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# ABSTRACT

Approximately 121.5 million individuals worldwide are diagnosed with cardiovascular diseases. Advancing age increases the risk of cardiovascular diseases in both genders. Circadian rhythm is accountable for well-ordered roles of many different body functions. The peak level of specific hormones and functions follow the biological interpretations of circadian rhythm, whether daylight or night time. Sleep disorders, aside from shift work, like obstructive sleep apnea, can induce circadian disruption that influences complex immunological, metabolic, and cardiovascular functions, eventually raising cardiovascular diseases risk. Online databases were systematically examined to investigate studies on randomized controlled trials (RCTs) from the past five years, assessing the impact of varying sleep disorders and shift work in inducing circadian disruption and its impact on the risk of cardiovascular diseases. After administering multiple inclusion and exclusion criteria, 18 studies were selected, but only eight documents were chosen to review after a comprehensive analysis of the studies. Each document was assessed for fitness of quality. Sleep-related disorders and shift work were discovered to induce circadian malfunction and disruption, and correlated with increased risk of cardiovascular diseases. Approaches to control disorders of cause should be developed to decrease the risk of cardiovascular diseases.

**Keywords:** circadian disruption, insomnia, shift work, cardiovascular risk, sleep

# INTRODUCTION

In 2016, around 121.5 million individuals worldwide were diagnosed with cardiovascular diseases, which is on par with 48% of the US population. Almost 47% of the US adult population is affected by hypertension [1]. The cardiovascular diseases incidence constantly progresses in men and women as their age advance. In a data retrieved in 2016, cardiovascular diseases are responsible for more than 2,303 deaths daily, having one person died every 38 seconds [1]. The high morbidity and mortality rates could be reduced with appropriate risk factors regulations. Beside primary risk factors, such as hypertension, obesity, diabetes, and metabolic syndromes, numerous other factors like stress and sleep disorders might impose a vital function. Additionally, circadian rhythm disruption is investigated to be a potential contributor to cardiovascular diseases.

Like the rest of mammals, humans have an internal timekeeper who maintains the schedule of multiple body functions. There is an interval where said functions peaked and an interval of stagnation when the functions are inactive. This internal timekeeper is known as the circadian rhythm, allocating 24 hours in a day to a 'biological daytime' and a 'biological night time', without regard to the environment daytime or night time [2].

This variance induces modifications in body heat and temperature and circulating levels of melatonin and cortisol [3, 4]. The circadian system comprises of the circadian oscillators and the suprachiasmatic nucleus. The suprachiasmatic nucleus is found in the hypothalamus, functioning as the center for control of the circadian system. However, circadian oscillators are located in multiple peripheral organs, such as the liver, pancreas, and. This finding emphasizes the variation and the cyclical activity of cardiovascular performance and metabolic capacities on differing occasions. Circadian oscillators produce their rhythm independently. Both of circadian system organs work in sync to deliver cyclical functions [2]. If the connection linking the peripheral and central circadian controllers is interrupted, the synchronization process may be compromised. Circadian rhythm is calibrated with the day timings of the external environment. The biological daytime is adjusted with the light time or the daytime; nevertheless, the biological night time is adjusted with the dark or night time. This adjustment is compromised when the internal timings work at an unmatched time to the real day time and harmonious with each other. This condition is described as circadian disruption. Disruption is initiated by shift work, jet lag, sleep disorders like obstructive sleep apnea, insomnia, et cetera. Circadian disruption induces many metabolic and cardiovascular health problems by damaging the physiological mechanism like blood pressure, immunity, insulin sensitivity, control of the cardiac autonomic system, and raise the risk of particular diseases [5].

This review focuses on the major risk factors of cardiovascular diseases and knowledge discrepancies concerning circadian disruption and sleep disorders as major risk factors for cardiovascular diseases or metabolic syndromes, such as diabetes, which later incite the development of cardiac diseases. This review will evaluate the impact of factors that provoke circadian disruption, such as sleep disorders or shift work, to cardiac diseases. By approaching problems to benefit prevention measures of cardiovascular diseases, improved health in those with cardiovascular diseases is expected.

# REVIEW

## Methods

Online database of PubMed was systematically searched as a means of data retrieval. Specific investigations of randomized controlled clinical trials (RCTs) were done, especially those evaluating the relationship of circadian disruption due to shift work or sleep disorders with cardiovascular diseases. The keywords being used are: circadian disruption, insomnia, shift work, cardiovascular risk, cardiac diseases, and arrhythmias. The keywords are used in combination or alone to examine published studies from the last five years. Fifty papers written in English were obtained, and twenty papers were finally selected following removals of duplicate papers and abstract reviews. Next, the application of inclusion and exclusion criteria were performed, which kept only 12 papers. Eight articles were concluded following comprehensive reviews. Chosen papers were all appraised for quality and peer-reviewed.

