NLRP3, or indirectly enhances their expression, amplifying the inflammatory response.[64] Although this methylation pattern is reversible, prolonged exposure establishes a persistent epigenetic memory that lowers the threshold for cytokine release.
2) Histone modifications: Uric acid- driven oxidative stress reshapes the histone modification landscape through three main routes:

- Histone acetylation: Activation of the TLR4/NF-κB pathway recruits HATs to pro-inflammatory gene promoters, elevates H3K27ac, and inhibits HDAC3, resulting in chromatin relaxation and enhanced transcription.[37,65]
- Histone methylation: Enhanced methyltransferase activity deposits H3K4me3 on pro-inflammatory genes, while genes involved in circadian rhythms (eg, CLOCK, PER2) may be downregulated due to H3K27me3 modifications, disrupting immune-metabolic homeostasis.[63,66]
- Other modifications: Include the phosphorylation and ubiquitination of signaling proteins, which further reinforce inflammatory signaling.

Consequently, the circadian secretion of pro-inflammatory cytokines becomes uncoupled from the sleep-wake cycle, undermining sleep-immune homeostasis and aggravating sleep disorders.[67,68] These events fuel a self-perpetuating cycle of chronic low-grade inflammation that increases the risk of metabolic syndrome, autoimmune diseases, and related

complications. Collectively, these findings identify uric acid-driven epigenetic remodeling as a pivotal hub linking metabolic stress to chronic inflammation and sleep-immune dysregulation, offering potential therapeutic targets for hyperuricemia-associated pathologies.

Redox Interference

Hyperuricemia induces persistent oxidative stress, which gradually depletes intracellular glutathione (GSH). As a key thiol antioxidant, GSH normally neutralizes free radicals and peroxides to maintain redox homeostasis. In a high-uric acid environment, however, uric acid's intrinsic pro-oxidant activity—and even its ability to inactivate endogenous antioxidant enzymes—promotes the accumulation of ROS.[69–71] Suppression of the Nrf2 pathway in this context further diminishes cellular antioxidant defenses, allowing ROS levels to rise unchecked. Elevated ROS not only cause direct molecular damage but also serve as second messengers to activate stress-responsive kinases. In particular, phosphorylation of p38 MAPK enhances the secretion of pro-inflammatory cytokines, which in turn exacerbates oxidative stress. This combined oxidative-inflammatory milieu disrupts central sleep-wake regulatory circuits, manifesting as prolonged sleep latency, increased light sleep, and reduced deep sleep.[37,72,73] Concurrent GSH depletion and oxidative stress impair the function of the hypothalamic-SCN-pineal axis, which governs circadian rhythms and melatonin synthesis. ROS-mediated suppression of Nrf2 signaling compromises cellular redox homeostasis, indirectly blunting AANAT—the rate-limiting enzyme in nocturnal melatonin biosynthesis—and downregulating other key enzymes such as HIOMT. The resulting decline in nocturnal melatonin secretion disrupts sleep architecture and reduces overall sleep quality.[41,51]

In summary, uric acid dysmetabolism disrupts sleep architecture via direct impacts on neurotransmitter regulation and molecular circadian mechanisms. It also aggravates sleep disturbances through the activation of neuroinflammatory and oxidative stress pathways, creating a vicious cycle of sleep impairment.

Sleep and Metabolic Regulation

Physiological Features of Sleep Architecture

Sleep consists of NREM and REM stages. NREM is further divided into N1 (a light transition phase with reduced cortical activity but maintained arousability), N2 (characterized by spindles and K-complexes, promoting autonomic stability), and N3 (slow-wave sleep, which supports energy homeostasis, immune recovery, insulin sensitivity, and lipid metabolism). In contrast, REM sleep exhibits wake-like EEG yet is accompanied by skeletal muscle atonia and phasic cholinergic–monoaminergic surges that facilitate emotional regulation, memory consolidation, and cardiovascular variability.[74–77] Together, deep NREM (particularly N3) and REM constitute an integrated neuroendocrine network that orchestrates systemic metabolism through complementary restorative mechanisms.

