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ORIGINAL ARTICLE

The Association between the Triglyceride-Glucose Index and the Incidence Risk of Parkinson's Disease: A Nationwide Cohort Study

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ABSTRACT

Objective We aimed to investigate the associations of the triglyceride-glucose index, which measures insulin resistance, and the incidence of Parkinson's disease.

Methods Our study used the Health Screening Cohort database of the National Health Insurance Service of South Korea (2002–2019). We included 310,021 participants who had no previous history of Parkinson's disease and for whom more than 3 triglyceride-glucose index measurements were available. A diagnosis of Parkinson's disease was determined via the International Classification of Diseases Tenth edition (G20) with a specific reimbursement code for rare intractable diseases and a history of prescriptions for anti-Parkinsonism drugs.

Results During a median of 9.64 years (interquartile range 8.72–10.53), 4,587 individuals (1.5%) had Parkinson's disease. Based on a multivariable time-dependent Cox proportional hazards model, a per-unit increase in triglyceride-glucose index score was associated with a significantly increased risk of Parkinson's disease (hazard ratio [HR]: 1.062; 95% confidence interval [CI] 1.007–1.119). In a sensitivity analysis, the triglyceride-glucose index was associated with the incidence of Parkinson's disease in a non–diabetes mellitus cohort (HR: 1.093; 95% CI 1.025–1.165), but not in the diabetes mellitus cohort (HR: 0.990; 95% CI 0.902–1.087). In a restricted cubic spline analysis, the association between the triglyceride-glucose index and the incidence risk of Parkinson's disease showed a nonlinear increasing (J-shaped) trend.

Conclusion Our study demonstrated that higher triglyceride-glucose index scores were associated with the incidence of Parkinson's disease in the general population, particularly in a nondiabetic mellitus cohort.

Keywords Insulin resistance; Triglyceride-glucose index; Parkinson's disease; Diabetes mellitus.

INTRODUCTION

Parkinson's disease (PD) is the second most frequently diagnosed neurodegenerative condition.[1,2] It predominantly affects people over the age of 60, with approximately 1% of this age group affected globally. The likelihood of developing PD increases with age. This disease progresses over time and is characterized by the deterioration of dopaminergic neurons in the nigrostriatal pathway, which leads to distinctive motor function–related symptoms such as rigidity, tremors, and bradyki-

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nesia. There is increasing evidence that the development of PD can begin up to two decades before motor symptoms become evident. Imaging studies and pathological examinations indicate that degeneration in the nigrostriatal region can be identified 5 to 10 years before motor symptoms become clinically apparent.[3,4] In the phase leading to noticeable neurodegeneration, PD is believed to undergo several stages that collectively form a molecular prodrome.[4,5] Despite the demonstrated efficacy of numerous compounds in laboratory or animal models, to date, none have been shown to be effective in altering the progression of PD in clinical trials.

Insulin resistance is a common metabolic disorder that is commonly linked with type 2 diabetes mellitus (DM).[6] This condition occurs when the body's cells become less responsive to insulin, a hormone essential for regulating blood sugar levels.[7] The implications of insulin resistance extend beyond DM and can affect a wide range of metabolic issues; it is closely associated with various conditions or poor prognoses, such as hypertension, dyslipidemia, liver diseases, cardiovascular diseases, certain types of cancer, obesity, and inflammatory and infectious diseases.[7-11] In recent years, the association between insulin and PD has attracted increasing research attention. Insulin, which is widely known for its role in managing blood glucose levels, also appears to have a protective effect on the brain. Insulin receptors are present in brain regions such as the basal ganglia and substantia nigra.[12] Growing evidence indicates that insulin sensitivity and resistance are crucial for maintaining neuronal health and growth, supporting dopamine-related neural transmission, and preserving synaptic connections in the brain.[13]

The triglyceride-glucose (TyG) index, which is calculated by fasting triglyceride (TG) and fasting blood glucose (FBG) levels, serves as a simple and practical surrogate marker for insulin resistance.[14] This index is easy to use and cost-effective, particularly in settings where more direct and complex measurements of insulin resistance are not readily available. It is a valuable tool for assessing metabolic health in various clinical settings and for identifying individuals at risk of developing complications associated with insulin resistance.[9,15] However, the association between insulin resistance and the risk of incident PD has rarely been investigated, and studies using repeatedly measured parameters in the general population are limited. We hypothesize that a higher TyG index score is associated with the development of PD. Our study aimed to investigate the association of the TyG index with the incidence risk of PD in a longitudinal setting in the general population.