## Inclusion and Exclusion Criteria

First, papers written in English from the past five years assessing the relationship of circadian disruption and cardiovascular diseases were included. Only papers that have been peer-reviewed were selected. Research articles in different languages other than English, unpublished studies, or review papers were eliminated. Papers which evaluate the immunologic or metabolic effects of circadian disruption were furthermore eliminated.

## Results

Of all eight clinical trials that are chosen, four of those evaluated the role of working in a shift as the cause of circadian*disruption* in cardiovascular diseases [6, 7, 8, 9]. Between those studies, five evaluated the issues which are related to sleep, like a lack of sleep, obstructive sleep apnea, and insomnia as the factors

contributing to cardiovascular diseases [8, 10, 11, 12, 13]. Only one of those studies evaluated all three of the mentioned factors as a potential factor which contribute to the development of cardiovascular diseases [7]. The chosen studies from the review are presented in Table 1 [6-13].

**Table 1.** A comparison table of randomized controlled trials included in the review

| No. | Author | Year | Study Type | Study Purpose |
|---|---|---|---|---|
| 1. | Morris et al. [6] | 2015 | RCT | Assessed circadian disruption impact in shift worker |
| 2. | Barger et al. [7] | 2017 | RCT | Shift work, sleep apnea, and sleep duration are each an independent cardi |
| 3. | Jarrin et al. [8] | 2018 | RCT | Evaluated the role of shift work and sleep abnormalities on heart failure c |
| 4. | Dutheil et al. [9] | 2017 | RCT | Contrasted the cardiac stress in Emergency Physicians during 14-hours sh |
| 5. | Kanno et al. [10] | 2016 | RCT | Reviewed insomnia's effect on heart failure |
| 6. | McGrath et al. [11] | 2017 | RCT | Determined the role of risk factor education compared to sleep interventio |
| 7. | Gheili et al. [12] | 2018 | RCT | Contrasted the role of Oxazepam and Melatonin insomnia management o |
| 8. | Carroll et al. [13] | 2015 | RCT | Revealed the comparative efficacy of TCC, CBT, and SS to decrease the |

Note: RCT = randomized controlled trial; ACS = acute coronary syndrome; STEMI = ST-elevation myocardial infarction; PCI = percutaneous cardiac intervention; CBT = cognitive behavioral therapy; SS = sleep seminar; TCC = Tai Chi CHIH

Limitations

As many as three clinical trials from the past five years were discovered to evaluate the impact of working in a shift on cardiovascular diseases. However, two studies did not assess the job characteristics in the shift, or the intensity and stress included that may heighten its impact on the risk of cardiovascular diseases. Consequently, the exact elevation in risk imposed in working in a shift could not be thoroughly estimated.

# DISCUSSION

The internal system, or known as the circadian rhythm, is accountable for well-ordered roles of the immunological and metabolic systems. The release of cortisol is correlated with the moderation of the circadian rhythm; cortisol begins to increase several hours after sleep, peaked in early in the morning and in the hours of awakening, promoting the body to shift from biological night time to biological daytime. Any sleep disturbances influence the release of circadian; it rises in wakefulness, insomnia, or reduced sleep. Likewise, working in shift disturbs the regular pattern of release, induces lethargy, and causes the release of epinephrine and norepinephrine, sequentially affecting the variability of the heartbeat, heart rate, and blood pressure. Melatonin begins to rise after nightfall, peaked by midnight, then progressively declines in the following half. Working conditions with rotating shift provoked abnormality in melatonin concentration [14]. Melatonin concentration is related to the occurrence of cardiovascular events. It was found to be decreased in coronary artery diseases (CAD) patients. The lower the concentration of melatonin, the more the risk of cardiovascular events, such as myocardial infarction (MI). It confirms that the severity of cardiovascular diseases was inversely proportional to melatonin levels [15]. Several cardiovascular variables were modified in a diurnal pattern with the circadian pattern, involving blood pressure, heart rate, and the activity of fibrinogen [16]; and also platelet activity, endothelial function, vascular tone, and lipid metabolism [17], which partially reveals high occurrence of cardiovascular events in the morning following the circadian rhythm [17]. In 2011, Sheer at al. explained the relationship between the activity of platelets with circadian rhythm [18], which was seen to be most eminent in early daylight [19]. These variations occur by the intrinsic circadian rhythm; hence, peripheral oscillators reflect the circadian rhythm and are influenced by circadian disruption. Added factor in predicting cardiovascular diseases' risk is the concentration of inflammatory markers, such as interleukins [20].

