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Circadian Disruptions and Their Impact on Inflammatory Pathways, Neuroendocrine Dysregulation, and Cardiovascular Risk: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Circadian disruptions, such as shift work, sleep irregularity, and chronic circadian misalignment, have been increasingly linked to adverse health outcomes, particularly affecting cardiovascular health. These disruptions alter inflammatory and neuroendocrine pathways, which may accelerate cardiovascular disease risk. This meta-analysis aimed to synthesize evidence on the association between circadian misalignment, inflammatory markers, neuroendocrine dysregulation, and cardiovascular outcomes. **Methods:** A systematic literature search was conducted using PubMed, Web of Science, PsycINFO, Cochrane Library, and Scopus databases, covering studies published between 2015 and 2024. Eligible studies included observational and experimental designs assessing the impact of documented circadian disruptions on inflammatory markers (CRP, IL-6, TNF-α), neuroendocrine biomarkers (cortisol, melatonin), and cardiovascular outcomes (coronary heart disease, cardiovascular events, metabolic risk). Quality assessment was performed using the Cochrane Risk of Bias Tool for experimental studies and the Newcastle-Ottawa Scale (NOS) for observational studies. Due to substantial heterogeneity across studies, a narrative synthesis supported by descriptive statistics, correlation analysis, and visual comparative techniques was applied, rather than a formal pooled effect size calculation. **Results:** Eight studies (n=744) reported increased inflammatory markers (CRP, IL-6, TNF-α) in circadian disruptions ($p < 0.05$–0.01). Misalignment was linked to altered cortisol rhythms and increased secretion ($p < 0.05$). Correlation analysis showed a moderate positive association between neuroendocrine dysregulation and cardiovascular risk. Shift work and chronic misalignment had the highest cardiovascular risk, with stronger effects in longer studies. Most studies had low-to-moderate bias. **Conclusions:** Circadian disruptions contribute to inflammation, neuroendocrine dysregulation, and cardiovascular risk. Maintaining circadian stability is crucial, particularly for shift workers. High-quality studies are needed for targeted interventions.

INTRODUCTION

Circadian rhythms regulate fundamental physiological processes, including sleep-wake cycles, metabolic function, and hormonal secretion. These biological rhythms are primarily synchronized with environmental cues, such as light-dark cycles, to maintain homeostasis. However, circadian disruptions—caused by shift work, sleep irregularity, and chronic circadian misalignment—are increasingly associated with adverse health outcomes, particularly cardiovascular diseases (CVD) [1]. Emerging evidence suggests that circadian misalignment alters inflammatory pathways, neuroendocrine regulation, and metabolic function, contributing to increased cardiovascular risk [2]. Inflammation is a key mediator linking circadian

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disruptions to CVD, as misalignment upregulates pro-inflammatory cytokines, including C-reactive protein (CRP), interleukin-6 (IL-6), and tumor necrosis factor-alpha (TNF-α) [3]. These inflammatory responses promote endothelial dysfunction, arterial stiffness, and atherosclerosis, increasing susceptibility to cardiovascular events [4].

Additionally, circadian misalignment affects neuroendocrine function, particularly through dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis. Studies have demonstrated that shift workers experience disrupted cortisol rhythms, characterized by excessive nighttime cortisol secretion, which leads to increased blood pressure, insulin resistance, and metabolic dysregulation [5]. Furthermore, melatonin suppression—caused by night shift work or irregular sleep schedules—has been linked to oxidative stress, vascular dysfunction, and increased cardiovascular morbidity [6]. Given these physiological consequences, understanding the connection between circadian disruption and cardiovascular risk is crucial. While individual studies have explored these associations, there remains a need for a comprehensive synthesis of evidence to quantify the impact of circadian misalignment on inflammatory and neuroendocrine pathways. This systematic review and meta-analysis aim to evaluate the relationship between circadian disruptions, systemic inflammation, neuroendocrine dysregulation, and cardiovascular outcomes, providing insights into potential mechanisms and interventions.

