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Review Article

Exploring the silent connection between sleep disorders and cardiovascular diseases: Pathophysiology and insights

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ABSTRACT

Sleep is a complex physiological phenomenon crucial for health. Despite this, millions suffer from sleep disorders, contributing to a range of health issues, particularly cardiovascular diseases (CVD). The pathophysiological mechanisms linking sleep disorders, such as insomnia and obstructive sleep apnea (OSA), to cardiovascular risk factors include disruptions in inflammatory, autonomic, and metabolic pathways. Increased sympathetic nervous system activity, chronic inflammation, and metabolic dysregulation stemming from poor sleep can lead to conditions like hypertension, obesity, and insulin resistance, significantly elevating the risk for CVD.

This article reviews the connection between sleep quality and cardiovascular disease risks. Sleep disorders (i.e., insomnia and OSA) have been found to impact cardiovascular risk factors adversely. Studies have found an association between abnormal sleep and increased cardiovascular morbidity and mortality by higher risks of hypertension, diabetes, obesity, and dyslipidemia.

The review also discusses non-pharmacological interventions, such as relaxation training, Cognitive behavioural therapy for insomnia (CBT-I), and red light therapy, which have shown efficacy in improving sleep quality and reducing cardiovascular risks. Dual orexin receptor antagonists and Ashwagandha promise to enhance sleep quality and cardiovascular health, but further research is needed. Addressing sleep disorders and promoting healthy sleep practices are essential for mitigating the global burden of cardiovascular diseases, underscoring the need for continued research and effective public health interventions.

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INTRODUCTION

Sleep is a multifaceted physiological phenomenon wherein the body and mind enter a state of rest for a duration.[1] The World Health Organization has acknowledged sleep as a crucial health state and activity; however, millions worldwide suffer from insufficient sleep, and approximately 50 to 70 million adults in the US experience a sleep disorder or report inadequate sleep.[2,3] People in various age groups need varying amounts of sleep depending on their physiological requirements. Infants can sleep up to 12-15 hours daily, which may benefit their growth and development. In contrast, children and teenagers should sleep an average of 9-11 hours and 8-10 hours per night, respectively. Meanwhile, the typical adult requires between 7-9 hours of sleep each night, but around sixty, the average night's sleep tends to be shorter, lighter, and more frequently interrupted by awakenings.[4] There are two main stages of sleep: REM (rapid eye movement) and NREM (non-rapid eye movement), which are divided into three stages (N1–N3) (Table 1). Each phase and stage of sleep involves changes in muscle tone, brain wave patterns, and eye movements, and the body cycles through these stages approximately 4 to 6 times each night, with an average cycle length of ninety minutes.[5] Several factors contribute to optimal sleep, including enough duration, excellent quality, appropriate scheduling, and the absence of sleep-related problems. Individuals' health and well-being are negatively impacted by sleep deprivation.[4] Getting adequate sleep is critical for maintaining good physical and mental health. Medical disorders such as obstructive sleep apnea, obesity, diabetes mellitus, insulin resistance, hypertension, depression, and anxiety are all significantly correlated with sleep deprivation.[6]

Cardiovascular disease (CVD) risk factors include non-modifiable factors such as age, sex, race, and family history, as well as modifiable factors such as hypertension, hyperlipidemia, diabetes, obesity, smoking, poor nutrition, stress, a sedentary lifestyle, all of which are also associated with sleep disorders.[7,8] In addition, studies have shown reduced sleep duration to seven out of the top 15 US causes of death, such as high blood pressure, diabetes, blood toxicity, cancer, heart disease, and stroke.[7] Studies show that inadequate sleep length and poor sleep quality are linked to a higher risk of CVD. Sleep has been related to cardiovascular health. CVD stands as a prominent global cause of mortality and impairment, and projections anticipate the number of cardiovascular-related deaths to surpass 24 million by 2030, imposing a substantial burden of disease.[9] Therefore, addressing risk factors such as obstructive sleep apnea (OSA) and insomnia is crucial in managing and preventing morbidity and mortality associated with CVD.[10]

In addition to short sleep, defined as less than seven hours, long sleep, or more than nine hours, is associated with a higher risk of CVD mortality, particularly in older adults and Asian populations.[10] For people with irregular sleep patterns, a one-hour reduction in sleep length per day is associated with a 3-11% increase in the risk of stroke, osteoporosis, coronary heart disease, and type 2 diabetes mellitus. On the other hand, those who are lengthy sleepers have a 7-17% increased risk of stroke mortality, coronary heart disease, stroke, and type 2 diabetes mellitus for every hour they sleep longer.[11] Studies reveal that people with sleep disorders or OSA are significantly more susceptible to metabolic disorders like obesity, type 2 diabetes mellitus, and dyslipidemia, as well as CVDs and cerebrovascular conditions like arrhythmias, atherosclerosis, coronary heart disease, heart failure, hypertension, and stroke.[3] This article aims to review the link between sleep quality and CVD risk.

