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NON-MOTOR SYMPTOMS IN PARKINSON'S DISEASE: A SYSTEMATIC REVIEW OF CARDIAC IMPLICATIONS

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НЕМОТОРНИ СИМПТОМИ ПРИ БОЛЕСТ НА ПАРКИНСОН: СИСТЕМАТИЧЕН ПРЕГЛЕД НА СЪРДЕЧНИТЕ ПОСЛЕДИЦИ

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Abstract.

Background: Parkinson's disease is a progressive neurodegenerative condition not only marked by motor impairment but also by a wide range of non-motor symptoms, such as cardiovascular complications. Cardiac dysfunction, traditionally ascribed to autonomic nervous system damage, is now more and more identified as a major cause of morbidity and mortality in PD patients. The present review intends to integrate current evidence regarding the cardiac manifestations of PD, highlighting their prevalence, mechanisms, and clinical relevance. **Methods:** A PRISMA-guided systematic review was carried out using the PECOS framework. Seven electronic databases were searched for articles published between January 2010 and January 2025 that explored cardiac involvement as a non-motor symptom in PD. The inclusion criteria included observational studies, clinical trials, and meta-analyses reporting on cardiac outcomes like orthostatic hypotension, arrhythmias, heart rate variability, and cardiovascular mortality. Data extraction and risk of bias evaluation were carried out independently by two reviewers. **Results:** Starting with a pool of 949 records, 20 studies were found to meet the inclusion criteria. These studies showed a uniform correlation between PD and enhanced cardiovascular risks, including stroke (up to OR 1.66), orthostatic hypotension, and decreased heart rate variability. Though some reports described a decreased risk of myocardial infarction (OR 0.80), autonomic dysfunction was the core mechanism underlying most cardiac events. The results also highlighted the need for individualized cardiovascular monitoring in the management of Parkinson's disease and indicated underutilization of diagnostic technologies such wearable sensors and HRV analysis. **Conclusion:** Cardiac failure in Parkinson's disease (PD), fueled by autonomic dysfunction, is underappreciated in spite of associations with hypotension, arrhythmias, and stroke. Early detection measures such as HRV and wearables are not utilized. Cardiovascular risk reduction, particularly with PD meds, and incorporating cardiac management can better enhance outcomes.

Key words: Parkinson's disease, non-motor symptoms, cardiac dysfunction, autonomic nervous system, orthostatic hypotension, heart rate variability, cardiovascular risk, neurodegeneration.

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Резюме.

Въведение: Болестта на Паркинсон е прогресивно невродегенеративно заболяване, което се характеризира не само с двигателни нарушения, но и с широк спектър от немоторни симптоми, като например сърдечносъдови усложнения. Сърдечната дисфункция, традиционно приписвана на увреждане на вегетативната нервна система, днес все по-често се определя като основна причина за заболяемост и смъртност при пациенти с болест на Паркинсон. Настоящият обзор цели да се обобщят актуалните данни относно сърдечните прояви при болест на Паркинсон, като се акцентира върху тяхната разпространеност, механизми и клинично значение. **Методи:** Беше проведен систематичен преглед, съобразен с насоките на PRISMA, като се използва рамката PECOS. Бяха претърсени седем електронни бази данни за статии, публикувани през периода януари 2010 г. – януари 2025 г., които разглеждат сърдечното засягане като немоторен симптом при болестта на Паркинсон. Критериите за включване

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обхващаха наблюдателни проучвания, клинични изпитвания и метаанализи, отчитащи сърдечни изходи като ортостатична хипотония, аритмии, вариабилност на сърдечната честота и сърдечносъдова смъртност. Извличането на данни и оценката на риска от пристрастие бяха извършени независимо от двама рецензенти. **Резултати:** От общо 949 записи бяха подбрани 20 проучвания, отговарящи на критериите за включване. Тези проучвания показаха еднозначна корелация между болестта на Паркинсон и повишените сърдечносъдови рискове, вкл. инсулт (с относителен риск до 1,66), ортостатична хипотония и намалена вариабилност на сърдечната честота. Въпреки че в някои доклади се посочва намален риск от миокарден инфаркт (относителен риск 0,80), автономната дисфункция бе основният механизъм, стоящ в основата на повечето сърдечни събития. Резултатите също така подчертаха необходимостта от индивидуализирано сърдечносъдово наблюдение при лечението на болестта на Паркинсон и посочиха недостатъчното използване на диагностични технологии като носими сензори и анализ на вариабилността на сърдечната честота (HRV). **Заключение:** Сърдечната недостатъчност при болестта на Паркинсон (БП), предизвикана от автономна дисфункция, е недооценена, въпреки връзките ѝ с хипотония, аритмии и инсулт. Мерките за ранно откриване, като HRV и носими устройства, не се използват. Намаляването на сърдечносъдовия риск, особено чрез медикаменти за БП, и включването на сърдечно лечение могат да подобрят резултатите.

Ключови думи: болест на Паркинсон, немоторни симптоми, сърдечна дисфункция, автономна нервна система, ортостатична хипотония, вариабилност на сърдечната честота, сърдечносъдов риск, невродегенерация.

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Introduction

Parkinson's disease (PD) is a neurodegenerative disorder characterized by progressive degeneration of dopaminergic neurons of the substantia nigra pars compacta with subsequent severe morbidity. Neuropathologically, PD is defined by the deposition of α-synuclein in the Lewy body and neurite type within affected neurons that are important in the pathogenesis of motor and non-motor symptoms of the disorder [1, 2, 3]. The significant neuronal loss tends to be expressed clinically in the form of a range of motor dysfunctions, such as bradykinesia, tremor, rigidity, and postural instability. Non-motor symptoms like cognitive impairment, autonomic dysfunction, and mood disorders have, however, become more subjects of interest in recent times because they have a major influence on the quality of life of patients [1, 4, 5].

Epidemiologically, PD is the most common neurodegenerative disorder, currently affecting 7-10 million people around the world with estimated prevalence between 1% and 2% in over 65 years of age patients [6, 7]. An unmistakable pattern of increasing incidence of PD by age is well established, and there has also been a clear demographic pattern toward geographic and genetic heterogeneity with studies showing prevalence variability among different ethnic groups as well as by geographic location [6, 7].

