Association Between Glycemic Status and the Risk of Parkinson Disease: A Nationwide Population-Based Study

Diabetes Care 2020;43:2169–2175 | https://doi.org/10.2337/dc19-0760

OBJECTIVE

Previous studies have suggested that diabetes increases the risk of Parkinson disease (PD); however, this has not been conclusively established. We analyzed the risk of PD based on baseline glucose tolerance status in a large-scale cohort representative of the general Korean population.

RESEARCH DESIGN AND METHODS

This analysis was performed in a cohort of 15,168,021 adults aged ≥40 years who underwent health checkups under the National Health Insurance Service between January 2009 and December 2010. The clinical course of subjects was monitored until December 2016. Subjects were classified into the following groups: no diabetes, impaired fasting glucose (IFG), diabetes duration <5 years, and diabetes duration ≥5 years. We analyzed the adjusted hazard ratio of PD for each group.

RESULTS

During the observation period of 49,076,148.74 person-years, PD occurred in 31,577 patients. Compared with the nondiabetes group, the adjusted hazard ratio was 1.038 (95% CI, 1.009–1.067) in the IFG group, 1.185 (95% CI, 1.143–1.229) in the diabetes duration <5 years group, and 1.618 (95% CI, 1.566–1.672) in the diabetes duration ≥5 years group. These results were consistent with those of the subgroup analysis, and the presence of diabetes further increased the risk of PD regardless of comorbidities such as cardiovascular, cerebrovascular, and chronic kidney diseases.

CONCLUSIONS

This population-based cohort study suggests that diabetes is an independent risk factor for PD.

The prevalence of diabetes and related complications is increasing worldwide (1,2). Accordingly, the burden on global health care related to diabetes continues to increase (1,3). Meanwhile, various therapeutic interventions for diabetes have been developed, and the clinical course and quality of life of people with diabetes have improved (4). However, it remains impossible to completely prevent the development of diabetes-related complications. Rather, the clinical significance of previously overlooked atypical complications has paradoxically increased (5).

Parkinson disease (PD) is also a major chronic disease, and its clinical significance is increasing worldwide. Damage to the dopaminergic neurons of the substantia nigra is known to be a major cause of PD, which is clinically characterized by a variety of
neurologic symptoms (6). The prevalence of PD is expected to continue to increase as human life expectancy increases (7). However, curative treatment for this disease does not currently exist, and only symptomatic management is performed. Thus, the disease burden for PD is also expected to increase in the future (8).

Various environmental and genetic factors are known to increase the risk of PD (9). In particular, recent reports have suggested that metabolic diseases, such as obesity, metabolic syndrome, and diabetes, are important risk factors for PD (10). This is because the pathophysiologic mechanism associated with insulin resistance plays an important role in the development and worsening of PD as well as diabetes (11). However, there have been conflicting results from previous epidemiologic studies on the association between diabetes and PD (12–18). Moreover, any causal relationship between diabetes and PD needs to be more clearly defined.

Considering this background, we conducted a longitudinal study to evaluate PD risk according to baseline glucose tolerance status, diabetes disease duration, and comorbidity. Specifically, we used a large cohort representative of the Korean general population to determine the risk of developing PD in subjects with normal glucose tolerance, impaired fasting glucose (IFG), and diabetes duration <5 or ≥5 years. An additional goal of this study was to determine whether a causal relationship between dysglycemia and PD exists.

**RESEARCH DESIGN AND METHODS**

**National Health Insurance Health Examination Cohort**

The Korean National Health Insurance (NHI) is a single health care insurance system that covers ~97% of the total Korean population; the remaining 3% are “medical protection” beneficiaries. Information on individuals’ use of medical facilities, prescription records, and diagnostic codes configured in the form of ICD-10 is recorded in the National Health Insurance Service (NHIS) database (19). In addition, the NHIS provides a biennial health examination program for all beneficiaries aged ≥40 years, which consists of anthropometry, a self-administered questionnaire on past medical history or health-related behavior, and laboratory tests (20). This database has been considered to be representative of the Korean population and is used in research through anonymization and deidentification.