Sleep Duration and Uric Acid Balance

Epidemiological data show short sleep (<7 h/night) increases hyperuricemia risk, while long sleep (≥8 h) is protective.[16] Sleep loss and fragmentation provoke insulin resistance, dyslipidemia, and pro-inflammatory cytokine release (IL-6, TNF-α), elevating oxidative stress and impairing renal uric acid clearance.[78,79] Conversely, intact slow-wave sleep sustains fatty acid oxidation and limits purine overload.[15,80] Emerging mechanisms include (a) the gut-brain purine axis, whereby sleep deprivation alters microbiota purine metabolism and enhances systemic xanthine load;[81,82] (b) neuroinflammatory breach of the blood-brain barrier, enabling peripheral uric acid entry and glial activation via TLR4/NF-κB pathways.[43,83–85] These mechanisms link sleep disruption to dysregulated uric acid homeostasis and increased risk of metabolic and neurodegenerative disorders.

Stage-Specific Sleep Effects on Uric Acid Metabolism

Sleep stages differ markedly in metabolic rate, with N1 (transition) having the highest among NREM, N2 (spindle/K-complex stage) being intermediate, and N3 (slow-wave) being the lowest. To date, few studies have explored the potential link between N1 duration or quality and uric acid turnover, and the relationship between N2—which constitutes 45–55% of total sleep—and serum uric acid or renal clearance remains largely uninvestigated.[11,86,87]

N3 slow-wave sleep minimizes cerebral and systemic ATP turnover, theoretically curbing uric acid production. Consistent with this, chronic insomnia—characterized by reduced N3—yields lower serum uric acid, likely due to excessive oxidative consumption of uric acid as an antioxidant.[11] In contrast, N3 disruption in obstructive sleep apnea (OSA) precipitates recurrent hypoxia-reoxygenation cycles; these cycles inhibit mitochondrial ATP synthesis yet accelerate its breakdown, elevating purine intermediates (eg, hypoxanthine) and driving uric acid generation via xanthine oxidase.[24] Thus, although N3 loss occurs in both insomnia and OSA, divergent oxidative-stress pathways produce opposite serum uric acid profiles.

REM sleep exhibits the highest brain metabolic rate of all stages, further amplifying ATP catabolism and uric acid synthesis.[87] In OSA, respiratory events peak in REM, intensifying intermittent hypoxemia and fueling excess uric acid production; nadir nocturnal oxygen saturation in REM strongly correlates with serum uric acid levels.[30,88,89] Clinically, nadir nocturnal oxygen saturation—typically occurring in REM—correlates strongly with serum uric acid concentrations in OSA patients, underscoring the impact of REM's unique neuro-metabolic environment on uric acid metabolism.[24,26,28] Collectively, these findings highlight that stage-specific variations in sleep architecture critically modulate uric acid homeostasis. Future research should integrate high-resolution polysomnography with real-time uric acid monitoring to quantify each stage's independent contribution to uric acid production and clearance, thereby informing stage-targeted interventions.

Sleep-Uric Acid Metabolism Confounders

Diet, exercise, medications, and lifestyle variables must be rigorously controlled in studies of the serum uric acid (SUA)-sleep relationship.

- Diet: purine-rich foods and alcohol increase SUA and disrupt sleep architecture, whereas caffeine lowers SUA but shortens sleep time and efficiency.[90–92]
- Exercise: acute high-intensity efforts transiently elevate SUA via lactate and may impair sleep;[93,94] habitual moderate exercise lowers SUA and improves sleep, yet vigorous or late-evening workouts can delay sleep onset.[95,96]
- Medications: thiazide diuretics, salicylates, and pyrazinamide reduce renal uric acid excretion and raise SUA,[97,98] whereas uric acid-lowering agents (allopurinol, febuxostat, etc) markedly decrease SUA and could mask true associations.[99,100] Benzodiazepines and Z-drugs alter sleep stages without affecting SUA;[101,102] failure to account for their use may overestimate sleep effects.
- Lifestyle: shift work and circadian misalignment increase hyperuricemia risk;[25,103] obesity, hypertension, and insulin resistance are shared risk factors for elevated SUA and sleep disorders;[104,105] Chronic psychosocial stress raises SUA and disturbs sleep.[106,107]

Most prior studies adjust only for age, sex, and BMI. Future work should prospectively collect detailed dietary, exercise, medication, and psychosocial data and include them as covariates to obtain unbiased estimates of the SUA-sleep association.

