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Review article

# Roles of sleep deprivation in cardiovascular dysfunctions

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ABSTRACT

It is widely recognized that inadequate sleep is associated with multiple acute and chronic diseases and results in increased mortality and morbidity for cardiovascular diseases. In recent years, there has been increasing interest in sleep related investigations. Emerging evidence indicates that sleep deprivation changes the biological phenotypes of DNA, RNA and protein levels, but the underlying mechanisms are not clear. We summarized the current research on the detrimental roles of sleep deprivation on the heart and elucidated the underlying mechanisms of sleep deficiency to improve our understanding of sleep deprivation and the emerging strategies to target this process for therapeutic benefit.

Abbreviations

| | |
|---|---|
| SD | sleep deprivation |
| TSD | total sleep deprivation |
| REMSD | rapid eye movement sleep deprivation |
| CSD | chronic sleep deprivation |
| SOD | superoxide dismutase |
| UPR | unfolded protein response |
| CVD | cardiovascular disease |
| MMPM | modified multiple platform method |
| MI | myocardium infarct/myocardium ischemia |
| STEMIs | ST-Segment Elevation Myocardial Infarction |
| SR | sleep restriction |
| PSD | partial sleep deprivation |
| ASD | acute sleep deprivation |
| ROS | reactive oxygen species |
| ER stress | endoplasmic reticulum stress |
| CHD | coronary heart disease |
| CRP | C-reactive protein |
| lncRNA | long non-coding RNA |
| miRNA | microRNA |
| ceRNA | competing endogenous RNA |

Long working hours and increasing shift-work in modern society have reduced sleep duration and altered sleeping patterns [1,2]. The 2017 China sleep quality report released by HUAWEI Sports Health showed that approximately 69.4% of cell phone users' sleep quality was not good, and 23% of young people had a habit of staying up late.

Significant attention has recently focused on the role of sleep deficiency and disturbance. These factors affect multiple organ systems and modulate an expanding list of disease processes. One study showed that people who sleep less than 7 h per night experience a 12% to 35% increased risk of death compared to people who sleep more than 7 h [3].

Sleep deprivation (SD) is related with the increased incidence of adverse cardiovascular disease (CVD) events. The cardiac diseases caused by sleep deprivation involve an intricate process that is orchestrated by a wide spectrum of causal and regulatory factors [4]. Nonetheless, there is a small but growing body of literature investigating the mechanisms of the detrimental effects of SD on cardiovascular pathophysiology. We review the current literature with particular emphasis on the mechanisms of SD influence on the cardiovascular system and further discuss the pharmacological approaches to treat SD-induced dysfunction and improve human health.

## 1. SD and cardiovascular diseases

Fig. 1 shows a model of signaling pathways that are involved in sleep deprivation and lead to cardiac accidents and the development of heart disease. Emerging evidence shows that sleep deprivation may be an important risk factor in obesity, type 2 diabetes, and hypertension, and it is a potentially independent predictor of stroke, CHD and CVD [5]. An increasing number of cross-sectional and prospective epidemiological studies provide evidence for an association between short