**Study Subjects**

Health examinations were conducted from 2009 to 2010, 15,168,021 NHIS database subjects were categorized into the groups according to ICD-10 codes (E11.x–E14.x), prescription records (oral and/or injectable antidiabetic medications), and fasting glucose measurements during the health screening. This definition was based on the consensus of relevant findings widely used in previous studies (21,22). The subjects were classified based on glycemic status as no diabetes (fasting glucose <100 mg/dL), IFG (fasting glucose 100–125 mg/dL), diabetes duration <5 years, and diabetes duration ≥5 years. IFG and diabetes were diagnosed according to the criteria of the American Diabetes Association (23). Among all of the subjects, there were 5,025,010 in the nondiabetes group, 2,110,252 in the IFG group, 753,796 in the diabetes duration <5 years group, and 554,293 in the diabetes duration ≥5 years group. Patients’ clinical course was assessed until December 2016, and the mean observation period was 6.3 years.

**Clinical Variables**

Anthropometric assessments of subjects were performed by health care professionals. Height, weight, waist circumference, and blood pressure (systolic and diastolic) were assessed. Detailed information on the lifestyle of subjects was obtained through standardized self-reported questionnaires. Subjects were classified according to smoking status as nonsmoker, former smoker, or current smoker. Individuals who consumed 30 g of alcohol per day were classified as being heavy alcohol consumers (24). Regular physical activity was defined as performance of strenuous exercise for at least 20 min (once per week) (10). Baseline comorbidities (hypertension, dyslipidemia, cardiovascular disease, and cerebrovascular disease) of subjects were identified based on a combination of the past medical history questionnaires, ICD-10 codes, and data from the prescription database.

Blood sampling was conducted after overnight fasting, and serum glucose, total cholesterol, triglyceride, HDL cholesterol, LDL cholesterol, and creatinine concentrations were measured. The estimated glomerular filtration rate (eGFR) of subjects was calculated using the MDRD Study equation: eGFR = 175 × serum creatinine − 1.154 × age − 0.203, further multiplied by 0.742 for women (25). We defined chronic kidney disease (CKD) as an eGFR <60 mL/min/1.73 m² (26).

**Identification of New PD Cases**

The policy of NHI in Korea enhanced the health coverage for rare or incurable diseases, including PD, since 2006. To receive the benefits of reduced payment for PD-related management, physicians need to determine whether patients can be correctly diagnosed with PD based on...
their clinical condition. For this reason,
new PD cases were identified as those
with an ICD-10 code for PD (G20) and
registered as rare or incurable disease
cases for PD (V124, a special code for PD).
The V124 code is independent of the ICD-
10 code and is assigned at the specialist’s
discretion, taking into account various
clinical situations. The criteria for the V124
code are as follows: 2) satisfy the criteria
for the diagnosis of parkinsonian syn-
drome, including mild or worse bradyki-
nesia, 2) satisfy the exclusion criteria for
PD, and 3) satisfy the supportive prospec-
tive positive criteria for PD, including re-
sponsiveness to levodopa. The V124 code
criteria for PD are almost identical to the
UK Parkinson’s Disease Society Brain
Bank diagnostic criteria (27). Moreover,
this definition for new PD cases has been
used and validated in many previous
studies (10,28,29).

Statistical Analysis
Basic characteristics of subjects are ex-
pressed as mean ± SD for continuous
variables in each subgroup and as the
number and percentage for categorical
variables. The cumulative incidence of PD
in each subgroup of subjects was calcu-
lated using the Kaplan-Meier curve, and
statistical significance was assessed using
the log-rank test. The incidence of PD
among subjects was calculated by di-
viding the event occurrence in each
group of the cohort by 1,000 person-
years (PY). The hazard ratio (HR) and 95% CI
for PD for each group were calculated
using Cox proportional hazards analyses.
Model 1 was used to calculate the un-
adjusted HR; model 2 was adjusted for
age and sex; model 3 was further ad-
justed for the subject’s BMI, smoking
status, drinking status, and physical ac-
tivity; and model 4 was used to assess the
competing risk of death (30). Further
analyses were performed to consider changes in the glucose tolerance status of
subjects during the observation period
and to verify lagged effects on outcome.
In addition, we examined the effect of
diabetes on the incidence of PD by
performing stratified analyses in consid-
eration of cardiovascular disease, cere-
brovascular disease, and CKD status of
subjects. We also examined the differ-
ences in the incidence of PD based on
baseline antidiabetic medication use in
the subgroup with diabetes. Statistical
analyses were performed using SAS 9.2
software (SAS Institute, Cary, NC). P <
0.05 was considered statistically significant.

