Risk of Parkinson disease in stroke patients: A nationwide cohort study in South Korea

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Abstract: BACKGROUND AND PURPOSE Previous studies have examined the risk of stroke in patients with Parkinson disease (PD), but the incidence of PD onset among stroke patients and its risk according to severity of poststroke disabilities have scarcely been investigated. This study aims to determine whether the risk of PD is increased among stroke patients using a retrospective cohort with a large population-based database. METHODS We used data collected by the Korean National Health Insurance Service from 2010 to 2018 and examined 307,361 stroke patients and 380,917 sex- and age-matched individuals without stroke to uncover the incidence of PD. Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval (CI), and the risk of PD was compared according to presence and severity of disability. RESULTS During 4.31 years of follow-up, stroke patients had a 1.67 times higher risk of PD compared to individuals without stroke (adjusted HR = 1.67, 95% CI = 1.57-1.78). The risk of PD was greater among stroke patients with disabilities than among those without disabilities, even after adjustment for multiple covariates (adjusted HR = 1.72, 95% CI = 1.55-1.91; and adjusted HR = 1.66, 95% CI = 1.56-1.77, respectively). CONCLUSIONS Our study demonstrated an increased risk of PD among stroke patients. Health professionals need to pay careful attention to detecting movement disorders as clues for diagnosing PD.

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ORIGINAL ARTICLE

Risk of Parkinson disease in stroke patients: A nationwide cohort study in South Korea

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Abstract

Background and purpose: Previous studies have examined the risk of stroke in patients with Parkinson disease (PD), but the incidence of PD onset among stroke patients and its risk according to severity of poststroke disabilities have scarcely been investigated. This study aims to determine whether the risk of PD is increased among stroke patients using a retrospective cohort with a large population-based database.

Methods: We used data collected by the Korean National Health Insurance Service from 2010 to 2018 and examined 307,361 stroke patients and 380,917 sex- and age-matched individuals without stroke to uncover the incidence of PD. Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% confidence interval (CI), and the risk of PD was compared according to presence and severity of disability.

Results: During 4.31 years of follow-up, stroke patients had a 1.67 times higher risk of PD compared to individuals without stroke (adjusted HR = 1.67, 95% CI = 1.57–1.78). The risk of PD was greater among stroke patients with disabilities than among those without disabilities, even after adjustment for multiple covariates (adjusted HR = 1.72, 95% CI = 1.55–1.91; and adjusted HR = 1.66, 95% CI = 1.56–1.77, respectively).

Conclusions: Our study demonstrated an increased risk of PD among stroke patients. Health professionals need to pay careful attention to detecting movement disorders as clues for diagnosing PD.

KEYWORDS
cohort studies, Parkinson disease, stroke

INTRODUCTION

Stroke is the second leading cause of death [1], and the burden of stroke has increased with its contribution to long-term disability. Stroke and Parkinson disease (PD) are common problems in the aged population, and the coexistence of these disorders can lead to particularly unfavorable outcomes [2, 3]. Previous studies have reported that PD patients with a history of stroke have increased risk of hospitalization [4, 5], and even a silent vascular burden can affect the motor and nonmotor symptoms of PD patients [6]. Therefore, the relationship between PD and stroke could be clinically important.

A case–control study [7] performed in the United Kingdom with 3637 PD cases and age- and sex-matched controls showed that stroke was more prevalent in PD cases compared to the control group (adjusted odds ratio [OR] = 1.65, 95% confidence interval [CI] = 2.00–2.47). Similar results were found in smaller studies from the United Kingdom (crude OR = 2.2, 95% CI = 1.1–4.6) [8] and China (OR = 2.58–6.77) [9]. A retrospective cohort study [10] enrolling a Korean population also found a greater risk of ischemic stroke in 5259 PD patients compared to age- and sex-matched controls (adjusted hazard ratio [HR] = 3.88, 95% CI = 3.17–4.75). Development of stroke in PD patients was explained by (i) their similar etiology, which is common among the elderly [11–13]; (ii) involvement of increased reactive oxygen species that damage dopaminergic neurons and promote atherosclerotic changes; and (iii) shared risk factors such as hypertension, diabetes mellitus, and dyslipidemia [14–17].

However, most previous studies examining the association between PD and stroke investigated stroke risk in PD patients, and there are limited studies that have directly investigated the incidence of PD among stroke patients (Table S1). Additionally, involuntary movement disorders including parkinsonism and the sequelae in poststroke patients may interfere with the diagnostic process of PD. Therefore, we designed a retrospective cohort study using a large population-based database to investigate the risk of PD development in stroke patients.