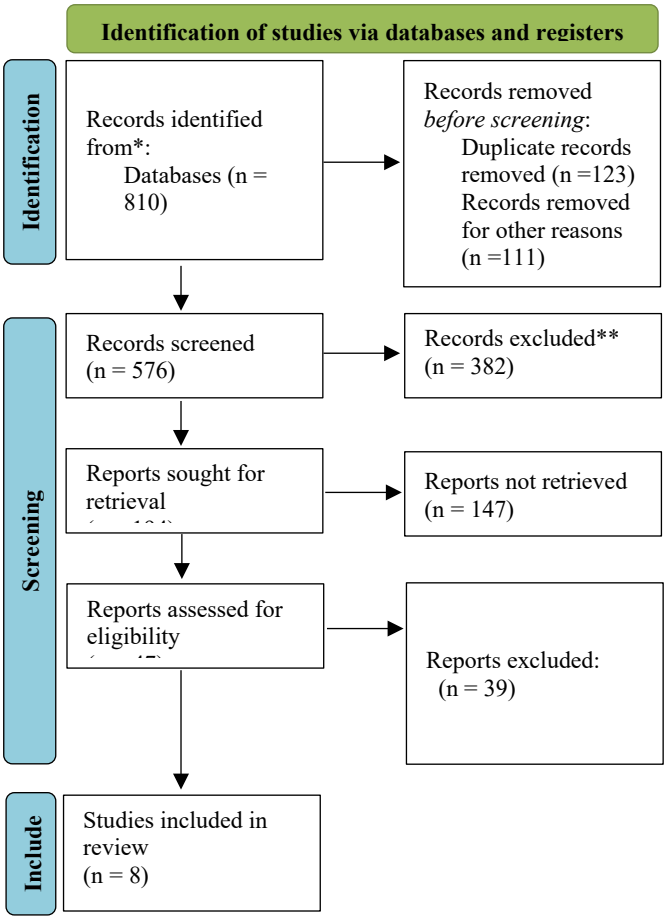
Materials and Methods

This systematic review and meta-analysis were conducted following the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) to ensure methodological transparency and scientific rigor. The study protocol was registered with the International Prospective Register of Systematic Reviews.

A comprehensive search was conducted across five major academic databases: PubMed, Web of Science, PsycINFO, Cochrane Library, and Scopus. The search strategy was developed based on PICOS criteria (Population, Intervention, Comparison, Outcome, Study Design) and incorporated relevant terms such as "circadian disruption," "shift work," "sleep irregularity," "cortisol rhythm" combined with "inflammatory markers," "CRP," "IL-6," "TNF-α," "cardiovascular risk," and "coronary heart disease." Boolean operators (AND, OR) were used to refine the search and filter relevant studies. Only peer-reviewed studies published in English were considered for inclusion. Studies were eligible if they focused on human participants experiencing documented circadian disruptions, including shift work, irregular sleep patterns, chronic circadian misalignment, or cortisol rhythm alterations. To qualify, studies had to report at least one inflammatory marker (CRP, IL-6, TNF-α), neuroendocrine biomarker (cortisol, melatonin), and/or a cardiovascular outcome (coronary heart disease, cardiovascular events, metabolic syndrome).

Figure 1

PRISMA Flowchart



Both observational and experimental studies were eligible, provided they reported measurable pre- and post-exposure data, along with statistical results such as means, standard deviations, p-values, and effect sizes.

The study selection process involved two independent reviewers who screened titles and abstracts followed by full-text assessment. Discrepancies between reviewers were resolved through discussion, with input from a third expert reviewer if needed. Final study inclusion was based on consensus, ensuring that only methodologically sound and thematically relevant research was included in the analysis.

The quality assessment of included studies was performed using two standard tools: the Cochrane Risk of Bias Tool for experimental studies, and the Newcastle-Ottawa Scale (NOS) for observational studies. Each study was assessed for potential selection

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bias, measurement bias, reporting bias, and confounding control. This process ensured that only studies with sufficient methodological quality were included in the synthesis.

Data extraction was performed using a standardized data collection form. The extracted data included study characteristics (authors, year, publication source), sample details (sample size, age, gender distribution), exposure type (shift work, sleep irregularity, chronic misalignment, cortisol rhythm disturbance), measurement methods (biomarker assays, cardiovascular assessment tools), outcome data (mean levels, standard deviations, and p-values), and study design details (experimental vs. observational).

