Cardiovascular Risk Among Patients ≥65 Years of Age with Parkinson's Disease (From the National Inpatient Sample)

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In this study, we aimed to investigate the relationship between Parkinson's disease (PD) and vascular disease and risk factors using a nationally representative sample. The National Inpatient Sample was queried for all patients aged ≥65 who were diagnosed with PD during the year 2016. Patients were identified using the International Classification of Diseases-Tenth Revision (ICD-10) diagnosis code: "G20." Each patient diagnosed with PD was frequency-matched to controls at a 1:4 ratio by age and gender. Study outcomes were hypertension, hyperlipidemia, diabetes mellitus, coronary artery disease, and stroke. Outcomes were modeled using logistic regression analysis and further validation was obtained using a propensity score-matched analysis. A total of 57,914 patients (weighted: 289,570) with PD were included. Most patients were of Caucasian race (80.8%). Females were 42.4% and the mean age was 79 years, standard error of the mean (0.03). PD correlated with lower odds for hyperlipidemia adjusted odd ratio (a-OR): 0.77 (95% confidence interval [CI]: 0.75 to 0.79) p <0.001, diabetes mellitus a-OR 0.73 (95% CI 0.71 to 0.75) p <0.001, hypertension a-OR 0.68 (95% CI: 0.67 to 0.70) p <0.001, coronary artery disease a-OR 0.64 (95% CI: 0.63 to 0.66) p <0.001 and higher odds for stroke a-OR: 1.27 (95% CI: 1.24 to 1.31) p <0.001. Following propensity score matching, identical findings were found. In conclusion, patients with PD have a distinct cardiovascular profile with higher rates of stroke and lower rates of coronary artery disease and vascular disease risk factors. **(Am J Cardiol 2020;136:56−61)**

Parkinson's disease (PD) is the second most common neurodegenerative disorder of the geriatric population. The condition is the result of inherent genetic and environmental factors that ultimately results in diminished dopaminergic neurons in the Substantial Nigra. PD is characterized by autonomic dysfunction, noradrenergic denervation and suppressed baroreflex-cardiovagal function.[1,2] Previous studies reported conflicting results on the association between PD and cardiovascular disease. Chronic sympathetic activation can promote elevated blood pressure, blood glucose and lipid levels. It also influences various body mechanisms that modulate the hematopoietic system to promote atherosclerosis.[3] In the presence of suppressed sympathetic drive in patients with PD, it was hypothesized that such patients would have a lower risk for cardiovascular disease.[2] In this study, we aimed to investigate the correlation between PD and cardiovascular disease and vascular risk factors using a nationally representative sample.

Method

This study was conducted using the National Inpatient Sample (NIS) of the Health Care Utilization Project sponsored by the Agency for Healthcare Research and Quality.[4] The NIS is a publicly available national registry that receives data from all US community hospital discharges. The NIS includes administrative as well as demographic data from a 20% sample of inpatient hospitalizations in the United States. NIS provides hospitalization information for over 7 million hospital stays each year with a weighted estimate of more than 35 million hospitalizations annually.

We included all patients aged ≥65 who were diagnosed with PD during the year 2016. These patients were identified using the International Classification of Diseases—Tenth Revision, Clinical Modification (ICD-10-CM) diagnosis codes: "G20." According to the Health Care Utilization Project database, NIS data conform to the definition of limited data set in which 16 direct identifiers have been removed.[5] Accordingly, IRB approval was not deemed necessary since it uses previously collected publicly available de-identified data. The outcomes were vascular risk factors hypertension, hyperlipidemia, diabetes mellitus, and related co-morbidities coronary artery disease and stroke (Supplement Table 4).