METHODS

Data sources and study setting

This retrospective cohort study used data from the Korean National Health Insurance Service (KNHIS) database, a single national insurer covering approximately 97% of the Korean population that collects all medical information on patients, such as visits to medical facilities, prescriptions, and diagnoses recorded as International Classification of Disease, 10th revision (ICD-10) codes. The remaining 3% of the Korean population is covered by a Medicaid program funded by the government, although their records also are managed by the KNHIS.

The KNHIS provides a biennial health screening program to all employees regardless of age or adults who are older than 40 years [18]. This program provides extensive information including anthropometric characteristics (blood pressure, height, weight, etc.), health behaviors (regular exercises, smoking status, alcohol consumption, etc.), and laboratory results (blood glucose, lipid profiles, urine analysis). The data obtained from this program have been widely used in various epidemiological studies [19].

Study subjects

This study included 800,646 patients diagnosed with stroke between 1 January 2010, and 31 December 2018. The definition of stroke was based on the recording of ICD-10 codes (I60–I64; includes both ischemic [I63, I64] and hemorrhagic stroke [I60, I61, I62]) with a claims code of brain magnetic resonance imaging or brain computed tomography [20–22]. These stroke patients were randomly matched 1:1 based on age and sex to a control group of individuals without stroke, with matching performed by year so that stroke patients diagnosed in a specific year were matched with control subjects alive in that same year. Among the participants, we included those who participated in the national health checkup program within 2 years from the index year and excluded those who were aged <40 years ($n = 6719$), had a previous history of traumatic brain injury ($n = 1039$), had a diagnosis of PD prior to stroke diagnosis ($n = 2898$), or were missing information ($n = 17{,}372$). This resulted in a total of 307,361 stroke patients. After applying the same inclusion and exclusion criteria to the matched control group of individuals without stroke, a total of 380,917 controls was selected for this study. The process of patient selection is illustrated in Figure 1.

This research was approved by the Institutional Review Board (IRB) of Samsung Medical Center (IRB no. 2020-12-068), and the requirement for informed consent from participants was waived due to the nature of deidentified retrospective data.

Severity of disability after stroke

Severity of disability after stroke was determined according to disability grades defined by the Korea National Disability Registration System (KNDRS) [23, 24]. Fifteen types of disability have been legally defined by the KNDRS, although the degree of disability was graded from 1 (most severe disability) to 6 (mild disability) during the study period. In the present study, disability was graded as severe or mild. As people with disability can obtain social benefits once registered with the KNDRS, almost all eligible people apply for registration. To be registered, people with a disability need to

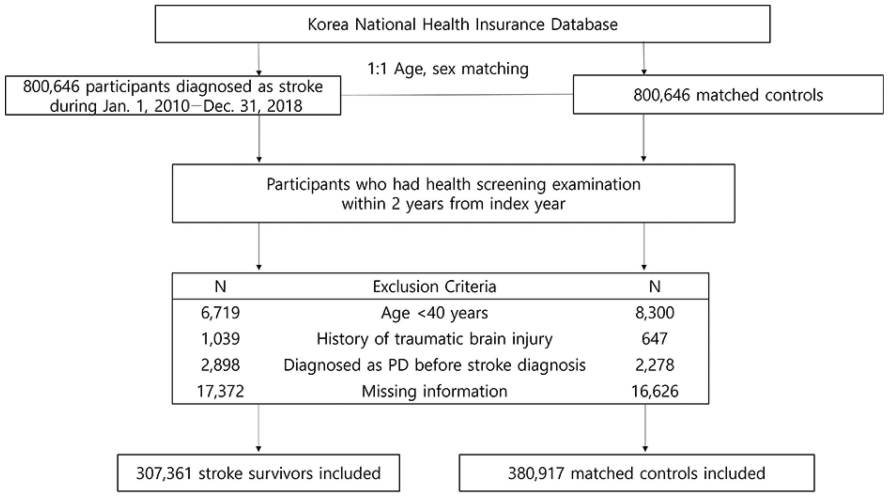

FIGURE 1 Flowchart of the study enrollment process. PD, Parkinson disease.

submit certified proof from a specialized physician who determines the severity of their disability based on the criteria provided by the government. In the case of stroke, people who meet the criteria can apply to KNDRS for "disability due to brain injury" 6 months after the date of stroke as their disease status becomes stable. Such patients should be assessed by neurologists, neurosurgeons, or physiatrists to determine of disability severity using the modified Barthel score; we dichotomized grades 1–3 as severe disability and grades 4–6 as mild disability for analysis (Table S2) [25].