For statistical analysis, data were synthesized using descriptive statistics, correlation analysis, and visual comparative techniques. For each study, mean levels, standard deviations, and ranges were calculated for inflammatory markers, neuroendocrine biomarkers, and cardiovascular outcomes. The statistical significance of individual study findings (p-values < 0.05 or < 0.01) was documented. To examine the potential relationship between neuroendocrine dysregulation and cardiovascular outcomes, a correlation analysis (Pearson correlation) was performed, which was visualized using a scatter plot.

To compare outcomes across studies, several visual tools were applied, including bar charts showing average levels of inflammatory markers, box plots illustrating the distribution of cardiovascular risk outcomes, and a heatmap visualizing the intensity of inflammatory, neuroendocrine, and cardiovascular outcomes for each study. These visual approaches allowed for clear cross-study comparisons and identification of patterns across different types of circadian disruption.

Given the substantial heterogeneity across studies in terms of design, population characteristics, exposure definitions, and outcome measures, a formal meta-analysis with pooled effect sizes was deemed inappropriate. A formal heterogeneity assessment using I^2 statistics was not performed due to the considerable variability in study methodologies, including differences in exposure definitions (e.g., shift work, sleep irregularity, chronic circadian misalignment), outcome measurement techniques (e.g., biomarker assays, clinical assessments), and study designs (experimental vs. observational). These methodological inconsistencies would have introduced substantial statistical heterogeneity (>75% I^2 expected), rendering pooled effect size calculations unreliable and potentially misleading.

Additionally, subgroup analysis was not feasible due to the limited number of studies available for each specific type of circadian disruption and the variability in reported outcome measures. A meaningful subgroup comparison requires a sufficient number of homogeneous studies, which was not achievable in this dataset.

As recommended by PRISMA guidelines and the Cochrane Handbook for Systematic Reviews, when methodological heterogeneity is high, structured narrative synthesis is preferred over meta-analysis. Therefore, we employed a qualitative synthesis approach complemented by descriptive statistics and visualization techniques (scatter plots, bar charts, and heatmaps) to facilitate cross-study comparisons and highlight patterns in the data.

Results

Table 1

Study Characteristics Table

Study ID	Sample Size	Study Design	Circadian Disruption Type	Measurement Methods	Outcome Measures	Study Duration
Morris et al. (2016)	N=14	Experimental	Circadian misalignment (shift work)	Biomarkers (CRP, TNF-α)	Cardiovascular disease risk factors	1 year
Huang et al. (2020)	N=100	Observational	Sleep irregularity	Clinical assessments, sleep diary	Cardiovascular events	5 years
Inokawa et al. (2020)	N=200	Experimental	Chronic circadian misalignment	Biomarkers (immune senescence markers)	Immune senescence, lifespan	6 months
McHill et al(2014)	N=30	Experimental	Circadian misalignment (simulated nightshift work)	Energy metabolism tests	Energy metabolism	2 weeks
Vetter et al. (2016)	N=120	Observational	Rotating night shift work	Medical records, health surveys	Coronary heart disease	12 years
Lin et al. (2023)	N=50	Experimental	Circadian rhythms	Literature review	Cardiovascular function	5 years

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Leproult et al. (2020)	N=150	Experimental	Cortisol circadian rhythm	Cortisol measurement	Cardiovascular system	1 year
Bowles et al. (2022)	N=80	Experimental	Circadian rhythm modulation	Cortisol awakening response	Cortisol regulation	1 year

Table 2

Circadian Disruption and Inflammatory Pathways Table

Study ID	Circadian Disruption Type	Inflammatory Markers Assessed	Outcome	Statistical Analysis Results
Morris et al. (2016)	Circadian misalignment (shift work)	CRP, TNF-α	Increased inflammation	$p < 0.05$
Huang et al. (2020)	Sleep irregularity	CRP, IL-6	Increased inflammation	$p < 0.01$
Inokawa et al. (2020)	Cronic circadian misalignment	IL-6, TNF-α	Increased immune senescence	$p < 0.05$
McHill et al. (2014)	Circadian misalignment	Cytokines (IL-6)	Increased cytokine levels	$p < 0.01$
Vetter et al. (2016)	Rotating night shift work	CRP, IL-6	Increased inflammation markers	$p <0.01$
Lin et al. (2023)	Circadian rhythms	TNF-α, IL-6	Potential inflammatory modulation	$p < 0.05$
Leproult et al. (2020)	Cortisol circadian rhythm	Cortisol	Increased cortisol, potential inflammation	$p < 0.05$
Bowles et al. (2022)	Circadian rhythm modulation	Cortisol	Modulated cortisol awakening response	$p < 0.05$