PATHOPHYSIOLOGY

Sleep disorders are known to affect the development of CVDs by impacting various physiological pathways such as inflammatory, autonomic, and metabolism. These pathways collectively contribute to the development of high blood pressure, glucose intolerance, visceral adiposity, dyslipidemia, and endothelial dysfunction, which can ultimately lead to cardiovascular problems.[12,13] These physiological mechanisms are used to illustrate links between sleep and CVD.

Blood pressure

Chronic insomnia has been linked to increased plasma and urine noradrenaline, which leads to increased sympathetic activation. Excess sympathetic nervous system activity causes peripheral vasoconstriction, activating the renin-angiotensin-aldosterone system.[14] Insomnia also causes stress dysregulation, which increases pulsatile cortisol release and causes hypothalamic-pituitary-adrenal (HPA) axis dysfunction. This dysregulation of the HPA axis raises ACTH (adrenocorticotropic hormone).[15] The activation of the renin-angiotensin-

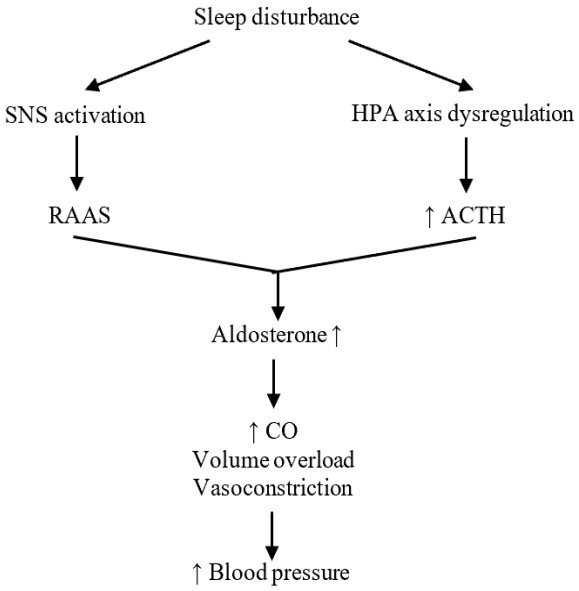

Figure 1. Pathway for sleep disturbances and blood pressure.
SNS: sympathetic nervous system, HPA: hypothalamic-pituitary-adrenal, RAAS: renin-angiotensin-aldosterone system, ACTH: adrenocorticotropic hormone, CO: cardiac output.

aldosterone system and ACTH release both increase the release of the aldosterone hormone.[14,15] This raised aldosterone hormone acts via the aldosterone receptor, which causes sodium retention and reabsorption, high cardiac output, volume overload, vasoconstriction, arterial stiffness, and vascular remodeling.[16] All of these effects result in elevated blood pressure (Figure-1). This increased blood pressure can damage arteries by making them less elastic, which decreases blood and oxygen flow to the heart and may lead to heart diseases.[17]

Inflammation

Inflammation has a major impact on the initiation and progression of CVD.[18] The hypothalamus-pituitary-adrenal (HPA) axis and the sympathetic nervous system are also in charge of preserving the inflammatory cells.[19,20] The sympathetic nervous system regulates pro-inflammatory cytokine production by releasing the neurotransmitter norepinephrine into peripheral tissues, primary and secondary lymphoid organs, and all other major organ systems, including the vasculature and perivascular tissues. Once released, norepinephrine modulates immune response gene transcription by stimulating β-adrenergic receptors.[19] This adrenergic signalling cascade also suppresses the transcription of antiviral type I interferon (IFN) genes and up-regulates transcription of the pro-inflammatory immune response genes IL (interleukin)-1, tumour necrosis factor (TNF), and IL6, leading to increases in systemic inflammatory activity.[20] The HPA axis, via glucocorticoids, regulates gene expression in practically every body cell. Hormone-induced glucocorticoid receptor activation in leukocytes results in a significant downregulation of proviral gene programs (e.g., transcription of type I IFN genes, e.g., IFNA and IFNB, mediated by interferon regulatory factors [IRF]) and pro-inflammatory gene networks (e.g., NF-κB-mediated transcription of pro-inflammatory cytokine genes, such as IL1B, IL6, and TNF).[19] This mechanism triggers pro-inflammatory cascades in sleep deprivation that promote pro-inflammatory markers (such as TNFα, IL-1, IL-6, and IL-17, C-reactive protein [CRP], cellular adhesion molecules, and visfatin) and the development of atherosclerotic plaques.[21]