MATERIALS & METHODS

Data source

This study sourced data from the National Health Insurance Service (NHIS) Health Screening Cohort (HEALS) database. As a government program, the NHIS provides health insurance to nearly 97% of the Korean population. It also provides a nationwide free health screening program every 2 years for all South Korean adults aged 40 years and over. The Medical Aid program, an affiliate of the NHIS, attends to 3% of the population not covered by the NHIS. Our study used the NHIS-HEALS cohort database for 2002–2019.[16] The NHIS-HEALS database includes measurements of blood pressure, body mass index (BMI), and blood biochemistry; the results of a self-administered questionnaire on medical history; and lifestyle records for smoking, alcohol consumption, and physical activity. Health claim data covering all hospital visits, diagnoses, surgeries, medical procedures, and prescriptions of participants from 2002 to 2019 are also included. Diagnoses at each hospital visit were recorded based on the International Classification of Disease, Tenth Revision (ICD-10). Demographic information such as sex, age, and household income was provided, and data regarding participants' health claims, insurance coverage maintenance, and deaths were available up to December 31, 2019.

Study population

From the NHIS-HEALS database, we included participants aged 40 years and older who participated in the national health screening program during the baseline years of 2009 and 2010. Among these 362,285 potential participants, those for whom data on demographic details, lifestyle, and laboratory findings were missing (n=9,047) were excluded from the study. The washout period extended from 2002 to the index date, during which patients with a history of PD were excluded (n=2,388). Participants with a follow-up duration of less than 1 year (n=56) (to avoid reverse causality or association) and those with fewer than 3 repeated measurements (n=40,773) were excluded. After applying these inclusion and exclusion criteria, the final cohort for analysis comprised 310,021 participants (Figure 1).

Data collection and definitions

Details of the participants' age, sex, BMI, waist circumference, household income, and lifestyle habits (smoking status, alcohol consumption, and regular physical activity) were collected through self-report questionnaires. BMI was calculated as weight (kg) divided by the square of height (m^2). Household income was categorized using quantiles of individuals' health insurance premiums, with those in the ninth decile and above considered high income. Smoking status was categorized into never,

