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Research Report

Association Between Parkinson's Disease and Coronary Artery Disease: A Systematic Review and Meta-Analysis

Shaun Kai Kiat Chua[a], Seyed Ehsan Saffari[b,c], Selene Joon Yan Lee[d] and Eng-King Tan[b,*]
[a]*Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore, Singapore*
[b]*National Neuroscience Institute, Singapore, Singapore*
[c]*Health Services & Systems Research, Duke-NUS Medical School, National University of Singapore, Singapore*
[d]*Duke-NUS Medical School, Singapore, Singapore*

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Abstract.
Background: The relationship between Parkinson's disease (PD) and coronary artery disease (CAD) is unclear.
Objective: This study aims to investigate whether PD and CAD are associated through systematic review and meta-analysis of observational studies.
Methods: Electronic database search of PubMed, EMBASE, and Web of Science for observational studies published from 1 January 2010 to 1 August 2021 was conducted using terms related to PD and CAD. Unadjusted risk ratios (RR) and odds ratios (OR) of included cohort and case-control studies respectively were used to ascertain the association between PD and CAD. Study heterogeneity was evaluated using the I^2 test.
Results: Forty-one full-text studies were initially retrieved for eligibility assessment. Five studies that satisfied the inclusion criteria, consisting of three cohort and two case-control studies, were eventually included in this meta-analysis. The five studies enrolled 35,237 PD patients and 650,866 non-PD patients. PD and CAD were found to be significantly associated in cohort studies (RR = 2.23, 95% CI = 1.08–4.59, $p = 0.03$; Fig. 2), which held after sensitivity analysis (RR = 1.45, 95% CI = 1.31–1.60, $p < 0.001$; Fig. 3). Case-control studies found a trend towards association of PD and CAD approaching significance (OR = 1.47, 95% CI = 0.84–2.56, $p = 0.18$; Fig. 2).
Conclusion: Overall, this meta-analysis suggests that PD is associated with CAD. The underlying mechanisms, as well as the role of ethnicity and other comorbidities on the relationship between PD and CAD should be further explored.

Keywords: Coronary artery disease, meta-analysis, observational studies, Parkinson's disease, systematic review

INTRODUCTION

Parkinson's disease (PD), clinically characterized by resting tremors, rigidity, and bradykinesia [1], is a common neurodegenerative disease in the elderly [2]. With increasing life expectancy, the prevalence and burden of PD have increased globally [3]. The prevalence of coronary artery disease (CAD) in the general population aged 20 and above is about 6.7% [4] and as high as 29% in the general elderly population [5]. However, the prevalence and relationship of CAD in the PD population is not well documented. Recent literature has increasingly described cardiovascular

*Correspondence to: Eng-King Tan, MD, Department of Neurology, National Neuroscience Institute, Duke NUS Medical School, Outram Road, Singapore 169608, Singapore. Tel.: +65 63265003; Fax: +65 62203322; E-mail: gnrtek@sgh.com.sg.

dysfunction as a non-motor manifestation in the prodromal phases of PD which worsens with disease progression [6, 7]. Moreover, PD and CAD might be linked due to shared vascular risk factors and cardiovascular dysautonomia from cardiac sympathetic denervation in PD [8]. In fact, recent studies also suggest that common risk factors for both PD and the general population such as diabetes and hypertension are prevalent conditions in both populations [9–11]. Increasing evidence seems to suggest an association between PD and CAD; however, the association between PD and CAD still remains unclear, with different studies yielding conflicting results. While some studies have shown that CAD was associated with PD [12] and that PD patients were associated with having acute myocardial infarction (AMI) [13], others have found similar [14] or even lower [15] rates of CAD among PD patients compared to controls. Previous studies [16, 17] have investigated the effects of PD on cardiovascular disease (CVD), including both CAD and cerebrovascular events, but none focusing on PD and CAD specifically.

