

The Interplay between Cardiovascular Health and Parkinson's Disease: Implications for Incidence, Severity, and Mortality

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Abstract

Parkinson's disease (PD) is a common neurodegenerative disorder that is becoming increasingly prevalent in the United States. Current research suggests a possible bidirectional relationship between cardiovascular disease (CVD) and PD. This review aims to synthesize relevant evidence to analyze the interplay between CVD and PD. Researchers utilized academic databases to find current and relevant studies that met the defined inclusion and exclusion criteria. After reviewing various articles, a majority of evidence suggests a correlation between CVD and worsening prognosis for PD patients regarding mortality, cardiac dysfunction, and blood pressure. Conflicting and inconclusive studies are acknowledged within this



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Abstract

review, showing the complexity of this subject and the need for continuing research to determine causality. Future research should adopt a prospective study design with stricter diagnostic methods and detailed sample demographics to identify confounding variables. The underlying biological and physiological background within these diseases should also be studied to help better understand the interplay between CVD and PD.

Keywords: Cardiology, cardiovascular medicine, heart, medicine

Introduction

Behind Alzheimer's, Parkinson's disease (PD) is the second-most common neurodegenerative disorder in the United States (US)⁽¹⁾. It is estimated that approximately one million Americans currently live with PD, with numerous others undiagnosed. Due to the progressive degeneration that accompanies PD, it further impacts thousands of spouses, children, and other caregivers.

The disruption of movement and emotion regulation in PD patients is often credited to the loss of dopamine-producing neurons. However, the actual cause of this phenomenon remains unknown. Approximately 80% of those diagnosed have an idiopathic form with no identifiable cause, while the remaining 20% are presumed to be genetically inherited. In the absence of genetic causes, environmental factors such as pesticide exposure, increasing age, and gender, among others, are thought to play a role⁽²⁾.

In recent years, researchers have also started to explore how cardiovascular disease (CVD) may be related to PD. However, these studies have yielded conflicting results. In a 2022 study published in the *Journal of the American Heart Association*, evidence showed that myocardial infarctions (MIs) were associated with a 20% decreased risk of PD and a 28% reduced risk of secondary Parkinsonism, which reflects an inverse relationship between cardiovascular risk factors and PD⁽³⁾. In contrast, a 2024 cohort-based study suggests that a history of CVD or MI may be a significant risk factor for the development of PD⁽⁴⁾. An additional cohort study utilizing data from

the National Health and Nutrition Examination Survey (NHANES) found that individuals with PD had a higher risk of CVD mortality compared to those without PD⁽⁵⁾.

Conflicting findings in current research reveal a crucial gap in understanding the connection between CVD and PD. These inconsistencies motivated a comprehensive literature review. The discrepancies highlight a critical gap in understanding the interplay between these two conditions. They force the question: What is the association between cardiovascular comorbidities and incidence rates, severity, and mortality of individuals diagnosed with PD compared to the general population?

This review aims to synthesize existing evidence, identify current gaps, and propose avenues for future research to better understand the complex interplay between CVD and PD.

Search Strategy

The objective of this analysis is to discuss the relationship between PD and CVD regarding incidence, severity, and mortality risk. In this review, databases such as PubMed and Google Scholar were used. A search was done to ensure a broad coverage of relevant literature. The search utilized a combination of various keywords in association with PD and cardiovascular health: "PD and cardiovascular health," "CVD and neurology," "Parkinson's Disease Associations," "cardiovascular and Parkinson's," "cardiovascular and motor impairment," "vascular disease and Parkinson's," "Parkinson's and heart," and "Parkinson's links."

Inclusion and Exclusion Criteria

Inclusion Criteria:

Studies were included if they:

1. Examined CVD in the context of PD.
2. Were published in high-quality, peer-reviewed journals to ensure credibility.
3. Utilized validated and reliable instruments to assess cardiovascular and neurological outcomes.
4. Followed established clinical guidelines or standards in the field.
5. Were initially published in English to facilitate the review process.

Exclusion Criteria:

Studies were excluded if they:

6. Were written in languages other than English.
7. Were inaccessible due to paywalls or a lack of open access
8. Did not explicitly discuss PD and/or cardiovascular health.
9. Were dissertations or non-peer-reviewed sources, which may not meet rigorous scientific standards.
10. Contained methodological flaws.
11. Provided insufficient data or poorly described outcomes.

Data Extraction and Synthesis

Data were systematically extracted from selected studies, focusing heavily on study design, population characteristics, outcomes, and key findings. Thirty-two studies were chosen to be reviewed based on the predefined inclusion criteria. The studies that were included provided diverse perspectives on the interplay between CVD and PD by utilizing the data included within the studies.

