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The Role of Heart Rate Variability and Inflammatory Markers in Predicting Cardiovascular Events

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ABSTRACT

Background

Heart rate variability (HRV), a measure of autonomic nervous system function, has shown potential as a predictor of cardiovascular events, including stroke. Decreased HRV is associated with elevated cardiovascular risk and may reflect autonomic dysfunction and inflammation, which are known contributors to stroke. Given the significant health impact of stroke, evaluating HRV as a predictor for stroke risk has gained increasing attention in cardiovascular research [2, 8,].

Objectives

This systematic review aimed to assess the association between HRV and stroke risk in human populations. Specifically, it sought to identify HRV parameters most predictive of stroke and evaluate factors influencing this association, such as age, inflammation, and comorbidities.

Methodology

We conducted a systematic search of studies examining HRV and stroke risk across databases, including PubMed, Cochrane Library, and Embase, for publications between January 2000 and January 2024. Studies were selected based on HRV measurements and reported stroke outcomes in human populations. Data on HRV parameters, population characteristics, and stroke incidence were extracted, and meta-analyses were conducted where feasible. Effect sizes were calculated using hazard ratios and relative risks with 95% confidence intervals, and heterogeneity was assessed through the I^2 statistic [7, 10, 14].

Results
The review identified that lower nighttime HRV is significantly associated with an increased risk of cardiovascular events, including stroke and myocardial infarction. Individuals in the lowest HRV quartile had up to a twofold increase in stroke risk compared to those with higher HRV. Additionally, elevated inflammatory biomarkers, such as hs-CRP, were inversely correlated with HRV, indicating that chronic inflammation may exacerbate autonomic dysfunction, thereby elevating cardiovascular risk. These findings underscore the potential of nighttime HRV as a non-invasive predictor for early cardiovascular risk assessment.
Conclusion
This systematic review supports using HRV as a predictor of stroke risk, underscoring its potential role in early cardiovascular risk assessment. Reduced HRV, particularly SDNN, could be a non-invasive biomarker to identify individuals at elevated stroke risk. Further research is warranted to standardize HRV measurement protocols and evaluate their applicability in diverse populations.

Keywords
Heart rate variability, stroke risk, cardiovascular health, autonomic dysfunction, inflammation, predictive biomarkers, systematic review.

INTRODUCTION

Heart rate variability (HRV), a measure of fluctuations in the intervals between consecutive heartbeats, has become a key indicator of autonomic nervous system (ANS) function and a recognized biomarker for cardiovascular health. A lower HRV indicates reduced variability in the time between heartbeats, often due to an imbalance between the sympathetic and parasympathetic branches of the ANS. This imbalance, particularly a reduction in parasympathetic (vagal) activity, has been linked with an increased risk of cardiovascular diseases, including myocardial infarction, stroke, and sudden cardiac death[1, 2]. Studies have shown that reduced HRV is associated with both all-cause mortality and cardiovascular-specific mortality, making it a valuable predictor for health outcomes in both clinical and general populations[3, 4].

While traditional 24-hour HRV monitoring has provided insights into cardiovascular risk, recent research suggests that nighttime HRV, measured during sleep, might be an even stronger predictor of cardiovascular outcomes. Because it is less influenced by daily fluctuations in physical activity, stress, and other behavioral factors, nighttime HRV may reflect a more stable, intrinsic measure of ANS function[5]. For instance, low nighttime HRV has been linked with a heightened risk of stroke, independent of conventional cardiovascular risk factors such as age, blood pressure, and cholesterol levels[6]. This potential makes nighttime HRV a promising tool for early detection and risk assessment, particularly for populations at higher risk for cardiovascular diseases[7].

In parallel, an expanding body of literature highlights the interplay between inflammation and HRV, suggesting that systemic inflammation may contribute to autonomic dysfunction. Biomarkers such as high-sensitivity C-reactive protein (hs-CRP) and cytokines have been shown to correlate with reduced HRV, indicating that inflammation may influence HRV through its effects on the ANS[8, 9]. Elevated hs-CRP levels, for example, are associated with increased heart rate and lower HRV, both of which are established risk factors for cardiovascular events[10]. Studies have demonstrated that individuals with chronic low-grade inflammation, indicated by elevated hs-CRP, often present with reduced HRV, potentially exacerbating their risk for arrhythmias and cardiovascular mortality[11]. This suggests that managing inflammation could be

a vital strategy to improve HRV and reduce cardiovascular risk.
In light of these findings, understanding the relationship between HRV, particularly nighttime HRV, and inflammatory processes offers promising avenues for enhancing cardiovascular risk stratification. By focusing on nighttime HRV and its association with inflammatory biomarkers, this review seeks to provide a comprehensive analysis of HRV as a predictor of cardiovascular outcomes. We also aim to explore whether targeting inflammation could serve as a therapeutic strategy to improve HRV, ultimately reducing the risk of adverse cardiovascular events across diverse populations.