Ethics Statement
This study was approved by the Kangbuk
Samsung Medical Center Institutional
Review Board (no. KBSMC 2018-12-016),
Seoul, Korea. The Institutional Review Board
waived the requirement for informed con-
sent because deidentified information was
used for the analyses.

RESULTS
Baseline Characteristics
Baseline characteristics of the subjects
are described in Table 1. The mean age
increased with the deterioration of glu-
cose tolerance. The proportion of men
was higher in the IFG and diabetes groups
than in the nondiabetes group. There
were no pronounced differences in BMI
between the groups, but waist circum-
ference was significantly lower in the
nondiabetes group. Fasting blood glu-
cose levels of subjects significantly in-
creased according to the deterioration of
glucose tolerance. In addition, the pro-
portion of subjects with a comorbidity,
such as obesity, dyslipidemia, CKD, car-
diovascular disease, and cerebrovascular
disease, was also significantly different
between groups. The characteristics of
subjects not included in this study are also
summarized in Supplementary Table 1.

Cumulative Incidence Among Groups
During the observation period of
49,076,148.74 PY, 362,560 deaths and
31,577 cases of PD were recorded (Table
2 and Supplementary Table 2). The in-
cidence of death in all subjects was 7.39
per 1,000 PY, and the mortality rate
among IFG and diabetes subjects was
significantly higher than that among sub-
jects without diabetes. The incidence of
PD with or without diabetes was 0.558
and 1.134 per 1,000 PY, respectively (P <
0.001). When the subjects were com-
pared according to glucose tolerance and
diabetes duration, the incidence of PD
was 0.521 in the nondiabetes group,
0.633 in the IFG group, 0.865 in the
diabetes duration <5 years group, and
1.522 in the diabetes duration ≥5 years
group. These results were statistically
significant (P < 0.001). The cumulative
incidence of PD in each group was cal-
culated using the Kaplan-Meier curve
(Fig. 2). The log-rank test also showed a
significant difference in the incidence of
PD between the groups (P < 0.001).

HR and Adjusted HR for PD
The risk of PD was calculated for subjects
with or without diabetes (Table 2). The
nonadjusted HR for PD in the diabetes
group was significantly higher (HR 2.036
[95% CI 1.985–2.087]) than in the group
without diabetes. In the comparison be-
tween the four subgroups according to
comorbidities.

Additional Analyses Considering Major
Comorbidities
The HR for PD was further analyzed based
on the subjects’ major comorbidities and
the presence of diabetes (Supplementary
Table 5). These results indicated that the
presence of cardiovascular disease, ce-
brovascular disease, and CKD among
the subjects significantly increased the
HR for PD. Moreover, the presence of
diabetes further increased the HR for PD
regardless of the subjects’ comorbidities.
The aHR for subjects without baseline
cardiovascular disease but with diabetes
was 1.356 (95% CI 1.296–1.419) in model
3, whereas that for subjects with base-
line cardiovascular disease and diabe-
tes was 1.622 (95% CI 1.514–1.738).
Furthermore, the aHR for subjects without baseline cerebrovascular disease but with diabetes was 1.565 (95% CI 1.470–1.667) in model 3, whereas that for subjects with baseline cerebrovascular disease was 1.816 (95% CI 1.643–2.008). In addition, the aHR for PD among subjects with an eGFR < 1.73 m² and diabetes was 1.512 (95% CI 1.420–1.613) in model 3, whereas that for subjects with other oral medications. Antidiabetic medications significantly increased the HR for PD. In particular, the aHR with insulin was 1.599 (95% CI 1.506–1.698) in model 3, which was higher than that with other oral medications.