To maintain consistency, qualitative and quantitative data related to cardiovascular risk factors, incidence rates, mortality rates, and associated symptoms of PD were analyzed. Conflicting reports were also noted. Studies focusing on the interrelation of CVD, cardiovascular

autonomic dysfunction, non-motor symptoms, and cognitive impairments were given priority because they present an interaction between PD and CVD.

It is worth noting that the typical forest plot seen in many meta-analyses and literature reviews was excluded. This was because many of the studies used were not combinable due to significant design differences.

Quality Assessment

To ensure reliability, the studies were reviewed based on author credibility, study design, and compliance with standard reporting guidelines. A quality checklist was used to evaluate methodological soundness, including sample size and control for confounding variables. The review aimed to balance studies supporting and contradicting the association between PD and cardiovascular risks to offer an unbiased blend of available evidence. All studies included were categorized as either “for,” “inconclusive,” or “against” to determine which conclusion the data supports.

Assistive Technology

Artificial intelligence (AI) models were used to assist in this literature review. The AI model GPT-4o was utilized to efficiently filter the initial pool of articles based on the predefined inclusion and exclusion criteria and to generate concise summaries of key findings to aid in rapid relevance assessment. Crucially, all AI-assisted tasks were subject to rigorous human oversight; each filtered article and summary was manually reviewed and verified by the research team to ensure accuracy, relevance, and appropriate application of criteria. AI was not used to write any part of the actual manuscript.

The relationship between CVD and PD when measuring mortality rates is a vital link to explore, with strong evidence in support of a link between the comorbidities of these diseases and a higher risk of adverse outcomes, as seen in Table 1. Numerous studies have reported that patients with PD and symptoms of CVD, such as autonomic dysfunction or orthostatic hypotension (OH), face a higher risk of mortality in comparison to patients

who do not present with CVD-like symptoms. In a population-based prospective analysis study using data from the NHANES and linking it with the national death index, there was substantial evidence suggesting that patients with pre-existing CVD symptoms were at higher risk of death. The researchers used the hazard ratio (HR) to compare the frequency of an event occurring in one group versus another, and verified statistical significance of the results through the use of confidence intervals (CIs) and p-values. In the context of these clinical trials, HR refers to the survival rate of patients in one group compared

to the other. An HR of 1 indicates no difference in risk between the groups. A value greater than 1 indicates an increased risk of the event (e.g. mortality) in the study group, while a value less than 1 indicates a decreased risk⁽¹²⁾. Results showed that people with PD had a higher risk of CVD-related death than those without PD (HR: 1.82; 95% CI: 1.24-2.69; p=0.002) and a similar increase in the risk of death from any cause (HR: 1.84; 95% CI: 1.44-2.33; p<0.001), as seen in Figure 1⁽⁵⁾. These results can be attributed to autonomic dysfunction and other cardiovascular symptoms in PD patients.

Table 1. Summary of key studies on the interplay between cardiovascular disease and Parkinson’s disease

Study (author, year) (reference)	Study design	Sample size	Key finding/outcome	Effect size/result
Mortality				
Ke, 2024 ⁽⁵⁾	Population-based prospective cohort (NHANES data)	28,242 participants (380 with PD; 27,862 without PD)	PD associated with a higher risk of both CVD-related and all-cause mortality	CVD death: HR: 1.82 (95% CI: 1.24-2.69; p=0.002) All-cause death: HR: 1.84 (95% CI: 1.44-2.33; p<0.001)
Bartl, 2022 ⁽⁶⁾	Analysis of plasma biomarkers (DeNoPa cohort)	109 drug-naïve PD patients 96 healthy controls	Biomarkers (e.g., IL-6, cystatin B) correlated with cognitive decline and motor progression	IL-6 vs. MMSE: Est. -0.33 (p<0.01) CSTB vs. MMSE: Est. -0.34 (p<0.01) IL-6 vs. MDS-UPDRS: Est. 0.28 (p=0.03)
Chen, 2024 ⁽⁷⁾	Two-sample mendelian randomization	GWAS data: PD (n=482,730) MI (n=462,933) AF (n=337,199) VTE (n=361,194)	Found a minimal, statistically significant protective association for PD on MI. No causal association found for PD on AF or VTE	PD on MI: OR: 0.9989 (95% CI: 0.9980-0.9998) PD on AF: OR: 1.0000 (95% CI: 0.9994-1.0007) PD on VTE: OR: 1.0000 (95% CI: 0.9994-1.0007)
CVD history & PD risk				
Acharya, 2024 ⁽⁴⁾	Cross-sectional observational study	676 idiopathic PD patients 874 non-PD controls	A history of CVD was associated with a higher risk of developing idiopathic PD, particularly in males	CVD history on idiopathic PD: OR 1.56 (95% CI: 1.09-2.08; p=0.013)
Sundbøll, 2022 ⁽³⁾	Nationwide population-based matched cohort (Danish registries)	181,994 MI patients 909,970 matched controls	Inverse relationship. MI survivors had a decreased risk of developing PD and secondary parkinsonism	PD risk (post-MI): aHR: 0.80 (95% CI: 0.73-0.87) Parkinsonism risk: aHR: 0.72 (95% CI: 0.54-0.94)

