RESEARCH ARTICLE

Visual Acuity and Development of Parkinson's Disease: A Nationwide Cohort Study

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ABSTRACT: Background: Visual dysfunction in Parkinson's disease (PD) is well known from previous reports, but the association of visual deficits with PD development has not yet been studied. The aim of this research was to evaluate the association of visual acuity with the risk of PD occurrence using a nationwide cohort in South Korea.

Methods: Among the population participating in the National Health Insurance Service, which is mandatory for all South Koreans, 6,055,113 individuals who had taken part in health screening programs between January 1, 2009, and December 31, 2012, were included in the cohort and followed until December 31, 2017. The hazard ratio was calculated for groups with high and low visual acuity using multivariate adjusted Cox regression analysis.

Results: A total of 22,872 subjects (0.38%) were diagnosed as having PD within the study period. Groups with low visual acuity showed a higher incidence of PD compared with groups with good visual acuity. Compared with the reference group (visual acuity better than 20/20), the adjusted hazard ratios and 95% confidence intervals (CIs) was 1.315 (95% CI, 1.261–1.371) for the group with visual acuity between 20/20 and 20/60, 1.357 (95% CI, 1.277–1.442) for the group with visual acuity between 20/60 and 10/100, and 1.267 (95% CI, 1.193–1.343) for the group with visual acuity less than 10/100.

Conclusions: Low visual acuity was associated with the development of PD. This suggests that visual dysfunction is one of the premotor symptoms for PD development. © 2020 International Parkinson and Movement Disorder Society

Key Words: nationwide cohort; Parkinson's disease; visual acuity

From the early stages of the disease, Parkinson's disease (PD) patients suffer from various nonmotor symptoms (NMSs) as well as classic motor symptoms, and NMSs can impact the quality of life even more than motor symptoms as the disease progresses.[1,2] Moreover, some NMSs can even precede parkinsonian motor symptoms.[2,3] PD may result in NMSs such as various visual disturbances, including defects in primary vision such as visual acuity (VA), color vision, and visual fields.[4] Anatomical changes in ocular structure that lead to visual dysfunction in PD patients have also been reported.[5,6] These visual disorders in PD are thought to

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be linked to retinal dopamine depletion.[7] Overall, visual impairment has been considered a consequence of PD progression. Because it is known that a number of oculovisual features are observed in early PD and could even be present in the prodromal phase,[8] the hypothesis that such visual features are antecedent to disease development cannot be dismissed.

Hence, the authors investigated the association between VA and PD using nationwide registry data, which are representative of the entire Korean population.

Materials and Methods

Data Source

The data analyzed in this study were derived from the National Health Information Database (NHID) of the National Health Insurance Service (NHIS). All individuals born in South Korea are given a unique resident registration number and are included in the NHIS system. The NHID is a public database of health care utilization, health screening, sociodemographic variables, and mortality for the entire population of South Korea created and maintained by the NHIS.[9] More than 50 million people, 97% of Korean residents, are included in the data. The health care utilization database includes information from records on inpatient and outpatient usage (diagnosis, length of stay, treatment costs, services received) and prescription records (drug code, days prescribed, daily dosage). The NHIS uses the Korean Classification of Diseases (KCD), an equivalent classification to the International Classification of Diseases.[10]

The NHID contains the health-screening database derived from the biennial national health screening program, in which the candidates are all National Health Insurance (NHI) members older than 20 years. The health-screening database includes information on health behaviors based on physicians' counseling and health examinees' questionnaire results, as well as bioclinical variables including anthropometric measurements, systolic and diastolic blood pressure, and VA, hearing, and blood laboratory tests. The participation rate in the health-screening programs was 74.8% in 2014.

Definition of "Patient With Parkinson's Disease"

Parkinson's disease is included on the list for the registration program of the South Korean government for copayment reduction. The list includes 138 rare intractable diseases. To register PD patients, documentation of a confirmed diagnosis by a neurologist, based on NHI criteria, is necessary. The NHI diagnostic criteria require that: (1) patients have more than a mild grade of bradykinesia and 1 of following: muscular rigidity, rest tremor, or postural instability; (2) the parkinsonism is not a secondary symptom of cerebral infarction, adverse drug effects, brain trauma, encephalitis, brain damage from hypoxia, or other conditions; and (3) the phenotype of parkinsonism must exhibit 3 or more of the following: symptoms began on 1 side of the body, the presence of a rest tremor, a progressive disease course, consistently asymmetric parkinsonism, a 70%–100% favorable response to levodopa, severe levodopa-induced dyskinesia, response to levodopa lasting more than 5 years, or a disease course of more than 10 years. The Health Insurance Review and Assessment Service (HIRA) reviews eligibility at the first registration and verifies the accuracy and reliability of the PD diagnosis. After registration, the Parkinson's disease registration code (V124) is given to PD-related claims for reduction of the copayment. As a result of this registration system, all patients with a PD registration code are assured of being diagnosed by a certificated neurologist with the definite criteria.