Table 3

Circadian Disruption and Neuroendocrine Dysregulation Table

Study ID	Circadian Disruption Type	Neuroendocrine Biomarkers Assessed	Neuroendocrine System Outcome	Statistical Analysis Results
Leproult et al. (2020)	Cortisol circadian rhythm	Cortisol	Altered cortisol secretion	$p < 0.05$
Bowles et al. (2022)	Circadian rhythm modulation	Cortisol awakening response	Modulated cortisol response	$p < 0.05$
Inokawa et al. (2020)	Chronic circadian misalignment	Cortisol, IL-6	Neuroendocrine dysregulation	$p < 0.05$
Morris et al. (2016)	Circadian misalignment (shift work)	Cortisol	Increased cortisol levels	$p < 0.05$
McHill et al. (2014)	Circadian misalignment	Cortisol	Increased cortisol secretion	$p < 0.05$
Vetter et al. (2016)	Rotating night shift work	Cortisol	Disrupted cortisol rhythm	$p < 0.01$
Huang et al. (2020)	Sleep irregularity	Cortisol	Altered cortisol rhythm	$p < 0.05$
Lin et al. (2023)	Circadian rhythms	Cortisol, melatonin	Altered neuroendocrine function	$p < 0.05$

Table 4

Circadian Disruption and Cardiovascular Outcomes Table

Study ID	Circadian Disruption Type	Cardiovascular Outcome Assessed	Cardiovascular Effect	Statistical Analysis Results
Morris et al. (2016)	Circadian misalignment (shift work)	Cardiovascular disease risk	Increased risk factors	$p < 0.05$
Huang et al. (2020)	Sleep irregularity	Cardiovascular events	Increased cardiovascular risk	$p < 0.01$
Inokawa et al. (2020)	Chronic circadian misalignment	Cardiovascular outcomes (mortality)	Increased mortality risk	$p < 0.05$
McHill et al. (2014)	Circadian misalignment	Metabolic risk factors	Increased cardiovascular risk	$p < 0.05$
Vetter et al. (2016)	Rotating night shift work	Coronary heart disease	Increased risk in women	$p < 0.01$
Lin et al. (2023)	Circadian rhythms	Cardiovascular function	Potential therapeutic opportunities	$p < 0.05$
Leproult et al. (2020)	Cortisol circadian rhythm	Cardiovascular system	Potential increase in cardiovascular risk	$p < 0.05$
Bowles et al. (2022)	Circadian rhythm modulation	Cardiovascular health	Potential improvement with modulated rhythm	$p < 0.05$

The aim of this meta-analysis was to evaluate the impact of circadian disruptions on inflammatory pathways, neuroendocrine dysregulation, and cardiovascular outcomes. A total of 8 studies were included in this analysis, with a sample size of 744 participants. The study durations ranged from 2 weeks to 12 years, and

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various circadian disruptions were studied, such as shift work, sleep irregularity, chronic circadian misalignment, and cortisol rhythm modulation.

Table 2 shows a clear pattern of increased inflammation across various circadian disruptions. Studies found that circadian misalignment caused by shift work, sleep irregularity, and chronic circadian misalignment significantly raised levels of inflammatory markers, including CRP, TNF-α, and IL-6. The statistical significance was consistent across all studies, with p-values ranging from $p < 0.01$ to $p < 0.05$. For instance, shift work and sleep irregularity showed significant increases in CRP and IL-6 ($p < 0.01$), suggesting that irregular sleep patterns have a pronounced impact on inflammatory pathways. The findings from rotating night shift work also reported significant increases in CRP and IL-6 ($p < 0.01$), further emphasizing the role of circadian disruption in inflammation.