Table 1. Continued

Study (author, year) (reference)	Study design	Sample size	Key finding/outcome	Effect size/result
Cardiovascular risk factors & events				
Vikdahl, 2015 ⁽⁸⁾	Population-based nested case-control study (NSHDS)	84 PD cases 336 matched controls	Inverse relationship. Lower S-TG and lower SBP 2-8 years prior to diagnosis were associated with an increased risk of PD	S-TG: HR 0.61 (95% CI: 0.39-0.96) SBP: HR 0.98 (95% CI: 0.97-0.99)
Han, 2021 ⁽⁹⁾	Nationwide population-based matched cohort (Korean National Health Insurance Service)	57,585 PD patients 57,585 matched controls	PD was an independent risk factor for new-onset AF. The risk was notably higher in younger patients	Overall AF risk: aHR 1.27 (95% CI: 1.18-1.36) Age 40-49: HR 3.06 (95% CI: 1.20-7.77)
Lim, 2024 ⁽¹⁰⁾	Retrospective, propensity-score matched cohort (Electronic health record data)	1,194 PD patients 4,574 matched controls	MACE were significantly higher in patients with more severe PD (measured by H&Y scale)	MACE incidence: 12.7% (low-severity) vs. 27.6% (high-severity) (p<0.01)
Abugroun, 2020 ⁽¹¹⁾	Cross-sectional (National Inpatient Sample)	57,914 PD patients 231,646 matched controls	PD associated with reduced odds of most vascular risk factors, but increased odds of stroke	Hyperlipidemia: aOR 0.77 (95% CI: 0.71-0.75) Diabetes: aOR 0.73 (95% CI: 0.71-0.75) Hypertension: aOR 0.68 (95% CI: 0.67-0.70) Stroke: aOR 1.27 (95% CI: 1.24-1.31)

AF: Atrial fibrillation, aHR: Adjusted hazard ratio, aOR: Adjusted odds ratio, HR: Hazard ratio, OR: Odds ratio, a-OR: Adjusted odds ratio, CI: Confidence interval, SBP: Systolic blood pressure, S-TG: Serum triglycerides, H&Y: Hoehn and Yahr, MACE: Major adverse cardiovascular events, MI: Myocardial infarction, MMSE: Mini-mental state examination, MDS-UPDRS: Movement disorder society-unified Parkinson's disease rating scale, VTE: Venous thromboembolism, PD: Parkinson's disease, CVD: Cardiovascular disease, IL-6: Interleukin-6

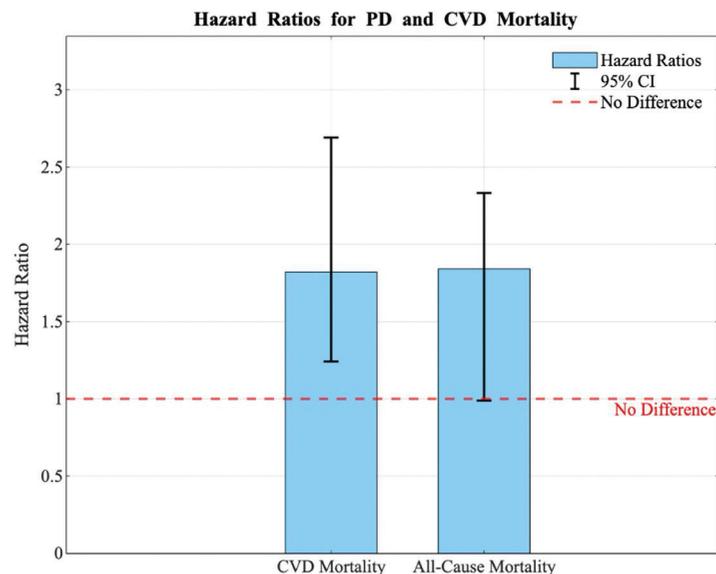


Figure 1. Hazard ratios for CVD and all-cause mortality in PD patients⁽⁵⁾
CVD: Cardiovascular disease, PD: Parkinson's disease, CI: Confidence interval



Figure 1. illustrates the HR values for cardiovascular and all-cause mortality in PD patients compared with non-PD individuals. The HR for CVD mortality significantly increases as its CI does not include 1. On the other hand, the HR for all-cause mortality shows a larger CI that narrowly contains 1. This suggests borderline statistical significance.