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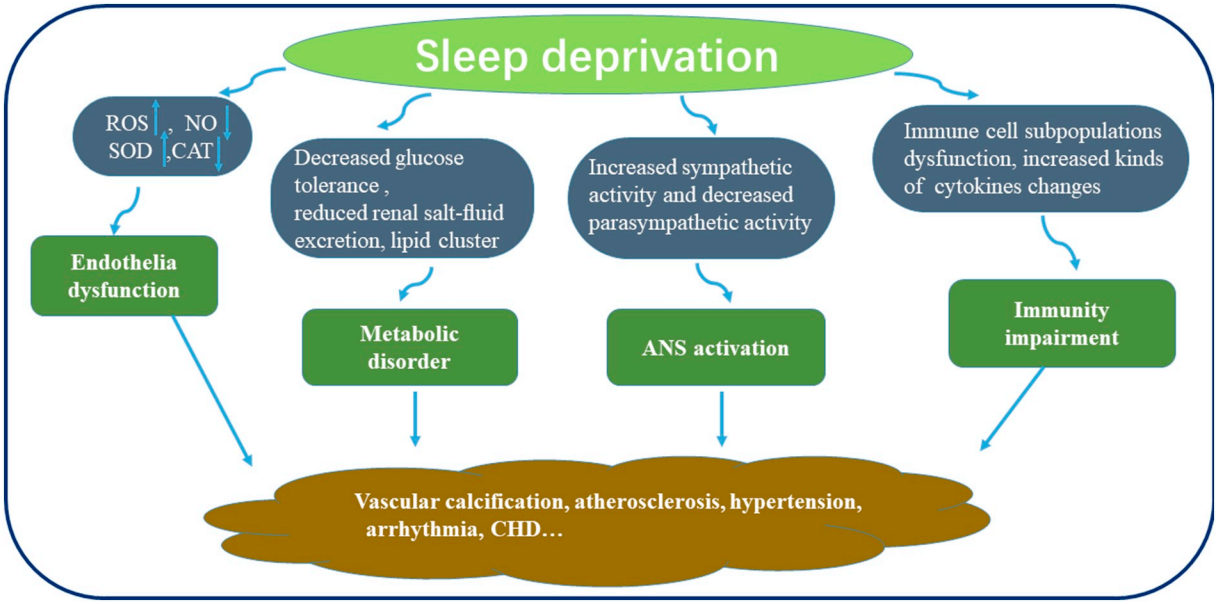


**Fig. 1.** Effects of sleep deprivation (SD) on cardiovascular diseases.
SD results in increased reactive oxygen species (ROS), nitric oxide (NO), superoxide dismutase (SOD) and catalase (CAT) levels, which further lead to endothelial dysfunction. SD decreases glucose tolerance and renal salt-fluid excretion and promotes lipid clustering, which will ultimately result in metabolic disorder. SD stimulates sympathetic activity and decreases parasympathetic activity. Immunity impairment includes immune cell subpopulation dysfunction, and increased changes in cytokine types. These effects are responsible explanations for the relationship of sleep deprivation and cardiovascular diseases, such as vascular calcification, hypertension, atherosclerosis, arrhythmia, and myocardial infarction.

sleep and cardiovascular diseases after controlling for age, body mass index (BMI) and various other confounders [6].

## 2. Potential effect on hypertension

Prospective cohort research of 18,958 initially healthy women who were followed up over 24 years showed that 5 years or more of rotating night shift work significantly increased their risk of CHD [9,10]. Poor sleep quality and short sleep duration produce fluctuations in blood pressure. Cross-sectional and longitudinal epidemiological studies revealed that a short sleep duration was involved in higher blood pressure and hypertension [7]. Kai Lu's group found that sleep duration shorter than 8 h was accompanied with increased hypertension using odds ratios [8]. The duration of sleep exerts a positive effect on serum homocysteine levels, which are strongly associated with H-type hypertension [9]. Sleep deprivation in hypertension is mainly caused by altered autonomic nerve activities and humoral factor changes.

## 3. Relationship with cardiac arrhythmia

A limited amount of total sleep time was also related to a greater reduction in high-frequency heart rate variability under stress conditions and caused prolonged elevations in the heart rate and diastolic pressure following tasks [6]. An increased probability of ventricular tachycardia and ventricular fibrillation occurrence was observed in sleep-deprived animal models [10], which indicates that there may be a link between sleep curtailment and cardiac arrhythmia. Disorder of autonomic nerve activities caused by sleep deprivation is a pivotal element in cardiac arrhythmia.

## 4. Vulnerability to CHD after SD

Short and long sleep durations are independently associated with a modestly increased risk of coronary events [11]. In addition to the acute effects observed, frequent night-calls over a longer period possibly elicit sustained alterations in cardiovascular homeostasis, which highlight the association of night shift with an increased risk profile for cardiovascular disease [12]. A large systematic review and meta-analysis composed of 34 observational studies concluded that shift work was associated with myocardial infarction risk [13]. Moreover, paradoxical sleep deprivation also produced significant damage to the cardiac structure and function, which was probably related to an autonomic dysfunction in the myocardial catabolic frame [14].