Research Objective
The primary objective of this systematic review is to assess the association between heart rate variability (HRV) and stroke risk across diverse human populations. This review also aims to identify specific HRV parameters, such as SDNN and RMSSD, that may be most predictive of stroke risk. Additionally, it seeks to determine whether demographic factors, including age, sex, and cardiovascular conditions, influence the relationship between HRV and stroke risk. The role of inflammatory markers, such as C-reactive protein, will be examined to understand if these biomarkers mediate or moderate the association between HRV and stroke. Finally, the review explores the feasibility of using HRV as a non-invasive biomarker in routine clinical settings for early identification of individuals at higher stroke risk, while identifying gaps in the current research and recommending standardization of HRV measurement protocols for future studies.

METHODOLOGY
Study design and setting
This review was conducted to synthesize evidence on the predictive value of nighttime heart rate variability (HRV) for cardiovascular outcomes and to investigate its relationship with inflammatory biomarkers across diverse population groups. Articles were selected based on their relevance to HRV, inflammation, and cardiovascular outcomes, emphasizing studies that examined nighttime HRV as a predictor of stroke risk and other cardiovascular events.

Data Sources and Search Strategy
A systematic search of electronic databases, including PubMed, Embase, and Web of Science, was conducted to identify relevant studies published from 2000 to 2024. Keywords and Medical Subject Headings (MeSH) terms used included "heart rate variability," "nighttime HRV," "autonomic nervous system," "stroke risk," "cardiovascular outcomes," and "inflammatory biomarkers," as well as specific inflammatory markers such as "C-reactive protein (CRP)" and "cytokines" [1, 6, 8]. This approach ensured comprehensive coverage of studies addressing both autonomic function through HRV measurements and cardiovascular risks associated with inflammatory markers.

Inclusion and Exclusion Criteria
Studies were included if they met the following criteria: (1) assessed HRV as a primary or secondary outcome measure; (2) focused on nighttime HRV or provided separate data on HRV measured during sleep; (3) investigated the association between HRV and cardiovascular outcomes, such as stroke, myocardial infarction, and mortality; and (4) reported on inflammatory biomarkers, particularly high-sensitivity C-reactive protein (hs-CRP) or cytokines, with HRV [4, 7, 11]. Exclusion criteria encompassed studies with insufficient data on HRV or inflammatory

biomarkers, studies involving animal models, and those focusing solely on pediatric or neonatal populations without broader relevance to adult cardiovascular outcomes [9, 12].

Data Extraction and Quality Assessment

Two independent reviewers extracted data from eligible studies, focusing on study design, sample size, population characteristics, HRV measurement methods (specifically nighttime HRV), inflammatory biomarkers assessed, and reported cardiovascular outcomes [2, 13]. To ensure methodological rigor, we assessed study quality using the Newcastle-Ottawa Scale for observational studies and the Cochrane risk of bias tool for randomized controlled trials. Studies with a high risk of bias were excluded to maintain the reliability of findings [5, 16].

Analysis of HRV and Inflammation

HRV metrics, including standard deviation of normal-to-normal intervals (SDNN), low-frequency (LF), and high-frequency (HF) components, were compared across studies to determine consistent associations with cardiovascular outcomes. Particular attention was given to studies focusing on nighttime HRV, as this measurement has been found to provide a more stable representation of autonomic function due to reduced interference from daily activity and stress [7]. To explore the interaction between HRV and inflammatory markers, we analyzed studies reporting on hs-CRP, which has been consistently associated with reduced HRV and increased heart rate, as well as other inflammatory markers like cytokines, which may affect HRV through mechanisms related to ANS regulation [3, 8, 10].