The interrelationship between PD motor and non-motor symptoms is multifaceted and frequently overlapping, calling for an overall understanding of the disease course. Although more classically stressed, motor symptoms have been, but current evidence indicates that non-motor symptoms may precede and, in fact, antedate the onset of motor impairment in most patients [2, 8, 9]. This changing attitude demands an integrated approach to PD management, and it challenges clinicians to view these non-motor symptoms as useful aspects of the total symptomatology that need to be identified early and treated [10, 11]. Identification and treatment of these non-motor symptoms can greatly improve diagnostic accuracy and patient outcomes, reaffirming the importance of integrated care strategies in the management of this disease [7, 12].

Non-motor symptoms (NMS) of Parkinson's disease (PD) are cardinal features that could potentially severely deteriorate the quality of life of patients even before the onset of motor symptoms. Research has shown that nearly 97% of patients with PD develop non-motor symptoms, and the most common of these are anxiety (78%), fatigue (78%), and sleep disturbance (75%) Habib et al. [13, 14]. These NMS could lead to cognitive impairment, mood disorders, and autonomic dysfunction and contribute to the complexity of patient care [15, 16]. It is remarkable to note that cognitive impairment affects about 40% of PD patients, and 80% are likely to develop Parkinson's disease dementia as the disease advances [15, 17].

The identification of NMS has treatment implications, with the latter frequently being directed mainly towards motor symptoms conventionally. A more integrated model of care for motor and non-motor symptoms is required for maximizing outcomes and quality of life in patients [18]. Optimizing the management of NMS has been reported to decrease burdens to a great extent, maximizing the overall therapeutic effect on PD patients [19, 20].

Classification of non-motor symptom (NMS) in Parkinson's disease (PD) suggests a complicated impact on the management of the patient, the symptoms usually evolving prior to motor symptoms and generating a significant influence on quality of life. NMS can broadly be categorized under autonomic, cognitive, psychiatric, sleep, gastrointestinal, and sensory disturbances. Specifically, autonomic dysfunction is characterized by symptoms like orthostatic hypotension, sialorrhea, and gastrointestinal manifestations such as constipation, which are also likely to be underdiagnosed and undertreated [21, 22, 23]. Cognitive impairments like memory impairment and executive dysfunction, which generally increase with deteriorating disease and affect daily function [24, 25].

Psychiatric symptoms, such as depression and anxiety, are also prevalent and may also aggravate the clinical burden of PD, illustrating the importance of comprehensive evaluations [13,17]. Sleep disorder, like REM sleep behavior disorder and insomnia, often presents itself in the prodromal state of PD and needs careful monitoring [26, 25].

The clinical handling of these non-motor symptoms usually lags behind, in that they will often go unseen by clinicians as well as by patients. Getting over this underdiagnosis is essential, however, since in-depth treatment regimens incorporating both the motor and non-motor symptoms can make patients' overall level of quality much better [21, 13, 27].

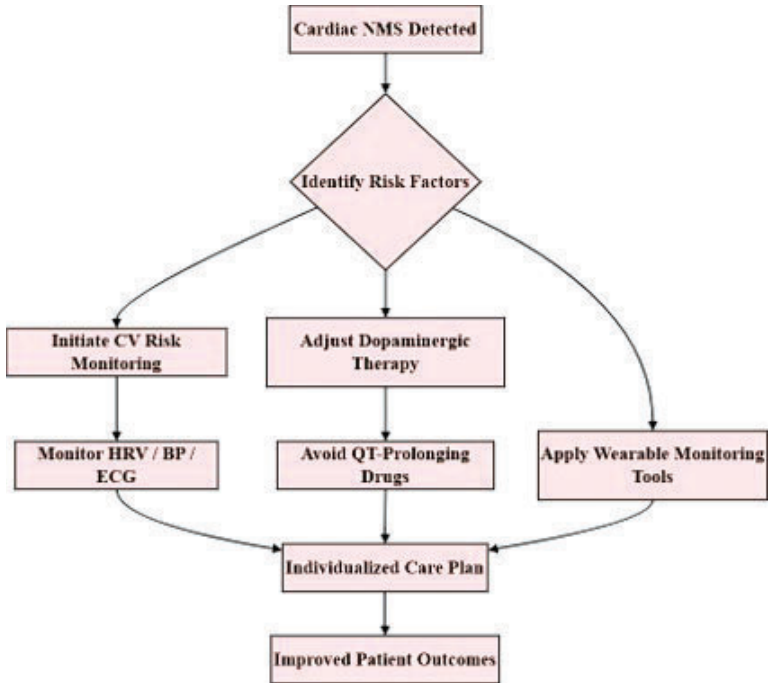

Fig. 1. Integrated Management of Cardiac Symptoms in PD

Autonomic nervous system participation in Parkinson's disease (PD) has a great influence on cardiovascular regulation, resulting in significant cardiac dysfunction without overt symptoms. Orthostatic hypotension owing to autonomic denervation affects about 30% of PD patients and can result in profound cardiovascular events like sudden cardiac death [28, 29]. Denervation of the heart, commonly before the development of motor symptoms, may express as high blood pressure variability and heart rate control abnormalities [30, 31].

Recent research illustrates that peripheral autonomic dysfunction, which is associated with α-synuclein pathology, can result in lethal consequences related to cardiac arrest, emphasizing the lethal character of these silent symptoms [30]. In addition, the current shortcomings in the systematic assessment of cardiac dysfunction in PD patients frequently lead to delayed diagnoses, increasing the burden of disease management. The absence of regular evaluation for cardiac function, with the incorporation of autonomic assessments, continues to be a key area of clinical improvement [28, 32]. At present, it is known that autonomic symptoms are related to more severe disease progression and shorter survival [29, 33]. A holistic approach to the diagnosis and treatment of these dysfunctions will be necessary to improve patient outcomes.