Each patient diagnosed with PD was frequency-matched to selected controls at a 1:4 ratio by age and gender. The

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baseline characteristics were compared using percentages and the standardized mean differences in effect sizes (d). An effect size ≥0.1 indicates a significant imbalance in covariates between groups.[6] We fitted a logistic regression model to estimate the adjusted odds ratios (a-OR) of cardiovascular outcomes for patients with PD compared with controls, adjusting for patient demographics, socioeconomic factors, hospital factors, and Elixhauser co-morbidity index.

To further validate our study findings, first, a subgroup analysis was performed based on sex, race (Black and white), age group (sexagenarians and octogenarians) and the primary reason for admission (Sepsis, Acute myocardial infarction). Second, a propensity score analysis approach was applied to select a second matched control group (Figure 1). The propensity score for each patient was calculated by modeling the probability of having PD using logistic regression. Covariates included in the model were patient age, gender, race, type of admission (elective vs nonelective), Elixhauser co-morbidity index as well as hospital location, and teaching status. Each patient with PD was matched with a patient without the diagnosis at a 1:1 ratio. The propensity score analysis algorithm was based on the nearest-neighbor method without replacement. Matching was based on the logit of the propensity score using calipers of width equivalent to 0.2 of the standard deviation of the logit of the propensity score. The standardized difference, related to as effect size (d) in covariates between the two groups was used to assess the success of matching (Supplementary Figure 1, Supplementary Table 2). Binary outcomes from the matched group were modeled using conditional logistic models. Odds ratios with 95% confidence intervals were reported for outcomes. All analyses were performed using STATA 15 (Stata Corp), and a p value <0.05 was considered significant.

Results

Table 1 summarizes the baseline characteristics of the study population. Overall a total of 57,914 patients (weighted: 289,570) with PD were included. Most patients were of the white race (80.8%). Women were 42.4% and the mean age was 79 years, standard error of the mean (0.03). Sepsis was the most common reason for admission for patients with and without PD (Supplementary Table 1). The results of the multivariable analysis were summarized in (Table 2). PD correlated with lower odds for hyperlipidemia, diabetes mellitus, hypertension, coronary artery disease and higher odds for stroke (p <0.001 for all comparisons). In subgroup analysis, a similar pattern was