Multi-Tiered Regulation of Sleep and Uric Acid Metabolism

Biological regulatory systems operate through complex, multi-layered networks that integrate signals across molecular, cellular, and systemic levels. Based on a comprehensive literature synthesis, these regulatory mechanisms can be broadly categorized into three hierarchical levels. Each level encompasses distinct biological processes and signaling pathways, ranging from gene and molecular regulation to organ-level coordination, together forming a dynamic and stratified framework of metabolic control (Figure 3).

Primary Regulation: Circadian Modulation of Uric Acid Metabolism via the Hypothalamic-Pituitary-Adrenal (HPA) Axis

The HPA axis is a central neuroendocrine system that governs both stress responses and circadian rhythms. Through rhythmic secretion of glucocorticoids—primarily cortisol—the HPA axis orchestrates a broad spectrum of metabolic

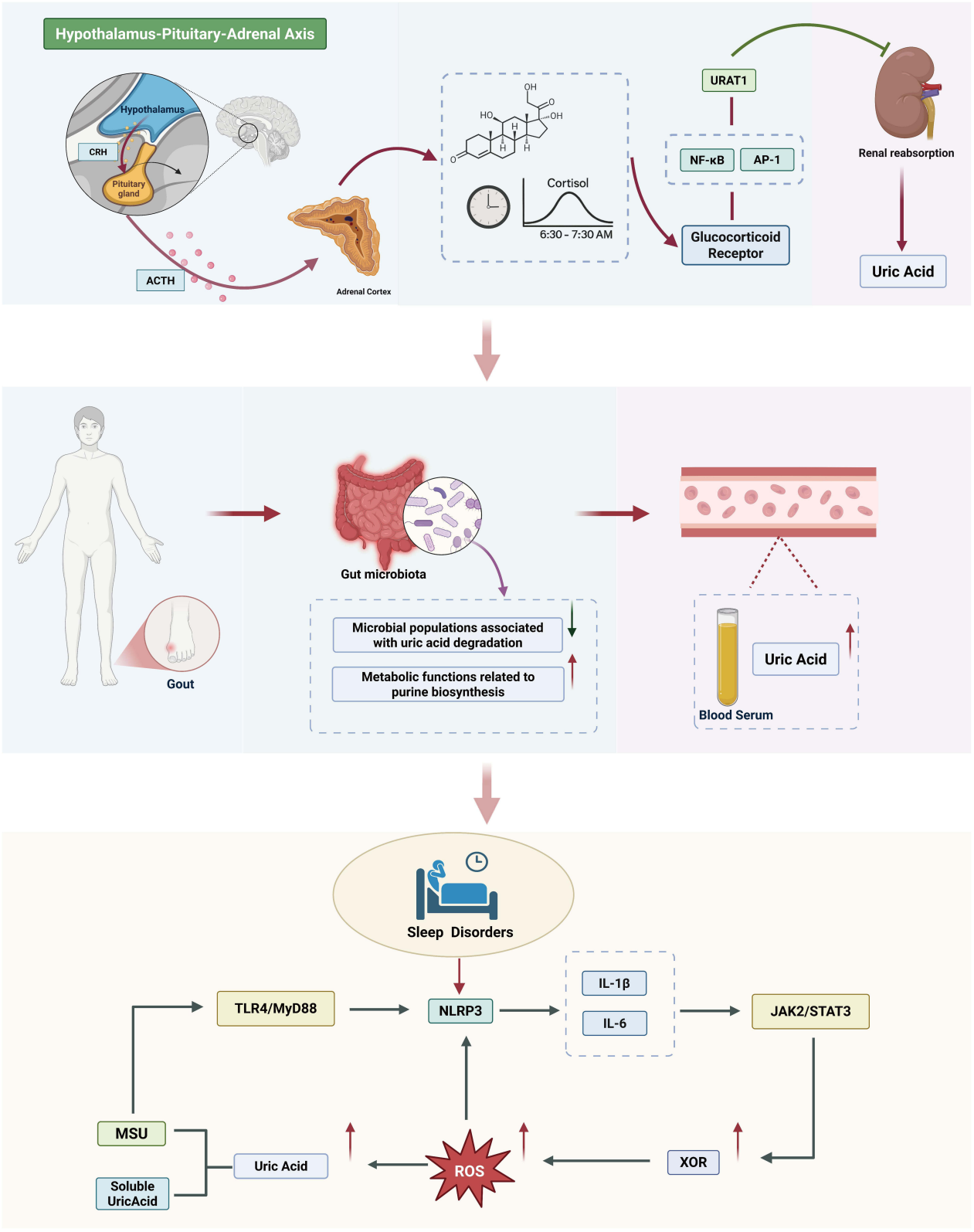

Figure 3 The schematic diagram of multilevel regulation of sleep and uric acid metabolism. Created in BioRender. Xie, Y. (2025) https://BioRender.com/woqjmyt.

activities, including uric acid metabolism. Under normal physiological conditions, cortisol levels peak approximately 30–60 minutes after awakening (around 06:30–07:30), aligning with a critical phase of the circadian cycle.[108]

Experimental studies have demonstrated that glucocorticoids, acting via the glucocorticoid receptor (GR), modulate downstream signaling pathways such as NF-κB and AP-1. This signaling cascade leads to the suppression of urate transporter 1 (URAT1) expression in the renal proximal tubules, thereby reducing uric acid reabsorption and enhancing renal uric acid excretion.[109] This mechanism highlights a direct link between circadian HPA axis activity and renal uric acid handling. Clinically, circadian misalignment—as observed in shift workers—has been associated with blunted diurnal fluctuations in serum uric acid and delayed phase shifts in 24-hour uric acid rhythms. These findings suggest that HPA axis dysregulation may be a critical contributor to disrupted uric acid homeostasis in populations exposed to circadian stress.[23,25] Collectively, the circadian regulation exerted by the HPA axis represents a fundamental, first-tier mechanism in the control of uric acid metabolism. Therapeutic strategies aimed at restoring HPA axis rhythmicity hold promise not only for improving sleep and endocrine balance but also for correcting uric acid dysregulation. This highlights its translational potential in the management of hyperuricemia and related metabolic disorders.