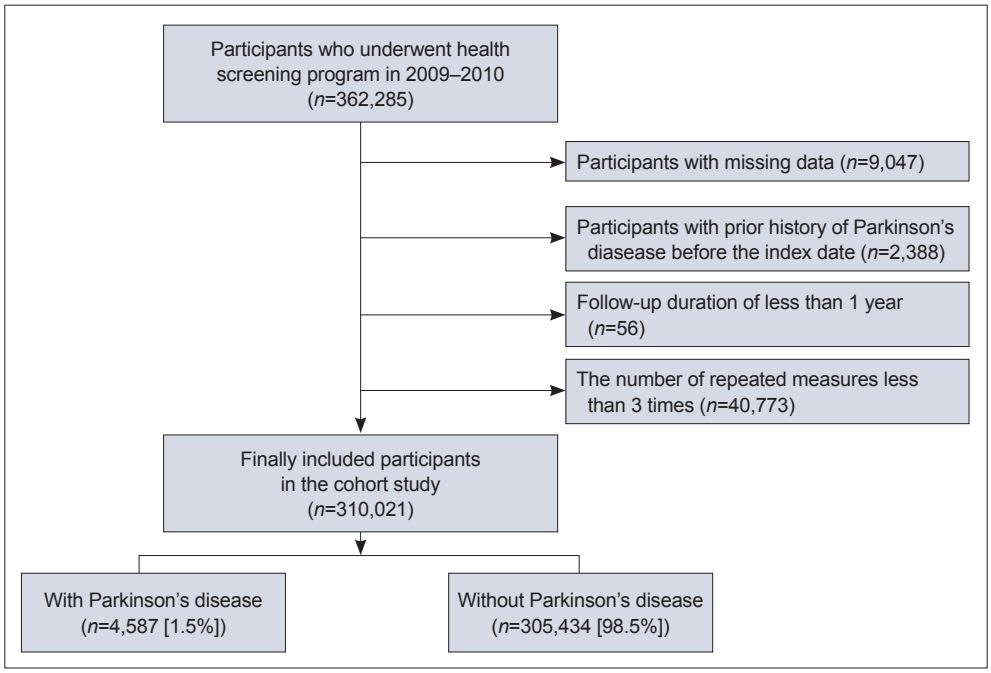


Figure 1. Flowchart of the inclusion and exclusion criteria.

former, and current smokers. The frequency of alcohol consumption was defined as the number of times alcohol was consumed per week (0, 1–2 times, 3–4 times, and ≥5 times). The frequency of regular physical activity was based on the number of days the participants engaged in exercise per week (0, 1–4 days, and ≥5 days). Biochemical measurements, including liver enzyme, lipid, and FBG levels, were collected from the health screening laboratory results. Hypertension, DM, dyslipidemia, renal disease, and liver disease were considered comorbidities, and the Charlson comorbidity index (CCI) was used to determine the burden of covariates. Information on the use of statins and antidiabetic medications (alpha-glucosidase inhibitors, sulfonylureas or meglitinides, dipeptidyl peptidase-4 [DPP-4] inhibitors, glucagon-like peptide-1 [GLP-1] agonists, sodium-glucose cotransporter-2 [SGLT2] inhibitors, biguanides, insulin, and thiazolidinedione) was collected. Detailed definitions for these can be found in the Supplementary Materials (in the online-only Data Supplement).[17-21]

Calculation of the TyG index

The TyG index was calculated as ln ([TG level]×[FBG level]/2).[9,22] In this study, the TyG index was considered a time-dependent covariate throughout the follow-up period. For further analysis, the average of repeated measures of the TyG index, calculated using values from at least three repeated measurements to reduce bias in the average value, was also utilized as a variable.

Outcome

Individuals were identified as having PD based on at least two or more related claims, with the initial date of diagnosis being noted. A diagnosis of PD was determined via the ICD-10 code of G20 and a reimbursement code of V124 for rare intractable diseases (RIDs) used by neurologists, neurosurgeons, or specialists in rehabilitation medicine, with a minimum of one annual claim for both hospital admissions and outpatient visits, along with a prescription history for any PD medication, such as amantadine, anticholinergics, catechol-O-methyltransferase inhibitors, dopamine agonists, or carbidopa/levodopa, selegiline, and rasagiline. To exclude cases of secondary parkinsonism, individuals with diagnoses of both PD (G20) and parkinsonism (G21–26) were not included as an incidence of PD.[23] Participants who have an RID must have their diagnoses confirmed by a physician using the standard diagnostic criteria provided by the NHIS. Following a physician's evaluation, the health care facility also examines the diagnosis prior to submitting it to the NHIS. This structured procedure guarantees the reliability of the data related to RIDs. The date of diagnosis for PD was considered the first prescription of anti-PD medication referred to from relevant ICD-10 codes on the claim record. Follow-up was carried out until December 31, 2019, death, or the first occurrence of PD.