In this study, patients with PD were identified by both the diagnostic code of Parkinson's disease (G20) and the rare intractable disease registration code (V124). If there were several claims with PD codes, the first instance it occurred was considered the time of PD diagnosis.

Visual Acuity and Visual Disability

VA was measured in the health-screening programs. Spectacle-corrected VA was recorded if participants were wearing glasses. Individuals were categorized into 4 groups by better VA (spectacle-corrected VA if possible) between both eyes: VA greater or equal to 20/20 as group 1, VA from 20/60 to 20/20 as group 2, VA from 10/100 to 20/60 as group 3, and VA less than 10/100 as group 4. Subjects with visual disability were defined as individuals who had visual disability certification from the government's Ministry of Health and Welfare, which requires a registration document from a certificated ophthalmologist. Grade was determined by the criteria found in Supplement Table 1. In this study, subjects with visual disability were divided into a higher group with grades 1, 2, and 3 and a lower group with grades 4, 5, and 6. Because the visual disability criteria include both VA and visual fields, analysis of the no-visual disability group was performed to eliminate mixed features of the cohort, according to the group as defined above.

Other Variables

Several studies of the risk factors for PD development[11-14] were reviewed, and the confounding variables included in the statistical regression model were selected from well-known positive or negative risk factors if

available. The selected factors were smoking, drinking habits, physical activity, diabetes, hypertension, and dyslipidemia.

Blood pressure (BP) was measured during the day with subjects in a seated position after 5 minutes of rest. Blood samples were collected after overnight fasting and measured for serum levels of glucose, total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol.

Subjects were considered to have hypertension, diabetes mellitus, or dyslipidemia if they were on hypertensive, diabetic, or lipid-lowering medication, respectively. Also, subjects with systolic BP (SBP) ≥ 140 mm Hg or diastolic BP (DBP) ≥ 90 mm Hg and fasting blood glucose level ≥ 126 mg/dL or TC ≥240 mg/dL were considered to have hypertension, diabetes mellitus, or dyslipidemia, respectively.

Subjects with an income level less than the lower 20th percentile were defined as low income.

The definition of lifestyle variables is as follows. Smoking status was categorized into 3 groups: nonsmokers, current smokers who had smoked 100 cigarettes or more in their lifetime, and ex-smokers who had smoked in the past but had quit for at least 1 month. Alcohol consumption status was categorized into 3 groups: nondrinkers, those who drank less than 30 g a day on average, and those who drank more than 30 g a day. Regular exercise was defined as strenuous physical activity performed for at least 30 minutes at least 5 times a week. Body mass index (BMI) was defined as weight in kilograms divided by the square of height in meters (kg/m^2). Increased waist circumference (WC) was defined as ≥90 cm for men and ≥ 85 cm for women according to the Korean Society for the Study of Obesity's cutoff point for central or abdominal obesity.

Hospitals where these health examinations were performed were certified by the NHIS and subjected to regular quality control.

Study Population

Inclusion criteria were individuals who were older than 40 years old and who participated in a health-screening program between January 1, 2009, and December 31, 2012. A total of 17,539,992 subjects who took part in a health-screening program at least once during this period were enrolled. Among these subjects, 4,815,596 younger than 40 years old, 6,410,544 without VA, and 183,670 with incomplete data (data in which some of variables described above were missing) were excluded. A total of 59,306 subjects who were previously diagnosed with PD were also excluded. After we applied a 1-year lag period, 15,763 subjects diagnosed with PD within 1 year after health screening were excluded. Finally, 6,055,113 subjects were included in the analysis. All included subjects were monitored for diagnosis of PD until December 31, 2017. Eligibility criteria and a flow diagram are presented in Figure 1. To exclude selection bias, baseline characteristics of groups with VA data (included in the analysis) and without VA data (excluded from the analysis) were compared and are presented in Supplement Table 2. Baseline characteristics of groups with/without VA data presented no obvious deviation in various covariates. A low possibility for selection bias could be presumed. Also, information on visual acuity, its distribution, presence of visual disability and visual disability grade in a previous PD diagnosis group that was excluded above compared with included subjects is presented in Supplement Table 3.