CAD, including ischemic heart disease (IHD) and AMI, is one of the top causes of death among the elderly [18]. CAD is a preventable disease for which patients and those at high risk of developing CAD can benefit from early detection and treatment [19]. Therefore, it is imperative to clarify the relationship between PD and CAD in facilitating early identification and pre-emptive management of a debilitating disease like CAD.

In this systematic review and meta-analysis, the aim was to determine the association between PD and CAD, through the analysis of observational (cohort, case-control, cross-sectional) studies published between 1 January 2010 to 1 August 2021 that studied the frequency of CAD in PD patients compared to control groups.

METHODS

Eligibility criteria

For this systematic review and meta-analysis, all published observational studies reporting the prevalence of CAD [CAD, MI (myocardial ischemia), and/or IHD] in both PD patients and controls, with clear determination of PD and CAD based on hospital records, doctor's diagnosis, disease identification codes, or self-reporting, were considered eligible.

Non-English articles, case reports, review articles, published abstracts, studies with duplicated study cohorts (the more recent one included), and studies where access to the full text was unavailable, were excluded. Studies with study groups which were non-representative of the general PD population, such as mortality studies, or control populations which had a natural higher predisposition to comorbidities like CAD than the general population, such as hospitalization studies, were also excluded.

Search strategy

All relevant articles published in English between 1 January 2010 to 1 August 2021 were identified by searching on PubMed, EMBASE, and Web of Science for studies that investigated the incidence and prevalence of AMI/IHD/CAD/CVD/coronary heart disease (CHD) in PD patients and non-PD controls. The search terms "coronary artery disease", "coronary heart disease", "heart failure", "acute coronary syndrome", "myocardial ischemia", "cardiovascular disease", "comorbidity", "Parkinson's disease", "Parkinson's", "epidemiological studies", "cohort studies", "case-control studies", and "observational studies" were used with appropriate Boolean operators for the identification of potential studies. The reference list of relevant studies was also manually examined for eligible studies that were not found using the search terms. The details of the search strategy are presented in Supplementary Material 1.

The articles were independently assessed by two authors (S.K.K.C and S.J.Y.L), to determine the eligibility to be included in the final review. Any disagreements were discussed with a third author (E.K.T) and resolved by consensus among the authors.

Data extraction

The title and abstracts were retrieved from the electronic database search for potentially relevant studies. The full reports of the potentially relevant studies were then retrieved and assessed to be included in the review based on the decided inclusion criteria.

The data extracted from the included studies were: sample size, patient and control demographics such as the mean age, gender distribution, and country where the study was conducted. Information regarding the study design, data source, outcomes of interest, and the adjustments applied to the outcome variables [risk

ratio (RR), hazard ratio (HR), odds ratio (OR)] were also extracted.

The type of study was categorized into case control and cohort studies.

Outcome

The outcome of interest for this study was determined to be CAD. The terms IHD, AMI, CHD, or acute coronary syndrome (ACS) were taken to be synonymous with CAD.

The common outcome variable for comparison between all studies was chosen to be the unadjusted RR and unadjusted OR for cohort and case-control studies respectively. If adjusted RR/HR/OR was provided, unadjusted RR was calculated manually using R software [20] with the raw frequency of the outcome of interest (CAD/IHD/AMI) and sample size in PD and non-PD populations.

Initial search of the electronic databases yielded 1,365 studies, with 41 full text articles subsequently retrieved for eligibility assessment and five studies eventually selected for meta-analysis (Fig. 1). Out of the five studies, two studies provided adjusted OR [21, 22] and three studies provided adjusted HR [8, 12, 13]. One study [8] did not report the raw AMI frequencies, but instead only reported the calculated HR. Effort was made to contact the authors of the paper for the raw data, which proved unsuccessful. Hence, back-calculation using the reported HR was performed to estimate the raw frequencies and subsequently the unadjusted HR.

Finally, the unadjusted RR of the three cohort studies and OR of the two case-control studies were pooled together and compared between PD and non-PD groups to determine the association between PD and CAD.