Metabolic dysregulation

Sleep deprivation has also been associated with hormonal changes that affect appetite, including increased hunger due to higher ghrelin levels and decreased satiety due to lower leptin levels.[22] The imbalance of leptin and ghrelin can impact glucose metabolism, cortisol levels, and growth hormone secretion.[23] Lack of sleep also raises cortisol levels because of dysregulation of the HPA axis and activation of the sympathetic nervous system. These

processes raise catecholamines and growth hormone levels, which reduces hepatic and peripheral insulin sensitivity and increases lipolysis.[24] The activation of lipolysis results in increased levels of non-esterified fatty acids and free fatty acids, further decreasing the hepatic insulin sensitivity and peripheral glucose uptake.[24,25] These high-free fatty acid and insulin resistance increase the risk of diabetes and obesity.[26] Chronic metabolic dysfunction in the form of insulin resistance and impaired glucose tolerance is a leading risk factor for CVD morbidity and mortality.[27]

Cardiovascular Diseases

Sleep disturbance leads to high blood pressure, insulin resistance, and a pro-inflammatory state. Increased visceral adiposity, blood pressure, glucose intolerance, and dyslipidemia characterise metabolic syndrome. Individually, these comorbidities induce endothelial dysfunction by increasing reactive oxygen species (ROS) and an imbalance between endothelium-derived relaxing (e.g., nitric oxide, prostaglandin [PG]-I2, endothelium-derived relaxing factor downregulation [EDRF]) and contracting factors (e.g., thromboxane [Tx]-A2, endothelin [ET]-1 upregulation).[12]

Endothelial dysfunction has several adverse impacts. Firstly, it could cause blood vessels to constrict, which would raise blood pressure; this may lead to inflammation within the arterial wall, which may contribute to the development of atherosclerosis (Figure-2). Moreover, it can stimulate an increase in platelet production, promoting the formation of blood clots. Lastly, it can compromise the integrity of blood vessel walls, making them leaky and exposing surrounding tissues to harmful lipoproteins and other toxic substances. It poses a multifaceted risk to cardiovascular health, leading to CVD.[28]

Arrhythmia

Poor sleep is an atrial fibrillation (AF) risk factor, directly affecting AF pathogenesis and other established risk factors.[29] Conditions like OSA, central sleep apnea (SLA), and restless legs syndrome (RLS) diminish sleep quality and harm the cardiovascular system.[30] Patients with OSA experience recurrent episodic airway obstruction resulting in negative intrathoracic pressure, hypoxemia, pulmonary hypertension, disturbances of autonomic tone, and sleep fragmentation.[31] These result in structural (increased left atrium [LA] volume, left ventricle [LV]) diastolic dysfunction, increased LV afterload, increased LA wall stress) and electrical disturbances (increased P wave duration and dispersion, disturbance in automatic tone, pro-inflammatory state may alter atrial electrical properties) that promote atrial arrhythmogenesis.[32]