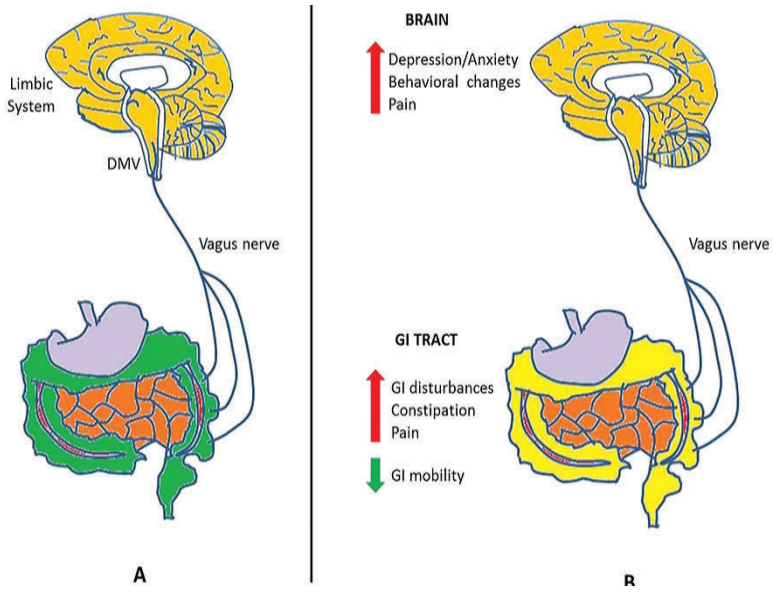

Fig. 2. Parkinson's disease and the brain-gut axis. (**A**) Bidirectional communication between the gut and the brain via the vagus nerve. (**B**) Non-motor symptoms of Parkinson's disease [26]

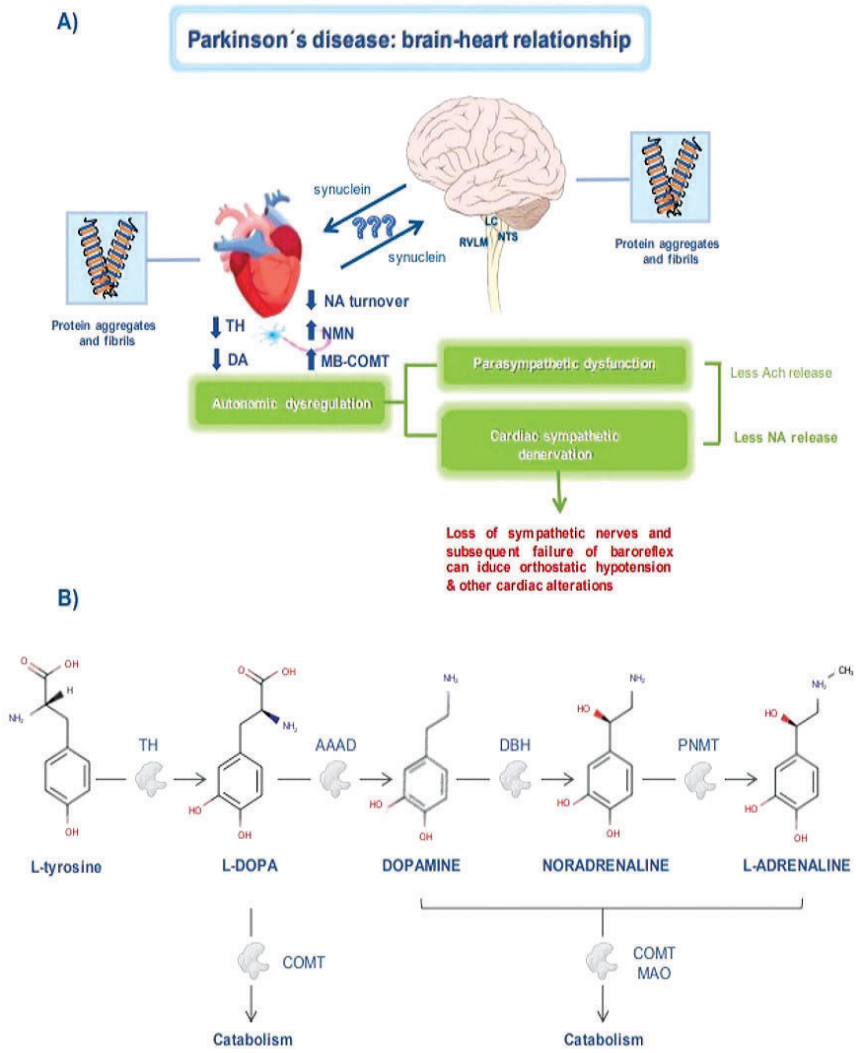

Fig. 3. Brain–heart interaction in Parkinson's disease. (**A**) Cardiac sympathetic pathway changes. The reduction in tyrosine hydroxylase either at the brain or cardiac level, causes alterations in noradrenaline metabolism. In PD patients, α-synuclein inclusions are present within the myocardial tissue and cardiac-related brain areas, including the locus coeruleus, nu cleus of the tractus solitarius, and the rostro ventrolateral medulla. Together, these autonomic abnormalities are linked with the development of cardiac dysfunction. (**B**) Schematic representation of catecholamines' biosynthesis pathway. Tyrosine hydroxylase, aromatic amino acid decarboxylase, dopamine-beta-hydroxylase, phenylethanola mine-N-methyltransferase, catechol-O-methyltransferase, monoamine oxidase. Chemical structures were obtained from the DrugBank database. these autonomic system abnormalities are associated with the progression of cardiac dysfunction. (**B**) Schematicrepresentation of the biosynthetic pathway of catecholamines. Tyrosine hydroxylase, aromatic amino acid decarboxylase, dopamine hydroxylase, phenylethanolamine N-methyltransferase, catechol-O-methyltransferase, monoamine oxidase. Chemical structures were retrieved from DrugBank database [54]

It is the goal of this review to systematically tabulate and critique the cardiac expressions of Parkinson's disease (PD) as part of its non-motor clinical manifestations, alongside the identification of the diagnostic modalities, causal mechanisms, and implications for optimum management.

Materials and methods

Review design

This systematic review's PECOS protocol (Population, Exposure, Comparison, Outcomes, Study design) followed the reporting guidelines of PRISMA so that it can be made transparent and reproducible.

Table 1. Inclusion and exclusion criteria devised for this review

Criteria	Inclusion	Exclusion
Population	Patients diagnosed with Parkinson's Disease (PD), any age or sex	Animal studies; patients with secondary parkinsonism or atypical parkinsonian syndromes
Exposure	Presence or assessment of non-motor symptoms with a focus on cardiac involvement instance arrhythmias, orthostatic hypotension, heart rate variability	Studies not addressing cardiac implications as a non-motor symptom
Comparator	Healthy controls or patients with PD without cardiac involvement	Studies without a comparator group
Outcomes	Cardiac manifestations in Parkinson's disease include cardiovascular autonomic dysfunction, ECG changes, heart rate variability, blood pressure changes, effects on disease progression, and reduced quality of life	Studies not reporting cardiac outcomes or insufficient outcome data
Study design	Observational studies cohort, case-control, cross-sectional, clinical trials, systematic reviews/meta-analyses	Case reports, conference abstracts, editorials, narrative reviews
Publication language	English only.	Non-English publications.
Publication year	Studies published from Jan 2010 to Jan 2025.	Studies published more than 15 years.