Assessment of study quality

To assess the quality of included studies, the Newcastle-Ottawa Scale (NOS) was used to perform risk of bias (RoB) analysis. Studies were then classified as 'Good', 'Fair', or 'Poor' quality based on Agency for Healthcare Research and Quality (AHRQ) ratings which were derived from the NOS scores.

The details of the RoB and AHRQ framework used for study quality assessment are presented in Supplementary Material 2.

Statistical analysis

Statistical analysis was performed using R software [20]. Random effects meta-analyses via restricted maximum-likelihood estimator were performed on end points and variables due to observed estimates and sampling variability between studies. Between-study heterogeneity was presented by the I^2 statistic test. p values for the I^2 statistics were computed by chi-square distribution of Cochran Q test. Statistical significance was set at $p < 0.05$.

Sensitivity analysis

Where I^2 values were high, sensitivity analysis was performed to reduce study heterogeneity in the meta-analysis. This was conducted through examination sources of heterogeneity among study cohorts and subsequently performing the meta-analysis after removing the corresponding study cohort contributing most to the study heterogeneity.

RESULTS

Included studies

Initial search of the electronic databases yielded 1,365 studies, and 41 full text articles were subsequently retrieved for eligibility assessment. Five studies were eventually selected for meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Fig. 1). Reasons for exclusion of studies retrieved for eligibility assessment are detailed in Supplementary Table 1.

The five studies, inclusive of three cohort studies and two case-control studies, enrolled 35,237 PD patients and 650,866 non-PD patients. Two [21, 22] studies were conducted in the United Kingdom (UK), while three [8, 12, 13] other studies were conducted in Asia, namely, Korea, China, and Taiwan respectively. Two studies [12, 13] compared AMI frequencies between PD and non-PD groups, while two studies [8, 21] and one other study [22] compared CAD and IHD frequencies respectively between PD and non-PD groups. One study, Li 2018 [8], investigated the outcomes of PD and controls between two separate populations, namely Malu and Wu Li Qiao (wlq). Hence, these studies were further split into two sub-groups, Li 2018 (malu) and Li 2018 (wlq), for analysis. Details of the five studies are summarized in Table 1.