INTERVENTIONS FOR PATIENTS WITH SLEEP DISORDERS AND THEIR ROLE IN THE MANAGEMENT OF CARDIOVASCULAR DISEASES

Non-pharmacological interventions

Cognitive behavioural therapy for insomnia

According to the American Academy of Sleep

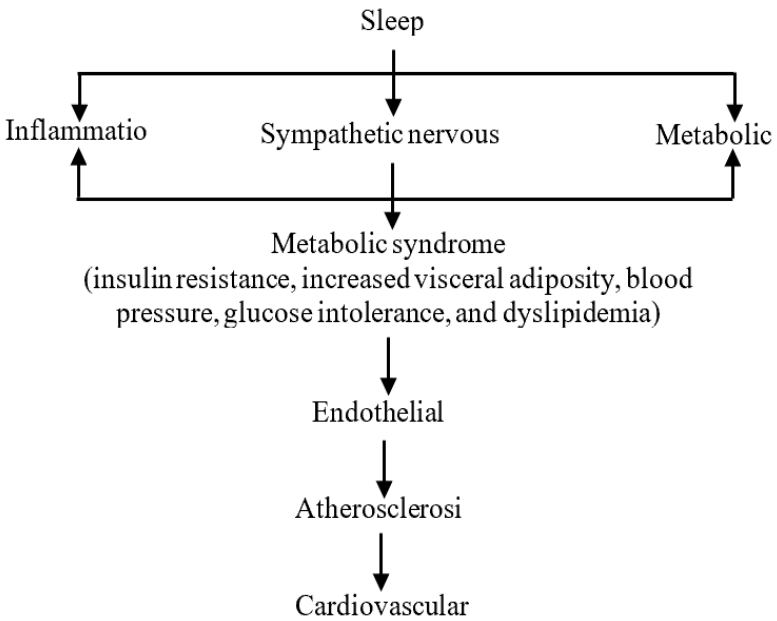

Figure 2. Flow diagram representing pathways and mechanisms for sleep disturbances leading to cardiovascular disease.

Medicine (AASM), cognitive behavioural therapy for insomnia (CBT-I) is recommended if insomnia has been determined due to intrusive thoughts or excessive worry, where a professional therapist helps manage the intrusive thoughts and behaviours that might be interfering with the sleep.[33] CBT-I comprises five components: sleep restriction, stimulus control, cognitive restructuring, sleep hygiene, and relaxation training (RT). Sleep restriction techniques limit the amount of time spent in bed and delay the sleep until the patient's sleep drive builds up, making them fall asleep easily. Stimulus control breaks the conditioning of using the bed for general activities like eating, drinking, and using a laptop and reserves the bed for sleep and sex. Cognitive restructuring targets the intrusive thinking patterns which restrict a person from falling asleep. Sleep hygiene, on the other hand, includes a set of guidelines that promote a healthy lifestyle, like daily exercise and avoiding alcohol and caffeine in the evening. Trauer et al.[34], in their meta-analysis, showed that CBT-I is an effective treatment for people with chronic insomnia. The application of CBT-I resulted in notable increases in overall sleep duration and efficiency and significant decreases in sleep latency.[34]

Relaxation training

Another non-pharmacological treatment option includes relaxation therapy, where progressive muscle relaxation starts at the feet and works one way up. It has been described as a useful technique for managing insomnia.[35] In a pilot study by Garcia et al.[36], evaluating the effect of RT on insomnia and quality of life in postmenopausal women, RT showed significant differences between the intervention and control groups with improvements in sleep quality, reduction in the severity of insomnia and vasomotor symptoms. RT has also been shown effective in the recovery of ischemic heart disease, as a therapy for secondary prevention, and in improving psychological and physical health in older patients with heart failure.[37]

Red light therapy

Many recent studies have shown a significant association of red light therapy in improving sleep quality and cognition.[38] In a cohort study involving female basketball players, whole-body irradiation with a red light over 14 days significantly improved the quality of sleep, serum melatonin levels, and endurance performance of the athletes. The Pittsburgh Sleep Quality Index questionnaire measured sleep quality, and the post-intervention analysis demonstrated a greater improvement in the Pittsburgh Sleep Quality Index score in the intervention group compared to the controls ($p<0.001$).[39] Therefore, red light therapy may improve outcomes in patients with co-morbid CVDs, possibly by improvement in overall sleep quality.[40] Some other trials have also shown the role of red-light therapy in mitigating cardiovascular ageing with significant results in its favour.[41]

Recent pharmacological advancements

Dual orexin receptor antagonists

Orexin A and B are neuropeptides demonstrated to induce sympathetic dysregulation and hypertension in animal and human studies.[42] Dual orexin receptor antagonists represent a novel class of drugs utilised for insomnia treatment, exhibiting superior efficacy compared to placebo, as evidenced in a systematic review conducted by Rocha in 2023.[43] Although the effects of Dual orexin receptor antagonists on the cardiovascular system are yet unknown, in animal models, their capacity to inhibit orexin receptors has demonstrated promise in lowering risk factors related to cardiovascular illnesses, such as hypertension.[44]