Study outcome and follow-up

The primary outcome of the study was newly diagnosed PD, which was identified by both ICD-19 code (G20) and registration code (V124) of the Rare Intractable Disease management program in Korea, as in prior studies [26–28]. Patients diagnosed with PD were identified with code V124, which is specified by criteria comparable to the UK Parkinson's Disease Society Brain Bank Diagnostic Criteria [29], and the diagnosis is confirmed by a neurologist or neurosurgeon. The study subjects were followed from the date of first diagnosis of stroke or matched index date for the individuals without stroke to the date of newly diagnosed PD or the end of the follow-up period (31 December 2019), whichever came first.

Covariates

We defined low household income as the lowest 20% of insurance premiums, which refers to the proxy for insurance demand, and categorized the place of residence into metropolitan, urban, and rural areas. Smoking status was divided into current, former, and never-smoker groups. Heavy alcohol consumption was defined as >30 g of alcohol per day. Participants who exercised ≥5 times per week at a moderate intensity for ≥30 min or 3 times a week at a high intensity for ≥20 min were defined as regular exercisers. Body mass index was calculated as weight in kilograms divided by height in meters squared. Fasting glucose and total cholesterol levels were measured after 8 h of fasting. Information on comorbidities was obtained from claims data (ICD-10 codes) and prescription information before the index date. Diabetes mellitus was defined as E10–14 and more than one claim for antidiabetic medication, hypertension was defined as I10–11 and more than one claim for antihypertensive medication, and dyslipidemia was defined as E78 and more than one claim for prescribing lipid-lowering medications. To assess the overall comorbidity load, the Charlson Comorbidity Index (CCI) was used [30].

Statistical analysis

Descriptive figures are presented as mean ± SD for continuous variables or *n* (%) for categorical variables. Kaplan–Meier analysis was conducted to show the incidence probabilities of PD in stroke patients compared to individuals without stroke. We calculated the HR and 95% CI for PD using Cox proportional hazards regression. In the multivariate model (Model 3), we adjusted variables related to PD development, such as age, sex, socioeconomic variables (household income and place of residence), health behaviors (smoking status, alcohol consumption, and regular exercise), comorbidities (type 2 diabetes, hypertension, and dyslipidemia), and CCI score [31]. Moreover, we compared the risk of PD according to presence and severity of disability. Additionally, we conducted 1-year lag sensitivity analysis to assess the potential presence of surveillance bias. Statistical analysis was conducted using SAS version 9.4 (SAS Institute, Cary, NC, USA), and $p < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics of the study population

Table 1 describes the baseline characteristics of the study population. In the stroke patient group, the mean age was 66.7 years and 56.26% were men. Stroke patients had lower household incomes,

TABLE 1 Baseline characteristics of the study population.

Variable	Matched controls, *n* = 380,917	Stroke survivors, *n* = 307,361	*p*
Age, years	66.5 ± 11.3	66.7 ± 11.1	<0.001
Sex, male	217,295 (57.05)	172,926 (56.26)	<0.001
Income, lowest 20%	72,072 (18.92)	66,782 (21.73)	<0.001
Place of residence, urban	163,631 (42.96)	119,285 (38.81)	<0.001
Current smoker	62,563 (16.42)	73,107 (23.79)	<0.001
Heavy alcohol consumption	24,152 (6.34)	23,346 (7.6)	<0.001
Regular exercise	82,808 (21.74)	55,020 (17.9)	<0.001
Body mass index, kg/m^2	24.06 ± 3.08	24.15 ± 3.23	<0.001
Systolic blood pressure, mmHg	127.35 ± 15.34	131.88 ± 17.40	<0.001
Diastolic blood pressure, mmHg	77.31 ± 9.81	79.98 ± 11.20	<0.001
Fasting glucose, mg/dL	103.78 ± 26.31	110.53 ± 38.17	<0.001
Total cholesterol, mg/dL	194.49 ± 38.56	197.08 ± 41.3	<0.001
Comorbidities			
Type 2 diabetes	72,613 (19.06)	95,310 (31.01)	<0.001
Hypertension	200,742 (52.7)	239,470 (77.91)	<0.001
Dyslipidemia	138,929 (36.47)	210,657 (68.54)	<0.001
Charlson Comorbidity Index	1.86 ± 1.92	4.54 ± 2.46	<0.001
Follow-up duration, years	5.3 ± 2.52	4.31 ± 2.73	<0.001

Note: Data are presented as mean ± SD or *n* (%).

more often were current smokers, and more frequently consumed alcohol compared to individuals without stroke. A lower proportion of stroke patients performed regular exercise and had higher body mass indices, systolic and diastolic blood pressures, fasting glucose, and total cholesterol before stroke diagnosis compared to individuals without stroke. Higher percentages of comorbidities of type 2 diabetes (31.01%), hypertension (77.91%), and dyslipidemia (68.54%) were found among stroke patients, and thus the CCI score. The mean follow-up duration was 4.31 ± 2.73 years for stroke patients and 5.30 ± 2.52 years for individuals without stroke.