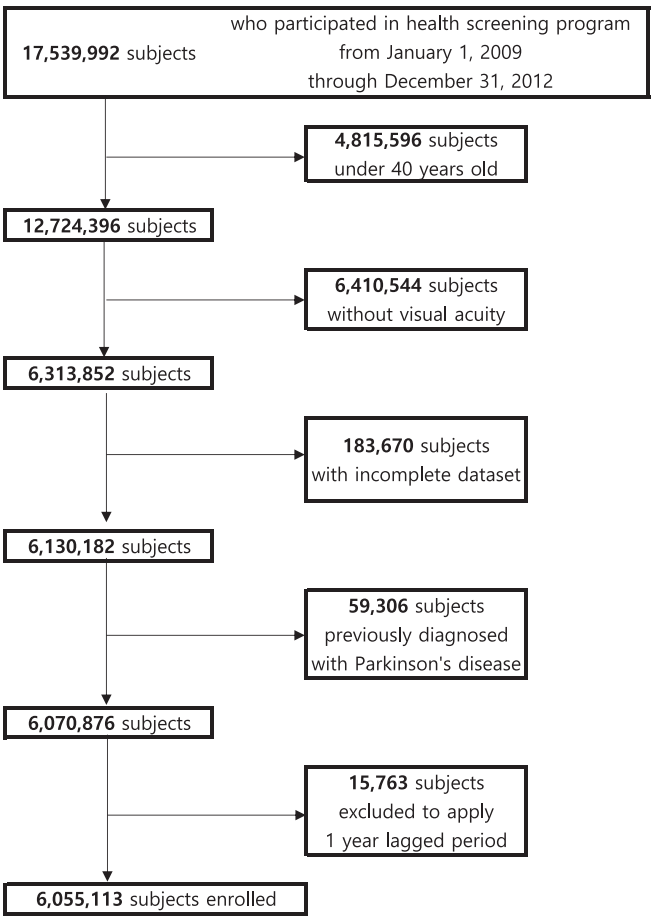

FIG. 1. Flow diagram for identifying the study population for incident Parkinson's disease.

Study Protocol Approvals and Registrations

The Deliberative Committee of the HIRA approved the conditional use of the database for this study. The study adhered to the Declaration of Helsinki, and the study protocol was reviewed and approved by the

institutional review board and Samsung Medical Center (SMC 2018-02-112).

Statistical Analysis

Data are described with mean ± SD and number (%). Differences between PD and non-PD groups were investigated by the independent *t* test for continuous data and the chi-square test for categorical data. A $P < 0.05$ was considered statistically significant. Kaplan-Meier analysis was used to assess the cumulative incidence of PD for the enrolled population. Crude and multivariate adjusted Cox regression analysis was conducted to examine the hazard ratio (HR) and 95% confidence interval (CI) to evaluate the risk of PD development associated with VA, visual disability presence, and visual disability grade. Including these visual factors as independent variables, 2 adjusted models were constructed for multivariate adjusted Cox regression analysis (age and sex for model 1 and age, sex, smoking

TABLE 1. Detailed characteristics of subjects with and without Parkinson's disease (PD)

	Parkinson's disease		
	Absent (n = 6,032,241)	Developed (n = 22,872)	Hazard ratio (95% CI)[a]
Sex (male)	2,971,741 (49.26)	10,729 (46.91)	0.910 (0.887–0.934)
Age (years)	54.29 ± 10.54	66.46 ± 8.97	1.097 (1.096–1.098)
Visual acuity of better eye (logMAR[b])	0.13 ± 0.48	0.41 ± 0.56	N/A
Hypertension	2,018,570 (33.46)	12,189 (53.29)	2.269 (2.210–2.329)
Diabetes	699,608 (11.6)	5004 (21.88)	2.135 (2.069–2.204)
Dyslipidemia	1,416,648 (23.48)	7444 (32.55)	2.135 (2.069–2.204)
Regular exercise[c]	3,028,123 (50.2)	9335 (40.81)	0.684 (0.666–0.702)
Smoking			
Nonsmoker	3,861,082 (64.01)	16,848 (73.66)	2.242 (2.151–2.342)
Ex-smoker	943,072 (15.63)	3635 (15.89)	1.133 (1.092–1.174)
Current smoker	1,228,087 (20.36)	2389 (10.45)	1 (reference)
Alcohol consumption			
None	3,556,467 (58.96)	16,882 (73.81)	2.174 (2.024–2.336)
<30 g/day	2,109,861 (34.98)	5191 (22.7)	1.931 (1.869–1.992)
>30 g/day	365,913 (6.07)	799 (3.49)	1 (reference)
Income low[d]	1,566,723 (25.97)	5515 (24.11)	0.906 (0.879–0.934)
Place (urban)	2,711,502 (44.95)	9727 (42.53)	0.906 (0.883–0.930)
Body mass index	23.95 ± 3.04	24.14 ± 3.07	1.020 (1.016–1.025)
Waist circumference	81.09 ± 8.63	83.36 ± 8.47	1.030 (1.029–1.032)
Fasting glucose	99.8 ± 24.5	104.81 ± 29.35	1.062[e] (1.058–1.066)
Systolic blood pressure	124.04 ± 15.35	127.71 ± 15.75	1.015 (1.014–1.016)
Diastolic blood pressure	77.08 ± 10.11	77.64 ± 9.96	1.005 (1.004–1.007)
High-density lipoprotein	54.74 ± 16.64	53.22 ± 19.33	0.993[e] (0.992–0.994)
Low-density lipoprotein	117.17 ± 34.19	116.23 ± 35.27	0.992[e] (0.988–0.996)