Another study researching blood markers of inflammation, neurodegeneration, and cardiovascular risk in early PD explores links to disease progression. The study identified inflammation and vascular pathology biomarkers in patients still in the early stages of PD. A proximity assay on 273 markers was applied to the plasma of 109 drug-naive at baseline PD patients and 96 healthy control patients⁽⁶⁾. At baseline, 35 plasma biomarkers showed downregulation of atherosclerosis risk factors such as E-selectin and B2-integrin, which both play key roles in stimulating endothelial contact and rolling with leukocytes⁽⁶⁾. Other contrasting results showed reduced markers in the plasminogen activation system, most notably the urokinase plasminogen activator⁽⁶⁾. Urokinase plasminogen activators and their reduction lead to decreased plasmin levels, the primary enzyme involved in dissolving blood clots. This study associated biomarker levels with disease progression, finding that higher plasma levels of parkers like interleukin-6 and cystatin B correlated with worse cognitive decline as measured by the Mini-Mental State Examination, and motor impairment, as measured by part III of the movement disorder society-unified PD rating scale⁽⁶⁾.

Additional studies examine the cardiac abnormalities associated with PD, emphasizing the role of autonomic dysfunction, which further supports the projected risk of adverse effects in PD patients. They report that PD patients experience a higher prevalence of arrhythmias, with one study cited indicating a 10-20% incidence of these cardiac issues in PD patients. Additionally, reduced heart rate variability (HRV) is common in PD patients, with a 25-30% decrease compared to healthy individuals, and is correlated with disease progression and motor

symptom severity⁽¹³⁾. The review also compares PD with other parkinsonisms, noting that while cardiac dysfunction is present in conditions like multiple system atrophy, PD patients exhibit more significant HRV reduction⁽¹³⁾. The authors advocate for routine monitoring of cardiac health, particularly HRV, as early intervention could improve cardiovascular outcomes.

PD patients also had prolonged electrocardiogram (ECG) parameters such as QTc, QRS, and QT. Having prolonged ECG parameters is associated with an increased risk of abnormal heart rhythms⁽¹⁴⁾. A study utilizing information from 28,242 patients, 380 of whom had PD, revealed that PD patients were, on average, older (mean 64.8 years vs. 60.1 years) and had a higher body mass index (BMI) (30.57 vs. 29.38 kg/m²) than their non-PD counterparts. The same patients were more likely to have diabetes (33.68% vs. 25.47%) and hypertension (68.16% vs. 56.49%) compared to others as well. Additionally, male PD patients exhibited higher CVD mortality rates, which may be related to the earlier onset of the disease and the lack of beneficial neuroprotective effects from the hormone estrogen⁽⁵⁾. This indicates that patients with PD face a higher risk of cardiovascular death and morbidity. Advanced age, greater BMI, diabetes, hypertension, abnormal heart rhythms, and earlier illness onset in male patients, together with the absence of estrogen's neuroprotective properties, are all associated with this higher risk⁽⁵⁾. These comorbidities not only raise the risk of CVD, but they may also exacerbate PD symptoms, resulting in a cyclical interplay that heightens the risk of serious cardiovascular events such as arrhythmias and sudden cardiac death. These findings underline the importance of an integrated clinical approach to addressing both PD and its accompanying comorbidities to reduce their combined impact on patient outcomes⁽⁵⁾.