Risk of PD in stroke patients compared to matched controls

Incidence probability of PD was higher among stroke patients than that of individuals without stroke (log-rank $p < 0.001$). Adjusted HR (aHR) for PD during the follow-up period among stroke patients was 1.67 (95% CI = 1.57–1.78) compared to individuals without stroke (Table 2, Figure 2).

The risk of PD was higher for both stroke patients with disabilities (aHR = 1.72, 95% CI = 1.55–1.91) and those without disabilities (aHR = 1.66, 95% CI = 1.56–1.77). Stroke patients with mild disability showed a higher aHR of 1.82 (95% CI = 1.62–2.05) than those with severe disability (aHR = 1.50, 95% CI = 1.25–1.79) compared to individuals without stroke. Sensitivity analyses with a 1-year lag period were consistent with main results, demonstrating 3.5-fold increased risk of PD in stroke patients within the first year. The risk slightly attenuated after the 1-year lag period (Table S3).

DISCUSSION

To the best of our knowledge, this is the first large population-based study to investigate the incidence of PD among stroke patients and to demonstrate that PD risk was 1.7 times higher in stroke patients than individuals without stroke. There could be concerns about meeting with neurologists more frequently leading to increased risk of PD incidence, so we conducted the sensitivity analysis with a 1-year lag period. The threefold increase within the first year is attributed to frequent medical contact. However, even after the first year, the risk remained slightly lower but consistently high, suggesting a potential association between stroke and PD.

The mechanism of developing PD after a stroke event needs to be elucidated but can include cerebral ischemia-induced aggregation of alpha-synuclein (α-syn), and loss of dopaminergic neurons can lead to PD development. Aggregated α-syn and loss of substantia nigra dopaminergic neurons were observed in rodents with infarction [32]. In parallel with this result, a comparative study of human red blood cells demonstrated increased levels of the oligomeric form of α-syn in both ischemic stroke and PD patients compared to normal participants [33]. Another study involving 54 patients with acute ischemic stroke revealed alterations in α-syn within red blood cells [34]. These studies with human red blood cells suggest that cerebral ischemia can trigger the abnormal aggregation of α-syn. In addition, recent review articles also emphasize that stroke can promote inflammation and oxidative stress, creating conditions conductive to the abnormal accumulation of α-syn [35, 36].

Second, shared risk factors in stroke and PD can be attributed to PD onset in stroke patients as well as development of stroke in

TABLE 2 Hazard ratios and 95% confidence intervals for incidence of Parkinson's disease among stroke survivors compared to the matched control group.

	Subjects, *n*	Events, *n*	Follow-up duration, person-years	IR	Model 1, HR (95% CI)	Model 2, HR (95% CI)	Model 3, HR (95% CI)
Comparison with the matched control group							
Matched controls	380,917	2600	2,018,389.5	1.3	1 (Ref.)	1 (Ref.)	1 (Ref.)
Stroke survivors	307,361	3174	1,323,560.8	2.4	1.86 (1.76–1.96)	1.57 (1.48–1.67)	1.67 (1.57–1.78)
Comparison according to presence of disability							
Matched controls	380,917	2600	2,018,389.5	1.3	1 (Ref.)	1 (Ref.)	1 (Ref.)
Stroke survivors							
No disability	269,400	2688	1,145,846.3	2.3	1.82 (1.72–1.92)	1.57 (1.47–1.66)	1.66 (1.56–1.77)
Disability	37,961	486	177,714.5	2.7	2.12 (1.92–2.34)	1.63 (1.47–1.81)	1.72 (1.55–1.91)
Comparison according to severity of disability							
Marched controls	380,917	2600	2,018,389.5	1.3	1 (Ref.)	1 (Ref.)	1 (Ref.)
Stroke survivors							
No disability	269,400	2688	1,145,846.3	2.3	1.82 (1.72–1.92)	1.56 (1.47–1.66)	1.66 (1.56–1.77)
Mild disability	25,260	353	119,738.9	2.9	2.29 (2.05–2.56)	1.72 (1.53–1.93)	1.82 (1.62–2.05)
Severe disability	12,701	133	57,975.7	2.3	1.78 (1.49–2.12)	1.44 (1.21–1.73)	1.50 (1.25–1.79)

Note: Model 1: unadjusted. Model 2: adjusted for age, sex, and Charlson Comorbidity Index. Model 3: adjusted for Model 2 + socioeconomic variables (household income and place of residence), smoking status, alcohol consumption, regular exercise status, and comorbidities (type 2 diabetes, hypertension, and dyslipidemia).