Numerical continuous parameters are described as mean ± standard deviation, and categorical parameters are described as total numbers (percentages). Crude hazard ratios and 95% confidence intervals were obtained by Cox proportional-hazard regression for each univariate.
[a]CI, confidence interval.
[b]logMAR, −log (Snellen visual acuity); lower values mean better visual acuity.
[c]Regular exercise was defined as strenuous physical activity performed for at least 30 minutes at least 5 times a week.
[d]Subjects with income of less than the lower 20th percentile were defined as low income.
[e]Calculated per each 10 units.

habits, alcohol consumption habits, physical activity, diabetes, hypertension, and dyslipidemia for model 2). Crude and adjusted Cox regression analyses were conducted to assess the effect of other covariates including age, sex, smoking, drinking habits, amount of physical activity, diabetes, hypertension, and dyslipidemia as possible risk factors of PD. Sensitivity analyses were performed with patients who had a repeated G20 code (2 or more). Additional subgroup analyses were performed to evaluate the interaction effect of visual disability in PD with other variables. Subjects were grouped by age, sex, smoking, drinking habits, amount of physical activity, diabetes, hypertension, and dyslipidemia. Statistical Analysis System software version 9.4 (SAS Institute, Inc., Cary, NC) was used for all analyses.

Results

Of the 6,055,113 subjects, 22,872 subjects (0.38%) were diagnosed with PD during the study period. Compared with subjects without PD, those with the disease were more likely to be female, older, nonsmoker, of higher income, nonuser of alcohol, rural inhabitant, with elevated WC and less regular exercise, and experiencing hypertension, diabetes, and dyslipidemia. Subjects with higher BMI, fasting glucose, SBP, DBP, and TG, and with lower HDL and LDL were more often included in the group with PD. The difference between the 2 groups was statically significant for all variables ($P < 0.001$), and the crude HR of PD by each variable was significant. Detailed characteristics are shown in Table 1.

VA in subjects who were excluded because of previous PD diagnosis (logMAR 0.20 ± 0.55; Supplement Table 3) and VA in subjects who were diagnosed with PD during the observation period (logMAR 0.41 ± 0.56; Table 1) were worse than subjects who were included in the analysis and not diagnosed for PD (logMAR 0.13 ± 0.48; Table 1). In sum, VA in PD patients was worse than in subject without PD.

Figure 2 shows the cumulative incidence of PD according to VA or disability. Subjects with VA ≥20/20 showed a significantly lower incidence of PD compared with the worse VA groups (Fig. 2A). Subjects without visual disability showed a significantly lower incidence of PD compared with the visual disability group (Fig. 2B).

Table 2 presents the association between VA/visual disability and PD diagnosis. Among 1,955,338 subjects with good VA ≥20/20), 2857 patients (0.15%) were diagnosed with PD. Among 271,780 subjects with worse VA (<10/100), 2206 patients (0.81%) were diagnosed with PD. Crude HRs of PD by VA group, in which group 1 was the reference group, were 3025