Vascular comorbidities in PD also require more attention and may significantly contribute to the mortality of these patients. One study's results show that PD patients are more likely to experience major adverse cardiovascular events (MACEs), according to some research. In contrast,

other studies suggest that PD may be linked to a reduced cardiovascular risk profile⁽¹⁰⁾. Patients must be screened more often for CVD if they have PD. Other studies have shown that physicians can monitor disease progression in PD by utilizing biomarkers while managing cardiovascular complications. Biomarkers include urate, protein DJ-1, and coenzyme Q10, all associated with neuroprotective effects⁽²⁾. Additional studies further confirmed this view, finding that in patients with PD and previous symptoms of CVD, the risk of cardiovascular and overall mortality is significantly higher⁽¹⁵⁾. For instance, one report found that biomarkers of inflammation and neurodegeneration found in early-stage PD patients are associated with disease progression and cognitive decline, especially in vascular pathology⁽⁶⁾. Biomarkers are measurable and detectable biological changes that can track and predict disease development. Cholesterol and blood pressure are common biomarkers for heart disease.

While most studies support this link, one study using a two-sample Mendelian randomization approach presents a counter, finding a minimal but statistically significant protective association of PD with MI, with an odds ratio (OR) of 0.9989⁽⁷⁾. Another study suggests that PD may be associated with a lower cardiovascular risk profile, contradicting the hypothesis that PD worsens cardiovascular outcomes. It reveals that cardiovascular biomarkers may indicate a lower cardiovascular risk profile in PD patients. However, the findings reveal minimal to no significant causal links between PD and other factors, such as atrial fibrillation (AF) or venous thromboembolism, as they both had ORs of 1.0000⁽⁷⁾.

Further studies reveal a nuanced relationship between PD and CVD, presenting multivariate reports. Supporting studies suggest that patients with PD are at an increased risk for cardiovascular complications. They reveal that ECG abnormalities have prolonged ramifications in PD patients, such as QTc, QRS, and QT intervals, which may indicate a predisposition to arrhythmias. Additionally, investigations have documented an increased trend in BMI, with higher incidences of diabetes and hypertension,

which all seem to be cardiovascular risk factors in elderly PD patients⁽¹⁶⁾.

Cardiac Dysfunction/Heart Failure

Cardiac dysfunction and heart failure significantly contribute to the non-motor symptoms of PD, highlighting a critical connection between cardiovascular health and cognitive function⁽¹⁶⁾. One cross-sectional study provides evidence that mild cognitive impairment has been seen to worsen with cardiovascular autonomic dysfunction in PD patients, establishing a link between autonomic regulation and cognitive decline⁽¹⁷⁾. Alterations in cardiovascular autonomic control, including impaired HRV, are present in patients with PD and may lead to the development and worsening of cognitive deficits. A systematic review of cardiac changes in PD further supports this idea, demonstrating that PD accelerates both autonomic dysfunction and cardiac dysregulation, underscoring the role of cardiac dysfunction in the overall progression of the disease⁽¹⁸⁾. Further research suggests that increased physical fitness reduces the prevalence of cardiac dysfunction and heart failure, reducing PD diagnosis rates⁽¹⁹⁾.

Studies have also identified links between the cardiovascular sympathetic system and PD, showing concurrent degeneration in motor symptoms and autonomic functions in individuals with PD. This connection is valuable because identifying cardiovascular dysfunction may enable providers to identify PD earlier, even before traditional motor symptoms like tremors or stiffness appear. A study utilizing metaiodobenzilguanidin (MIBG) scintigraphy reports that PD patients often have reduced heart nerve activity (sympathetic denervation) on MIBG scans before experiencing motor symptoms. This diagnostic tool involves injecting a radioactive substance into the bloodstream to measure cardiac uptake and nerve function⁽²⁰⁾. These findings indicate that sympathetic denervation may precede motor issues, demonstrating the diagnostic value of MIBG scintigraphy for heart-related problems in PD patients and its role in revealing a link between PD and cardiovascular autonomic dysfunction.



As mentioned, impaired nerve activity is one of many cardiovascular ramifications caused by PD-induced neurodegeneration. PD is ascribed to progressive loss of motor function and coordination due to enduring degeneration of the substantia nigra, decreasing dopamine production, which impacts autonomic regulation⁽²¹⁾. White matter hyperintensity (WMH) is the pathological manifestation of damage and a radiological hallmark of cerebral small vessel disease, which involves endothelial dysfunction and compromises the integrity of the blood-brain barrier. This disruption leads to the formation of lacunes and microhemorrhages, which damage structural networks inside the brain. Neuropathological conditions like WMH adversely affect the autonomic nervous system (ANS), disrupting homeostasis and eliciting complications such as ischemia and arrhythmia, reflecting underlying vascular pathology. Specifically, sympathetic neuronal degeneration caused by PD can impair the cardiovascular system⁽²²⁾. The concept of a neurovascular unit highlights the tight, bidirectional relationship between the neurons, glia, and vascular cells, illustrating that vascular protection contributes to neuronal protection. Following this concept, interventions that protect vascular health may help preserve neuronal function and delay neurodegenerative consequences. These adverse cardio-related effects have been shown to impact the efficacy of therapeutic Levodopa treatment in PD patients by increasing the risk of OH. Presentation of OH can diminish brain dopamine levels, limiting Levodopa's use as a dopamine prodrug. Moreover, neurogenic OH results from ANS dysfunction; WMH can impair baroreceptor function, and neurodegeneration can affect vascular regulation and heart rate⁽²²⁾.