Obviously, sleep loss affects the occurrence and progression of cardiovascular disease, but it also significantly impacts disease recovery and prognosis. Sleep-deprived recipients suffer more STEMIs compared to non-sleep-deprived subjects [15]. Additionally, in sleep deprived females compared to control females, the post ischemic recovery of cardiac function is worsened by sleep deprivation [16]. Sleep deprivation leads to an increase in PCI surgeries in patients who are more likely to present with cardiogenic shock or cardiac arrest, and these patients received fewer elective PCI surgeries and more emergent PCI surgeries [17].

After illustrating the cardiac dysfunctions caused by sleep deprivation, we next focus on the pathologies that emerge in sleep-deprived subjects.

## 5. Sleep deprivation and types of cardiac pathologies

The most acknowledged and recently proposed links are reviewed below and presented in Fig. 1.

### 5.1. SD-induced endothelial dysfunction

Sleep deprivation-mediated inflammation may be responsible for mild to moderate multi-organ damage in mice [18]. Sauvet's study demonstrated that 24 h of wakefulness in rats produced a decrease in endothelial-dependent vasodilation that was not related to changes in blood pressure or sympathetic activation [19]. Moreover, sleep deprivation induces inflammatory mediator products by activating the sympathetic system and increasing oxidative reactions [20]. Lungato's study demonstrated that SD produced an imbalanced redox status in spleen cells, which was confirmed by increasing SOD activity and expression and a reduction in catalase activity (Fig. 1). These changes

stemmed from mitochondrial metabolism dysfunction and vulnerability in cell signaling pathways, which may explain some of the cytotoxic action of SD [21]. Recent studies found that inhibition of inflammation pathways exhibited beneficial effects in SD animal models. For example, the over-expression of cryptochrome-1 (CRY-1) inhibited sleep deprivation-induced vascular inflammation, which may involve the NF–κB and cAMP/PKA pathways [22]. We know that sleep deprivation induces inflammation and increases oxidative stress, which may exacerbate some disease processes or influence the prognosis of patients who suffer from poor sleep. Conversely, poor health may further worsen sleep quality.

### 5.2. Sleep restriction accelerates metabolic disorder processes

Modern lifestyles promote diabetes, hypercholesterolemia, obesity, and other metabolic syndromes. Short sleep duration is involved in metabolic disorders in many epidemiological studies [23]. Short-term physiological studies revealed that insufficient and/or inadequate sleep slowed undesirable glucose metabolism and increased the levels of inflammatory mediators, which suggest that sleep is an important homeostatic regulator of factors that contribute to the development of metabolic syndrome and cardiovascular disease [20]. Koban found that the following pathologies were reliably produced: hyperphagia, weight loss, elevated energy expenditure, hypothyroidism, reduction in core temperature, deterioration in physical appearance, and reduced levels of anabolic hormones [24]. Several studies found that sleep deprivation also altered α, β-cell function, which resulted in decreased glucose tolerance and compromised insulin sensitivity in diabetes [25–27]. Leptin and ghrelin are a pair of hormones that provide information about the energy status to regulate human appetite and modulate hunger and food intake to sustain normal insulin function. Sleep deprivation decreases leptin levels [28], and increased ghrelin levels are found in sleep deprivation with an increased diabetes risk [29,30]. Sleep deprivation is considered a stressful condition, and it promotes salt intake and suppresses renal salt-fluid excretion [30], which ultimately leads to hypertension. Vilma Aho's study indicated that prolonged sleep deprivation modified the cholesterol pathways at the level of gene expression and serum lipoproteins, and specific metabolic modulations induced by SD likely explain the association between restricted sleep and atherosclerosis, which is characterized by a slow build-up of lipid plaques in arterial walls [31]. Sleep deprivation also influenced serum levels of HDL and LDL lipoproteins, and the increased acyl carnitine levels after short sleep duration may be a marker of altered metabolic processes [32]. These studies suggest sleep deprivation as the catalyzer of metabolic system dysfunctions, and the consequences of sleep deprivation on metabolic system are equally applicable in heart diseases.