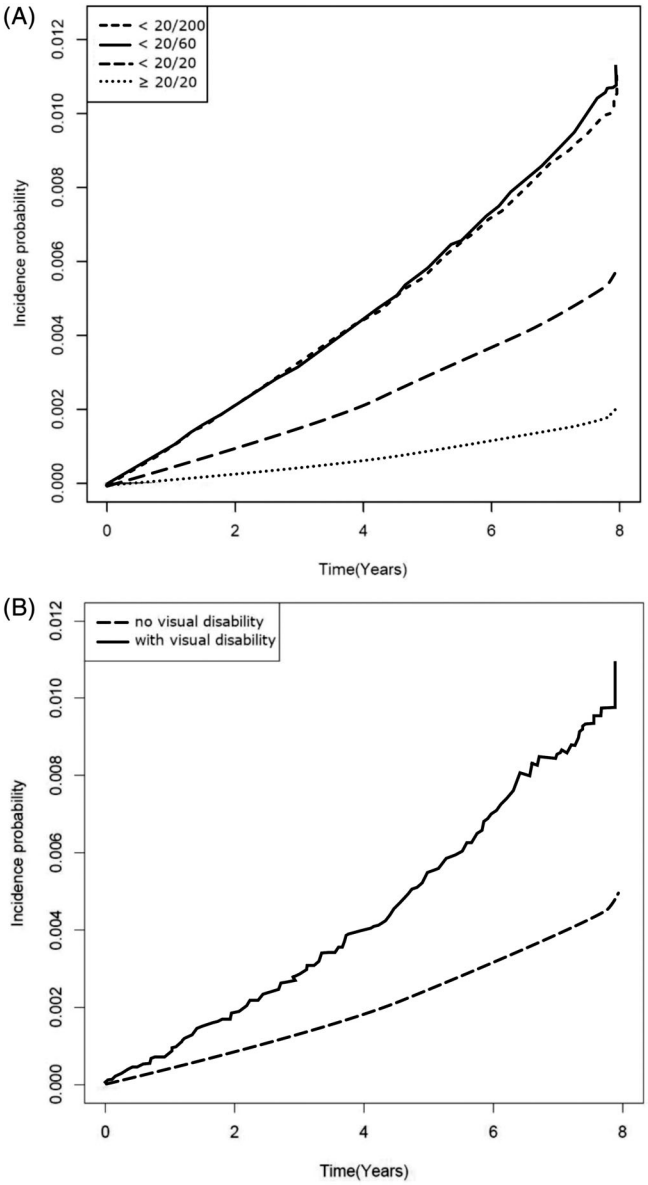

FIG. 2. (**A**) Graph of cumulative incidence probability of Parkinson's disease grouped by visual acuity (upper graph). Visual acuity is presented with the Snellen visual acuity system. All categories excluded inferior categories (ie, category [< 20/20] contains individuals with visual acuity ≥20/60 and < 20/20). (**B**) Graph of cumulative incidence probability of Parkinson's disease grouped by the presence of visual disability (lower graph).

(95% CI, 2.907–3.148) in group 2, 6060 (95% CI, 5.727–6.412) forgGroup 3, and 5.840 (95% CI, 5.524–6.174) in group 4. After adjusting for age, sex, and other covariates (model 2), the HRs were 1.315 (95% CI, 1.261–1.371) in group 2, 1.357 (95% CI, 1.277–1.442) in group 3, and 1.267 (95% CI, 1.193–1.343) in group 4.

Subjects with visual disability were more likely to be diagnosed with PD. Using the group with no visual disability as a reference, the crude HR of PD patients presenting with visual disability was 2.218 (95% CI,

1.956–2.514). The adjusted HR of PD was 1.195 (95% CI, 1.054–1.355) in model 2. Among subjects with visual disability, the higher-grade groups were more susceptible to PD. Compared with subjects with no visual disability, the crude HRs of PD stratified by visual disability grade were 2.064 (95% CI, 1.786–2.387) for the low-grade group and 2.812 (95% CI, 2.192–3.608) for the high-grade group. The adjusted HRs were 1.181 (95% CI, 1.021–1.365) for the lower-grade group in model 2 and 1.235 (95% CI, 0.963–1.585) for the higher-grade group in model 2. The adjusted HRs by groups categorized by VA with and without subjects of visual disability showed similar results.

In the adjusted model, the effect of covariates on PD development is presented in Table 2 and Supplement

TABLE 2. Cox regression analysis on Parkinson's disease (PD) development by visual acuity and visual disability