Overall, neurodegeneration linked to PD is associated with various sources of damage to the ANS, manifesting as cardiovascular regulation malfunctions. Despite this association between cardiovascular dysautonomia and PD, contradictory findings also exist. A referenced Danish cohort addressed in the focal study found an inverse relationship between CVD and PD, reporting that patients with MI had a 20% decreased risk of

developing PD and a 28% reduced risk of developing secondary parkinsonism. The focal study suggests that these results may be influenced by confounding factors, such as demographic variability, comorbidities, and age, which impact the external validity of the data. Despite this counterclaim in the Danish study, a case-control study used univariate and multivariate logistic regression analysis to assess the association between CVD history and idiopathic PD development. The univariate analysis substantiates a direct correlation between CVD history and idiopathic PD, finding that PD and CVD associations remained statistically significant despite removing common confounds (i.e., Age, BMI, hypertension, diabetes, etc.) (OR: 1.56, 95% CI: 1.09-2.08, $p=0.013$)⁽⁴⁾. This analysis supports a direct relationship between PD and CVD, independent of comorbid conditions and additional risk factors such as those removed from the data set. Furthermore, PD and CVD exhibit bilateral effects, substantiating the intersectionality between neurologic and cardiovascular functions.

Together, these studies underline the significant relationship between cardiac dysfunction and heart failure with the incidence and progression of PD, reinforcing the need for expanded research targeting cardiovascular indicators of PD. This may improve the disease's prognosis through early diagnosis and intervention.

Blood Pressure/Cholesterol Increasing PD Rates

Cardiovascular risk factors, such as high blood pressure and high cholesterol, are associated with increasing PD rates. Researchers aimed to further investigate this and conducted a prospective study using data from the Northern Sweden Health and Disease Study, a population-based cohort study in Västerbotten County, Sweden. The study, led by researchers from Umeå University, had 101,790 subjects. Cases were identified through the Newly Diagnosed Parkinson in Umeå study from 2004 to 2009. The data sets were linked, and in doing so, researchers examined cardiovascular metrics 2-8 years before PD diagnosis to determine their association with PD risk. This nested case-control design minimized recall

and selection biases, improving the reliability of findings. One prospective study found an inverse relationship between systolic blood pressure, serum triglycerides (S-TG), and PD risk. Study participants with lower blood pressure had an HR of 0.98 (95% CI: 0.97-0.99). This shows a slightly lower risk of developing PD for those individuals. It was also found that lower S-TG values were associated with a greater risk of developing PD, and participants had an HR of 0.61 (95% CI: 0.39-0.96)⁽⁸⁾. These results highlight the idea that while lower systolic blood pressure and S-TG levels may be associated with better cardiovascular health in general, they paradoxically correlate with an increased risk of PD. This suggests a complex interplay between cardiovascular health and neurodegenerative processes. All of this evidence shows that specific cardiovascular health metrics substantiate a higher likelihood of PD development. However, further research is necessary to explore potential mechanisms and reconcile these findings with conflicting evidence from other studies.

Another study involving 57,585 patients with newly diagnosed PD who had matched controls showed that PD patients have a significantly higher risk of AF. Their adjusted HR was reported to be 1.27 (95% CI: 1.18-1.36).

The HR of 3.06 shows that patients aged 40-49 had a substantially greater risk than individuals in the control group⁽⁹⁾. This data supports a positive association between autonomic dysfunction onset in PD patients and AF. These findings highlight the role of autonomic dysfunction in PD and show its correlation to AF, which covaries with a patient’s cardiovascular and neurological morbidity.

An additional study using electronic health records from two tertiary hospitals examined the occurrence of MACEs among 1,194 PD patients. MACE occurrence was found to be much higher for patients with more severe cases of PD. Researchers used the Hoehn and Yahr (H&Y) scale to measure disease severity. Results showed that MACE incidence ranges from 12.7% in low-severity PD patients to 27.6% in high-severity PD patients (p-trend <0.01)⁽¹⁰⁾.