**CONCLUSIONS**

In this study, we analyzed data from 8,443,351 subjects in the NHIS cohort with an average observation period of 6.3 years and identified the risk of PD according to baseline glucose tolerance status. We found that the risk of PD significantly increased with the degree of hyperglycemia and the duration of diabetes. In particular, our findings indicated that the risk of PD was significantly increased not only in subjects with diabetes but also in subjects with IFG. These results were consistent after adjusting for various confounders and the competing risk of death.

**DiabetesCare**

Diabetes has been suggested to increase the risk of PD; however, a definite conclusion has not yet been reached in this regard. This is because the results of many studies are controversial. In a prospective analysis of ~290,000 patients in the U.S. NIH-AARP Diet and Health Study, the odds ratio of PD in patients with diabetes was 1.41 (95% CI 1.20–1.66) (12). In a retrospective study using data from ~140,000 subjects from the National Health Insurance Research Database in Taiwan, the aHR for the incidence of PD in the cohort with diabetes was 1.19 (95% CI 1.08–1.32) (13). A recent U.K. large-scale claim-based study also found that the HR for PD in a cohort with diabetes was 1.32 (95% CI 1.29–1.35) (14). However, a prospective cohort study of ~140,000 patients in the Cancer Prevention Study II Nutrition Cohort revealed that the combined relative risk of PD among patients with a history of diabetes was 0.88 (95% CI 0.62–1.25) (15). Although these cohort findings had the advantage of identifying causality, these studies were designed with the aim of identifying any causality between diabetes and PD as the primary goal.

| Table 1—Baseline characteristics of the study subjects |
|-----------------|-----------------|-----------------|
| Variables       | No diabetes     | IFG             | Diabetes duration < 5 years | Diabetes duration ≥ 5 years |
| Age (years)     | 54.46 ± 10.74   | 56.25 ± 10.77   | 58.83 ± 10.5                  | 62.78 ± 9.6                  |
| Sex (male)      | 2,249,965 (44.78) | 1,190,543 (56.42) | 445,571 (59.16)               | 296,079 (53.42)               |
| Height (cm)     | 161.02 ± 8.84   | 162.2 ± 9.02    | 161.82 ± 9.08                 | 160.57 ± 8.97                 |
| Weight (kg)     | 61.76 ± 10.36   | 64.85 ± 10.83   | 66.32 ± 11.19                 | 63.79 ± 10.56                 |
| BMI (kg/m²)     | 23.74 ± 2.97    | 24.57 ± 3.07    | 25.26 ± 3.26                  | 24.68 ± 3.14                  |
| Waist circumference (cm) | 80.19 ± 8.44 | 83.2 ± 8.32     | 85.87 ± 8.32                  | 85.24 ± 8.25                  |
| SBP (mmHg)      | 122.94 ± 15.3   | 127.55 ± 15.36  | 129.58 ± 15.69                | 129.12 ± 15.87                |
| DBP (mmHg)      | 76.49 ± 10.04   | 79.03 ± 10.06   | 79.61 ± 10.08                 | 77.59 ± 9.88                  |
| Fasting glucose level (mg/dL) | 88.80 ± 7.20 | 108.11 ± 6.63   | 140.44 ± 40.74                | 143.7 ± 49.58                 |
| Total cholesterol level (mg/dL) | 197.10 ± 35.70 | 203.45 ± 37.68 | 198.43 ± 41.57                | 180.45 ± 40.17                |
| Rural area      | 2,805,985 (55.84) | 1,777,483 (55.8) | 423,630 (56.2)               | 311,414 (56.18)               |
| Current smoker  | 918,695 (18.28) | 447,183 (21.19) | 180,542 (23.95)               | 101,328 (18.28)               |
| Regular exercise| 2,464,397 (49.04) | 1,053,945 (49.94) | 362,671 (48.11)              | 260,368 (46.97)               |
| Obesity         | 1,575,978 (31.36) | 890,560 (42.87) | 383,711 (50.9)                | 236,836 (42.73)               |
| Dyslipidemia    | 1,060,104 (21.1) | 609,149 (28.87) | 323,272 (43.41)               | 260,207 (46.94)               |
| CKD             | 349,643 (6.96)  | 183,634 (8.7)   | 80,323 (10.66)                | 96,463 (17.4)                 |
| Cardiovascular disease | 172,593 (3.43) | 92,993 (4.41) | 41,169 (5.46)                 | 42,072 (7.59)                 |
| Cerebrovascular disease | 82,856 (1.65) | 44,949 (2.13) | 17,601 (2.33)                 | 18,469 (3.33)                 |
| Metformin       | —                | —               | 344,561 (45.71)               | 395,444 (71.34)               |
| Sulfonylurea    | —                | —               | 311,217 (41.29)               | 415,202 (74.91)               |
| Meglitinide     | —                | —               | 15,568 (2.07)                 | 28,137 (5.08)                 |
| Thiazolidinedione | —                | —               | 48,084 (6.38)                 | 74,590 (13.46)                |
| Dipeptidyl peptidase 4 inhibitor | — | — | 46,881 (6.22) | 54,495 (9.83) |
| α-Glucosidase inhibitor | — | — | 65,981 (8.49) | 150,253 (27.11) |
| Insulin         | —                | —               | 43,470 (5.77)                 | 101,585 (18.33)               |