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate per 1000 person-years.

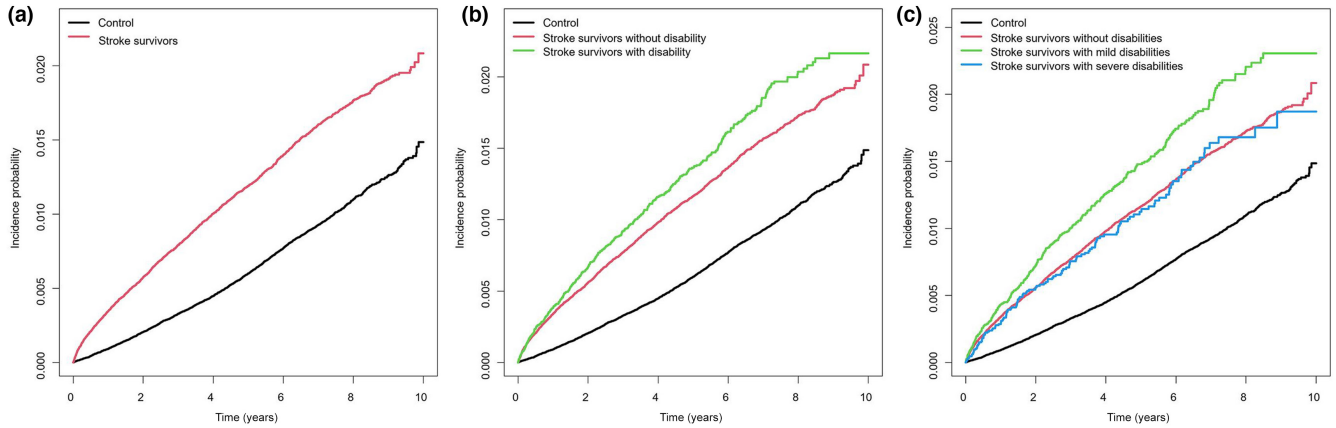

FIGURE 2 Kaplan–Meier curves of estimated incidence probability for risk of Parkinson disease (PD). (a) Risk of PD in stroke patients and control group. (b) Risk of PD in stroke by presence of disability. (c) Risk of PD in stroke by severity of disability.

PD patients. Known stroke risk factors such as age, hypertension, diabetes, heart failure, and obstructive sleep apnea were reported to increase the risk for PD [37], suggesting similar pathophysiology between the two disorders [38]. Although we adjusted all available health behavioral and comorbidity factors, there might be a pathophysiological link between stroke and PD that was not fully addressed by our multivariate model.

Additionally, shared genetic factors can explain the increased PD risk in stroke patients. A genome-wide association study [39] revealed that stroke and PD share five common genes (*PX7*, *LBH*, *ZCCHC10*, *DENND2A*, and *NUDT14*), which were expressed differentially in stroke and PD patients compared to healthy subjects. These studies help to understand the causal relationship between stroke and PD and to elucidate the mechanism to support our results.

Last, structural brain lesions from stroke could have lowered the threshold of PD symptoms by altering the "motor reserve." Previous models explain the discrepancy between the clinical and pathological severity of PD using the concept of motor reserve. Motor reserve in PD may compensate for the dopaminergic degeneration in PD, and parkinsonian symptoms can present when motor reserve fails to compensate for the dopaminergic degeneration in PD patients. Motor reserve in PD is associated with various brain structures, including the basal ganglia and extrabasal ganglia structures, and brain structural lesions from stroke can damage

the motor reserve in PD [40–42]. In our study, PD was more common in stroke patients; thus, our results support the connection between PD and stroke.