Secondary Regulation: The Role of the Gut Microbiota in Purine and Uric Acid Metabolism

Recent advances have highlighted the gut microbiota as a key modulator of host circadian rhythms and metabolic homeostasis. A growing body of evidence suggests that the gut-brain axis facilitates bidirectional communication between microbial communities and the host's central clock system, thereby contributing to the regulation of sleep-wake cycles and circadian alignment.[110–112] Beyond circadian control, the gut microbiota plays an increasingly recognized role in uric acid metabolism. Clinical and microbiome studies have consistently shown that individuals with gout exhibit significant dysbiosis—characterized by a depletion of microbial taxa involved in uricolysis, alongside an enrichment of pathways associated with de novo purine biosynthesis.[82] Large-scale metagenomic analyses have confirmed substantial alterations in both taxonomic composition and metabolic potential of the gut microbiota in hyperuricemia individuals, with these changes correlating closely with aberrant uric acid handling and chronic low-grade inflammation.[113] Mechanistically, certain gut microbes express xanthine oxidase homologs, contributing directly to the microbial conversion of purines into uric acid. Importantly, microbial purine metabolism exhibits circadian rhythmicity, which may exert time-dependent effects on host serum uric acid levels.[114,115] Animal models have further substantiated the pivotal role of the gut microbiota in maintaining purine homeostasis, particularly in modulating systemic uric acid concentrations.[115] Taken together, the gut microbiota functions as a secondary regulatory layer in uric acid metabolism, exerting multifaceted control over host purine flux and uric acid balance. Its circadian rhythmicity offers novel insight into the temporal dynamics of metabolic regulation and opens promising avenues for microbiota-targeted interventions in hyperuricemia and related disorders.