Figure 2 illustrates the MACE and CV risk across H&Y tertiles as outlined in a study by Lim et al.⁽¹⁰⁾ Data from the source was taken to formulate this figure, which illustrates the trend of increasing MACE occurrence and very high CV risk percentages across H&Y tertiles. This indicates worsening cardiovascular health alongside PD progression. The decrease in low-moderate CV risk

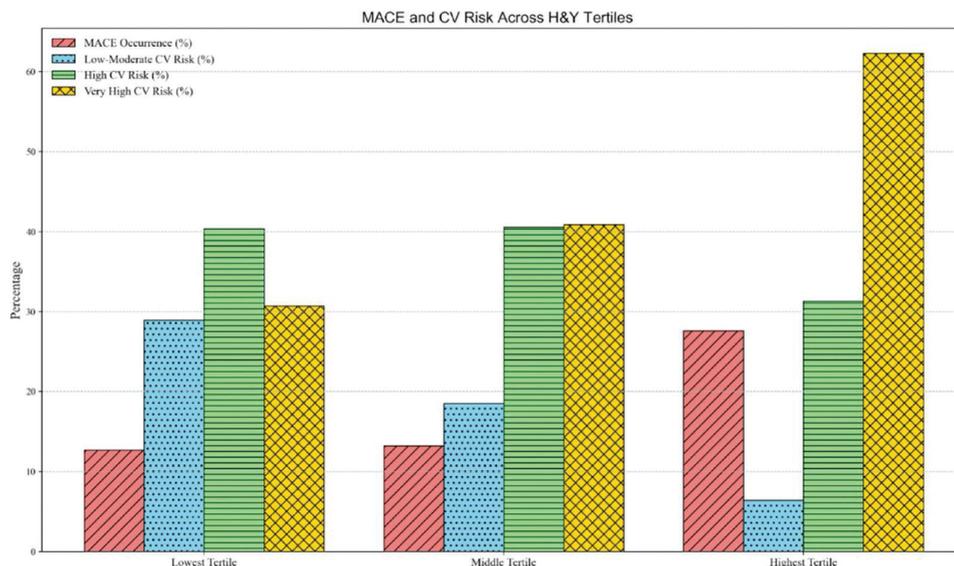


Figure 2. MACE and cardiovascular risk across H&Y tertiles⁽¹⁰⁾
H&Y: Hoehn and Yahr, MACE: Major adverse cardiovascular event, CV: Cardiovascular

highlights how cardiovascular complications can be more pronounced as PD severity increases. This data emphasizes the importance of cardiovascular risk management strategies for patients with PD that is advancing.

These findings highlight a significant correlation between the severity of PD and cardiovascular events, emphasizing the need to assess PD patients for cardiovascular risk factors such as hypertension and hyperlipidemia⁽²⁰⁾. While some studies have produced inconclusive or contradictory results, a growing body of evidence underscores the comorbidity of PD and CVD⁽²⁰⁾. However, limited research has explored the specific impact of CVD on PD progression. Recent advancements, such as those involving myocardial MIBG imaging, suggest that cardiac uptake decline often precedes motor symptoms and dopamine depletion in PD patients⁽²⁰⁾. These insights indicate that CVD plays a crucial role in influencing PD progression and overall prognosis, warranting further investigation into its potential as a therapeutic target⁽²⁰⁾.

PD patients were also found to have reduced rates of hyperlipidemia with an adjusted OR (a-OR): 0.77 (95% CI: 0.75-0.79), diabetes mellitus a-OR 0.73 (95% CI: 0.71-0.75), and hypertension a-OR 0.68 (95% CI: 0.67-0.70). This data compares PD patients with control individuals aged 65 or older. PD patients, however, had a significantly higher risk of a stroke, a-OR 1.27 (95% CI: 1.24-1.31), indicating a unique cardiovascular profile⁽¹¹⁾. Concerning vascular control and stroke prevention in particular, these findings raise significant concerns regarding the involvement of autonomic dysfunction in changing cardiovascular risk profiles in PD disease.

A previous systematic review investigated standard risk variables such as diabetes and inflammation, which are linked to both PD and CVD, further complicating the situation. Both of these factors contribute to an increase in cholesterol. While this complicates the picture, the study also found an inverse relationship between PD risk and other conventional cardiovascular risk factors, including smoking and high low-density lipoprotein cholesterol⁽²³⁾.

These results imply that although there is a strong correlation between cardiovascular health and PD outcomes, the underlying association remains unclear.