In terms of disability from stroke, PD was more common in stroke patients with disability. Considering various brain structures associated with poor motor reserve, more structural lesions or larger brain area involvement could be related to the development of PD. However, when we divided participants into stroke patients with mild or severe disabilities, PD was more common in those with a mild disability compared to those with a severe disability. Even though we also discussed various possible mechanisms that cause PD in stroke patients, parkinsonism could be masked by severe disability from stroke. Because PD is a neurodegenerative disease, development of parkinsonism can be insidious and slowly progressive. It is reported that people with disabilities constitute an unrecognized health disparity population [43]. Therefore, if stroke patients already exhibit severe disability such as hemiparesis or limitations in daily activity, they may encounter barriers to accessing health care. Detection of parkinsonism by a physician or caregivers might not be easy, potentially leading to potential underdiagnosis of PD. Consequently, the diagnosis rate in stroke patients with severe disabilities could be lower than in those with mild disabilities.

Our study has important clinical implications. It would be detrimental for stroke patients to develop PD in terms of morbidity and mortality. Previous studies have reported that stroke patients with PD experience longer hospitalization stays; higher rates of morbidities such as pneumonia, sepsis, and acute kidney injury; and increased mortality rates compared to those without PD [5, 44]. Deteriorated movements due to PD can negatively affect the outcome of rehabilitation in stroke patients [45]. Therefore, clinicians should be encouraged to screen for symptoms of PD in stroke patients to achieve early diagnosis, provide timely dopamine replacement therapy, and introduce early rehabilitation to stroke patients with disabilities to maintain quality of life.

There are several limitations in our study. First, a misdiagnosis of PD instead of vascular parkinsonism should be considered; it has been reported that the rate of misdiagnosis of PD accounts for approximately 15%–30% of cases, although the typical features of the two disorders are regarded as different [46]. However, PD is classified as a rare intractable disease with special financial aid in Korea; thus, the diagnostic process for PD is very thorough, to rule out secondary parkinsonism (G21), including vascular parkinsonism (G21.4) based on dopamine transporter scan, widely used in Korea, or the response to levodopa clinically. Second, a potential ascertainment bias should be considered in the study, as stroke patients have a higher chance of being diagnosed with PD due to increased medical attention. However, as we have discussed earlier, sensitivity analysis with 1-year lag time periods was consistent with the main results, suggesting such bias does not fully explain the association and that a potential association between stroke and PD exist. Last, because emerging data suggest ethnic variations in the incidence and manifestations of PD [47–49], our results should not be generalized, as we considered only the Korean population.

CONCLUSIONS

In conclusion, this nationwide population-based cohort study demonstrated that stroke patients have an increased risk of developing PD. Future studies are needed to further elucidate the underlying mechanism of PD onset in stroke patients and to observe their association in various ethnic groups.

AUTHOR CONTRIBUTIONS

Bong Sung Kim: Formal analysis; software. **Dong Wook Shin:** Validation; conceptualization; methodology; supervision; writing – review and editing; investigation; project administration. **Jinyoung Youn:** Conceptualization; writing – review and editing; supervision. **Hea Lim Choi:** Writing – original draft; formal analysis; writing – review and editing; visualization; investigation. **Kyungdo Han:** Methodology; formal analysis; data curation; software. **Jong Hyeon Ahn:** Writing – review and editing. **Won Hyuk Chang:** Writing – review and editing. **Wonyoung Jung:** Writing – review and editing.

CONFLICT OF INTEREST STATEMENT

The authors have no financial conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

ETHICS STATEMENT AND CONSENT TO PARTICIPATE

There were no patients directly involved in the overall process of our study. All human studies included in this analysis were conducted according to the Declaration of Helsinki.

CONSENT FOR PUBLICATION

All authors agreed to the publication of this article.

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REFERENCES

1. GBD 2019 Stroke Collaborators. Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the global burden of disease study 2019. *Lancet Neurol*. 2021;20(10):795-820.
2. Levine RL, Jones JC, Bee N. Stroke and Parkinson's disease. *Stroke*. 1992;23(6):839-842.
3. Liu Y, Xue L, Zhang Y, Xie A. Association between stroke and Parkinson's disease: a meta-analysis. *J Mol Neurosci*. 2020;70(8):1169-1176.
4. Hommel ALAJ, Krijthe JH, Darweesh S, Bloem BR. The association of comorbidity with Parkinson's disease-related hospitalizations. *Parkinsonism Relat Disord*. 2022;104:123-128.
5. Perdomo-Lampignano JA, Pana TA, Sleeman I, et al. Parkinson's disease and patient related outcomes in stroke: a matched cohort study. *J Stroke Cerebrovasc Dis*. 2020;29(7):104826.
6. Stojkovic T, Stefanova E, Soldatovic I, et al. Exploring the relationship between motor impairment, vascular burden and cognition in Parkinson's disease. *J Neurol*. 2018;265(6):1320-1327.