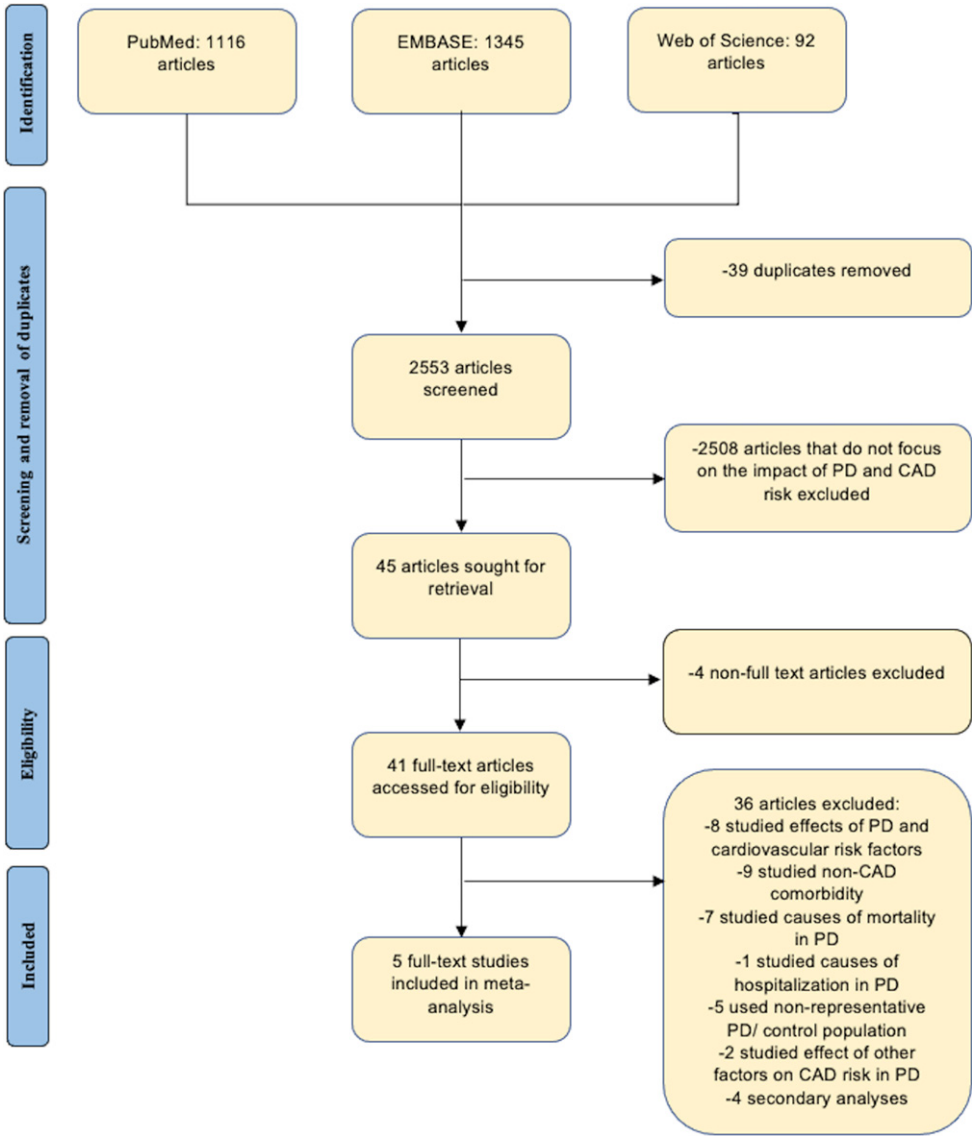

Fig. 1. PRISMA flowchart detailing database search procedure and exclusion criteria.

The reporting quality of the included studies were all 'Good' except for Li 2018 [8] which used questionnaires and self-reporting for outcome assessment, in contrast to other studies which only used registries and databases. Details of the reporting quality of the included studies are summarized in Table 2.

Meta-analysis

This study found that PD was associated with CAD (RR = 2.23, 95% CI = 1.08–4.59, $p = 0.03$; Fig. 2) for cohort studies. A greater association between PD and CAD was found among the cohort studies as compared to case-control studies (OR = 1.47, 95% CI = 0.84–2.56, $p = 0.18$; Fig. 2).

The I^2 value obtained before sensitivity analysis was 94.7% and 98.4% for cohort and case-control studies respectively.

Sensitivity analysis

After sensitivity analysis to reduce study heterogeneity, the positive association found between PD and CAD in cohort studies held with I^2 value at 0% (RR = 1.45, 95% CI = 1.31–1.60, $p < 0.001$; Fig. 3) after removal of one study cohort (Li 2018 (malu))