### 5.3. Sleep insufficiency stimulates autonomic nerve activities

Research showed an impairment of autonomic regulation in healthy young subjects with acute sleep deprivation (ASD) [4]. The same results were found in different populations, in which ASD increased sympathetic activity and decreased parasympathetic activity in the hearts of healthy humans [33]. Blood pressure dips an average of 10%–20% during sleep, and short sleep duration in the summer results in higher daily blood pressure, and chronically insufficient sleep may produce and maintain hypertension [7]. Many epidemiological studies found that the sympathetic nervous system affected heart rate variability. Musa Cakici M.D.'s study found that even one night of SD was intensively relevant and produced subclinical left ventricular diastolic functional changes, higher TpTe intervals and TpTe/QT ratios in healthy young adults [34]. Poor sleep quality and short sleep duration may lead to unhealthier heart rate variability patterns in children by sympathetic over parasympathetic dominance [35]. Our former study focused on partial sleep deprivation (PSD) and observed abnormal cardiac electric activity in deprived rats, which indicated that the myocardial cell damage may due to PSD and suggested that sleep deprivation increased the risk of CHD [36]. Taken together, sleep deprivation exerts strong effects on autonomic nerve activities, which further results in various heart diseases.

### 5.4. Sleep loss weakens our immunity and makes us vulnerable to infectious heart diseases

There is strong evidence showing that reduced sleep quality and quantity are detrimental to the immune system and that sleep deprivation increases the susceptibility to viral, bacterial, and parasitic infections [37]. Many studies have demonstrated that total sleep deprivation (TSD) and rapid eye movement sleep deprivation (REMSD) could modify components of the immune system, such as the percentage of cell subpopulations (e.g., CD4+, CD8+, and NK) and cytokine levels [13,38,39]. In addition, a shorter sleep duration in the natural setting was associated with the down-regulation of specific immune and inflammatory programs in circulating leukocytes [40]. A. Zager's study found that the spleen weight, total leukocytes, and lymphocytes decreased after 21 days of sleep restriction (SR) and that the complement C3 and corticosterone concentrations increased after 96 h PSD in contrast to the control group [41]. Moreover, some experimental evidence links sleep deprivation to paradoxical findings on the immune defense system. Both decreased and increased numbers of lymphocytes and NK cells were observed in SD groups [42,43]. Enhancement of post-infection sleep is a conserved behavioral response that has a beneficial function to the host during bacterial infection. Tzu-Hsing Kuo observed that acute sleep deprivation elevated NF-κB activity, longer post-infection sleep time, and improved survival during bacterial infection [44]. Infectious heart diseases, such as infective endocarditis, bacterial or viral myocarditis, are strongly related with impaired levels of immune-relevant molecules (macrophage, T-cell, Th2, and cytokine types) dysfunction [45]. Collectively, it is obvious that sleep deprivation influences the stability of the immune system. Moreover, the interaction between sleep loss and immune disorders is bi-directional, which means that sleep deprivation modulates the immune system, and the immune response alters sleep patterns [37].

### 5.5. Increased CRP after sleep deprivation induces CHD

It has been found that poor sleep quality is independently related to higher hs-CRP (high sensitivity C-reactive protein) in females [46], and one night of partial sleep deprivation increases the level of ultra-sensitive c-reactive protein (us-CRP) [47]. However, different experimental conditions and objectives produced different outcomes. Giampa's study showed no differences in CRP serum levels [14]. Michael R et al. suggested that sleep disturbance and a long sleep duration, but not a short sleep duration, were associated with increases in markers of systemic inflammation, including CRP [48]. Additionally, epidemiologic studies have proposed CRP (C-reactive protein) as a predictor of the risk CHD [49,50]. Hs-CRP may bind and transfer ox-LDL to macrophages, which is a strong risk factor for the early, but not the advanced, stage of CHD [49]. Therefore, it is not difficult to propose that CRP mediates sleep deprivation and increases the CHD risk.

### 5.6. SD produces other cardiovascular pathological changes

Diane S Lauderdale also found that sleep deprivation increased coronary artery calcification incidence, which is a subclinical predictor of coronary heart disease [51]. However, few articles on this subject were retrieved, which suggests that it may be a potential research point.