7. Becker C, Jick SS, Meier CR. Risk of stroke in patients with idiopathic Parkinson disease. *Parkinsonism Relat Disord*. 2010;16(1):31-35.
8. Patel M, Coutinho C, Emsley HC. Prevalence of radiological and clinical cerebrovascular disease in idiopathic Parkinson's disease. *Clin Neurol Neurosurg*. 2011;113(10):830-834.
9. Li Q, Wang C, Tang H, Chen S, Ma J. Stroke and coronary artery disease are associated with Parkinson's disease. *Can J Neurol Sci*. 2018;45(5):559-565.
10. Kim WY, Kim H, Hong JB, Sheen SH, Han IB, Sohn S. Association of Parkinson's disease with ischemic stroke in Korea: a nationwide longitudinal cohort study in Korea. *J Cerebrovasc Endovasc Neurosurg*. 2021;23(3):233-239.
11. Collier TJ, Kanaan NM, Kordower JH. Ageing as a primary risk factor for Parkinson's disease: evidence from studies of non-human primates. *Nat Rev Neurosci*. 2011;12(6):359-366.
12. Wafa HA, Wolfe CDA, Emmett E, Roth GA, Johnson CO, Wang Y. Burden of stroke in Europe: thirty-year projections of incidence, prevalence, deaths, and disability-adjusted life years. *Stroke*. 2020;51(8):2418-2427.
13. Pringsheim T, Jette N, Frolkis A, Steeves TD. The prevalence of Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. 2014;29(13):1583-1590.
14. Schernhammer E, Hansen J, Rugbjerg K, Wermuth L, Ritz B. Diabetes and the risk of developing Parkinson's disease in Denmark. *Diabetes Care*. 2011;34(5):1102-1108.
15. Sun Y, Chang YH, Chen HF, Su YH, Su HF, Li CY. Risk of Parkinson disease onset in patients with diabetes: a 9-year population-based cohort study with age and sex stratifications. *Diabetes Care*. 2012;35(5):1047-1049.
16. Qiu C, Hu G, Kivipelto M, et al. Association of blood pressure and hypertension with the risk of Parkinson disease: the national FINRISK study. *Hypertension*. 2011;57(6):1094-1100.
17. Pilotto A, Turrone R, Liepelt-Scarfone I, et al. Vascular risk factors and cognition in Parkinson's disease. *J Alzheimers Dis*. 2016;51(2):563-570.
18. Shin DW, Cho J, Park JH, Cho B. National General Health Screening Program in Korea: history, current status, and future direction. *Precis Future Med*. 2022;6(1):9-31.
19. Shin DW, Cho B, Guallar E. Korean national health insurance database. *JAMA Intern Med*. 2016;176(1):138.
20. Lee HR, Yoo JE, Choi H, et al. Tuberculosis and risk of ischemic stroke: a Nationwide cohort study. *Stroke*. 2022;53(11):3401-3409.
21. Jeong SM, Lee HR, Han K, et al. Association of change in alcohol consumption with risk of ischemic stroke. *Stroke*. 2022;53(8):2488-2496.
22. Choi EK. Cardiovascular research using the Korean National Health Information Database. *Korean Circ J*. 2020;50(9):754-772.
23. Choi HL, Yang K, Han K, et al. Increased risk of developing depression in disability after stroke: a Korean Nationwide study. *Int J Environ Res Public Health*. 2023;20(1):842.
24. Shin DW, Park J, Yeob KE, et al. Disparities in prostate cancer diagnosis, treatment, and survival among men with disabilities: retrospective cohort study in South Korea. *Disabil Health J*. 2021;14(4):101125.
25. Shin DW, Yu J, Cho J, et al. Breast cancer screening disparities between women with and without disabilities: a national database study in South Korea. *Cancer*. 2020;126(7):1522-1529.
26. Jeong SM, Lee HR, Jang W, et al. Sex differences in the association between nonalcoholic fatty liver disease and Parkinson's disease. *Parkinsonism Relat Disord*. 2021;93:19-26.
27. Kwon S, Jung SY, Han KD, et al. Risk of Parkinson's disease in multiple sclerosis and neuromyelitis optica spectrum disorder: a nationwide cohort study in South Korea. *J Neurol Neurosurg Psychiatry*. 2022;93:1209-1215.
28. Jeong SM, Han K, Kim D, Rhee SY, Jang W, Shin DW. Body mass index, diabetes, and the risk of Parkinson's disease. *Mov Disord*. 2020;35(2):236-244.