Statistical analysis

Comparisons between groups based on quartiles of the TyG index were made via one-way analysis of variance for continu-

ous variables and chi-square tests (or Fisher's exact test) for categorical variables. Survival curves for the time-to-event outcomes were plotted via Kaplan–Meier curves, and a log-rank test was used to compare the survival curves across TyG index groups. To explore the linear relationship between the TyG index per standard deviation (x-axis) and the incidence of PD (y-axis), restricted cubic splines were applied. The optimal change point in the spline curve analysis was estimated via a regression model with piecewise linear relationships.

To evaluate the incidence risk of PD in relation to repeated measurements of the TyG index during the follow-up period, a time-dependent Cox proportional hazards model was applied. The participants were divided into 3 groups based on tertiles (T1, T2, and T3) of the average TyG index during the follow-up period. To determine the risk of PD according to quartile groups, a conventional Cox proportional hazards model was used. The proportionality of the hazard assumption was evaluated via the Grambsch and Therneau test of Schoenfeld residuals, which yielded satisfactory results.

The results of time-dependent Cox regression and conventional Cox regression analyses are presented as hazard ratios (HRs) and 95% confidence intervals (CIs) for an unadjusted model, Model 1, and Model 2, depending on the adjustment of covariates. Model 1 was adjusted for age and sex, whereas Model 2 was adjusted for Model 1 plus BMI, household income, smoking status, alcohol consumption, regular physical activity, hypertension, DM, renal disease, liver disease, and CCI. Antidiabetic medication was further adjusted only for the DM cohort. Blood biomarkers, such as aspartate transaminase and alanine transaminase levels and liver disease, were not adjusted for in Model 2 because of multiple collinearity factors. For covariates, in cases where participants underwent multiple health check-ups from 2009 to 2019, data from their latest examination were used in the statistical analysis. Subgroup analyses were performed according to the presence of DM. Sensitivity analyses regarding the association of the TyG index with PD were performed according to demographic data, lifestyle habits, and covariates, suggesting *p* values for interactions. To confirm the association between anti-diabetic medication and the risk of PD, further analysis was conducted in the cohort that received anti-diabetic medication at least once during the follow-up period from the time of inclusion. In the case of combination antidiabetic drugs, each drug was considered to have been taken. In addition, a time-dependent Cox proportional hazards model was applied according to the duration of each antidiabetic medication. All the statistical analyses were conducted via SAS version 9.4 (SAS Inc.) and R version 4.2.1 (R Foundation for Statistical Computing), with statistical significance defined as a two-sided *p* value <0.05.

Ethical standards

Ethical approval and participation consent followed the Helsinki Declaration guidelines. The institutional review board of Ewha Womans University Hospital approved our study (EUMC-2022-02-018). Given that the data are accessible to the public through the NHIS database, the need for ethical approval and informed consent was waived.

RESULTS

Baseline characteristics of the participants

The number of measurements repeated during the follow-up period is described in Supplementary Table 1 (in the online-only Data Supplement), and the characteristics of the variables for each year are described in Supplementary Table 2 (in the online-only Data Supplement).

Table 1 presents the baseline characteristics of the entire cohort divided into 3 groups on the basis of the tertiles of the average TyG index score (T1: <9.129; T2: 9.129–9.539; and T3: >9.539). The members of the T2 group were older than those in the other groups were. The members of the T3 group were more likely to be male and more likely to be obese. The income level of the T3 group was lower than that of the other groups. Members of the T3 group were also more likely to be smokers and consumers of alcohol and exercise less frequently (≥ 5 days/week). With respect to laboratory data, the levels of liver enzymes, total cholesterol, triglycerides, and FBG were highest in the T3 group, and the proportions of those with comorbidities, including hypertension, DM, dyslipidemia, renal disease, liver disease, and a CCI score of 2 or more, were significantly greater in the T3 group (Table 1).