		Total	Number of PD patients	Hazard ratio (95% confidence interval)		
				Crude	Model 1[a]	Model 2[b]
		(N = 6,055,113)	(n = 22,827)			
Visual acuity						
<10/100		271,780	2,206	5.840 (5.524–6.174)	1.262 (1.188–1.34)	1.267 (1.193–1.346)
≥10/100, <20/60		242,758	2,073	6.060 (5.727–6.412)	1.348 (1.268–1.433)	1.357 (1.277–1.442)
≥20/60,<20/20		3,585,237	15,736	3.025 (2.907–3.148)	1.327 (1.273–1.384)	1.315 (1.261–1.371)
≥20/20		1,955,338	2,857	1 (reference)	1 (reference)	1 (reference)
Age				1.097 (1.096–1.098)	1.101 (1.099–1.102)	1.095 (1.094–1.097)
Sex (male)		2,982,470	10,729	0.910 (0.887–0.934)	1.111 (1.082–1.142)	1.389 (1.342–1.435)
Smoking						
Nonsmoker		3,877,930	16,848	2.242 (2.151–2.342)		1.583 (1.509–1.662)
Ex-smoker		946,707	3,635	1.133 (1.092–1.174)		1.414 (1.343–1.490)
Current smoker		1,230,476	2,389	1 (reference)		1 (reference)
Alcohol						
None		3,573,349	16,882	2.174 (2.024–2.336)		1.344 (1.247–1.447)
<30 g/day		2,115,052	5,191	1.931 (1.869–1.992)		1.131 (1.050–1.219)
>30 g/day		366,712	799	1 (reference)		1 (reference)
Regular exercise[c]		3,037,458	9,335	0.684 (0.666–0.702)		0.954 (0.929–0.981)
Hypertension		2,030,759	12,189	2.269 (2.210–2.329)		1.351 (1.308–1.395)
Diabetes		704,612	5,004	2.135 (2.069–2.204)		1.043 (1.014–1.072)
Dyslipidemia		1,424,092	7,444	1.572 (1.529–1.616)		1.134 (1.102–1.167)
Visual disability						
Yes		30,307	246	2.218 (1.956–2,514)	1.227 (1.082–1.392)	1.195 (1.054–1.355)
No		6,024,806	22,626	1 (reference)	1 (reference)	1 (reference)
Visual disability and groups by visual acuity						
Yes		30,307	246	5.746 (5.044–6.545)	1.573 (1.379–1.794)	1.524 (1.336–1.738)
No	<10/100	249,372	2,013	5.830 (5.507–6.172)	1.237 (1.163–1.316)	1.247 (1.173–1.327)
	≥10/100, <20/60	240,922	2,057	6.072 (5.737–6.426)	1.346 (1.266–1.430)	1.356 (1.276–1.441)
	≥ 20/60, <20/20	3,580,452	15,707	3.030 (2.912–3.154)	1.329 (1.274–1.386)	1.316 (1.262–1.373)
	≥20/20	1,954,060	2,849	1 (reference)	1 (reference)	1 (reference)
Grouped by visual disability grade						
Higher (1,2, 3)		24,105	62	2.812 (2.192–3.608)	1.296 (1.010–1.663)	1.235 (0.963–1.585)
Lower (4, 5, 6)		6,202	184	2.064 (1.786–2.387)	1.205 (1.042–1.393)	1.181 (1.021–1.365)
No disability		6,024,806	22,626	1 (reference)	1 (reference)	1 (reference)

Hazard ratios (95% CIs) were calculated using a Cox proportional hazards model.
For the first multivariable Cox regression analysis according to visual acuity, crude and adjusted hazard ratios of other covariates are shown in this table. In the rest of the analysis that visual acuity was classified by visual disability, visual disability, and groups by visual acuity and grouped by visual disability grade, the adjusted hazard ratios of other covariates except for visual acuity–related variable are shown in Supplement Table 3. Crude hazard ratios for other variables are shown in Table 1.
[a]Adjusted for age and sex.
[b]Adjusted for age, sex, smoking habits, alcohol consumption habits, physical activity, diabetes, hypertension, and dyslipidemia.
[c]Regular exercise was defined as strenuous physical activity performed for at least 30 minutes at least 5 times a week.