29. Clarke CE, Patel S, Ives N, et al. Clinical effectiveness and cost-effectiveness of physiotherapy and occupational therapy versus no therapy in mild to moderate Parkinson's disease: a large pragmatic randomised controlled trial (PD REHAB). *Health Technol Assess*. 2016;20(63):1-96.
30. Kim KH. Comparative study on three algorithms of the ICD-10 Charlson comorbidity index with myocardial infarction patients. *J Prev Med Public Health*. 2010;43(1):42-49.
31. Pupillo E, Cricelli C, Mazzoleni F, et al. Epidemiology of Parkinson's disease: a population-based study in primary Care in Italy. *Neuroepidemiology*. 2016;47(1):38-45.
32. Lohmann S, Grigoletto J, Bernis ME, et al. Ischemic stroke causes Parkinson's disease-like pathology and symptoms in transgenic mice overexpressing alpha-synuclein. *Acta Neuropathol Commun*. 2022;10(1):26.
33. Zhao HQ, Li FF, Wang Z, Wang XM, Feng T. A comparative study of the amount of alpha-synuclein in ischemic stroke and Parkinson's disease. *Neurol Sci*. 2016;37(5):749-754.
34. Wu Z, Li X, Zeng M, et al. Alpha-synuclein alterations in red blood cells of peripheral blood after acute ischemic stroke. *Int J Clin Exp Pathol*. 2019;12(5):1757-1763.
35. Wu S, Du L. Protein aggregation in the pathogenesis of ischemic stroke. *Cell Mol Neurobiol*. 2021;41(6):1183-1194.
36. Guo M, Ji X, Liu J. Hypoxia and alpha-Synuclein: inextricable link underlying the pathologic progression of Parkinson's disease. *Front Aging Neurosci*. 2022;14:919343.
37. Kummer BR, Diaz I, Wu X, et al. Associations between cerebrovascular risk factors and parkinson disease. *Ann Neurol*. 2019;86(4):572-581.
38. Song L, Zhang S, Li H, Hansson O, Sonestedt E, Borne Y. Comparison of risk factors for Parkinson's disease, coronary events and ischemic stroke. *NPJ Parkinsons Dis*. 2022;8(1):107.
39. Lang W, Wang J, Ma X, et al. Identification of shared genes between ischemic stroke and Parkinson's disease using genome-wide association studies. *Front Neurol*. 2019;10:297.
40. Youn J, Won JH, Kim M, et al. Extra-basal ganglia brain structures are related to Motor Reserve in Parkinson's disease. *J Parkinsons Dis*. 2023;13(1):39-48.
41. Kim YJ, Park CW, Shin HW, et al. Identifying the white matter structural network of motor reserve in early Parkinson's disease. *Parkinsonism Relat Disord*. 2022;102:108-114.
42. Chung SJ, Kim HR, Jung JH, Lee PH, Jeong Y, Sohn YH. Identifying the functional brain network of Motor Reserve in Early Parkinson's disease. *Mov Disord*. 2020;35(4):577-586.
43. Krahn GL, Walker DK, Correa-De-Araujo R. Persons with disabilities as an unrecognized health disparity population. *Am J Public Health*. 2015;105(Suppl 2):S198-S206.
44. Harnod D, Harnod T, Lin CL, Hsu CY, Kao CH. Poststroke parkinsonism associates with an increased mortality risk in patients. *Ann Transl Med*. 2020;8(7):471.
45. Ciftci S, Kuran B, Duman Z, et al. The effect of associated parkinsonism on rehabilitation in stroke patients: a case series. *Sisli Etfal Hastan Tip Bul*. 2018;52(1):64-69.
46. Bansil S, Prakash N, Kaye J, et al. Movement disorders after stroke in adults: a review. *Tremor Other Hyperkinet Mov (N Y)*. 2012;2:tre-02-42-195-191.
47. Ben-Joseph A, Marshall CR, Lees AJ, Noyce AJ. Ethnic variation in the manifestation of Parkinson's disease: a narrative review. *J Parkinsons Dis*. 2020;10(1):31-45.
48. Van Den Eeden SK, Tanner CM, Bernstein AL, et al. Incidence of Parkinson's disease: variation by age, gender, and race/ethnicity. *Am J Epidemiol*. 2003;157(11):1015-1022.

49. Dahodwala N, Siderowf A, Xie M, Noll E, Stern M, Mandell DS. Racial differences in the diagnosis of Parkinson's disease. *Mov Disord*. 2009;24(8):1200-1205.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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