## 6. Mechanisms of SD-induced cardiac dysfunction

Fig. 2 shows a model of the possible mechanism of cardiovascular

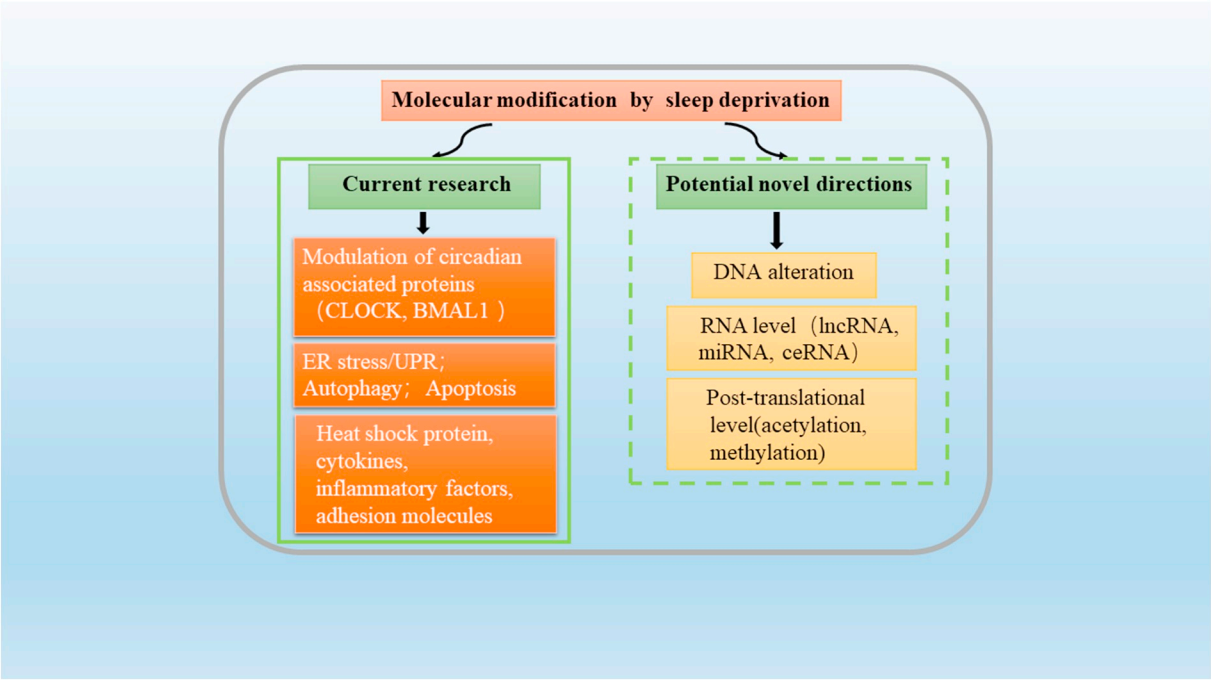


**Fig. 2.** Molecular modifications of sleep deprivation.
Centering on the effects of sleep deprivation on molecular changes, the contents presented in solid indicate the viewpoints in current research: alterations in circadian modulation protein levels, endoplasmic reticulum (ER) stress/unfolded protein response (UPR), autophagy and apoptosis. Inflammation-related molecules, such as cytokines, heat shock protein, inflammatory factors, and adhesion molecules. The contents in dotted type suggest potential novel directions for sleep deprivation investigations, such as alterations of DNA and RNA levels (lncRNA, miRNA, ceRNA), and post-translational levels (acetylation and methylation).

dysfunction in sleep deprivation.