Relationship of the TyG index with incidence risk for PD

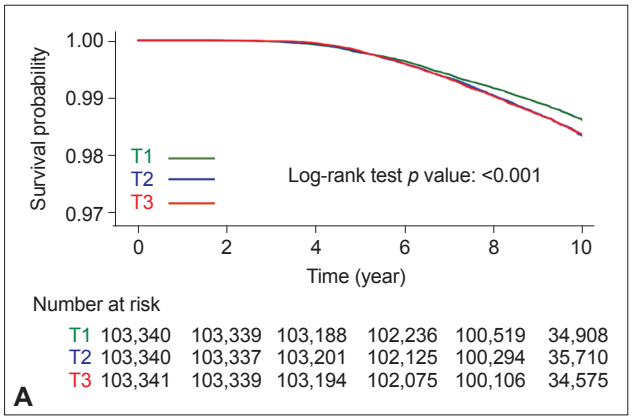
During a median of 9.64 years (interquartile range 8.72–10.53), 4,587 individuals (1.5%) experienced PD. Survival curves depicting the incidence of PD across tertiles of the average TyG index score are presented in Figure 2. The incidence of PD depended on the TyG index tertiles in the entire cohort (log-rank test: $p<0.001$) and the non-DM cohort ($p=0.002$). In contrast, the incidence of PD did not depend on TyG index tertiles in the DM cohort ($p=0.122$).

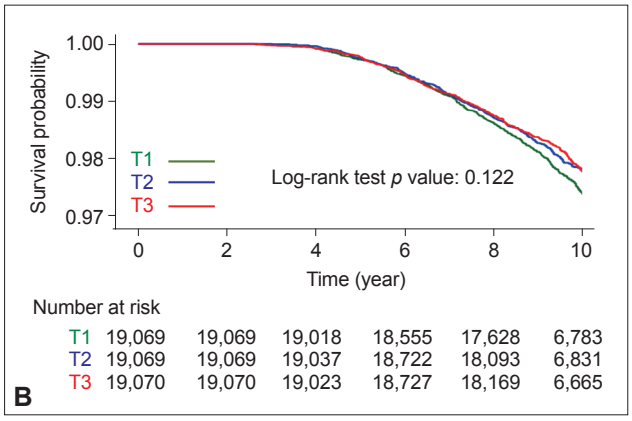
For the multivariable time-dependent Cox proportional hazards model with repeated measures of average TyG index scores, a per-unit increase in TyG index score significantly increased the risk of PD in the entire cohort (HR: 1.062; 95% CI 1.007–1.119). In the sensitivity analysis, repeated measures of average TyG index scores were associated with the incidence risk of PD in the non-DM cohort (HR: 1.093; 95% CI 1.025–1.165). Repeated