Database search protocol

To ensure an all-inclusive capture of literature, a database search strategy was conceptualized. The databases searched include PubMed, Embase, Scopus, Web of Science, Cochrane Library, CINAHL, and PsycINFO. The precision of the search was maximized using Boolean operators and MeSH keywords. It included combinations such as:

("Parkinson Disease"[Mesh] OR "Parkinson's disease" OR "PD")

AND

("Non-Motor Symptoms" OR "Autonomic Dysfunction" OR "Cardiovascular Dysfunction" OR "Cardiac Implications" OR "Orthostatic Hypotension" OR "Heart Rate Variability" OR "Arrhythmias" OR "ECG abnormalities")

AND

("Systematic Review" OR "Observational Study" OR "Clinical Trial")

Data extraction protocol and data items

Application of data extraction was conducted by using a form of pre-designed data extraction. Data extraction used two independent reviewers to limit error and bias. Included are study characteristics such as author, year, location, study design, sample size, and demographics; Parkinson's disease–specific details such as diagnostic criteria, disease duration, and severity; cardiac non-motor symptom details such as type of cardiac involvement, diagnostic methods, and assessment tools; outcomes such as prevalence, severity, quality of life impact, morbidity, and mortality; major findings including associations with treatment or disease progression; the statistical outputs that included odds ratios, hazard ratios, or beta coefficients; and any noted environmental or medication-related exposures. Third, reviewers compared and resolved inconsistencies by cross-checking in consensus.

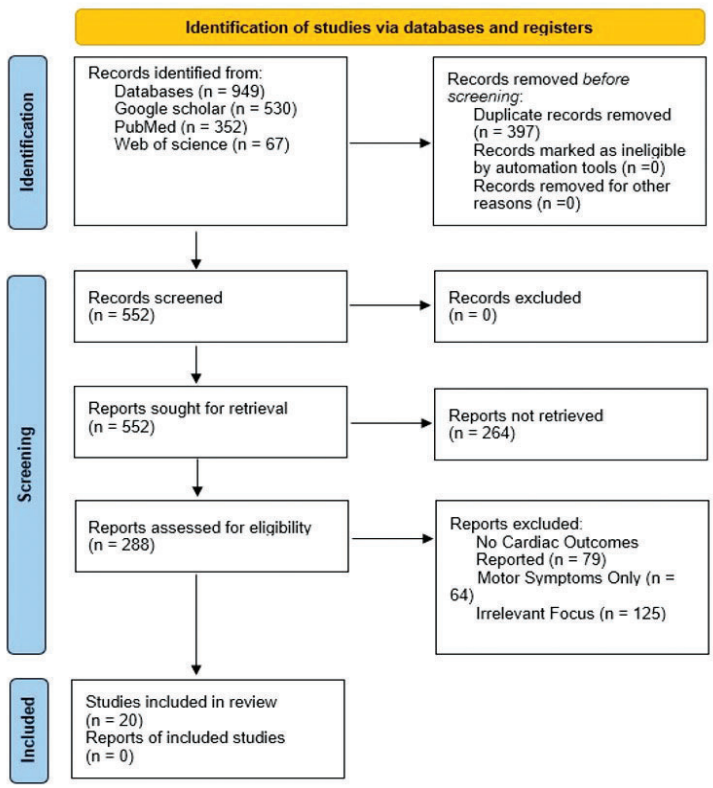

Fig. 4. PRISMA flowchart

Results

The database search initially identified 949 records from three sources: Google Scholar (n = 530), PubMed (n = 352), and Web of Science (n = 67). After the removal of 397 duplicate records, 552 unique records were screened, with none excluded at this stage. All 552 records were sought for full-text retrieval, but 264 reports could not be retrieved. Subsequently, 288 reports were assessed for eligibility, of which 268 were excluded due to reasons such as the absence of cardiac outcomes (n = 79), a focus on motor symptoms only (n = 64), or an irrelevant focus (n = 125). Finally, 20 studies [34-53] were included in the review.

Demographic Characteristics

The reviewed studies for ascertaining cardiac implications as a non-motor symptom in Parkinson's disease (PD) were geographically representative, including international or multinational research teams, and single country-based studies from the USA [41, 52], the UK [43, 45, 53], South Korea [40, 51], Taiwan [38], and Italy [44] (Table 2), with high generalizability and usability of outcomes in various healthcare settings. Participant demographics were extremely variable, ranging in mean ages from approximately 60 to over 79 years, as expected, based upon the general age of onset and progression of PD. While a few studies, e.g., Liang et al. [38] and Abugroun et al. [41], had cohorts that were gender-balanced or close to being balanced, the majority did not report gender, and only a few, e.g., Nabizadeh et al. [50] and Ukenenye et al. [52], made specific mention of gender-specific eligibility. Follow-up durations ranged widely from short evaluations like one-year observational studies [41, 53] to long cohort studies spanning over a decade [40, 45]. Most studies employed some form of control group matching, e.g., 1:1 and 1:4 matching, propensity score matching [51], or database-based matched analyses [52], thereby enhancing comparability between PD and non-PD populations. Inconsistencies in reporting demographic or methodology variables such as age, gender, and follow-up durations

were observed in some studies, which may have limited interpretability. But the extensive range in study setting and design, e.g., meta-analyses [49], longitudinal cohort studies [40, 44], and multinational database studies [46], provides an extensive range synthesis of the cardiac characteristics of non-motor symptoms in PD.