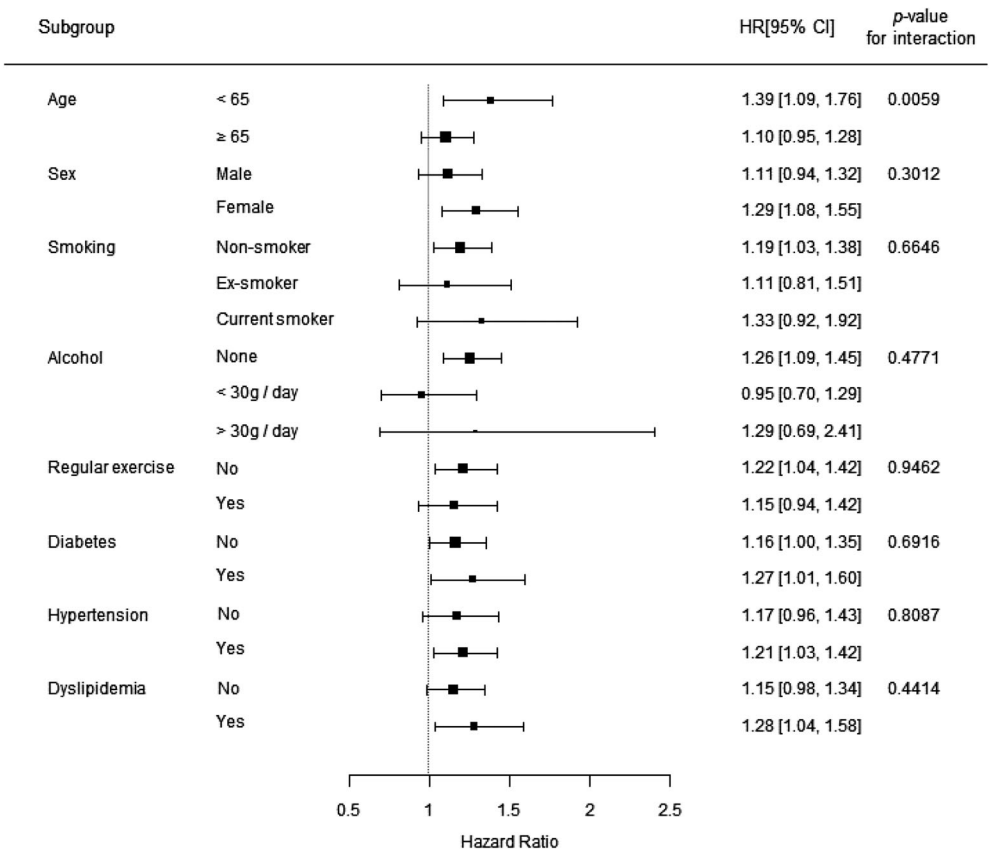

FIG. 3. Forest plot for subgroup analyses of Parkinson's disease development by the presence of visual disability. Subjects without visual disability were set as a reference group for each subgroup category and adjusted hazard ratios (95% CIs) were calculated using a Cox proportional hazards model. Regular exercise was defined as strenuous physical activity that was performed for at least 30 minutes at least 5 times a week.

Table 4. Old age, male sex, nonsmoking, nonalcohol, less exercise, hypertension, diabetes, and dyslipidemia were significant risk factors for PD development. The results were reversed after adjusting other confounders, especially sex. The crude HR for being male on PD was 0.910 (95% CI, 0.887–0.934), and the adjusted HR was 1.389 (95% CI, 1.342–1.435).

In the sensitivity analysis using 2 or more G20 diagnostic codes, the Cox regression analysis showed the same results as described above. The number of repeated G20 PD patients was 21,358. Detailed results of repeated G20 analysis are in Supplement Table 5.

A forest plot for subgroup analyses of PD by the presence of visual disability is presented in Figure 3. Subjects without visual disability were set as a reference group for each subgroup category. In crude and adjusted Cox regression analysis, the presence of visual disability significantly increased the risk of PD for subjects younger than age 65 compared with those 65 or older (adjusted HR, 1.386 for age younger than 65 years, 1.104 for age 65 or older, P for interaction <0.006, group with no visual disability as reference). Other variables did not show significant interaction with visual disability on PD (P for interaction >0.05).

Discussion

In the current study, we found a different incidence of PD according to VA. Multivariable Cox regression analysis showed individuals with low VA or visual disability had a higher risk of PD development. Old age, being male, nonsmoking, nondrinking, less exercise, hypertension, diabetes, and dyslipidemia also increased the risk of PD. In the subgroup analysis, the population younger than age 65 was more susceptible to PD according to visual disability.

Based on the results of the present study, low VA might be considered as a premotor sign of PD. Visual dysfunction has been considered a consequence of PD during the disease course.[15,16] Vision is one of the nonmotor systems altered in PD, and foveal vision is especially impaired.[17] Several studies have demonstrated retinal thinning in PD patients compared with healthy subjects,[18,19] and progressive changes in the retinal nerve fiber layer associated with disease progression have also been reported.[6] Therefore, retinal changes could have existed before the diagnosis of PD and may have contributed to low VA. In addition, in terms of the concept of Parkinson's-associated risk syndrome, in

which at-risk patients may have genetic factors predisposing to PD or exhibit early nonmotor symptoms,[20] this study's findings suggest that visual dysfunction is one of the nonmotor symptoms.

Visual deficits in PD are known to influence overall motor function.[21] Therefore, it is worthwhile to evaluate whether visual dysfunction not only affects the severity of PD but also the development of PD. Individuals with visual dysfunction are less likely to engage in physical activity, which is a protective factor for PD.[22-24] However, groups with low VA still showed a higher risk for PD even after adjustment for regular exercise. Several studies have demonstrated that good VA was correlated with a lower dementia level, and visual dysfunction was associated with poorer cognitive function. Because cognitive activity is associated with brain health in general[25] and considering that the pathogenesis of PD lies in a neurodegenerative pathway, development of low VA can be considered a risk factor for PD onset. As seen in an animal study in which dopamine synthesis reduction was found in surgically induced blinded anosmic rats,[26] sensory deprivation such as visual dysfunction might be associated with deterioration of dopamine pathways, which leads to PD development.

The results of this study do not present specific evidence for a dose-response relationship (ie, lower VA did not mean higher PD incidence), but we did observe a trend in which higher incidence and HR were associated with lower VA, except for the lowest VA group (less than 10/100). This disparity could be attributed to the possibility that if subjects with lower VA (especially less than 10/100) had subclinical PD or other NMSs, it serves as another hurdle to getting the necessary health-screening programs. This would lead to an underestimation of PD incidence in lower VA groups.

There is another possibility that the severity of visual deficit that existed in the prodromal phase of PD is not directly correlated to decreased level of VA. Among known visual changes in PD, color vision change, visual field deficits,[4] and changes in the retinal nerve fiber layer[6] are not linearly related to VA, although they would result in VA change if advanced.