Table 1
Summary of studies included in the meta-analysis

No.	Author, year	Study design	Country	Sub-group	Sample size		# Male (%)		Mean age (SD)		Data source	PD diagnosis	CAD diagnostic tool	Matching	Outcome assessment	Outcome adjustment	Reported outcome (risk of CAD)
					PD	Non-PD	PD	Non-PD	PD	Non-PD							
1	Liang, 2015 [13]	Cohort	Taiwan	Nil	3,211	3,211	1,652 (51.4)	1,620 (50.5)	71.9 (9.3)	72.0 (9.0)	National Health Insurance Claim Database	International Classification of Disease diagnosis codes	Medical information from health care database	Age, Sex	AMI	propensity score matching (based on age, sex, preexisting comorbidity, socioeconomic status)	Higher
2	Park, 2020 [12]	Cohort	Korea	Nil	25,624	128,120	10,890 (42.5)	54,451 (42.5)	69 (10.2)	69 (10.2)	National Health Insurance Service and National Rare Intractable Disease Registry Database	International Classification of Disease diagnosis codes	Medical information from health care database	Age, Sex	AMI	age, sex, lowest quartile income, diabetes mellitus, hypertension, and dyslipidemia	Higher
3	Mclean, 2017 [21]	Case-Control	UK (Scotland)	Nil	2,640	507,862	1,459 (55.3)	232,602 (45.8)	76.4 (9.1)	68.2 (9.7)	Primary Care Clinical Informatics Unit Database	Read Codes (NHS Scotland Information)	Medical information from health care database	NR	CAD	age, gender, and deprivation (carstairs) score	Higher
4	Li, 2018 [8]	Cohort	China	Malu	63	4,483	34 (54.0)	1,906 (42.5)	74.9 (8.6)	66.5 (9.4)	Door to door assessment (PD) and questionnaire (CAD)	UK Parkinson's Disease Society Brain Bank Clinical Diagnostic Criteria	Questionnaire	NR	CAD	age, sex, smoking status, alcohol consumption, hypertension, diabetes mellitus, tea consumption, hypercholesterolemia and BMI	Higher
				Wuliqiao (wlq)	62	3,553	26 (41.9)	1,134 (31.9)	75.7 (9.5)	69.4 (10.6)							
5	Becker, 2010 [22]	Case-Control[†]	UK	Nil	3,637	3,637	2,167 (59.6)	2,167 (59.6)	NR	NR	General Practice Research Database	Oxford Medical Information System or Read codes	Medical information from health care database	Age, gender, general practice, PD diagnosis date, years of history in GPRD prior to PD diagnosis date	IHD	age, sex, smoking status, BMI, other comorbidities	Higher

[†]Nested case-control. No., number; UK, United Kingdom; PD, Parkinson's disease; CAD, coronary artery disease; IHD, ischemic heart disease; AMI, acute myocardial infarction; NR, not reported; BMI, body mass index; NHS, National Health Service; GPRD, General Practice Research Database.

Table 2A
Risk of Bias Analysis for Cohort studies

Author	Selection				Comparability	Outcome			Total quality score	Quality rank
	Representativeness of exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts based on the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohort		
Liang, 2015 [13]	+	+	+	+	++(age, sex, comorbidities, socioeco-nomic status)	+(National Health Insurance claim database)	+(from index visit to the first occur-rence of AMI, death, or end of follow up)		8	Good
Park, 2020 [12]	+	+	+	+	++(age, sex)	+(National Health Insurance Service and National Rare Intractable Disease Registry database)	+(from 2010 to 2016)		8	Good
Li, 2018 [8]	+	+	+		++(age, sex, smoking status, alcohol consumption, hypertension, diabetes mellitus, tea consumption, hypercholes-terolemia, and body mass index)	(Questionnaire, Self-Report)	+(from April 2013 to October 2013 for Malu, 2014 for Wuliqiao)		6	Poor

Table 2B
Risk of Bias Analysis for Case-control studies

Author	Selection				Comparability	Exposure			Total	Quality
	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definitionof controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertain-ment for cases and controls	Non-response rate	quality score	rank
Mclean, 2017 [21]	+	+	+		++(age, gender, socioeconomic deprivation)	+(Primary Care Clinical Informatics Unit Database)	+		7	Good
Becker, 2010 [22]	+	+	+	+	++(age, gender, calendar time)	+(General Practice Research Database)	+		8	Good