Table 1. Baseline characteristics of study participants

Variables	Total (*n*=310,021)	T1 (*n*=103,341)	T2 (*n*=103,340)	T3 (*n*=103,340)	*p* value
Age (yr)					<0.001
<65	246,238 (79.4)	84,153 (81.4)	79,956 (77.4)	82,129 (79.5)	
≥65	63,783 (20.6)	19,188 (18.6)	23,384 (22.6)	21,211 (20.5)	
Sex					<0.001
Female	142,741 (46.0)	55,597 (53.8)	49,427 (47.8)	37,717 (36.5)	
Male	167,280 (54.0)	47,744 (46.2)	53,913 (52.2)	65,623 (63.5)	
Body mass index (kg/m^2)					<0.001
<25	201,853 (65.1)	80,566 (78.0)	66,590 (64.4)	54,697 (52.9)	
≥25	108,168 (34.9)	22,775 (22.0)	36,750 (35.6)	48,643 (47.1)	
Waist circumference (cm)					<0.001
Male <90, female <85	249,265 (80.4)	92,374 (89.4)	83,164 (80.5)	73,727 (71.3)	
Male ≥90, female ≥85	60,756 (19.6)	10,967 (10.6)	20,176 (19.5)	29,613 (28.7)	
Household income					0.001
Low	197,765 (63.8)	65,639 (63.5)	65,741 (63.6)	66,385 (64.2)	
High	112,256 (36.2)	37,702 (36.5)	37,599 (36.4)	36,955 (35.8)	
Smoking status					<0.001
Never	199,495 (64.4)	75,243 (72.8)	67,956 (65.8)	56,296 (54.5)	
Former	58,781 (19.0)	17,024 (16.5)	19,438 (18.8)	22,319 (21.6)	
Current	51,745 (16.7)	11,074 (10.7)	15,946 (15.4)	24,725 (23.9)	
Alcohol consumption (days/week)					<0.001
None	185,044 (59.7)	67,040 (64.9)	63,498 (61.5)	54,506 (52.7)	
1–2 times	82,200 (26.5)	25,591 (24.8)	26,618 (25.8)	29,991 (29.0)	
3–4 times	28,073 (9.1)	6,951 (6.7)	8,684 (8.4)	12,438 (12.0)	
≥5 times	14,704 (4.7)	3,759 (3.6)	4,540 (4.4)	6,405 (6.2)	
Regular physical activity (days/week)					<0.001
None	76,285 (24.6)	24,444 (23.6)	25,960 (25.1)	25,881 (25.1)	
1–4	138,580 (44.7)	45,347 (43.9)	45,828 (44.4)	47,405 (45.9)	
≥5	95,156 (30.7)	33,550 (32.5)	31,552 (30.5)	30,054 (29.1)	
Laboratory findings					
AST (U/L)	26.3±16.2	25.1±15.4	25.7±15.4	27.9±17.4	<0.001
ALT (U/L)	25.2±18.7	21.8±17.4	24.4±17.7	29.2±20.2	<0.001
Total-C (mg/dL)	200.2±37.1	192.0±34.0	201.4±36.4	207.0±39.3	<0.001
HDL-C (mg/dL)	54.7±23.7	59.5±20.6	54.6±25.5	49.9±23.8	<0.001
LDL-C (mg/dL)	118.8±35.8	116.4±32.4	122.7±35.0	117.3±39.4	<0.001
Triglyceride (mg/dL)	137.3±83.4	81.9±32.1	125.0±48.2	204.9±98.8	<0.001
FBG (mg/dL)	100.6±24.2	92.7±13.4	98.4±18.4	110.5±32.7	<0.001
Comorbidities					
Hypertension	94,511 (30.5)	22,888 (22.2)	32,234 (31.2)	39,389 (38.1)	<0.001
Diabetes mellitus	57,208 (18.5)	7,328 (7.1)	15,709 (15.2)	34,171 (33.1)	<0.001
Dyslipidemia	50,141 (16.2)	11,161 (10.8)	16,544 (16.0)	22,436 (21.7)	<0.001
Renal disease	40,930 (13.2)	11,899 (11.5)	13,845 (13.4)	15,186 (14.7)	<0.001
Liver disease	52,228 (16.9)	15,154 (14.7)	16,884 (16.3)	20,190 (19.5)	<0.001
Charlson comorbidity index					<0.001
0	160,823 (51.9)	57,338 (55.5)	53,722 (52.0)	49,763 (48.2)	
1	128,525 (41.5)	40,258 (39.0)	43,141 (41.8)	45,126 (43.7)	
2 or more	20,673 (6.7)	5,745 (5.6)	6,477 (6.3)	8,451 (8.2)	
Use of statin					<0.001
No	267,849 (86.4)	94,456 (91.4)	89,158 (86.3)	84,235 (81.5)	
Yes	42,172 (13.6)	8,885 (8.6)	14,182 (13.7)	19,105 (18.5)	

Values are presented as number (%) or mean±standard deviation. The tertiles for the average TyG index scores are as follows: T1: <9.129; T2: 9.129–9.539; and T3:>9.539.
AST, aspartate aminotransferase; ALT, alanine aminotransferase; total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBG, fasting blood glucose; TyG, triglyceride-glucose.