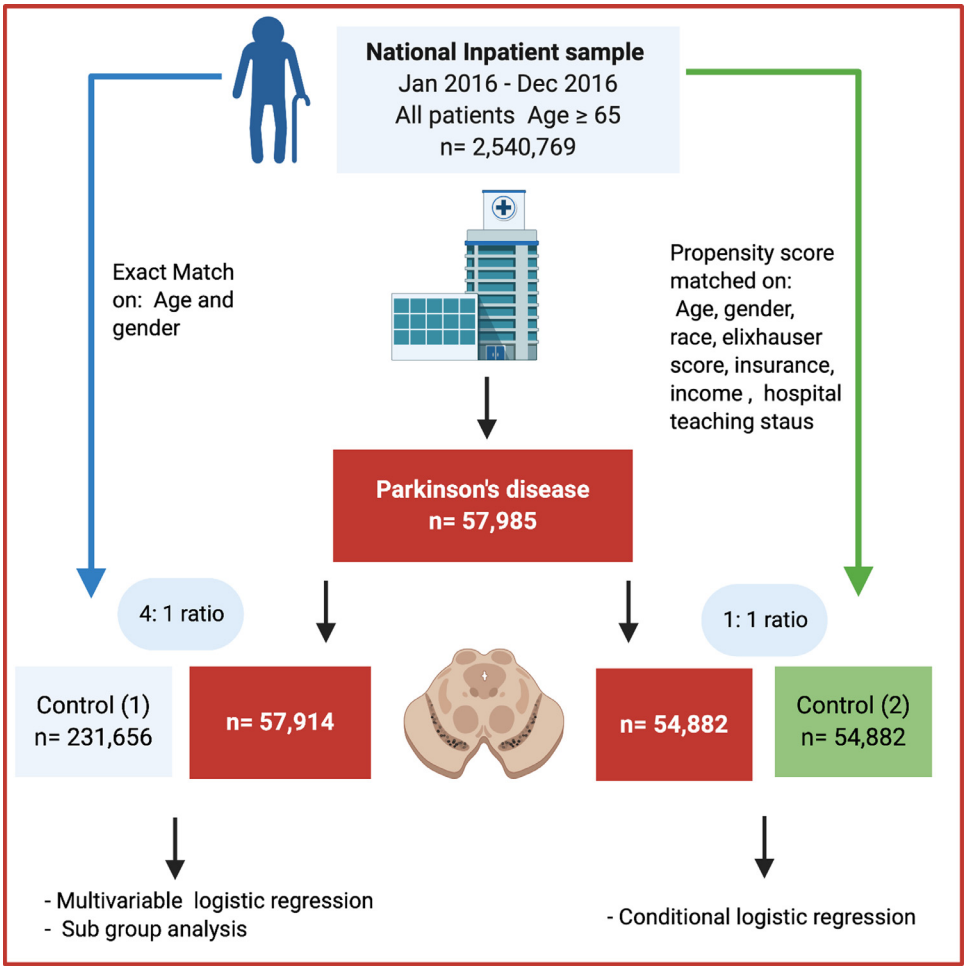

Figure 1. Algorithm for the selection of study population.

Table 1
Baseline characteristics of the study population

Variable	Control	Parkinson's disease	Effect size (d)
N (unweighted)	231,656	57,914	
N (weighted)	1,158,279	289,570	
Age (Mean, SEM)	79.0 [0.03]	79.0 [0.03]	0.0
Women	42.4 %	42.4%	0.0
White	78.6%	80.8%	Ref
Black	9.5%	6.6%	−0.1
Hispanic	6.9%	7.4%	0.0
Asian or Pacific Islander	2.4%	2.5%	−0.0
Native American	0.4%	0.3%	0.0
Other	2.2%	2.4%	−0.1
Primary expected payer			
Medicare	90.2%	92%	
Medicaid	1.3%	1.2%	−0.0
Private insurance	6.5%	5.1%	−0.1
Self-pay	0.5%	0.4%	−0.0
Other	1.5%	1.4%	−0.0
Median household income percentile			
0-25th	27.3%	25.4%	Ref
26th to 50th	26.2%	25.9%	0.0
51st to 75th	24.7%	24.9%	0.0
76th to 100th	21.8%	23.8%	0.0
Hospital Location/teaching status			
Rural	10.8%	11.5%	
Urban nonteaching	28.7%	30%	0.0
Urban teaching	60.5%	58.5%	−0.0
Elective admission	18.6%	12.8%	−0.2
Elixhauser score (Mean, SEM)	4.2 [0.01]	4.7[0.01]	0.2
Comorbidities			
Hyperlipidemia	46.4%	41.6%	−0.1
Hypertension	76.2%	71.5%	−0.1
Diabetes mellitus	34.5%	31.6%	−0.1
Coronary artery disease	36.4%	30.9%	−0.1
Prior Stroke	11%	14%	0.1

Table 2
Multivariable analyses. The relation between Parkinson's disease and cardiovascular outcomes

Comorbidities	a-OR	LCI	UCI	p Value
Stroke	1.27	1.24	1.31	<0.001
Coronary artery disease	0.64	0.63	0.66	<0.001
Diabetes Mellitus	0.73	0.71	0.75	<0.001
Hypertension	0.68	0.67	0.70	<0.001
Hyperlipidemia	0.77	0.75	0.79	<0.001

observed in an analysis restricted to men, women, the White race, Black race, sexagenarian, octogenarians age groups, patients who were primarily admitted for sepsis and those who were admitted for acute myocardial infarction (Table 3, Figure 2). Also, similar results were obtained following propensity score based matched analysis (Supplupplementary Tables 2, 3).