A number of studies have assessed the cardiovascular risk of Parkinson's Disease (PD), which always demonstrated a raised risk of stroke (OR 1.66 and OR 1.49, respectively). This raised risk is due to susceptibility of the cerebrovascular, most probably secondary to autonomic dysfunction. In these studies, an increased risk of myocardial infarction (MI) or cardiovascular mortality was not observed [34, 37]. Increased risk of circulatory disease and all-cause mortality (HR 2.09) has also been documented, for which personalized cardiovascular monitoring and comprehensive strategy for PD treatment are required [40]. Increased risk of heart failure (HF) in PD patients receiving dopamine agonists, especially those of ergot origin, has been documented by Tran et al. and caution is advised in patients with established cardiovascular disease [35]. Autonomic dysfunction was found to be one of the most frequent causative factors in cardiac complications associated with PD. Heimrich et al. found an increased risk of AMI and indicated alterations in heart rate variability (HRV) [38, 46]. The side effects of dopaminergic drugs, orthostatic hypotension (OH), and prolongation of QT interval were also found to be significant predictors in cardiac risk evaluation prior to starting such treatment [47]. In addition, studies have shown an increased risk of coronary artery disease (CAD) in PD caused by autonomic dysregulation and inflammation, highlighting the need for CAD risk assessment during treatment in PD. The use of diagnostics of autonomic dysfunction, as well as systematic cardiovascular risk surveillance particularly in the context of stroke and cardiac ischemia, has been established [49]. Early identification of cardiovascular non-motor symptoms through wrist-worn sensors has also been proposed as a preventive care tool [42]. Drug-related risk factors were studied as well. A study identified increased risk of ischemic heart disease (IHD) and death in PD patients treated with first-generation antipsychotics and suggested the use of alternative antipsychotics with ongoing cardiovascular monitoring [53]. Lastly, increased hospitalization rates from cardiovascular complications among PD patients have been documented, while others observed short-term symptom relief in PD patients with atrial fibrillation on admission possibly reflecting a reduced arrhythmogenic tone in this subgroup [43, 44, 52].

Assessment of bias

Risk of bias assessment was performed with the ROBINS-I tool that assessed seven domains in twenty studies. The most frequent affected domain was bias

Table 2. Overview of study demographics, follow-up duration, and control group matching

Study (Year)	Location	Mean Age (Years)	Male:Female Ratio	Gender Data Eligible?	Follow-up Period	Control Group Matching
Alves et al. (2020) [34]	Europe (Multiple)	~65–80	Not Reported	No	Varied	Yes
Tran et al. (2015) [35]	International	Not reported	Not Reported	No	Not reported	Yes
Heimrich et al. (2021) [36]	International	Not specified	Not Reported	No	NA	Yes
Hu & Xu (2023) [37]	International	Not reported	Not Reported	No	Varied	Yes
Liang et al. (2015) [38]	Taiwan	Not specified	1.0 : 1.0	Yes	3 years	Yes
Alves et al. (2020) [39]	Global	Not reported	Not Reported	No	NA	Placebo-arm only
Choi et al. (2019) [40]	South Korea	≥ 60	Mixed	Partial	12 years (2002–2013)	Yes (1:4 matching)
Abugroun et al. (2020) [41]	USA	79 (± 0.03 SE)	~1.35 : 1.0	Yes	1 year	Yes
Okunoye et al. (2022) [43]	UK	≥ 50	Not Reported	No	Median: 5.1 years	Yes
Braga et al. (2014) [44]	Italy	Mean: 76.7	Not specified	No	7 years (2000–2007)	Yes
Hobson & Meara (2018) [45]	UK	Not specified	Not Reported	No	18 years	Yes
Li et al. (2021) [46]	Global (Multi-national)	Not reported	Not Reported	No	Not specified	Yes
Bacchi et al. (2017) [47]	Global	Not reported	Not Reported	No	Not reported	NA
Chua et al. (2022) [48]	International	Not specified	Not Reported	No	Not specified	Yes
Cereja et al. (2023) [49]	International	Not specified	Not Reported	No	Varied (meta-analysis)	Yes
Nabizadeh et al. (2023) [50]	International	Not specified	Similar for M & F	Yes	Varied (multi-database)	Yes
Lim et al. (2024) [51]	South Korea	Not specified	Not Reported	No	Retrospective (multi-year)	Yes (propensity score-matched)
Ukenenye et al. (2023) [52]	USA	PD: 78.1, No-PD: 70.5	PD: 56.3% M / 43.7% F	Yes	Hospital stay-based	Yes (NIS database analysis)
Orayj (2021) [53]	UK (SAIL databank)	≥ 40	Not reported	Partial	1 year	Yes (1:1 matched)

Table 3. PD involves cardiac risks and autonomic dysfunction, requiring tailored monitoring and care