Tertiary Regulation: Positive Feedback Between Oxidative Stress and Inflammatory Signaling

Oxidative stress and inflammation constitute a central mechanistic axis linking sleep architecture disruption to altered uric acid metabolism. Sleep fragmentation (SF), a hallmark of disturbed sleep structure, has been shown to activate the NLRP3 inflammasome, resulting in elevated secretion of pro-inflammatory cytokines such as interleukin-1β (IL-1β), which in turn amplifies both systemic and local inflammatory responses.[116,117] Certain cytokines, notably IL-6, can further activate the JAK2/STAT3 signaling cascade, upregulating the transcription and expression of xanthine oxidase (XOR), a key enzyme in purine catabolism, thereby accelerating uric acid production.[118] Moreover, urate crystals function as DAMPs, capable of perpetuating immune activation via the TLR4/MyD88 pathway. This establishes a self-reinforcing inflammatory loop, which is critically implicated in the pathogenesis of gout and uric acid-associated nephropathies.[119] Experimental models support this mechanism: antioxidant intervention using agents such as N-acetylcysteine (NAC), alone or in combination with bioactive phytochemicals, has been shown to improve serum uric acid levels and renal function, underscoring the therapeutic value of targeting oxidative stress in uric acid-related disorders.[120] Collectively, oxidative stress and inflammation form a tertiary regulatory layer in uric acid metabolism, wherein sleep disturbance triggers

inflammatory and oxidative signals that synergistically exacerbate uric acid accumulation. This pathological feedback loop serves as a key mechanistic substrate for the development and progression of hyperuricemia and related metabolic diseases.

In summary, the regulation of uric acid metabolism by sleep architecture is a complex, multilayered physiological process. Primary regulation is mediated by the circadian rhythmicity of the HPA axis, which modulates endocrine output and renal uric acid excretion. Secondary regulation involves the composition and metabolic activity of the gut microbiota, influencing purine metabolic flux and circadian oscillations of uric acid levels. Tertiary regulation comprises the oxidative stress-inflammation feedback loop, which sustains inflammatory signaling and promotes uric acid synthesis under conditions of sleep disruption. These three regulatory tiers interact synergistically to maintain uric acid homeostasis. This multidimensional framework not only advances our mechanistic understanding of uric acid metabolism but also identifies promising therapeutic targets for the precision management of hyperuricemia and associated metabolic disorders.

Research Directions and Clinical Perspectives

Research Priorities

Elucidating the Bidirectional Regulation Between Uric Acid Metabolism and Sleep

The bidirectional regulatory mechanisms between uric acid and sleep remain incompletely elucidated at the molecular level. Future studies should focus on the role of uric acid in modulating sleep architecture and circadian rhythms, particularly its detailed mechanisms of action via oxidative stress, neuroinflammation, and clock genes (eg, BMAL1 and CLOCK). Employing cutting-edge technologies, researchers should dissect how uric acid influences sleep quality by affecting neuronal functions, neurotransmitter homeostasis, and inflammatory responses within the central nervous system. Additionally, the role of uric acid metabolism in neuroendocrine regulation warrants investigation, especially the complex interactions between uric acid metabolism and various neurotransmitters. Further exploration of clock genes as molecular hubs linking uric acid metabolism and sleep regulation may reveal novel therapeutic targets for clinical intervention.

Integrating Traditional Chinese Medicine (TCM) in Uric Acid and Sleep Regulation

TCM has a long history of regulating uric acid metabolism and improving sleep quality, offering a unique complement to modern medicine through its holistic approach and individualized treatment methods. Future research could explore the application of classical TCM formulas in addressing uric acid metabolism disorders and the associated sleep disturbances. Clinical randomized controlled trials, combined with modern scientific technologies such as metabolomics and genomics, should be conducted to investigate the molecular mechanisms by which herbal medicine influences uric acid metabolism. Additionally, traditional TCM therapies such as acupuncture and tuina massage warrant further investigation for their potential to regulate sleep quality and alleviate uric acid-related symptoms. A comprehensive intervention strategy combining both Western and Chinese medicine should be a research priority, focusing on multi-target, multi-level treatment models that integrate TCM with pharmacological therapies to optimize the combined therapeutic effects on uric acid metabolism and sleep quality.

Clinical Perspectives

Personalized Therapeutic Strategies in Precision Medicine

A structured "Assessment-Intervention-Monitoring-Follow-up" paradigm is proposed to address the bidirectional interplay between hyperuricemia and sleep disturbances, aiming for precise optimization of serum uric acid levels and restorative sleep.