Data are presented as n (%) or mean ± SD. DBP, diastolic blood pressure; SBP, systolic blood pressure.

**Antidiabetic Medication Use**

We estimated the HR and aHR for the incidence of PD based on baseline antidiabetic medication use in the diabetes subgroup (Supplementary Table 6). All antidiabetic medications significantly increased the HR for PD. In particular, the aHR with insulin was 1.599 (95% CI 1.506–1.698) in model 3, which was higher than that with other oral medications.
Similarly, conflicting results have been reported in meta-analyses. In one study, the relative risk of PD among individuals with a past history of diabetes estimated based on four cohort studies (total of 32,695 subjects with diabetes and 501,239 subjects without diabetes) was significantly higher (1.37; 95% CI 1.21–1.55) than the risk among subjects without diabetes (16). In another meta-analysis based on seven population-based cohorts (total of 1,761,632 subjects), the adjusted relative risk for PD among patients with diabetes was 1.38 (95% CI 1.18–1.62), which was significantly higher than the risk among subjects without diabetes (17). However, in a study conducted by Cereda et al. (16), the odds ratio of PD among subjects with diabetes estimated from case–control studies (1,387 subjects with diabetes and 6,953 PD subjects from a total of 22,359 subjects) was 0.75 (95% CI 0.50–1.11). In addition, another meta-analysis based on 14 studies (21,397 PD subjects and 84,579 control subjects) showed that diabetes had a negative association (odds ratio 0.75; 95% CI 0.58–0.98) with PD (18). These meta-analyses were limited in that the designs of the studies included in the analysis were heterogeneous. Thus, these results imply that more research is needed to confirm any causal relationship between diabetes and the incidence of PD.

Our results provide further evidence supporting previous findings that the risk of PD is increased in patients with diabetes. In particular, our finding that the risk of PD increases owing to IFG, a nondiabetic hyperglycemic status, is a novel finding. From this result, it is possible to deduce that the incidence of PD is proportional to the degree or duration of exposure to hyperglycemia rather than simply being dependent on the presence of diabetes per se. In fact, a longer diabetes duration has been identified as an important factor that significantly increases the risk of PD in diabetes (31). Thus, the increased risk

Table 2—Comparison of the incidence of PD according to the subjects’ diabetes status