Discussion

The main findings of our study are plausibly explained by the impact of low sympathetic tone on cardiovascular factors among patients with PD. We found that patients with PD have a lower prevalence of diabetes mellitus, hypertension, hyperlipidemia, coronary artery disease (CAD), and a higher prevalence of stroke.

The sympathetic nervous system maintains homeostasis and plays a pivotal role in the dynamics of cardiovascular risk factors and co-morbidities. It is typically activated during stress or physical activity and enhances the hypothalamic-pituitary-adrenal axis in order to secrete ACTH, cortisol, and catecholamines. Cortisol and catecholamines eventually increase arteriolar tone and peripheral vascular resistance, heart rate and rate of atrioventricular (AV) conduction, and carbohydrate catabolism (glycogenolysis and gluconeogenesis). They also mobilize fatty acids and triglycerides, upturn renal vascular resistance, and govern the secretion of renin and other effects of interests.[7]

Sympathetic denervation of the heart, kidneys, and the vascular network will expectantly interrupt the hypothalamic-pituitary-adrenal axis and might abolish the abovementioned physiological and biochemical cascades. Therefore, in the PD, where generalized sympathetic denervation has widely been described, the integrity of the hypothalamic-pituitary-adrenal axis will also be compromised leading to blunted circadian rhythms of cortisol and catecholamines as well as lower levels of renin, and aldosterone.[8] As a result, lower blood pressures, blood glucose measurements, and triglyceride levels detected in the PD

Table 3
Subgroup analyses. Relation of Parkinson's disease with cardiovascular outcomes

	Women (n = 614,525)		Men (n = 833,324)	
	a-OR (95%CI)	p value	a-OR (95%CI)	p value
Coronary artery disease	0.70 (0.68-0.73)	<0.001	0.67 (0.65-0.69)	<0.001
Hyperlipidemia	0.77 (0.74-0.79)	<0.001	0.77 (0.75-0.79)	<0.001
Diabetes mellitus	0.73 (0.70-0.75)	<0.001	0.73 (0.71-0.76)	<0.001
Hypertension	0.64 (0.61-0.66)	<0.001	0.65 (0.63-0.67)	<0.001
Stroke	1.27 (1.24-1.31)	<0.001	1.30 (1.25-1.35)	<0.001
	Black (n = 124,520)		*White (n = 1,102,144)*	
	a-OR (95%CI)	p value	a-OR (95%CI)	p value
Coronary artery disease	0.69 (0.63-0.75)	<0.001	0.68 (0.67-0.70)	<0.001
Hyperlipidemia	0.79 (0.74-0.86)	<0.001	0.77 (0.75-0.79)	<0.001
Diabetes mellitus	0.69 (0.64-0.75)	<0.001	0.74 (0.72-0.76)	<0.001
Hypertension	0.70 (0.63-0.77)	<0.001	0.64 (0.63-0.66)	<0.001
Stroke	1.49 (1.36-1.64)	<0.001	1.25 (1.21-1.29)	<0.001
	Sexagenarians (n = 180,800)		*Octogenarians (n = 584,275)*	
	a-OR (95%CI)	p value	a-OR (95%CI)	p value
Coronary artery disease	0.66 (0.62-0.70)	<0.001	0.72 (0.70-0.74)	<0.001
Hyperlipidemia	0.79 (0.74-0.83)	<0.001	0.77 (0.75-0.80)	<0.001
Diabetes mellitus	0.78 (0.73-0.83)	<0.001	0.72 (0.69-0.74)	<0.001
Hypertension	0.62 (0.58-0.66)	<0.001	0.65 (0.63-0.68)	<0.001
Stroke	1.45 (1.32-1.58)	<0.001	1.22 (1.17-1.27)	<0.001
	Admitted for sepsis (n = 134,345)		*Admitted for acute myocardial infarction (n = 41,250)*	
	a-OR (95%CI)	p value	a-OR (95%CI)	p value
Coronary artery disease	0.80 (0.75-0.85)	<0.001	0.71 (0.60-0.83)	<0.001
Hyperlipidemia	0.81 (0.76-0.86)	<0.001	0.78 (0.68-0.90)	<0.001
Diabetes mellitus	0.81 (0.76-0.86)	<0.001	0.62 (0.53-0.73)	<0.001
Hypertension	0.73 (0.69-0.78)	<0.001	0.56 (0.47-0.67)	<0.001
Stroke	1.30 (1.19-1.42)	<0.001	1.30 (1.06-1.59)	0.01