- Assessment: During the initial consultation, quantify sleep disturbances by using the Pittsburgh Sleep Quality Index (PSQI). Supplement subjective data with objective measures—such as portable or wearable sleep monitors—to record nocturnal awakenings and the proportion of deep sleep. Simultaneously, document gout flare characteristics (severity and frequency), pain-related nighttime awakenings, mood disorders, and exposure histories (diet, alcohol, caffeine) to identify interactive risk factors linking sleep disturbances and hyperuricemia.

- Intervention: Prioritize nonpharmacological strategies—particularly cognitive behavioral therapy for insomnia (CBT-I) and sleep environment optimization. When pain impairs sleep initiation, short-term use of low-dose zolpidem may be considered. Concurrently, colchicine or non-steroidal anti-inflammatory drugs (NSAIDs) administered at night can suppress inflammatory surges. To control uric acid levels in the long term, it is recommended to take allopurinol or febuxostat in the evening to maintain stable plasma concentrations. For diet, a low-purine, high-fiber dinner is advised, avoiding foods rich in purines. Engaging in light stretching or yoga 1.5 hours before bedtime can help relax the body and improve sleep quality. Additionally, melatonin supplementation may be considered to improve sleep, potentially helping to reduce nocturnal uric acid peaks.
- Monitoring: Reassess biomarkers of inflammation and oxidative stress (interleukin-1β, tumor necrosis factor-α, malondialdehyde, superoxide dismutase), eGFR, serum uric acid, and 24-hour urinary uric acid excretion every 1–3 months to gauge intervention impact on the inflammation-oxidative stress-renal function axis. Reevaluate the PSQI at 1, 3, and 6 months; if indicated, escalate to polysomnography to screen for sleep-disordered breathing.
- Follow-up: Coordinate follow-up within a multidisciplinary team—led by rheumatology and endocrinology and supported by sleep medicine, psychiatry, nutrition, and physical therapy. During acute flares, adjust the analgesic-hypnotic regimen weekly; in the remission phase, fine-tune uric acid-lowering and sleep-maintenance strategies monthly. The ultimate goal is bidirectional optimization and precise management of both serum uric acid levels and sleep quality (Figure 4).

Management Strategies for Special Populations

Intervention strategies for elderly individuals, pediatric patients, and pregnant women should adhere to three overarching principles: non-pharmacological first-line therapy, individualized pharmacotherapy, and regular monitoring. All groups benefit initially from sleep hygiene education (eg, regular sleep-wake schedules, pre-sleep relaxation, minimization of noise and light), CBT-I, and acupuncture. When medication is indicated, it must be short-term, low-dose, and fast-acting. Elderly patients should avoid long-term benzodiazepines and antihistamines due to the risk of falls and cognitive decline.[121–123] Children require caution with sedatives to prevent neurodevelopmental impairment, and only minimal doses should be used when necessary.[124] Pregnant women may, after specialist risk assessment, receive minimal doses of lorazepam, but their intake should be strictly controlled.

For hyperuricemia management:

- Elderly individuals, who experience reduced N3 sleep and have compromised hepatic and renal clearance, should begin allopurinol at doses of less than 100 mg/day, with dose titration based on serum uric acid levels and clinical response.[125] Acute gout flares in this population warrant low-dose colchicine or a brief course of corticosteroids, along with vigilant monitoring of hepatic and renal function.[126]
- Although children have higher renal uric acid clearance and greater slow-wave sleep needs, lifestyle modification remains paramount. Under pediatric guidance, allopurinol or uricosuric agents may be used when necessary.[127]
- In pregnant women, the focus should be on dietary control, fluid-electrolyte balance, left lateral decubitus positioning with pillow support, and avoidance of standard uric acid-lowering drugs.[128] Acute gout in pregnancy is managed preferentially with low-dose corticosteroids and prophylactic colchicine.[129]

Tiered Multi-Target Interventions

Building on the three-level regulatory framework, future research may implement combined multi-target interventions:

- **Tier I modulation**: Optimization of uric acid excretion via circadian rhythm adjustment (eg, standardized sleep-wake schedules, phototherapy, or chronobiotic agents) and hormonal pathway modulation (eg, glucocorticoid receptor modulators).
- **Tier II modulation**: Intervention in the gut microbiota (eg, probiotic supplementation, increased dietary fiber intake, or fecal microbiota transplantation) or direct targeting of microbial purine-metabolizing enzymes (eg, engineered bacterial strains) to regulate host uric acid levels.