### 6.1. AMPK-mTOR

Sleep determines transcription and translation aspects of the destiny of cells. However, most investigations focus on the nervous system, and little is known about how sleep and sleep deprivation influence cardiovascular signaling pathways. AMP-activated protein kinase (AMPK) is a critical regulator of cellular metabolism and plays an important role in diabetes, cancer, and vascular disease [52], as well as the additional cellular processes that may contribute to cardiomyocyte function and survival in healthy and diseased hearts [53]. The mechanistic target of the rapamycin (mTOR) signaling pathway regulates many important cellular processes and is implicated in an increasing number of pathological conditions, including cancer, obesity, type 2 diabetes, and neurodegeneration [54]. The AMPK signaling pathway is a positive regulator of autophagy, and AMPK acts as a metabolic checkpoint in the metabolic monitoring system and stimulates autophagy by inhibiting mTOR, which is implicated in many diseases [55]. Sleep deprivation is a potent circadian rhythm destroyer that plays a pivotal role in autophagy regulation primarily via modulating circadian proteins, and AMPK-mTOR may participate in rhythm-associated diseases [56]. However, there are few investigations on the effects of sleep deficiency and deprivation on AMPK-mTOR, especially in heart.

### 6.2. UPR/ER stress

Alterations of endoplasmic reticulum (ER) homeostasis lead to the accumulation of unfolded or misfolded proteins in the ER lumen, which is known as ER stress. ER stress activates the unfolded protein response (UPR). UPR activation promotes cell survival or death when ER stress is chronic or severe [57]. Many cardiac diseases trigger ER stress, including ischemia and hypoxia, and whether the effect is survival or lethal is contradictory [58]. Furthermore, recent investigations have shown that sleep can influences ER stress. Nirinjini Naidoo's study provided evidence that modest sleep deprivation induced cellular stress and activated adaptive response in brain, in which ER stress was involved [59]. This phenomenon was observed in the central nervous system and peripheral tissues. It was found that aging and SD cooperate to induce the UPR in pancreatic tissue, leading to some accompanying metabolic dysfunctions [60]. Paul J. Shaw demonstrated that flies carried a mutation for heat-shock protein (Hsp)83 after sleep deprivation; Hsp83 protective during cellular stress [61], which indicates that sleep deprivation lowers the ability to defend against outer stress. Ron C Anafi et al. identified that protein synthesis was significantly different between sleep and sleep deprivation in the mouse heart and lung because of the unfolded protein response activated by ER stress and showed that sleep reduced CHOP, Bip, Casepase12 and other specific markers of ER stress both in the heart and lung as well as enhanced metabolic processes in an organ in specific way, promoting cellular survival [62]. Sleep deprivation induces hyperphagic behaviors and reduces leptin signaling in the hypothalamus, both of which are mediated by the activation of ER stress, potentially resulting in a SF-induced weight gain and metabolic dysfunction [63].

### 6.3. Circadian rhythm disorders

Sleep is regulated by the suprachiasmatic nucleus, the central biological clock in circadian and circannual cycles [64]. The 2017 Nobel prize for medicine was awarded to three American scientists for their discoveries of the molecular mechanisms of circadian rhythm. Disorders of the circadian rhythm have been shown to be caused by numerous pathological processes, including genome transcription, protein synthesis, protein post-translational modification [65]. Human diseases, such as age-dependent cardiovascular diseases, metabolic diseases and neuronal diseases, exhibit a strong relationship to circadian rhythm impairment [66–68]. CLOCK/BMALL1 is the central regulator of circadian rhythm and controls many physiological functions [65,69,70]. Disruption of Clock leads to age-dependent cardiomyopathy [68], and the lack of Bmal1 in bone marrow-derived progenitor cells (BMPCs) further

aggravates endothelial injury due to the inability of these cells to adequately participate in vascular repair [71]. Sleep loss alters the epigenetic and transcriptional profiles of circadian clock genes, including BMAL1, CLOCK, CRY1, and PER1 [71]. Sleep deprivation notably disrupts the circadian rhythm, which further supports the detrimental effects of sleep deprivation on health.