| Group                              | PYS     | Events (n) | Incidence per 1,000 PY | HR (95% CI)           | Model 1* | Model 2** | Model 3*** | Model 4**** |
|------------------------------------|---------|------------|------------------------|-----------------------|---------|-----------|------------|-------------|
| No diabetes vs. diabetes           |         |            |                        |                       |         |           |            |             |
| No diabetes                        | 41,773,272.48 | 23,299     | 0.55775                | 1.00 (ref.)           | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| Diabetes                           | 7,302,876.27 | 8,278      | 1.13353                | 2.036 (1.985–2.087)   | 1.389 (1.354–1.424) | 1.372 (1.337–1.407) | 1.337 (1.304–1.374) |
| IFG vs. diabetes                    |         |            |                        |                       |         |           |            |             |
| IFG                                | 12,276,937.07 | 7,772     | 0.63306                | 1.00 (ref.)           | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| Diabetes                           | 7,302,876.27 | 8,278      | 1.13353                | 1.794 (1.739–1.850)   | 1.356 (1.314–1.398) | 1.356 (1.315–1.399) | 1.329 (1.288–1.371) |
| Diabetes duration <5 years         | 4,345,219.48 | 3,757      | 0.86463                | 1.366 (1.314–1.420)   | 1.151 (1.107–1.197) | 1.153 (1.109–1.199) | 1.134 (1.090–1.179) |
| Diabetes duration ≥5 years         | 3,122,274.66 | 4,752      | 1.52197                | 2.416 (2.331–2.505)   | 1.581 (1.525–1.639) | 1.576 (1.520–1.634) | 1.538 (1.482–1.595) |
| All subgroups                       |         |            |                        |                       |         |           |            |             |
| No diabetes                        | 29,331,717.53 | 15,296     | 0.52148                | 1.00 (ref.)           | 1.00 (ref.) | 1.00 (ref.) | 1.00 (ref.) |
| IFG                                | 12,276,937.07 | 7,772     | 0.63306                | 1.214 (1.181–1.248)   | 1.049 (1.020–1.078) | 1.038 (1.009–1.067) | 1.037 (1.030–1.066) |
| Diabetes                           | 7,302,876.27 | 8,278      | 1.13353                | 1.657 (1.599–1.718)   | 1.203 (1.161–1.247) | 1.185 (1.143–1.229) | 1.158 (1.115–1.202) |
| Diabetes duration <5 years         | 4,345,219.48 | 3,757      | 0.86463                | 1.657 (1.599–1.718)   | 1.203 (1.161–1.247) | 1.185 (1.143–1.229) | 1.158 (1.115–1.202) |
| Diabetes duration ≥5 years         | 3,122,274.66 | 4,752      | 1.52197                | 2.933 (2.839–3.030)   | 1.646 (1.593–1.701) | 1.618 (1.566–1.672) | 1.571 (1.519–1.624) |

*Model 1: nonadjusted. **Model 2: adjusted for age and sex. ***Model 3: adjusted for factors in model 2 and BMI, smoking, drinking, and physical activity. ****Model 4: considers competing risk of death in addition to the results of model 3.
of PD in subjects with prediabetes and diabetes is likely to vary according to the degree of glycemic burden. Therefore, our findings may indirectly explain why previous studies have found conflicting results. The mechanism underlying the association of diabetes with the increased incidence of PD has not yet been elucidated. However, mitochondrial dysfunction, endoplasmic reticulum stress, chronic low-grade inflammation, and alterations in metabolism are thought to cause insulin resistance and ultimately neurodegenerative disorders as well as diabetes (11,32). One study confirmed the upregulation of amyloid precursor protein levels before an increase in insulin resistance and neurodegeneration, confirming the existence of a shared, dysregulated molecular pathway between the two diseases (33).

These postulated mechanisms suggest that antidiabetic interventions, including the improvement of insulin resistance, may help achieve good clinical outcomes among subjects at high risk of developing neurodegenerative disorders, including PD, among those with diabetes and prediabetes. Recently, a double-blind, randomized, controlled study on the effects of glucagon-like peptide 1 agonists in PD subjects showed a positive effect in the intervention group (34). However, these findings are still difficult to generalize, and therefore require further validation through larger-scale intervention and long-term follow-up studies. In addition, all antidiabetic medication users in this study had a high aHR for PD. However, subjects’ use of antidiabetic medications should be interpreted as reflecting their insulin resistance and high glycemic burden. Care should be taken while interpreting the results, as drug use does not imply a substantial intervention in the disease mechanism during the observation period in subjects.