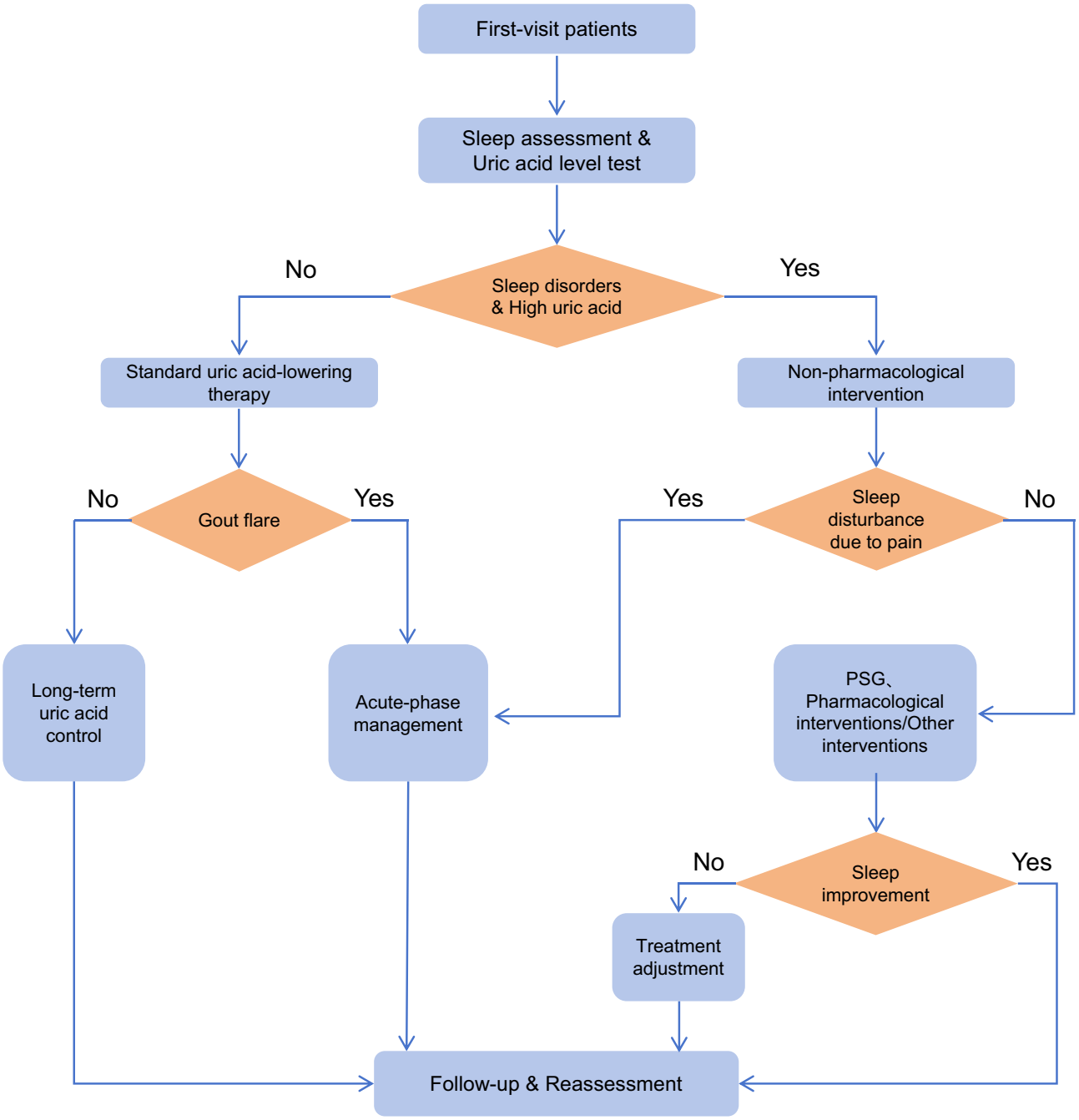

Figure 4 Decision Tree for Uric Acid Management Based on Sleep Assessment in Patients with Hyperuricemia.