Ashwagandha

Ashwagandha, also known as Indian Ginseng, is a shrub shown to improve sleep disorders in recent clinical trials. In a randomised controlled trial comprising 150 men and women aged 18 to 65 with insomnia, they were randomised to take Ashwagandha root and leaf extracts and a placebo. The study concluded with improvements in sleep in both groups; however, improvements were significantly higher in the Ashwagandha group (72%) than in the control group (29%).45 Similarly, many other studies have shown significant results for Ashwagandha in improving sleep efficiency, overall sleep time, and sleep latency through mechanisms involving increased expressions of gamma-aminobutyric acid A (GABAA), gamma-aminobutyric acid B1 (GABAB1), and serotonin receptors in the brain.[46,47] Ashwagandha has also been reported to demonstrate beneficial effects on the cardiovascular system by enhancing overall cardio-respiratory endurance (CRE). For instance, a trial by Tiwari et al.[48] found

that Ashwagandha significantly improved athletes' maximum aerobic capacity (a measure of CRE) (p=0.0074) over 8 weeks. The mouse models of myocardial infarction have also demonstrated cardio-protective properties of Ashwagandha through mechanisms involving upregulation of anti-apoptotic pathways and reduction of lipid peroxidation.[49] However, there is no data on actual human subjects being treated with Ashwagandha alone or as an adjunct to standard therapy for CVD like myocardial infarction or heart failure. Although Ashwagandha has shown physiological enhancements in healthy subjects, its use in patients with cardiovascular comorbidities is questionable. In terms of safety, trials have demonstrated that Ashwagandha has been well tolerated over several weeks of consumption, however, few case reports of hepatic adverse effects have raised concerns. Other studies have also claimed Ashwagandha may affect thyroid functions, but no specific dose has been studied. There is also a possibility of interactions with other drugs, which is scope for further research.[50]

DISCUSSION

Sleep disturbances associated with poor sleep, including quantity, quality, and associated sleep disorders, have been shown to negatively impact the risk factors for CVDs like diabetes, hypertension, obesity, and dyslipidemia, leading to increased cardiovascular morbidity and mortality.[50] In a systematic review conducted by Laksono et al.[51], short sleep was significantly and consistently associated with an increased incidence of hypertension and a high risk of developing heart failure. In contrast, both short and long sleep have been shown to increase the risk of AF and coronary heart disease, where short sleep duration was defined as sleep less than or equal to 4.9 hours to less than 7 hours, while long sleep duration was defined as sleep more than or equal to 7.5 hours to more than or equal to 10 hours in the study.[51] In a large-scale cross-section study conducted by the National Health Interview Survey (NHIS), people with both extremes of sleep duration have shown a higher prevalence of hypertension (<6 hours/night, prevalence of 32.4%; ≥10 hours/night, prevalence of 32.5%) compared to the referent category (8 hours/night, prevalence of 23.2%).[52] The sleep heart health study, another cross-sectional study, suggests similar findings. According to the findings, people who sleep less than 6 hours or more than 7 hours a day had adjusted odds ratios for hypertension of 1.66 (95% confidence interval [CI]: 1.35-2.04) and 1.19 (1.02-1.39), respectively; those who sleep between 8 and 9 hours a night and those who sleep for 9 hours or more had adjusted odds ratios of 1.19 (1.04-1.37) and 1.30 (1.04-1.62), respectively (p<0.0001 for the association between sleep duration and hypertension).[53] Although cross-sectional studies have proven the association of both short and long duration of sleep with hypertension, observational studies have only been able to prove the temporal association of short sleep but not long sleep with hypertension.[54] Multiple studies have shown an association between abnormal sleep duration and the prevalence of coronary heart disease. The NHIS discovered that the multivariate odds ratio of CVD was 2.20 (with a 95% CI of 1.78-2.71), 1.33 (1.13-1.57), 1.23 (1.06-1.41), and 1.57 (1.31-1.89) for sleep durations of <5 h, 6 h, 8 h, and ≥9 h when compared to a referent's 7 h of sleep.[55]