Author (Year)	Study Type	Sample Size (PD / Control)	Cardiac Manifestations Studied	Diagnostic Tools	Key Findings (Risk Ratios, ORs, etc.)	Proposed Mechanisms	Management Implications
Alves et al. (2020) [34]	Systematic Review & Meta-analysis	11 studies (varied)	Stroke, MI, CV mortality	Clinical diagnosis	Increased Stroke (OR 1.66); No Increased MI or CV death	Autonomic dysfunction	Stroke risk assessment
Tran et al. (2015) [35]	Systematic Review	13 (CVR), 4 (HF)	Valve regurgitation, HF	Echo, imaging	Higher CVR (IRR up to 7.10); Higher HF w/ DAs	Dopamine agonist toxicity	Limit ergot DA in CV patients
Heimrich et al. (2021) [36]	Meta-analysis	47 studies, 2772 pts	HRV changes	HRV (RMSSD, HFms2)	Decreased Parasympathetic tone	Vagal involvement	HRV as a diagnostic tool
Hu & Xu (2023) [37]	Meta-analysis	101,712 PD / 204,901 ctrl	Stroke, MI, CV mortality	Clinical data	Increased risk of Stroke (OR 1.49), cohort: Increased MI, CV death	Autonomic dysfunction, age	Tailored CV monitoring
Liang et al. (2015) [38]	Cohort Study	3211 PD / 3211 ctrl	AMI	Claims data	HR for AMI: 1.67	Autonomic, metabolic stress	Monitor cardiac ischemia risk
Alves et al. (2020) [39]	Meta-analysis (placebo arms)	14704 PD	CV adverse events	Trial data	CV AEs: 3.3%; most common: hypotension	BP instability	BP monitoring needed
Choi et al. (2019) [40]	Cohort (Korea)	3510 PD / 14040 ctrl	Mortality (CV, neuro, etc.)	National registry	HR 2.09 for mortality; Increased circulatory disease	Comorbidity & vulnerability	System-wide health approach
Abugroun et al. (2020) [41]	Cross-sectional	57,914 PD (aged ≥65)	Stroke, CAD, HTN, diabetes	Inpatient dataset	Increased Stroke (OR 1.27), Decreased CAD/HTN/DM	Selective risk profile	Emphasize stroke prevention
Mughal et al. (2022) [42]	Systematic Review	More than 50 studies	Cardiac NMS, monitoring	Wearable sensors	Wearables underused for CV NMS	Early detection, remote tracking	Develop cardiac sensor tools
Okunoye et al. (2022) [43]	Cohort Study	9998 PD / 55554 controls	Hospitalization reasons	THIN database	Increased Hospitalizations due to falls, stroke, CV issues	NMS burden	Preventive CV care & fall reduction
Braga et al. (2014) [44]	Case-Control Study	367 admissions	Hospitalization reasons incl. CV	Hospital records	Increased infections, trauma; CV mortality more in controls	Mixed comorbidity load	Early CV risk assessment may help
Hobson & Meara (2018) [45]	Longitudinal Cohort	166 PD / 102 controls	Mortality patterns, cardiac deaths	Death certificates, clinical records	21% cardiac-related deaths; Increased pneumonia (53%); HR for pneumonia death: 2.03	Undiagnosed cardiac/ PNS dysfunction, aspiration-related CV strain	Improve CV risk documentation and palliative care planning
Li et al. (2021) [46]	Meta-analysis	13 references (16 studies)	Heart Rate Variability (HRV)	LF, HF spectral analysis	Reduced LF in PD (g = -0.27), decreased HF in late-stage PD	Sympathovagal imbalance	HRV can guide early autonomic monitoring
Bacchi et al. (2017) [47]	Systematic Review	22 studies	Orthostatic hypotension (OH), QT prolongation, VT/SCD	BP readings, ECG	Domperidone may help OH but increased QT/VT/SCD risk in heart disease	Interaction between dopaminergic therapy and domperidone	Screen for cardiac risk before prescribing domperidone
Chua et al. (2022) [48]	Systematic Review & Meta-analysis	35,237 PD / 650,866 control	Coronary Artery Disease (CAD)	Observational data	Increased CAD in cohort studies (RR = 2.23); trend in case-control (OR = 1.47)	Autonomic dysregulation, inflammation	CAD risk needs consideration in long-term PD care
Cereja et al. (2023) [49]	Meta-analysis	7 studies	Atrial fibrillation (AF)	Clinical diagnosis, ECG	No increased AF overall (OR 1.10), but increased in early PD (OR 1.55)	Autonomic dysfunction in early PD	AF screening may be warranted early in PD
Nabizadeh et al. (2023) [50]	Meta-analysis	80,441 PD / 802,857 contro	Myocardial infarction (MI)	Clinical data	Decreased MI risk in PD (OR 0.80); MI prevalence ~5%	Possibly reduced traditional CV risk profile in PD	Tailor cardiac risk assessments differently in PD
Lim et al. (2024) [51]	Retrospective Cohort	1194 PD / matched controls	Major adverse CV events (MACE)	EHR, hospital records	No difference in MACE rates; severity not an independent predictor	Common CV risk factors dominate outcome	Manage CV risk factors regardless of PD status
Ukenenye et al. (2023) [52]	Nationwide Analysis	1.86M AF hospitalizations (19,490 PD)	In-hospital mortality, VT, AHF	NIS database	No increased mortality in PD with AF; decreased AHF (OR 0.79), decreased VT (OR 0.77)	Reduced arrhythmogenic tone	Favorable short-term outcomes in AF hospitalizations
Orayj (2021) [53]	Propensity-matched cohort	1837 PD	Ischemic heart disease (IHD), mortality	SAIL databank, Cox regression	Increased IHD with FGAs (HR 2.60); increased mortality with all antipsychotics, esp. FGAs	Cardiometabolic effects of antipsychotics	Avoid FGAs in PD when possible, monitor CV risk

due to confounding (D1), and there was a severe risk in some of the studies such as Braga et al. [44], Bacchi et al. [47], and Orayj [53]. This indicates that control over potential confounding variables may not have been achieved in these studies. Participant selection bias (D2) and intervention classification bias (D3) were mostly low or moderate, reflecting good methodological control in these categories. High risk was present in some studies, though, such as Abugroun et al. [41], Mughal et al. [42], and Braga et al. [44], perhaps due to indeterminate eligibility criteria or exposure misclassification.

Deviation in planned intervention (D4) was kept under control throughout all the studies and graded as uniformly low risk. Missing data bias (D5) and outcome measurement bias (D6) were more variable. Such studies, e.g., Mughal et al. [42] and Braga et al. [44], graded as serious risk in these categories, and problem with outcome data completeness and consistency of outcome measurement, potentially secondary to the absence of blinding. Selective report bias during outcome reported choice (D7) was mainly low, yet some studies, such as Abugroun et al. [41] and Braga et al. [44], presented high risk, which was indicative of potential selective outcome reporting.