- **Tier III modulation**: Emphasis on anti-inflammatory and antioxidant strategies (eg, IL-1β/IL-6 inhibitors and xanthine oxidase inhibitors) to disrupt the inflammation-uric acid positive-feedback loop.

By integrating Tier I (circadian-rhythm and hormonal regulation), Tier II (gut-microbiota modulation and microbial enzyme targeting), and Tier III (anti-inflammatory and antioxidant) interventions into a unified, multi-tiered framework, mechanistic synergy is achieved. This synergy optimizes uric acid homeostasis and disrupts pro-inflammatory feedback loops. Furthermore, by tailoring the combination of interventions to each patient's individual circadian rhythm, gut-microbiota profile, and inflammatory status, a personalized, multi-tiered strategy can not only optimize therapeutic efficacy but also minimize drug-related side effects, thereby improving quality of life—particularly for patients with

refractory hyperuricemia or gout. This comprehensive, multi-modal approach is expected to restore metabolic balance and substantially improve clinical outcomes.

Limitations

While preliminary evidence indicates an association between sleep disturbances and uric acid dysregulation, most findings to date rely on indirect observational data or small cohort studies. This reliance limits causal inference, especially given the lack of experimentally validated mechanistic data. Notably, shared pathophysiological mediators —for example, inflammatory cytokines (such as IL-1β and TNF-α) and oxidative stress markers (such as malondialdehyde) —may drive both conditions simultaneously and could exacerbate hyperuricemia. To address these gaps, future research should focus on several key areas:

- Randomized controlled trials that target the bidirectional links between sleep and uric acid.
- Longitudinal human studies with repeated measurements of biomarkers, in order to clarify how changes in sleep architecture and uric acid homeostasis influence each other over time.
- Integrated multi-omics analyses to uncover new molecular pathways and therapeutic targets involved in the comorbidity of sleep disorders and hyperuricemia.

By pursuing these approaches, the field can establish stronger mechanistic connections between sleep disturbances and uric acid dysregulation. Ultimately, this will facilitate a more stratified and effective clinical management of patients suffering from coexisting sleep disorders and hyperuricemia.

Conclusion

There exists a bidirectional regulatory relationship between uric acid metabolism and sleep architecture: elevated uric acid levels contribute to sleep disruption via pro-inflammatory and oxidative mechanisms, while sleep disturbances in turn exacerbate metabolic dysregulation of uric acid. This study highlights the necessity of an integrated therapeutic strategy that concurrently modulates uric acid homeostasis and improves sleep quality for the management of hyperuricemia and related metabolic disorders. Optimizing sleep as an adjunctive therapeutic strategy holds significant clinical promise and should be incorporated into the comprehensive treatment framework to enhance treatment efficacy and improve long-term patient outcomes.

Abbreviations

NREM, non-rapid eye movement; REM, rapid eye movement; XO, xanthine oxidase; HIF-1α, hypoxia-inducible factor-1α; ROS, reactive oxygen species; AMPK, AMP-activated protein kinase; DAMPs, damage-associated molecular patterns; DNMT3A, DNA Methyltransferase 3A; GSH, glutathione; HPA, hypothalamic-pituitary-adrenal; GR, glucocorticoid receptor; URAT1, urate transporter 1; SF, sleep fragmentation; IL-1β, interleukin-1β; XOR, xanthine oxidase; NAC, N-acetylcysteine; TCM, Traditional Chinese Medicine; PSQI, Pittsburgh Sleep Quality Index; CBT-I, cognitive behavioral therapy for insomnia; NSAIDs, non-steroidal anti-inflammatory drugs.

Data Sharing Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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Author Contributions

Guodong Ha and Jiawei Wu contributed to conceptualization, writing—review & editing, and writing—original draft. Jing Hu, Xun Wang, Yijie Xie, Zhengyu Zhao, and Dingjun Cai, as the subsequent authors, all participated in formal

analysis, supervision, and writing-review & editing. All authors have contributed substantially to the drafting, writing, or critical revision of this paper. They have collectively agreed on the target journal for submission, reviewed and approved all versions of the paper at each stage—including submission, revision, final acceptance, and proofreading—and have accepted responsibility and accountability for the content of the paper.

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Disclosure

The authors report no conflicts of interest in this work.

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