Intima media thickness (IMT) indicates the thickness of the inner layers of arteries, specifically the intima and media. It is utilised as a surrogate marker for atherosclerosis, as outlined in research conducted by Kastelein in 2003.[56] Moreover, a study by Zhang et al. in 201457 revealed a subtle connection between carotid IMT (CIMT) and the likelihood of developing coronary artery disease. In the Study of Health in Pomerania (SHIP), individuals who averaged 7-8 hours of sleep showed the lowest IMT values (0.76±0.15 and 0.79±0.16 mm, respectively). Conversely, IMT increased with both shorter and longer sleep durations. For instance, subjects sleeping only 5 hours displayed age- and sex-adjusted differences of 0.042 mm IMT (95% CI 0.008-0.076 compared to those sleeping 8 hours). Similarly, individuals with 11-12 hours of sleep showed increased IMT values (adjusted differences vs 8 hours of sleep: 0.084 mm [0.040-0.128] IMT).[58]

A greater incidence of AF has also been linked to sleeplessness, as per a meta-analysis of prospective cohort studies. It is found to increase the risk of AF by a standardised rate ratio (SRR) of 1.30 (95% confidence interval of 1.26 to 1.35), CVDs by 1.45 (1.29 to 1.64), coronary heart disease by 1.28 (1.10 to 1.50) and myocardial infarction by 1.42 (1.17 to 1.72).59 According to another meta-analysis by Sofi et al.[60], those with insomnia were more likely to experience CVD-related complications or death (relative risk

[RR]1.45, 95% CI: 1.29-1.62, p<0.00001).

The symptoms of OSA include repeated hypoxia caused by episodes of hypopnea or apnea during sleep. It has been shown to cause numerous cardiovascular complications, including hypertension, AF and other arrhythmias, heart failure, coronary artery disease, stroke, pulmonary hypertension, metabolic syndrome, diabetes, and increased cardiovascular mortality.[61] OSA has been shown to increase the odds of hypertension by 1.184 (95% CI: 1.093-1.274, p<0.05) for mild OSA, 1.316 (95% CI: 1.197-1.433, p<0.05) for moderate OSA and 1.561 (95% CI: 1.287-1.835, p<0.05) for severe OSA[62], the severity of OSA being graded by the apnea-hypopnea index (AHI) (AHI 5-15 being mild OSA, 15-30 being moderate OSA and more than 30 being severe OSA). Subjects with OSA compared to those without OSA had greater rates of AF, non-sustained ventricular tachycardia, and complex ventricular ectopy (non-sustained ventricular tachycardia or bigeminy, trigeminy, or quadrigeminy): 4.8 vs 0.9% (p=0.003) for AF; 5.3 vs 1.2% (p=0.004) for non-sustained ventricular tachycardia; and 25.0 vs 14.5% (p=0.002) for complex ventricular ectopy.[63] A grouping of many cardiovascular risk factors, such as diabetes, hypertension, dyslipidemia, and abdominal obesity, characterises metabolic syndrome.[64] Sleep duration has been suggested to play a role in the development of metabolic syndrome. A systematic review has shown that both short and long sleep was associated with metabolic syndrome (RR=1.15, 95% CI: 1.09-1.22, p<0.001) and (RR=1.19, 95% CI: 1.05-1.35, p<0.001).[65]

CONCLUSIONS

Getting enough sleep is crucial for preserving both mental and physical health. Sleep disorders like insomnia and OSA can affect inflammatory, autonomic, and metabolic pathways, potentially impacting cardiovascular health. Research also suggests that abnormal sleep duration, both short and long, is associated with an increased risk of hypertension, diabetes, obesity, and dyslipidemia, leading to elevated cardiovascular morbidity and mortality. Non-pharmacological interventions like CBT-I, RT, and red-light therapy have shown promise in improving sleep quality and mitigating cardiovascular risk factors. Dual orexin receptor antagonists have been suggested to enhance sleep quality and reduce cardiovascular morbidity, but only animal studies are supporting this. Ashwagandha also promises to improve sleep quality and cardiovascular health, but further research is needed. By addressing sleep disorders and promoting healthy sleep habits, the burden of CVDs can be significantly reduced worldwide.

Conflict of Interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Authors' Contribution

Study Conception: MD; MT; PA;FA; DD; BS; Study Design: MD; MT; PA;FA; DD; BS; Literature Review: FA, DD; Critical Review: BS; Manuscript preparing: MD, MT, PA.

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