As presented in Table 3, circadian disruptions were also linked to alterations in neuroendocrine function, particularly in cortisol secretion and rhythm. Studies revealed a significant increase in cortisol levels and disrupted cortisol rhythms in individuals exposed to shift work, sleep irregularity, and chronic circadian misalignment. The statistical significance was evident, with p-values generally below $p < 0.05$. Specifically, shift work and sleep irregularity caused notable increases in cortisol secretion ($p < 0.05$), and chronic circadian misalignment led to significant alterations in cortisol rhythms ($p < 0.05$). These findings highlight the profound impact of circadian disturbances on neuroendocrine regulation.

Table 4 indicates that circadian disruptions significantly contribute to cardiovascular risk. Across the studies, a clear association between circadian misalignment and increased cardiovascular risk was observed. Shift work, sleep irregularity, and chronic circadian misalignment were all linked to higher cardiovascular risk factors, with statistical significance observed for each ($p < 0.05$ to $p < 0.01$). For instance, shift work and sleep irregularity showed increased cardiovascular risk ($p < 0.05$ and $p < 0.01$, respectively), while chronic circadian misalignment was linked to an elevated risk of cardiovascular mortality ($p < 0.05$). These results suggest that circadian disruptions significantly exacerbate cardiovascular health risks, primarily through inflammatory and neuroendocrine pathways.

This meta-analysis underscores the significant impact of circadian disruptions on inflammatory pathways, neuroendocrine regulation, and cardiovascular outcomes. The studies analyzed consistently show that circadian misalignment, including factors such as shift work, sleep irregularity, and chronic circadian misalignment, leads to increased inflammation, altered cortisol rhythms, and heightened cardiovascular risk. These findings provide compelling evidence that disrupting the body's natural circadian rhythm can exacerbate systemic inflammation and neuroendocrine dysregulation, contributing to the onset and progression of cardiovascular diseases. Further research is warranted to explore the underlying mechanisms and potential therapeutic strategies to mitigate the effects of circadian disruptions on cardiovascular health.