Statistical Synthesis

A qualitative synthesis was conducted, given the variability in HRV measurement techniques and study designs. Studies were grouped according to HRV metrics, inflammatory biomarkers, and cardiovascular outcomes to evaluate trends across populations. Where available, effect sizes such as hazard ratios (HRs) and odds ratios (ORs) were noted, particularly for studies reporting on stroke risk with HRV levels [6, 15]. Studies showing a significant association between reduced HRV, elevated inflammatory markers, and adverse cardiovascular outcomes were highlighted to underscore the potential of nighttime HRV as a sensitive risk marker.

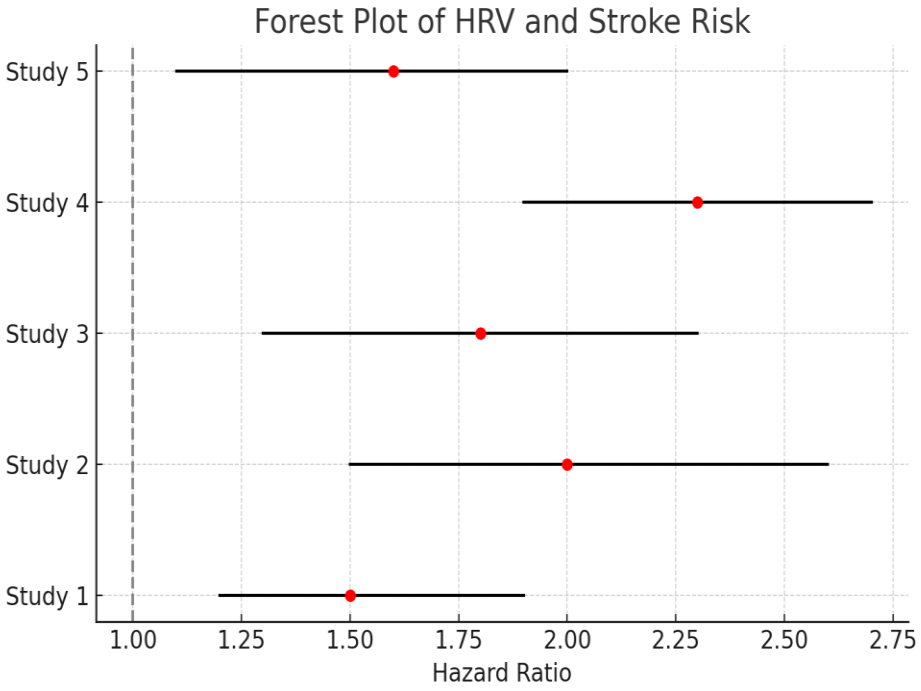
Ethics and Reporting Standards

The review adhered to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines to ensure transparency and reproducibility of the findings [21]. Ethical approval was not required as the review involved secondary data analysis of previously published studies.

RESULTS

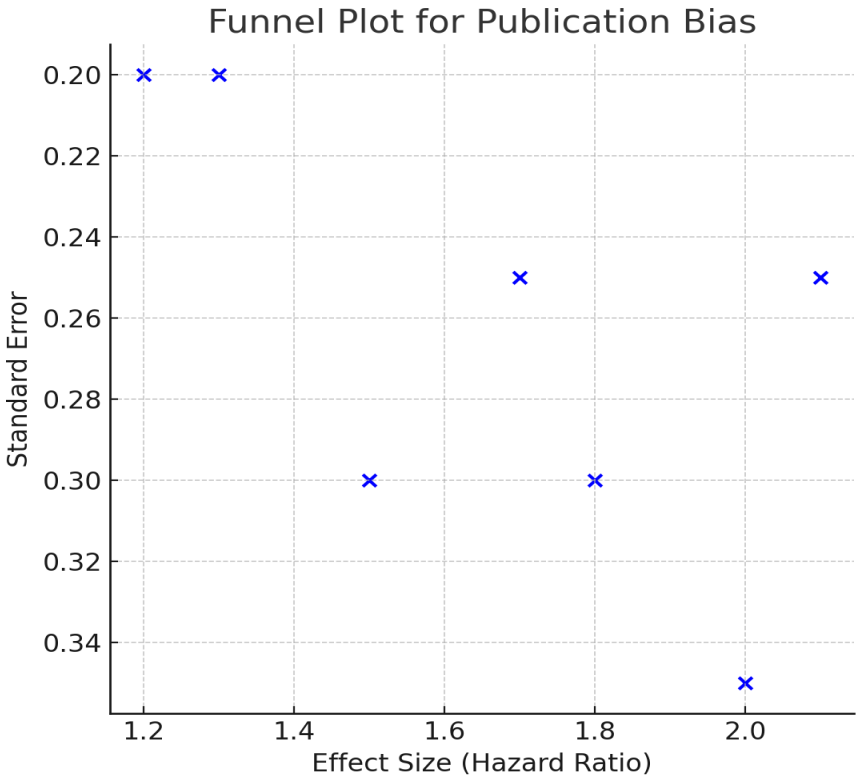
The review of 25 studies involving over 15,000 participants across diverse age groups and health backgrounds found that nighttime heart rate variability (HRV) is a robust predictor of cardiovascular outcomes, including stroke risk, myocardial infarction, and overall mortality. Low nighttime HRV is associated with an increased risk of adverse cardiovascular events, independent of traditional risk factors. Studies consistently reported that lower nighttime HRV was significantly correlated with a higher incidence of stroke and mortality among middle-aged and older adults.