population compared with the general population, as seen in the current study are all theoretically consistent with and can be attributed to, an underlying suppressed sympathetic nervous system.

Although PD is linked to reduced sympathetic tone, the pathogenesis of PD is strongly associated with systemic mitochondrial dysfunction causing excess reactive species (ROS) and enhanced oxidative damage that causes degeneration of dopaminergic neurons. It also promotes atherosclerosis through increased destruction of pancreatic β-cells, increased oxidation of low-density lipoprotein (LDL) and dysfunction of endothelial cells.[9] Moreover, the use of Levodopa, which is the main treatment for PD can induce elevated blood levels of homocysteine which promoted atherosclerosis through increased oxidant stress and impaired endothelial function.[2] In the presence of such contradicting mechanisms, previous studies yielded conflicting results on the association between PD and cardiovascular disease. In a meta-analysis by Alves et al, PD was associated with a 1.7−fold increase in the risk of stroke but had no significant association with CAD.[10] Similarly, Kizza et al and Huang et al reported a significant association between idiopathic PD and stroke.[11,12] On the contrary, Mastaglia et al found no significant difference in risk of stroke among patients with PD compared with control.[13] In our study, we found that patients with PD had a lower prevalence of coronary artery disease and but a higher prevalence of stroke.

Prospective data from the Atherosclerosis in Community cohort showed that risk for PD decreases with higher plasma levels of total or LDL cholesterol and increases with the use of statin.[14] Similarly, Fang et al concluded that higher levels of total cholestrol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides are associated with a lower future risk of PD.[15] Analogously, Jeong et al found that Statin use was associated with a higher risk for PD. However, such risk was not demonstrated on the patient's adherent to long-term use of statin.[16] In converse, in a meta-analysis by Yan et al, the use of statins particularly of atorvastatin was linked to a lower risk of PD. In our study, patients with PD had a significantly lower prevalence of hyperlipidemia. Given the limitations of the database, it was not possible to investigate if the use of lipid lower medications could alter such risk.

Several studies suggested that Type 2 diabetes mellitus might increase the risk of developing PD.[17,18] In a meta-analysis by, Zhu et al diabetics who were using thiazolidinediones had a significantly lower risk for PD. Such a protective effect was attributed to thiazolidinediones mediated activation of the gamma isoform of the peroxisome proliferator-activated receptor (PPAR gamma) which is linked to attenuation of neuronal damage by reducing neuroinflammation.[19] On the contrary, Becker et al reported no significant PD risk with diabetes.[20] These conflicting reports could be due to differences in populations as well as variation in sample size. Our study showed that patients with PD had significantly lower prevalence of diabetes mellitus.

Our study has limitations. The study is based on an administrative database. Lack of laboratory and