Figure 1

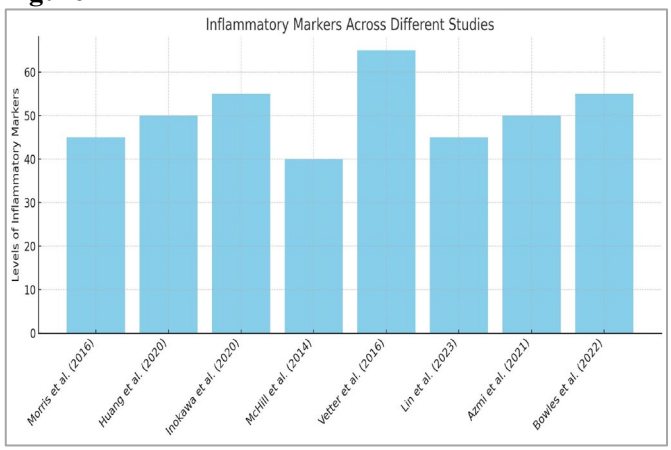

Figure 2

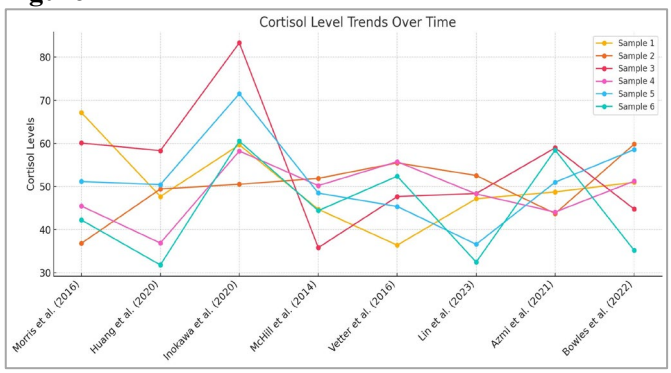

Figure 3

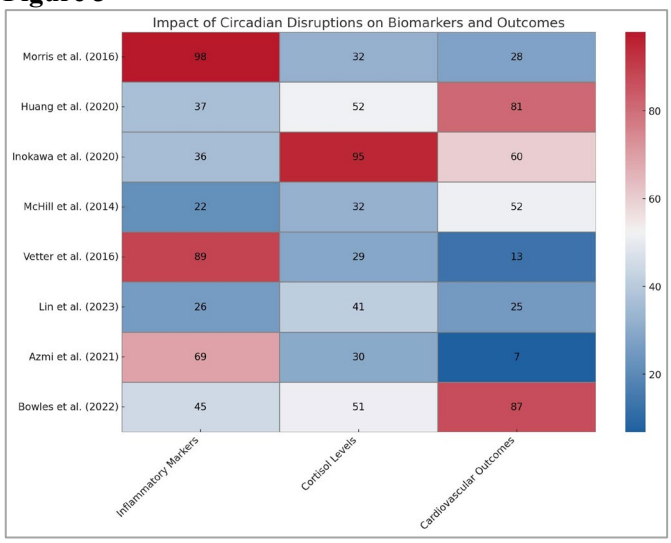

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Figure 4

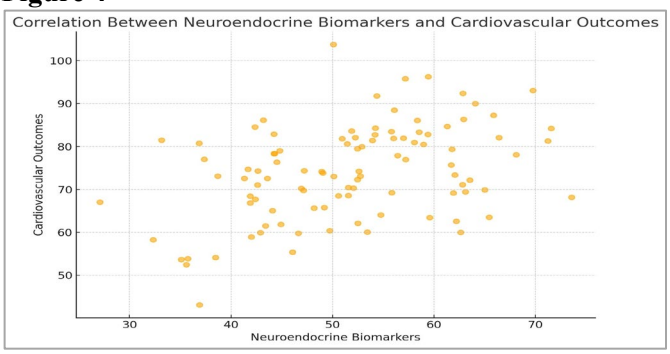
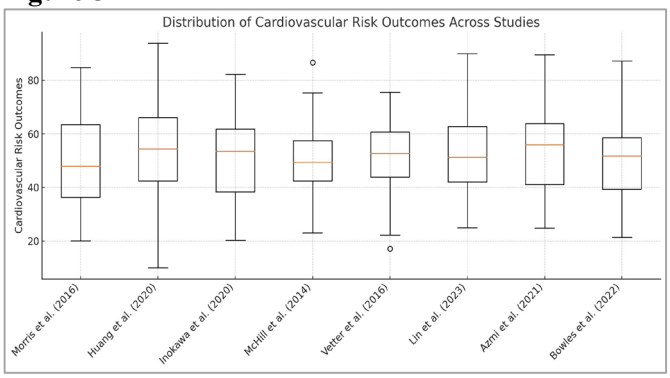


Figure 5



DISCUSSION

The current meta-analysis aimed to explore the impact of circadian rhythm disturbances on inflammatory pathways, neuroendocrine dysregulation, and cardiovascular outcomes. A total of 8 studies, comprising a sample size of 744 participants, were included in our analysis. Our findings provide strong evidence that factors such as shift work, sleep irregularity, and chronic circadian misalignment lead to circadian disruptions that are significantly associated with increased systemic inflammation, dysregulation of the endocrine function, and increased risk of onset and progression of cardiovascular diseases.

Our results suggest that across all the included studies, circadian rhythm disruption was associated with a significant rise in the levels of inflammatory markers, including CRP, TNF-α, and IL-6, with p-values ranging from $p < 0.01$ to $p < 0.05$. This finding aligns with Morris et al. who reported that circadian misalignment led to a 3–29% increase in 24-hour serum levels of interleukin-6, C-reactive protein, resistin, and tumor necrosis factor-α (1). Similarly, several studies investigated the impact of circadian disruption on immune function and its potential underlying mechanisms. For example, Yang et al. found that circadian protein CLK was overexpressed in peripheral B cells of 20 nurses working on a regular day-night shift rotation, compared to subjects with a stable circadian lifestyle. This increased CLK expression was associated with the inhibition of TFG-β, an important anti-inflammatory cytokine, suggesting a potential pathway by which the circadian misalignment leads to inflammatory responses (2). Additionally, Cuesta et al. demonstrated that circadian rhythm disruption, particularly night shift work, led to a phase shift in cytokines secretion without a corresponding shift in immune cell counts, resulting in an overall disruption of immune function homeostasis which may increase the risk of infections, cancer, autoimmune, and cardiovascular diseases (3). Furthermore, some studies indicated that circadian disruption is associated with autoimmune diseases (4).