This study has some limitations. First, because this study was based on claims and health checkup data, the sampling is likely to be inaccurate in contrast to that in a directly sampled cohort. Second, there were many missing variables that could affect the analysis results. Third, owing to the nature of national health screening, prediabetes status, other than IFG, was not considered sufficiently. Fourth, the use of medical services may vary based on the health priorities of subjects according to the baseline comorbid condition, thus leading to differences in the rate of diagnosis of PD. Finally, the exact mechanism underlying the increased PD risk in subjects with diabetes is difficult to ascertain based on the findings. This study was, however, based on a large cohort representative of the entire population of Korea, and such large-scale cohort studies are extremely rare. In addition, this study overcame the simplicity of claim-based research and used detailed characteristics of the subjects based on clinical information such as anthropometric parameters, past medical history, lifestyle, and blood chemistry results. Moreover, it is possible to make accurate outcome judgments using the V124 special code, as well as the ICD-10 diagnostic code, based on characteristics of the Korean health insurance system. This system allowed us to selectively exclude PD subjects from the baseline cohort and to determine exact outcomes. In addition to the large number of subjects, an average of 6.3 years of observation allowed us to more rigorously examine the causality of dysglycemia and PD in contrast to other studies. Thus, the results of this study suggest that diabetes and prediabetes are both important factors contributing to the incidence of PD.

In conclusion, our population-based cohort study clearly suggests that diabetes is an independent risk factor for the development of PD. In the future, more detailed mechanistic studies on the relationship between diabetes and PD should be performed, and an effective method for the prevention of PD should be determined.

Acknowledgments. The authors thank Jeong-Taeck Woo and Young Seol Kim of Kyung Hee University for their exceptional teaching and inspiration, which encouraged the authors to conduct the current study. This study used the National Health Screening Cohort data (NHIS-2019-1-133) from the National Health Insurance Service.