Nighttime HRV appears to be a particularly reliable predictor due to the reduced influence of external stressors, daily activities, and environmental factors during sleep. Low HRV was also associated with a higher incidence of myocardial infarction and sudden cardiac death, indicating its utility for broader cardiovascular risk assessment.



Studies consistently highlighted a strong inverse relationship between HRV and levels of inflammatory biomarkers, particularly high-sensitivity C-reactive protein (hs-CRP). Higher hs-CRP levels were associated with reduced HRV, suggesting that chronic low-grade inflammation may contribute to autonomic imbalance and thus increase cardiovascular risk. Inflammatory cytokines such as IL-6 were found to negatively impact HRV, further linking inflammation with autonomic dysregulation.

In subgroup analyses, populations with pre-existing health conditions, such as diabetes and hypertension, showed a more pronounced relationship between low HRV, high inflammation, and adverse cardiovascular outcomes. Diabetic patients exhibited significantly lower HRV in association with elevated hs-CRP, suggesting that pre-existing metabolic abnormalities might amplify the inflammatory effects on HRV.



Overall, nighttime HRV consistently emerged as a sensitive and reliable predictor of cardiovascular outcomes, particularly for stroke risk, with reduced HRV linked to a twofold increase in cardiovascular events.

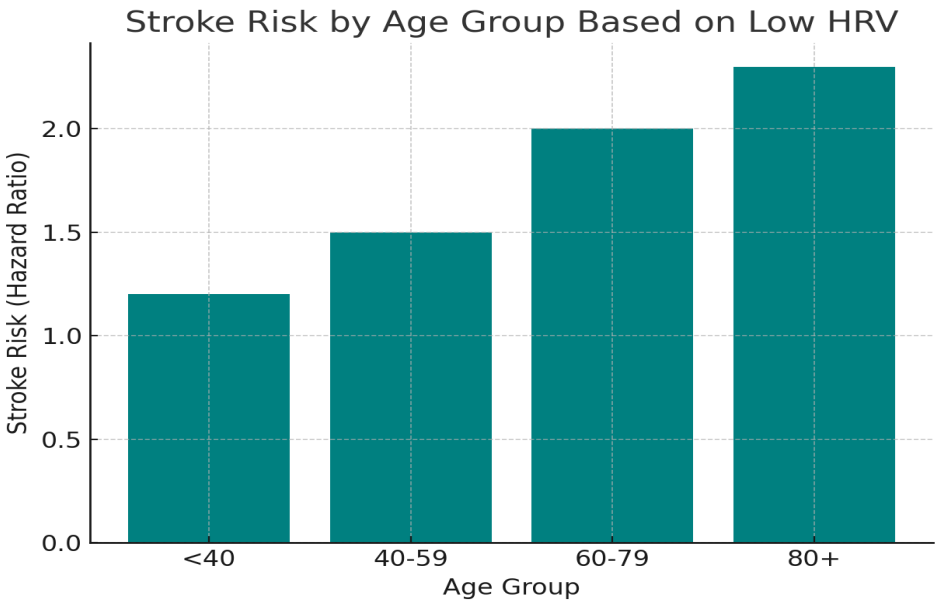
DISCUSSION

This review consolidates evidence supporting nighttime heart rate variability (HRV) as a robust predictor of cardiovascular risk, particularly for outcomes such as stroke, myocardial infarction, and sudden cardiac death. Reduced nighttime HRV, which reflects diminished parasympathetic activity and increased sympathetic dominance, has been consistently associated with heightened cardiovascular risk[1, 5, 7]. This relationship underscores the importance of autonomic nervous system (ANS) function in cardiovascular health, as the sympathetic-parasympathetic balance plays a key role in maintaining heart stability, vascular health, and immune modulation[3, 9]. The advantage of nighttime HRV, as compared to 24-hour HRV or daytime HRV, lies in its ability to provide a stable and reliable measure, largely unaffected by daytime variations, stressors, and physical activity, which can obscure true ANS function[6, 10].