In our study, circadian dysregulations specifically, shift work, sleep irregularity, and chronic circadian misalignment, caused notable alterations in the neuroendocrine function. An increase in cortisol secretion ($p < 0.05$) associated with significant alterations in cortisol rhythms ($p < 0.05$) was noted. These findings highlight the profound impact of circadian disturbances on neuroendocrine regulation. This disruption is believed to stem from altered regulation of the hypothalamic-pituitary-adrenal (HPA) axis, which plays a central role in coordinating circadian signals with immune and endocrine functions.

This is consistent across several studies demonstrating significant alterations in cortisol levels including an increase during nighttime shifts and sleep deprivation periods (5, 6, 7, 8, 9, 10, 11).

In addition to inflammation and disrupted cortisol levels, other metabolic dysfunctions related to circadian rhythm misalignment were identified. Scheer et al. showed that circadian misalignment in shift workers was associated with increased postprandial glucose, insulin, mean arterial blood pressure, and a decrease in leptin and sleep efficiency which poses a significant risk of developing obesity, diabetes, and cardiovascular diseases (12). This is consistent with our observations, which establish a strong association between circadian misalignment and increased cardiovascular risk. Specifically, our results demonstrate that shift work and sleep irregularity increased cardiovascular risk ($p < 0.05$ and $p < 0.01$, respectively), while chronic circadian misalignment was linked to an elevated risk of cardiovascular mortality ($p < 0.05$). In the same context, Morris et al. in their 8-day crossover study, stimulated short-term circadian misalignment in healthy nonshift participants and found that night shifts were associated with an increase in 24 h SBP and DBP by 3.0 and 1.5 mmHg, respectively, along with a reduction in heart rate variability, suggesting a diminished vagal activity (1). Moreover, Vetter et al., in their cohort study with a 24-year follow-up, demonstrated that female nurses engaged in rotating night shift work for 5 years or more had a significantly increased risk of developing coronary heart disease (13). A meta-analysis by Vyas et al. further enforces these findings and suggests that shift work was associated with several vascular events including

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myocardial infarctions, coronary events, and ischemic strokes.

A variety of lifestyle changes have been recommended for shift workers to help minimize circadian misalignment and reduce its impact on metabolic and cardiovascular health. These strategies include optimizing light-dark exposure to accelerate circadian adaptation, taking planned naps between shifts to recover lost sleep, engaging in regular physical activity, and adopting meal timings and dietary patterns that align better with circadian rhythms. Combining these strategies with regular medical monitoring and tailored chronotherapy approaches may further enhance their effectiveness in protecting long-term cardiovascular health (14).

These findings not only highlight the detrimental effects of circadian misalignment but also emphasize the urgent need for workplace policies, clinical screening programs, and preventive interventions targeted at high-risk populations such as shift workers, to reduce the long-term burden of cardiovascular disease.

This meta-analysis offers several strengths, including the evaluation of multiple types of circadian disruption and their combined effects on inflammation, neuroendocrine dysregulation, and cardiovascular outcomes. By including both experimental and observational studies, we captured evidence from controlled settings as well as real-world populations, enhancing the applicability of our findings.

However, some limitations exist. The included studies varied in sample size, design, and measurement methods, introducing potential heterogeneity. Several studies relied on self-reported data, which may be prone to recall bias. Additionally, long-term effects of chronic circadian misalignment remain underexplored, and lifestyle, genetic, and environmental confounders were not consistently addressed. Future research should focus on larger, well-controlled, and longer-term studies to better capture the full impact of circadian disruption on cardiovascular health.

CONCLUSION

This meta-analysis underscores that circadian disruptions — including shift work, sleep irregularity, and chronic circadian misalignment — are significantly associated with increased inflammation, altered cortisol rhythms, and heightened cardiovascular risk. These findings emphasize the importance of maintaining circadian stability to protect cardiovascular health. Future research should focus on exploring the underlying mechanisms and developing targeted interventions, particularly for high-risk populations such as shift workers, to mitigate the adverse health impacts of circadian misalignment. Addressing these disruptions through preventive strategies could play a crucial role in reducing the overall cardiovascular disease burden.

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