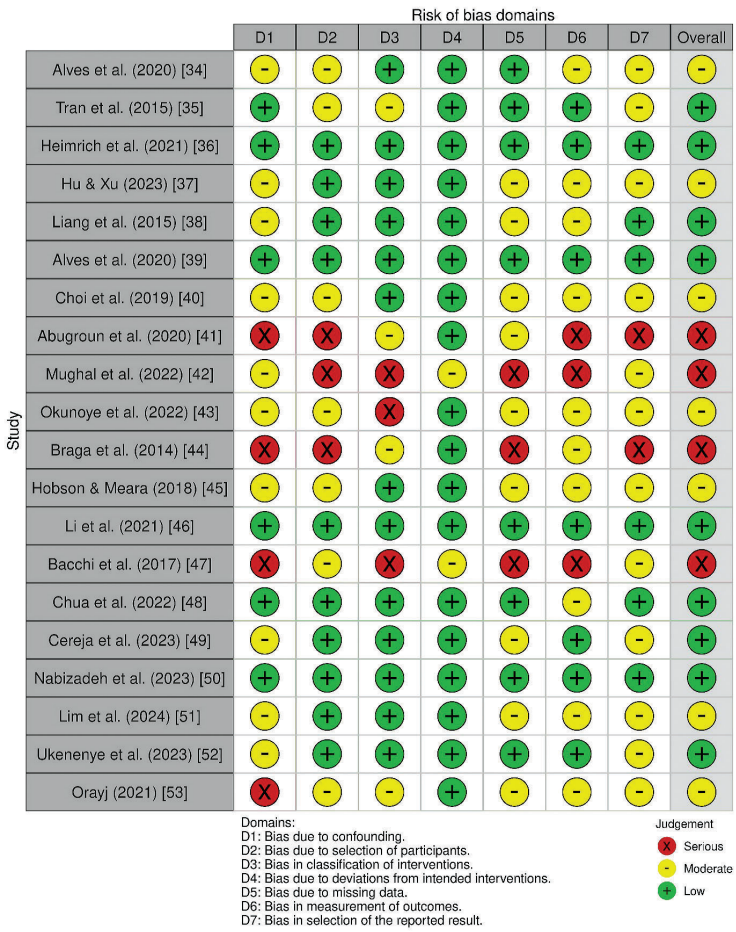

Fig. 5. Bias assessment using the ROBINS-I tool

In general, most of the included studies were at moderate risk of bias. Mughal et al. [42], Braga et al. [44], and Abugroun et al. [41] had the greatest overall risk with several key domain-level issues. Tran et al. [35], Heimrich et al. [36], and Hu & Xu [37] were at low overall risk, indicating greater methodological quality. These findings highlight the necessity of managing confounding, providing robust outcome measurement techniques, and full reporting of data to minimize bias and enhance the validity of research results (Fig. 5).

Discussion

The present study in view presents a broad overview of the cardiac presentation of Parkinson's disease (PD) manifesting with varied cardiac conditions, modes of diagnosis, mechanisms, and modes of management engaged. Notably, cardiovascular (CV) events of stroke, myocardial infarction (MI), and heart failure (HF) are very common in PD patients and are usually the result of native autonomic dysfunction inherent in the disease. The association of PD neurodegenerative disorders with cardiovascular comorbidities requires greater focus and intervention. The application of augmented diagnostic methods and treatment protocols to prevent such risks also becomes evident.

Other research has identified increased stroke risk in PD patients, with odds ratios (ORs) ranging from 1.27 to 1.66 (Alves et al., 2020 [34]; Hu & Xu, 2023 [37]), and this emphasizes the importance of intensification of stroke risk evaluation among these patients. Moreover, Liang et al.'s (2015) [38] cohort study also shows the high prevalence of acute myocardial infarction (AMI) in PD patients, again highlighting the need for cardiovascular monitoring. While PD per se is not directly related to CAD or MI development, comorbid conditions occurring in PD like autonomic dysfunction and metabolic stress are accountable for heightened cardiovascular susceptibility. In addition, studies like those of Choi et al. (2019) [40] arrive at the conclusion that PD-related cardiovascular mortality is considerably greater in comparison to controls, with evidence of synergistic interaction of comorbidities among the latter (Fig. 6).

Notably, Nabizadeh et al. (2023) [50] results reveal a reduced risk of myocardial infarction (OR 0.80) in PD patients owing to potentially changed cardiovascular risk profile. These results reveal the complexity of cardiovascular risk in PD where varying factors, i.e., autonomic dysfunction and changed lipid metabolism, affect outcomes differently for varying cardiovascular

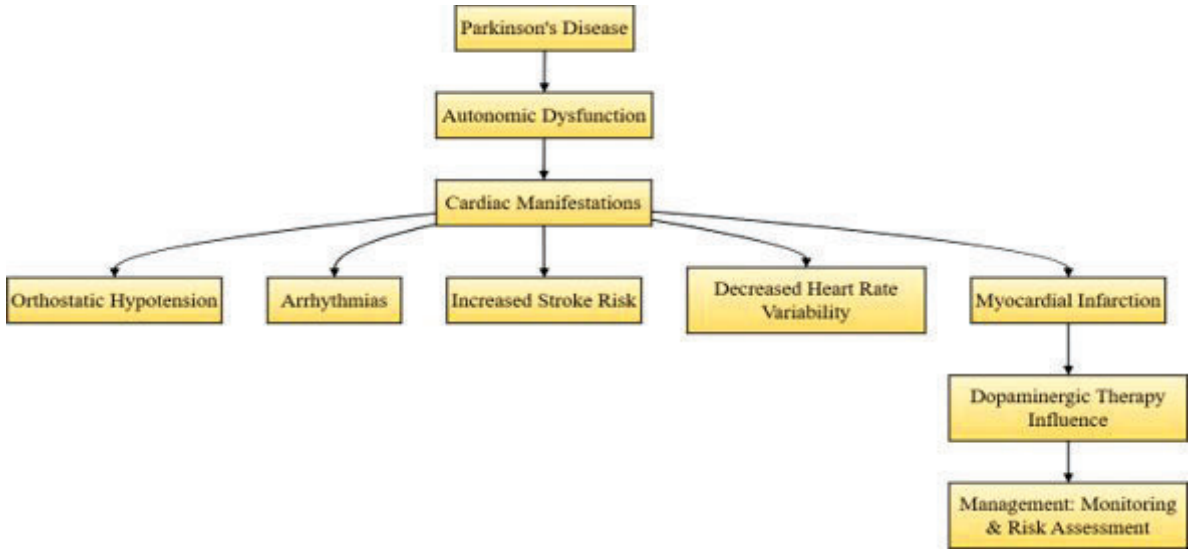

Fig. 6. Cardiac Manifestations in PD

events. This highlights the requirement for risk assessment on an individual basis to manage and identify cardiovascular risks efficiently among PD patients.

Diagnostic strategies differ in studies, such as clinical diagnosis, imaging methods (e.g., echocardiography), and wearable technology as major modalities for cardiac function assessment in PD. For example, Heimrich et al. (2021) [36] and Li et al. (2021) [46] suggest that heart rate variability (HRV) could be a potential diagnostic indicator of autonomic dysfunction, offering valuable information regarding parasympathetic and sympathetic tone imbalance. In addition, electrocardiography (ECG) screening for atrial fibrillation (AF) and arrhythmias is emphasized in several studies (Cereja et al., 2023) [49].

However, wearable sensors, as reported by Mughal et al. (2022) [42], are underutilized, and there is a suggested area of early detection and remote monitoring of cardiac non-motor symptoms (NMS). The underutilization of the diagnostic tools indicates the necessity for further integration into practice to facilitate early detection and management of cardiac disease in PD.