## Effect of Shift Work and Sleep Disorders

Multiple experts have advised that working in shift prompted circadian disruption by proceeding the body to work adversely to the physiological cycle, later affecting to cardiovascular events [21, 22]. A meta-analysis pointed that irregular sleep duration of fewer than seven hours or longer than eight hours was responsible to adult mortality. Decreased sleep duration is particularly correlated with congenital heart diseases and cardiovascular diseases [1]. Working in shift exhibits an individual to the light at an abnormal periods. Additionally, sleep disorders like obstructive sleep apnea, insomnia, and altered pattern or reduced sleep duration induces failure of synchronization among the body's physiological circadian rhythm and functions. In turn, the condition heightens the risk of cardiovascular diseases [23, 24]. This circadian disruption induces floods of unnecessary hormones when they are not needed in that much concentration, and decreased concentration when they are most needed. The condition will further change stress response flexibility; eventually leading to excess glucocorticoid and incites its cognitive and metabolic consequences. These consequences raise the risk of cardiovascular diseases.

Moris et al. in 2016 condcuted an RCT which pointed that the circadian disruption evoke increased blood pressure and biomarkers for inflammatory states, such as interleukin-6 (IL-6), C-reactive protein (CRP), and tumor necrotic factor (TNF), having each as an independent cardiovascular diseases' risk factor. These outcomes were enhanced along with prolonged duration of circadian disruption [6]. Rising blood pressure in circadian disruption occur in systolic and diastolic blood pressure [6]. A different multicenter study called SOLID-TIMI 52 trial, implemented long-term followups of 13,026 subject. The study reveals the connection within the causes of circadian disruption, such as various sleep disorders and working in shift, heightened the chance for cardiovascular disorders. Individually, each cause is an independent risk factor. Moreover, the consequence is magnified if an individual holds more than one risk factor [7]. In 2018, Jarrin et al. carried a study to re-evaluate the data from two earlier trials. They investigated the connection of two insomnia phenotypes, one with normal, conventional sleep duration and one with insufficient sleep duration, with outcomes affecting cardiovascular system. They discovered that insomnia with insufficient sleep duration decreased the activation of parasympathetic nervous system, eventually prompting sympathovagal imbalance [8]. The heart rate and its variation varied among individuals with normal sleep duration and individuals with less than six hours of sleep. The result was observed across shorter duration but not in longer period [8]. The outcomes are produced by weakened parasympathetic activity, leading to increased blood pressure and tachycardia; it further reduces insulin secretion and increases markers for inflammation, such as cytokines, having the definite alterations to portray circadian disruption. Weakened parasympathetic activity adds to the development of cardiovascular morbidity [25, 26]. Suppose shift work is blended with stressful circumstances. In that case, as was confirmed by Dutheil et al., the condition commences to more persistent and frequent tachycardia. They observed emergency physicians throughout a 14-hours shift and a 24-hours shift. The emergency physicians displayed recurrent tachycardia occurrences, reaching up to 180 beats per minute. The cardiac stress was experienced doubly on the shift day as opposed to the non-shift days [9].

Changes in body physiological functions tax an additional stress and worsen the disease prognosis in patients with previous history of cardiovascular events. A Japanese study by Kanno et al. investigated the impacts of insomnia on heart failure patients and exhibited that insomnia has the ability to worsen heart failure's prognosis [10]. Insomniac patients expressed markedly elevated aldosterone ($p=0.047$) and renin concentrations ($p=0.042$) [10]. Likewise, insomniac and ST-elevation myocardial infarction (STEMI) patients found that melatonin decreased their anxiety and increased the quality of sleep compared to oxazepam, and also perceived to have a beneficial effect on cardiovascular health [12]. However, SLEPT trial confirmed that, despite increasing psychosocial health, sleep intervention did not improve the reading of systolic blood pressure in a short period (24 hours) [11]. Intervention therapies for sleep, such as Tai Chi Chih (TCC) or cognitive behavioral therapy (CBT), recorded improvement in cardiovascular hazard in a year, as confirmed in a research which assessed the impacts of sleep on markers, such as insulin, inflammatory markers, and lipid profile [13].

# CONCLUSIONS

The circadian rhythm is accountable for a coordinated and well-ordered purposes of numerous functions in cardiovascular, immunological, and metabolic systems. Cyclical peaks and fluctuations control these functions, as well as numerous other hormonal and biological system. Working in shift and several sleep disorders, such as obstructive sleep apnea, insomnia, and reduced sleep contribute to the disposition of circadian disruption, which later raises the risk cardiovascular diseases. The effect can be immediately associated to melatonin or cortisol concentrations, or indirectly by its impacts on metabolic and immunological systems. If supplemented by stressful work circumstances as experienced by healthcare professionals, shift work can further increase the risk of cardiovascular diseases. Therefore, it is inferred that the cardiovascular disorders' risk can be lessened by managing and treating the disorders which cause circadian disruption. While assessing the risk of cardiovascular diseases in patients, the possibility of treating the root cause for circadian disruption should perpetually be regarded.

# DISCLOSURE


## Funding

None.


## Conflict of Interest

The author declares there is no conflict of interest regarding all aspect of the study.

## Author Contribution

PHW is responsible for the study from the literature search, data gathering, data analysis, until reporting the results of the study.


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