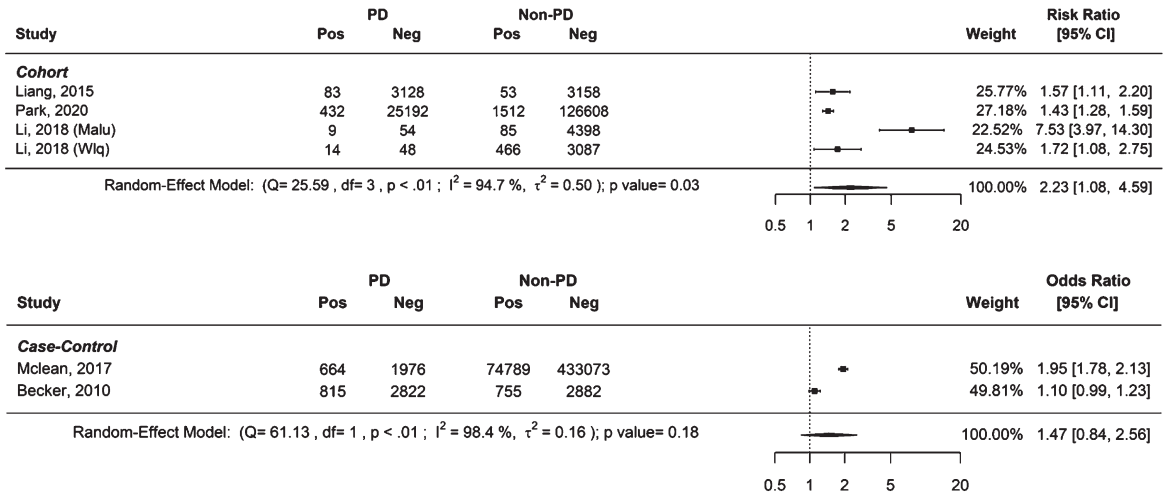

Fig. 2. Forest plots of cohort and case-control studies.

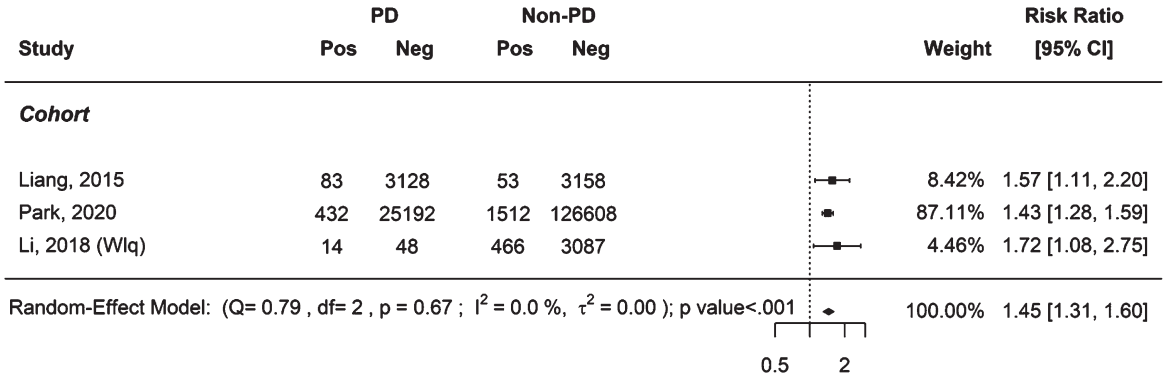

Fig. 3. Forest plot of cohort studies after sensitivity analysis.

that contributed significantly to the study heterogeneity, further supporting our findings.

DISCUSSION

Association between PD and CAD

This study found an association between PD and CAD in cohort studies, providing new evidence to address the uncertainty surrounding the relationship between the two. Several reasons have been proposed to explain this correlation.

First, while the pathophysiology of PD remains poorly understood, it has been hypothesized that the neurodegenerative disease may be caused by oxidative stress that leads to mitochondrial dysfunction and damage to the substantial nigra [23]. Moreover, neurodegeneration in PD have also been thought to be contributed by chronic central and systemic inflammation [24]. Both oxidative stress and systemic inflammation are possible underlying mechanisms in the pathogenesis of atherosclerosis [25, 26] and CAD [27–29], suggesting a possible common pathophysiology in both PD and CAD that could explain their association.

Second, autonomic dysfunction, specifically an increased sympathetic activity and decreased parasympathetic activity, in PD patients have been proposed to be a possible mechanism through which PD may predispose to vascular diseases like CAD [30]. Significantly, orthostatic hypotension (OH) is a known non-motor manifestation of PD that is thought to be caused by autonomic dysfunction in PD [31, 32]. OH has been associated with an increased risk of CAD and suggested to be a consequence of decreased myocardial perfusion leading to ischemia [33, 34]. Hence, OH is a possible mechanism for

which PD could be associated with CAD. Moreover, beyond autonomic dysfunction, the concept of a "Parkinsonian heart" in recent literature further describes the cardiovascular dysfunction in PD patients not only due to sympathetic denervation, but also changes that occur at the functional, structural, and molecular level of the heart [35, 36].