In this study, PD was defined by the diagnostic code G20 and the intractable disease registration code V124. PD criteria for registration in rare intractable disease is very strict, which can potentially lead to underestimation of PD incidence. However, considering that the registration offers financial benefits to patients by paying 90% of their medical cost, it can be assumed that PD patients are willing to register in the rare intractable disease registry. Consequently, PD diagnoses by certificated neurologists are very accurate. Sensitivity analysis with a repeated G20 code showed similar results. Therefore, we could be assured that the definition for PD from registry data was robust. Also, previous literature used the same definition in epidemiological studies on PD from Korea.[27,28]

VA of prevalent PD was worse than that of included subjects for the study and better than that of incident PD patients. We postulated the reason why excluded prevalent PD patients showed better VA than newly developed PD patients was that "excluded PD patients in our study" do not represent the whole of prevalent PD patients, but PD patients with mild disease course or better general condition. Chronic or severe PD patients might not participate in the national health-screening program because they were already checking their health status regularly by their own neurology clinic and had no need to get health screening separately. Furthermore, severe PD patients cannot perform VA measurement. So, VA of prevalent PD in our study can be overestimated. VA of excluded prevalent PD patients in our study was measured at different times during the disease course, and only selected PD patients who examined VA and who could measure VA (ie, with a mild disease course) were included in the prevalent PD group, and it could have caused biased results. In addition, baseline characteristics of these groups might differ from each other.

The current study revealed that men have a higher risk of PD, with an adjusted HR of 1.389 (95% CI, 1.342–1.435). Although subjects with PD were more likely to be female compared with those without the disease, and the crude HR for being male was 0.910 (95% CI, 0.887–0.934), all adjusted Cox regression analyses revealed that being male is a risk factor for PD. The conversion of the sex effect in the regression model is considered the effect of adjusting for age and other confounders.

In the present study, subjects with alcohol intake tended to be less likely to develop PD compared with subjects with no alcohol intake, regardless of the intake amount. Ex-smokers and nonsmokers showed higher risk of PD compared with current smokers. Smoking[29-31] is a well-known protective factor for PD, and the prevalence of PD related to alcohol consumption is concordant with a previous study.[32]

Regarding the effect of diabetes and hypertension on PD, the results of our study did not correspond to previous studies. Both hypertension and diabetes were positively associated with the risk of PD in our study, with adjusted HRs of 1.351 (95% CI, 1.308–1.395) and 1.043 (95% CI, 1.014–1.072), respectively. Previously, the effect of diabetes for PD risk was inconclusive.[33,34] Hypertension and blood pressure were not associated[35] or negatively associated.[12] Secondary PD patients, including vascular PD, were excluded when we defined PD in the study. Although there might be some patients with atypical or secondary parkinsonism in our study, the majority would be patients with Parkinson's disease.

BMI and HDL and LDL levels are also still controversial as risk factors for PD.[28,36-39] In our study, the crude incidence and HR for these variables were higher, but they were not adjusted for other confounders. The findings with these factors for PD development did not assess risk factors for PD.

This study has several limitations. First, detailed clinical ophthalmologic information such as refractive power, retinal status, or cataract grading was not available from our source database. Thus, the etiology of poor vision reported could not be detailed. However, the diagnosis of PD, measurement of VA, and confirmation of visual disability were performed by specialists, so the association between VA and PD is robust regardless of low VA etiology. There is another possibility that VA was measured under a dim-light condition in some health-screening centers, although regular quality assurance training and quality control are performed by the NHIS. In consequence, the VA of patients who had diminished contrast sensitivity might be measured as lower values. Second, PD is a slowly progressive disease, so it cannot be assured that the results of this study (obtained over 8 years of longitudinal observation) could uncover the entire effect of VA associated with PD development. Third, we cannot ignore the possibility that atypical or secondary parkinsonism, such as vascular parkinsonism patients were enrolled because patients' detailed clinical information is not included in the NHID, but the disease code for PD is made based on clinical symptoms by a certified neurologist who affirmed the criteria for intractable disease registration for copayment reduction by the government. In addition, there are separate codes for vascular parkinsonism, multiple systemic atrophy, and progressive supranuclear palsy. Therefore, we assumed that the PD diagnoses were accurate and that the majority of enrolled patients had PD. Fourth and last, based on study results, we postulated low VA to be a premotor symptom of PD; however, there is a lack of clinical trials and laboratory studies to support this interpretation. Additional research regarding the association of VA and PD development should be conducted in the future.

In conclusion, this study showed that individuals with low VA were more likely to develop PD. This suggests that low VA might be a premotor symptom of PD and could potentially contribute to multidimensional prodromal risk scores. ●

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.