Findings from an additional cohort study focused on how people with PD had both an elevated risk of CVD and overall mortality⁽²⁴⁾. This supports the hypothesis that cardiovascular health is closely linked to PD outcomes, influencing disease severity, mortality rates, and overall quality of life.

Current research both supports and contradicts a link between blood pressure, cholesterol, and PD outcomes. Some research shows a protective effect, while other supports the idea that poor cardiovascular health accelerates the progression of PD. To address the impact of both neurological and cardiovascular disorders, the numerical evidence emphasizes the vital necessity for thorough cardiovascular examinations and individualized therapy options for patients with PD.

Hypothesis Confirmation

We hypothesized a bidirectional relationship between CVD and PD. The findings of this literature review revealed partial support for this hypothesis. Although substantial evidence supports the idea that PD worsens cardiovascular complications through mechanisms like autonomic dysfunction, reduced HRV, and neurovascular dysregulation, the reverse relationship we also hypothesized CVD acting as a causative factor for PD is less clear.

Multiple studies show that pre-existing cardiovascular conditions in patients may worsen PD outcomes and even contribute to PD progression. Even so, conflicting evidence from Mendelian randomization studies and analyses of MI risk suggests that CVD might not directly cause PD. These studies show how complex the relationship is and that more longitudinal research is needed to find potential causality.

Clinical Implications

An overwhelming portion of the literature examined suggests a correlation between CVD and worsening prognosis for PD patients. PD patients either concurrently have or are at an increased risk for developing cardiovascular conditions such as heart failure, hypertrophic cardiomyopathy, and ECG abnormalities, such as AF. Additionally, neurodegeneration linked to PD can worsen cardiac regulation, as damage to the ANS can disrupt electrical conduction within the heart, affecting cardiac rhythm. The mechanism described above hinders adequate perfusion to the brain, further exacerbating an individual's cognitive impairment. When either cardiovascular or neurological comorbidities remain unmanaged, patients face an increased risk of mortality.

These findings suggest that a holistic approach to treatment may be beneficial for PD patients, addressing both the management of PD and associated comorbidities⁴. Managing risk factors such as diabetes and hypertension could be done earlier in a patient's treatment to potentially manage cardiovascular and neurological status better. Cardiac assessments, such as monitoring ECG abnormalities or using the Head-up tilt test, could be utilized to prevent further complications and consequences. Clinicians should prioritize recognizing potential adverse reactions such as ECG abnormalities, arrhythmias, and increased risk for cardiac events when prescribing PD medications⁽¹⁰⁾. Patients with both CVD and PD are likely to be on multiple medications. Therefore, side effects and drug interactions should be analyzed thoroughly. Outside the clinical setting, patients could be educated on lifestyle modification, such as getting adequate exercise and maintaining at-home blood pressure diaries to monitor their cardiovascular health, control PD progression, and maintain their independence in daily tasks⁽¹⁹⁾.

Conclusion

This study aimed to examine the bilateral relationship between CVD and PD. Our findings included results concerning the link between CVD and PD mortality,

cardiac dysfunction/heart failure, and blood pressure/cholesterol-increasing PD rates. Findings examining the link between CVD and PD mortality suggest that this relationship remains complex and multifaceted. Some studies support the conclusion that PD patients face an increased risk of cardiovascular mortality due to autonomic dysfunction and systemic inflammation; other studies suggest that PD serves as a protective factor against MI. Moreover, regarding cases of cardiac dysfunction and heart failure, symptoms of cognitive impairment, ANS malfunction, and motor symptoms were most commonly influenced. Cardiovascular issues were also observed to complicate the efficacy of PD treatment. Examination of the codependency between CVD risk factors such as blood pressure, cholesterol levels, and PD progression also occurred; the search strategy prompting these results employed databases such as PubMed and Google Scholar.

Additionally, stringent criteria were constituted to ascertain high-quality peer-reviewed studies. Our meta-analysis was limited to studies written in English, accessible within our departments, and ones that distinctly examined PD and CVD. Due to the inconclusive nature of our results, future research is necessary to refine clinical management and the use of biomarkers to predict disease progression and to find more evidence for conclusive CVD-PD comorbidity and risk factors. Ultimately, understanding the relationship between these two diseases will help clinicians improve early diagnosis, treatment strategies, and disease prognosis.

Ethics

Footnotes

Authorship Contributions

Surgical and Medical Practices: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M, Patel D, Nguyen P, Concept: George C, Sidhu G, Dave H, Sonthalia S, Ramirez G, Rupp L, Wasniewski R, Burnidge A, Punzalan M, Ahmed A, Warren P, Maskey M,

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