Third, PD and CAD could be linked via a common molecular pathway involving matrix metalloproteinases (MMPs). MMPs are a family of proteins that are responsible for tissue remodeling and degradation of extracellular matrix (ECM) proteins. MMPs play a key role in the pathogenesis of atherosclerosis and CAD [37], and vascular endothelial cell damage from CAD can further activate MMPs through the release of free radicals and proinflammatory cytokines [38]. Activation of MMPs causes ECM degradation and Blood-Brain-Barrier leakage, which could facilitate microglial activation and dopaminergic neurodegeneration [39]. Moreover, MMPs activation could cause alteration and aggregation of α-synuclein protein, a key protein in the pathogenesis of PD [40]. Therefore, MMPs implicated in both CAD and PD could possibly mediate both pathologies.

Fourth, PD patients have a high tendency for physical inactivity [40] due to both non-motor (dementia, depression) and motor (bradykinesia, tremors, rigidity) symptoms, which is a significant risk factor for CAD [41, 42]. Regular physical activity has known cardioprotective effects [42], and PD patients have markedly reduced levels of physical activity with greater disease severity [40]. Therefore, it is plausible that as PD, a chronic progressive disease, worsens with time, the eventual loss of ability to be physically active and its cardioprotective effects could make PD patients more vulnerable to cardiovascular diseases like CAD.

Fifth, medication given for the treatment of PD such as Levodopa have been known to cause adverse cardiovascular effects through an increased serum homocysteine level which induces atherosclerosis [43, 44]. Specifically, many ergot-derived dopamine agonist have been associated with valvulopathies and fibrosis of the heart leading to cardiovascular impairment [45, 46]. Anti-psychotic medications prescribed to PD patients who develop psychosis also increases risk of cardiovascular mortality [47–49]. Therefore, pharmacological treatment commonly initiated in the management of PD patients could also be a possible pathophysiological mechanism affecting cardiovascular health in PD patients. Nonetheless, while PD treatment may be the cause of increased CAD risk rather than PD itself, a recent meta-analysis [50] found that the cardiac complication associated with PD were more related to the degenerative disease itself rather than exposure to cardiotropic drugs.

Furthermore, several PD-related genes may be potentially involved in the relationship between PD and CAD. The PARK family proteins related to PD such as α-synuclein (PARK1), Parkin (PARK2), PINK1 (PARK6), DJ-1 (PARK7), and LRRK2 (PARK8) have been proposed to play a role in the association of PD and cardiac dysfunction, including CAD [51–53]. These genes have also been thought to be found in heart tissue and implicated in oxidative damage and loss of cardioprotective effects in gene mutations or depletions [54]. Nonetheless, there are still limited data on the molecular and genetic links of PD and CAD, and more studies are needed in the future to decipher the potential links between PD and cardiovascular health.

It is also plausible that patients with PD or comorbidities such as CAD are innately more likely to visit healthcare facilities for their treatment or follow-up, putting them in a more likely position for health related problems such as PD and CAD to be presented and diagnosed by a healthcare professional. Studies have shown that the combination of PD related symptoms, as well as the associated treatment side-effects and comorbidities have led to an increase in healthcare utilization and expenditure, with increased healthcare seeking behavior in populations where there is higher prevalence and awareness of PD [55, 56]. Therefore, there could be increased health seeking behavior in populations with either PD or comorbidities which increases their chances of being diagnosed with either diseases compared to the general population.

While some previous studies have proposed a negative correlation between PD and CAD [15], comparison was made with a hospital-based control group which were subject to selection bias as hospital-based populations are more likely to have comorbidities like CAD compared to the general population. As such, these studies were not included in this review which aims to investigate the association of CAD with PD patients versus the general population.