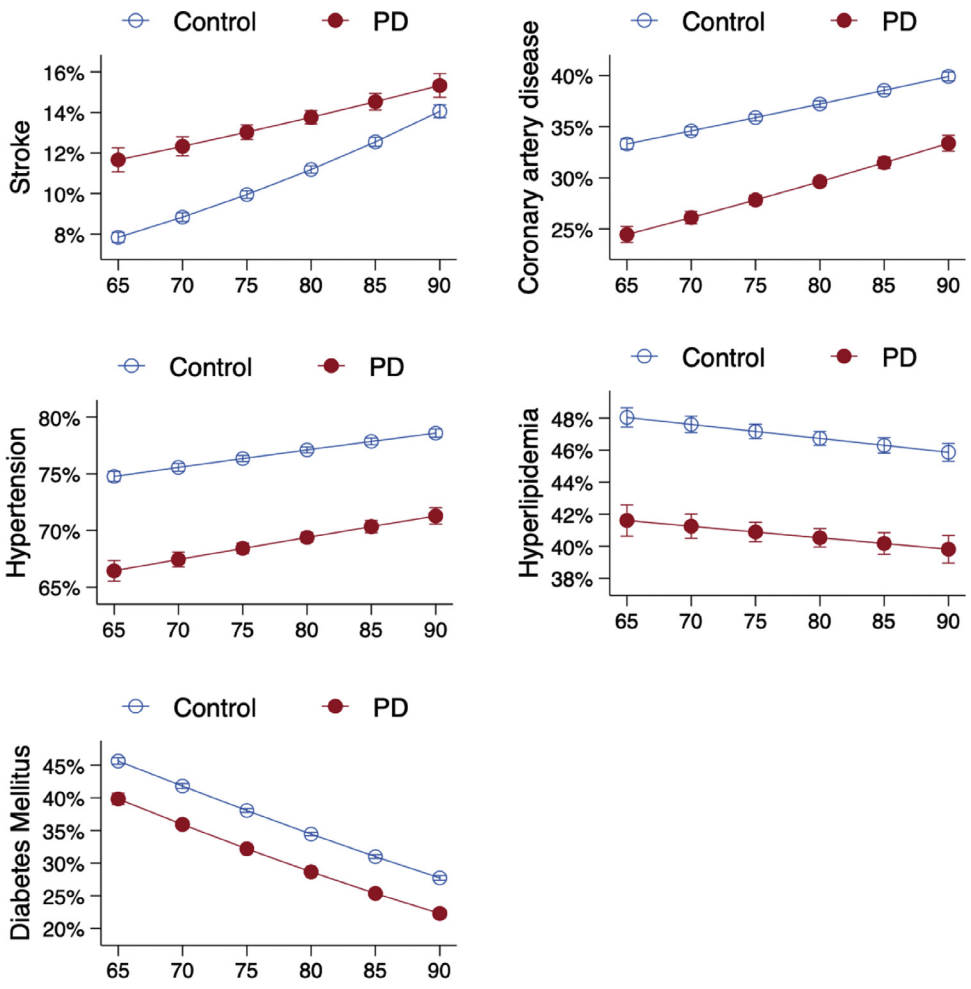

Figure 2. Predicted probability of cardiovascular risk factors and co-morbidities among different age groups of patients with PD.

radiological data including neuroimaging and neuropathological results limited our ability to study the direct association between PD and cardiovascular risk factors. In addition, patients with PD were identified based on ICD Codes with no information about the duration and severity of the illness. There is a risk of an underreporting of PD in the ICD-codes system. Moreover, no information was available about the medications that were used by the patients. The study is cross-sectional; thus, the timing of the onset of reported co-morbidities in relation to the diagnosis of PD was not determined. In the presence of these limitations, the study also had a number of strength points. The study had a large sample size and was representative of the entire USA population. The control groups were selected from same hospitalization population.

In summary, the findings of this national cross-sectional study suggest that patients with PD have a significantly lower prevalence of cardiovascular risk factors with a lower prevalence of cardiovascular co-morbidities except for an increased prevalence of stroke. Such association was demonstrated in all patient age groups irrespective of their age, gender or race.

Authors Contribution

AA: conceptualization, methodology, resources, formal analysis, visualization, writing - original draft. AT: writing - review & editing. MA: formal analysis, review & editing. PP: Writing - review & editing. IA: writing - review & editing. LK: supervision, writing - review & editing.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.amjcard.2020.09.021.

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