In addition, the application of clinical data, such as electronic health records (EHRs), has been helpful in large cohort studies to obtain a broader view of cardiovascular outcomes among PD patients (Ukenenye et al., 2023 [52]; Okunoye et al., 2022 [43]). The instruments facilitate tracking hospitalization trends that can be utilized to direct preventive care interventions. For instance, Ukenenye et al. (2023) established that AF patients had reduced incidence rates of AHF and VT, casting reassurance on short-term outcomes but indicating a need for ongoing surveillance.

Autonomic dysfunction is still the most frequently mentioned mechanism of cardiac presentation in PD, leading to conditions such as OH, arrhythmias, and ischemic heart disease. Bacchi et al. (2017) [47] and Choi et al. (2019) [40] studies indicate that the dopaminergic treatments, more so the dopamine agonists, play a causative role in worsening such conditions. Secondly, sympathetic-vagal imbalances indicated by Li et al. (2021) [46] could be responsible for the diminished heart rate variability and increased frequency of arrhythmias and other CV events. This autonomic dysfunction not only worsens cardiovascular disease but also contributes to the burden of disease, thus rendering cardiovascular complications in PD more challenging to manage.

Coexistence of other pathophysiological processes like chronic inflammation, endothelial dysfunction, and metabolic alterations (e.g., obesity, dyslipidemia) has also been described in the majority of studies (Chua et al., 2022 [48]; Nabizadeh et al., 2023 [50]). These mechanisms interact with the neurodegenerative processes of PD to increase the risk of cardiovascular disease. The importance of identifying these regions of overlap cannot be overstated, as they determine treatment modalities and clinical management. For instance, the increased prevalence of atrial fibrillation in early PD, as hypothesized by Cereja et al. (2023) [49], may be a distinct expression of autonomic dysfunction that merits early treatment.

Cardiovascular management in PD entails a multi-component strategy with an emphasis on personalized cardiovascular surveillance and control of cardiovascular risk factors. Alves et al. (2020) [34] and Tran et al. (2015) [35] encourage preventive measures for stroke and heart failure with particular emphasis on limitation of some of the dopaminergic treatments in the setting of established cardiovascular comorbid conditions. Early identification of autonomic dysfunction using HRV or wearable devices can potentially

lead to early treatment of cardiac NMS, leading to improved symptom control and averts complications. On the other hand, pharmacological interventions such as the beneficial use of domperidone in orthostatic hypotension Bacchi et al., 2017 [47] need to be analyzed under the possible cardiac risk.

The study also stresses the importance of managing classic cardiovascular risk factors (e.g., hypertension, diabetes, hyperlipidemia) in PD patients because they have a significant role in predicting cardiovascular outcomes (Lim et al., 2024 [51]). In defining personal risk profiles, care should be used in interpreting Nabizadeh et al. (2023) [50] data that PD patients can have a low classical CV risk profile. This could be a result of the impact of the disease on metabolism and autonomic regulation.

Furthermore, the potential benefit of pharmacogenomics and precision medicine in optimizing cardiovascular care in PD patients is a promising prospect. Tailoring drug regimens based on individual genetic profiles and treatment response would enhance cardiovascular outcome, especially since PD patients have complex drug interactions (Orayj, 2021 [53]).

In conclusion, although PD patients are more likely to experience cardiovascular events, the overlap between PD's neurodegenerative processes and cardiovascular comorbidities presents the possibility of early detection and targeted interventions. Through the integration of cardiac monitoring technology, treatment protocols designed to meet individual needs, and routine risk assessment, clinicians can individualize care to PD patients, improving both cardiac outcomes and overall quality of life. Moreover, concurrent treatment of the neurological and cardiovascular aspects of the illness is crucial to the limitation of PD burden and optimization of patient outcomes. More studies on novel diagnostic drugs, therapies, and long-term management methods will be essential to the care improvement in this high-risk population of patients.

Limitations

In spite of the vast quantity of data yielded by the studies covered by this review, a few limitations need to be noted. Most studies were observational, which restricts determination of causal associations between Parkinson's disease (PD) and cardiovascular events. Population heterogeneity across study populations, diagnostic definition, and outcomes limit generalizability of results, while sample size heterogeneity impacts statistical power, particularly in studies of unique presentations of cardiovascular disease. In addition, use of retrospective data and claims data may create biases toward data quality. The absence of standardized diagnostic criteria for cardiac non-motor symptoms (NMS) in PD also affects consistency to the same extent, and the improper use of wearable technologies for early cardiac detection highlights the necessity for broader application. Finally, most of the studies do not account for examining the effects of disease duration or changes in PD treatment regimens on cardiovascular health, potentially with implications on outcomes and treatment planning.

Future directions

Some of the areas that have future directions of study to more comprehensively understand and treat cardiovascular risk in Parkinson's disease (PD) are. Large-scale prospective multicenter cohort studies are required to determine causal associations between PD and certain cardiovascular diseases, with particular interest in long-term cardiovascular complications and the impact of various PD treatments, including dopaminergic treatments, on the heart. Further research is also required to solidify diagnostic strategies for cardiac NMS in PD, including the development and validation of biomarkers and wearable devices for early detection. Biomarker assessment, for example, inflammatory markers or autonomic function measures, might enable the identification of patients with increased cardiovascular risk and more focused interventions. Pharmacogenetic research into the influence of gene variants on cardiovascular events in PD would guide individualized treatment regimens, whereas interventional potential of cardiovascular risk factor management, including statins, antihypertensive, and antidiabetic therapy, is but partly discussed and requires further attention. Lastly, comparative clinical trials of interventions like lifestyle interventions, exercise therapy, and new pharmacologic agents are essential to maximizing cardiovascular management in PD patients and overall health and quality of life.

Conclusion

Cardiac dysfunction is an underemphasized but important non-motor symptom of Parkinson's disease (PD) mainly caused by autonomic nervous system dysfunction. The review brings out uniform evidence of PD causally associated with cardiovascular conditions like orthostatic hypotension, arrhythmias, decreased heart rate variability, and stroke risk. The application of early diagnosis by HRV analysis, ECGs, and wearable devices although not yet fully utilized can enhance outcomes. Clinical management, especially dopaminergic and antipsychotic treatment, must take into account cardiovascular risk. Future studies must establish causality, confirm biomarkers, and investigate individualized therapies. The integration of cardiac care into multidisciplinary PD management can significantly improve patient quality of life and survival.

No conflict of interest was declared

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