Nonetheless, it is interesting to note that while previous studies have documented a lower prevalence of vascular risk factors such as diabetes, hypertension, and dyslipidemia and smoking rate among PD patients [23, 57], our findings suggest that PD and CAD are associated. Therefore, despite the reduced prevalence of vascular risk factors, patients with PD

should still be monitored for CAD which could be mediated by various mechanisms as proposed above.

Cohort versus case-control studies

Methodological factors may have played a role in the results with cohort studies showing a more significant CAD association in PD patients compared to case-control studies. The cohort studies included predominantly Asian populations whereas the case-control studies selected a predominantly Caucasian population in the UK. Studies have shown that Asians are more predisposed to developing CAD compared to non-Asians [58, 59], suggesting that ethnic differences may have contributed to the greater association found in cohort studies.

Study heterogeneity

For cohort studies, the study cohort that contributed to significant heterogeneity within the results and subsequently removed in the sensitivity analysis was Li 2018 (malu). The study cohort could have attributed to significant study heterogeneity as it included a rural study population, in contrast to the other cohort studies that included populations from more developed areas or countries. Nonetheless, the positive association found in cohort studies held with low heterogeneity after sensitivity analysis and reanalysis of the remaining cohorts after removal of Li 2018 (malu), further supporting our findings.

For case-control studies, sensitivity analysis could not be performed as there were only two studies [21, 22]. Mclean et al. [21] found a significant positive association between PD and CAD in contrast to Becker et al. [22] which found an insignificant positive association. Study heterogeneity between the case-control studies may be attributed to differences in methodology of subject recruitment as Becker et al. [22] had gender and age (year) matched cases and controls in contrast to Mclean et al. [21] where cases and controls were matched by gender, age groups (55 to 64, 65 to 74, 75 to 84, and over 85) and socioeconomic deprivation.

Potential implications

The positive association between PD and CAD found in this study emphasizes the greater need for early screening and prevention of CAD in PD patients. Healthier lifestyle choices and more regular follow up to prevent and slow down the progression of CAD should be encouraged especially among younger PD patients. PD patients, especially those with PD onset at 50 years or younger who have a longer disease trajectory, should undergo cardiovascular risk screening at a younger age and be put under closer cardiac monitoring involving cardiac assessments such as treadmill exercise stress test and cardiac echocardiogram for early detection of any present cardiac abnormalities. Early control is then warranted for any abnormalities found in the cardiovascular screen or cardiac assessment. Furthermore, the possible involvement of MMPs and OH in the pathogenesis of PD and CAD sets up plausible new therapeutic angles that should be further investigated, where treatment inhibiting MMPs or reducing OH could reduce the risk of PD or CAD.

Study strengths

Our meta-analysis was a novel investigation of the association between PD and CAD. Two previous meta-analysis [16, 17] explored the relationship between PD and CAD. However, Hong et al. [17] investigated the effects of PD on both cerebrovascular and cardiovascular disease as one entity, and in contrast to Alves et al. [16], this study excluded studies which focused solely on specific subgroups of PD patients, such as PD mortality and hospital admission studies, hence selecting a more representative PD population. Furthermore, this study only included more recent publications in the last ten years with a more updated view on the subject matter.

Study limitations

First, inherent publication bias may be present in the selection of studies. Studies with positive findings may be more publishable and replicable, hence having a greater chance of selection by this meta-analysis. Second, while this meta-analysis included studies from a diverse population consisting of Europe and Asia, it had a small number of available studies with limited capture of all ethnic races, affecting the generalizability of this study to both the global and certain populations.

Conclusions

In this systematic review and meta-analysis, we found an association between PD and CAD. However, to prove a direct cause and effect relationship between the two conditions, more large-scale

prospective studies and experimental data will be required. Future studies should also explore the contributions of ethnicity, comorbidities, and other lifestyle factors on the relationship between PD and CAD.

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CONFLICT OF INTEREST

The authors have no conflict of interest to report.

SUPPLEMENTARY MATERIAL

The supplementary material is available in the electronic version of this article: https://dx.doi.org/10.3233/JPD-223291.

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