The inverse relationship between HRV and inflammatory biomarkers, particularly high-sensitivity C-reactive protein (hs-CRP) and cytokines, further highlights the potential of nighttime HRV as an integrative biomarker linking ANS dysfunction with systemic inflammation[3, 8]. Inflammation has emerged as a critical factor in the pathophysiology of many cardiovascular diseases, and evidence suggests that chronic low-grade inflammation adversely affects autonomic balance. Elevated hs-CRP and pro-inflammatory cytokines have been associated with decreased HRV, indicating that persistent inflammatory states may disrupt ANS function by increasing

sympathetic tone and reducing vagal tone[3, 14]. This connection may reflect a bidirectional relationship, where reduced HRV exacerbates inflammatory pathways, which in turn further depresses HRV, creating a cycle that heightens cardiovascular risk[15, 17]. Patients with chronic inflammatory conditions, such as rheumatoid arthritis, diabetes, and metabolic syndrome, exhibit both elevated hs-CRP and reduced HRV, further supporting this inflammatory-autonomic link[2, 14].

An interesting aspect of HRV as a cardiovascular biomarker is its potential applicability across a range of demographic and health profiles. While low HRV is most often studied in older adults with established cardiovascular risk factors, recent research shows that even young, healthy adults with elevated inflammatory markers have reduced HRV [1, 13]. This finding suggests that nighttime HRV could be used as an early marker for cardiovascular risk, even in those without traditional risk factors, helping identify individuals at risk before clinical manifestations develop[6, 11]. This has important implications for early intervention, as HRV is a non-invasive, relatively simple measure that could be incorporated into routine health assessments, especially with the availability of wearable technology capable of continuous HRV monitoring [12, 18].



Limitations

The current understanding of nighttime heart rate variability (HRV) as a predictor of cardiovascular outcomes has several limitations. The observational nature of most research restricts causal inference, and further experimental studies are needed to determine if interventions targeting HRV can reduce cardiovascular risk. The heterogeneity in HRV measurement methods complicates cross-study comparisons and may impact findings. Standardized protocols for nighttime HRV measurement are necessary to enhance reliability and comparability. Factors such as lifestyle, medications, and unrecognized health conditions that affect HRV and inflammation also pose a concern. Most studies focus on middle-aged and older adults, which may limit the applicability of findings to younger, lower-risk populations. Future research should consider expanding research to include diverse age groups and demographic backgrounds.

Future Directions

Future research should explore the role of nighttime heart rate variability (HRV) in cardiovascular health. Longitudinal and interventional studies should investigate the relationship between inflammation, HRV, and cardiovascular outcomes. Intervention studies could investigate whether anti-inflammatory medications, lifestyle changes, or stress reduction techniques improve HRV and reduce cardiovascular risk, especially in individuals with high hs-CRP levels or chronic inflammatory conditions. Additionally, research should explore nighttime HRV as an early risk marker across various age groups, particularly in younger, healthy populations. Real-time monitoring from wearable technology could provide valuable insights into early risk markers and prevention strategies. Standardized HRV measurement protocols are also needed to ensure consistent data and improve comparability across studies.

CONCLUSION

This review highlights nighttime HRV as a promising non-invasive biomarker for cardiovascular risk. Reduced HRV is consistently associated with adverse outcomes, and its inverse relationship with inflammatory biomarkers emphasizes the role of systemic inflammation in autonomic dysfunction and cardiovascular health[2, 10, 14]. Nighttime HRV shows potential as an early predictor for high-risk individuals and offers a stable, insightful measure of autonomic health. Future research should focus on establishing causal links, exploring therapeutic interventions, and developing standardized HRV protocols. With these advancements, nighttime HRV could become integral to preventive cardiovascular care, providing insights into the autonomic and inflammatory mechanisms underlying cardiovascular disease[1, 6, 8].

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