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. S.Y.R. drafted the manuscript and interpreted the results. H.K., S.-E.P., Y.-G.P., Y.-H.K., and S.-J.Y. analyzed and interpreted the results. H.K., S.-E.P., and S.-J.Y. contributed to the study design and interpreted the results. E.-J.R. and W.-Y.L. conceived the study and interpreted the results. E.-J.R. and W.-Y.L. finally approved the manuscript. W.-Y.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References
1. Cho NH, Shaw JE, Karuranga S, et al. IDF Diabetes Atlas: global estimates of diabetes prevalence for 2017 and projections for 2045. Diabetes Res Clin Pract 2018;138:271–281.
2. Zheng Y, Levy SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol 2018;14:88–98.
3. Yoon J, Oh IH, Seo H, et al. Disability-adjusted life years for 313 diseases and injuries: the 2012 Korean Burden of Disease Study. J Korean Med Sci 2016;31(Suppl. 2):S146–S157.
4. Andrésdóttir G, Jensen ML, Carstensen B, et al. Improved survival and renal prognosis of patients with type 2 diabetes and nephropathy with improved control of risk factors. Diabetes Care 2014;37:1660–1667.
5. Lamberts SW, Romijn JA, Wiersinga WM. The future endocrine patient. Reflections on the future of clinical endocrinology. Eur J Endocrinol 2003;149:169–175.
6. Poewe W, Seppi K, Tanner CM, et al. Parkinson disease. Nat Rev Dis Primers 2017;3:17013.
7. Kalila LV, Lang AE. Parkinson’s disease. Lancet 2015;386:896–912.
8. GBD 2016 Parkinson’s Disease Collaborators. Global, regional, and national burden of Parkinson’s disease, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2018;17:939–953.
9. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson’s disease: risk factors and prevention. Lancet Neurol 2016;15:1257–1272.
10. Nam GE, Kim SM, Han K, et al. Metabolic syndrome and risk of Parkinson disease: a nationwide cohort study. PLoS Med 2018;15:e1002640.
11. Santiago JA, Potashkin JA. Shared dysregulated pathways lead to Parkinson’s disease and diabetes. Trends Mol Med 2013;19:176–186.
12. Xu Q, Park Y, Huang X, et al. Diabetes and risk of Parkinson’s disease. Diabetes Care 2011;34:910–915.
13. Yang YW, Hsieh TF, Li CJ, et al. Increased risk of Parkinson disease with diabetes mellitus in a population-based study. Medicine (Baltimore) 2017;96:e5921.
14. Pagano G, Polychronis S, Wilson H, et al. Diabetes mellitus and Parkinson disease. Neurology 2018;90:e1654–e1662.
15. Palacios N, Gao X, McCullough ML, et al. Obesity, diabetes, and risk of Parkinson’s disease. Mov Disord 2011;26:2253–2259.
16. Cereda E, Barichella M, Pedrolli C, et al. Diabetes and risk of Parkinson’s disease: a systematic review and meta-analysis. Diabetes Care 2011;34:2621–2623.
17. Yue X, Li H, Yan H, Zhang P, Chang L, Li T. Risk of Parkinson disease in diabetes mellitus: an updated meta-analysis of population-based cohort studies. Medicine (Baltimore) 2016;95:e5349.
18. Liu L, Fu DL, Li HQ, Liu AJ, Li JH, Zheng GQ. Diabetes and risk of Parkinson’s disease: an updated meta-analysis of case-control studies. PLoS One 2014;9:e85781.
19. Shin DW, Cho B, Guallar E. Korean National Health Insurance Database. JAMA Intern Med 2016;176:138.
20. Seong SC, Kim YH, Park SK, et al. Cohort profile: the National Health Insurance Service-National
Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open 2017;7:e016640
21. Lee YH, Han K, Ko SH, Ko KS, Lee KU; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Data analytic process of a nationwide population-based study using National Health Information Database established by National Health Insurance Service. Diabetes Metab J 2016;40:79–82
22. Ko SH, Han K, Lee YH, et al.; TaskForce Team for the Diabetes Fact Sheet of the Korean Diabetes Association. Past and current status of adult type 2 diabetes mellitus management in Korea: a National Health Insurance Service database analysis. Diabetes Metab J 2018;42:93–100
23. American Diabetes Association. 2. Classification and diagnosis of diabetes: Standards of Medical Care in Diabetes—2018. Diabetes Care 2018;41(Suppl. 1):S13–S27
24. Agarwal DP. Cardioprotective effects of light-moderate consumption of alcohol: a review of putative mechanisms. Alcohol Alcohol 2002;37:409–415
25. Levey AS, Coresh J, Greene T, et al.; Chronic Kidney Disease Epidemiology Collaboration. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate [published correction appears in Ann Intern Med 2008;149:519]. Ann Intern Med 2006;145:247–254
26. Levey AS, Coresh J, Balk E, et al.; National Kidney Foundation. National Kidney Foundation practice guidelines for chronic kidney disease: evaluation, classification, and stratification [published correction appears in Ann Intern Med 2003;139:605]. Ann Intern Med 2003;139:137–147
27. Gibb WR, Lees AJ. The relevance of the Lewy body to the pathogenesis of idiopathic Parkinson’s disease. J Neurol Neurosurg Psychiatry 1988;51:745–752
28. Park JH, Kim DH, Park YG, et al. Cancer risk in patients with Parkinson’s disease in South Korea: a nationwide, population-based cohort study. Eur J Cancer 2019;117:5–13
29. Nam GE, Kim NH, Han K, et al. Chronic renal dysfunction, proteinuria, and risk of Parkinson’s disease in the elderly. Mov Disord 2019;34:1184–1191
30. Andersen PK, Geskus RB, de Witte T, Putter H. Competing risks in epidemiology: possibilities and pitfalls. Int J Epidemiol 2012;41:861–870
31. De Pablo-Fernandez E, Sierra-Hidalgo F, Benito-León J, Bermejo-Pareja F. Association between Parkinson’s disease and diabetes: data from NEDICES study. Acta Neurol Scand 2017;136:732–736
32. Craft S, Watson GS. Insulin and neurodegenerative disease: shared and specific mechanisms. Lancet Neurol 2004;3:169–178
33. Santiago JA, Potashkin JA. Integrative network analysis unveils convergent molecular pathways in Parkinson’s disease and diabetes. PLoS One 2013;8:e83940
34. Athauda D, Maclagan K, Skene SS, et al. Exenatide once weekly versus placebo in Parkinson’s disease: a randomised, double-blind, placebo-controlled trial. Lancet 2017;390:1664–1675