### 6.4. Genome-wide landscape modifications

Sleep deprivation affects the DNA structure, transcription and translation. Total sleep deprivation (TSD), alone or on combination with psychological stress, does not produce a significant increase in DNA damage, and radiation-induced DNA damage decreased significantly in response to TSD [72]. However, different results indicated that partial sleep deprivation (PSD) increased DNA damage responses (DDR), the senescence-associated secretory phenotype (SASP), and senescence indicator p16 expression in older adult humans [73]. M.L. Andersen's group found that PSD promoted genetic damage in the blood, brain and liver in rodents, but a recent study showed that SD did not produce genetic damage in skin cells of old, hairless mice [73]. One possible explanation is that the aging process resists SD-induced DNA damage. The large numbers of genes that are affected by sleep deprivation reflects the great complexity of the genomic response triggered by sleep, including c-fos, Zif-268, Arc, and Homer1 [74]. As for epigenetic modifications, a study in the brain showed that SD altered the cortical genome-wide distribution of two major epigenetic marks: DNA methylation and hydroxymethylation [75,76]. DNA methylation partially regulates the sleep-wake cycle and the genes connected to CLOCK/BMAL1, cryptochrome 1 (CRY1) and PER1 [71]. One study showed that many CpG sites were group-wise associated with the same gene [77]. DNA methylation in cardiac hypertrophy is dynamic [78]. A preliminary study provided evidence that CHD patients had relatively lower methylation levels in the angiopoietin-like protein 2 (ANGPTL2) promoter region than controls [79]. On the basis that sleep and sleep loss induce changes in many mRNA species, it was demonstrated that sleep loss changes microRNA levels, which regulates synaptic protein synthesis in the brain [80]. Sleep deprivation downregulates the expression of microRNA (miR)-19b, which inhibits hematopoietic stem cell (HSC) migration and homing and further impairs HSC transplantation [81]. Sleep deprivation alters hypothalamic lncRNA expression, which varies by strain, including 1700020I14Rik, 9430037G07Rik, A330023F24Rik, Gm15832, Gm17275, Neat1, Gm15050 and Gm17337 [82]. Interestingly, heart disease-associated miR-1, miR-30c and let7d were downregulated in sleep-deprived rats [83]. However, limited strong evidence is available in the literature, and investigations are urgently needed to explain the molecular changes influenced by sleep deprivation on cardiovascular system protein, DNA, and RNA levels. ncRNA regulation may be a novel and promising direction for further study.

### 6.5. Further pharmacological approaches to sleep deprivation

Chinese medicine treatment for the side effects of sleep deprivation was investigated. Melatonin improved sleep deprivation-induced neuronal disorders by reducing ROS levels [84]. Gongjin-dan was beneficial for fatigue under insufficient sleep conditions in endocrine and immunological mechanisms [85]. Traditional Chinese medicine tranquilization methods improved the pathological factors of sleep deprivation via a multiple component, multiple target and multiple pathway approach, which reflects the purpose of psycho-cardiology treatment [86]. Walnut (*Juglans regia*) peptides reversed sleep deprivation-induced memory impairment in rats by reducing oxidative stress and apoptosis in PC12 cells [87]. The beneficial effect of Jiao-tai-wan on ameliorating inflammation and insulin resistance was demonstrated in partially sleep-deprived rats by up-regulating hypothalamic and peripheral circadian clock gene CRY and activating PI3K/AKT signaling in partially sleep-deprived rats [88]. In summary, an early diagnosis and appropriate treatment of subjects with SD are essential to reduce the risk of cardiovascular and metabolic diseases in the general population.

## 7. Conclusion

Study on sleep disorders is a hot topic. Currently, an increasing number of people suffer from sleep disturbances, but our understanding of the regulation and molecular mechanisms of sleep deprivation on cardiovascular diseases remains rudimentary. Hence, the investigations on sleep deprivation should be diversified in gender, age, other conditions and experimental models. The findings of sleep deprivation on the cardiovascular system are controversial, but it is clear that the quality and quantity of sleep is important to maintain normal cardiovascular functions [89].

Although we concentrated on sleep loss, it is known that longer sleep duration can also increase the mortality and incidence of cardiac diseases [90]. Integrating sleep into public health research is appropriate for identifying a novel approach and closing the gap in health disparities. Optimization of sleep is beneficial to human well-being, and further research is warranted to clarify the regulation and function of sleep on the heart before the related molecules may be considered therapeutic targets and disease biomarkers. Future large population and experimental studies are needed to evaluate the influence of sleep deprivation on cardiovascular diseases.

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## Conflict of interest statement

The authors declare that there are no conflicts of interest.

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