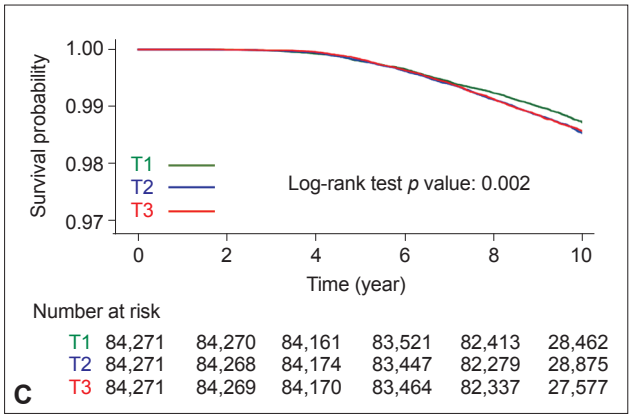


Figure 2. Kaplan–Meier survival curves of PD outcomes according to TyG index quartiles. A: Total cohort. B: Diabetes mellitus cohort. C: Non-diabetes mellitus cohort. PD, Parkinson's disease; TyG, triglyceride-glucose.

measures of average TyG index scores were not associated with the incidence risk of PD in the DM cohort (HR: 0.990; 95% CI 0.902–1.087) in fully adjusted multivariable models (Table 2 and Supplementary Table 3 in the online-only Data Supplement). In a subgroup analysis, no statistically significant interaction was found according to demographic data or covariates except for sex (Figure 3). Additionally, the multivariable Cox proportional model for average TyG index tertiles during follow-up is detailed in Table 3 and Supplementary Table 4 (in the online-only Data Supplement). The highest tertiles of the TyG index were positively associated with the incidence of PD in the entire cohort and non-DM cohort but not in the DM cohort.

Restricted cubic spline analysis (Figure 4) revealed a clear, nonlinear and increasing trend (U- or J-shaped) in the risk of PD as measured by the TyG index per standard deviation in the entire cohort and in the DM and non-DM cohorts.

In the sensitivity analysis, participants whose TyG index was less than three were analyzed (Supplementary Tables 5 and 6 in the online-only Data Supplement). A multivariate time-dependent Cox proportional hazards model of average TyG index scores and TyG index tertiles revealed a consistent association of the risk of PD with the TyG index in all participants and non-DM participants with more than one measurement. However, there was no correlation between the TyG index and the risk of PD in patients whose PD was measured less than 2 times.

Detailed information on DM medication is described in Supplementary Tables 7–10 (in the online-only Data Supplement). Among participants taking antidiabetic medications, the risk of PD was greater in the insulin group (HR: 1.161; 95% CI 1.005–1.340) than in the sulfonylurea group (Supplementary Table 11 in the online-only Data Supplement).

DISCUSSION

The key findings of our study were that the TyG index was associated with the incidence risk of PD in a general population based on a time-dependent analysis of the TyG index and a conventional Cox regression analysis with averages of the re-

Table 2. Results of risk of Parkinson's disease considering the TyG index as a time-dependent covariate

Groups	*n*	Events	Person-years	Incidence rate (per 1,000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Total	310,021	4,587	2,998,495	1.530	1.104 (1.052–1.159)	1.103 (1.049–1.160)	1.062 (1.007–1.119)
DM	57,208	1,234	549,862	2.244	0.909 (0.831–1.004)	0.984 (0.897–1.079)	0.990 (0.902–1.087)
Non-DM	252,813	3,353	2,448,633	1.369	1.063 (1.001–1.129)	1.082 (1.016–1.152)	1.093 (1.025–1.165)

The estimated HR (95% CI) was calculated using time-dependent Cox regression model. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, body mass index, household income, smoking status, alcohol consumption, regular physical activity, hypertension, diabetes mellitus, dyslipidemia, renal disease, liver disease, and Charlson comorbidity index.
TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus.

peatedly measured values of the index. This association was evident for the entire cohort and the non-DM cohort, and the relationship between the TyG index and the incidence risk of PD exhibited a J shape regardless of the accompanying DM history.

The TyG index is linked to several health conditions with respect to disease presence and progression and related adverse

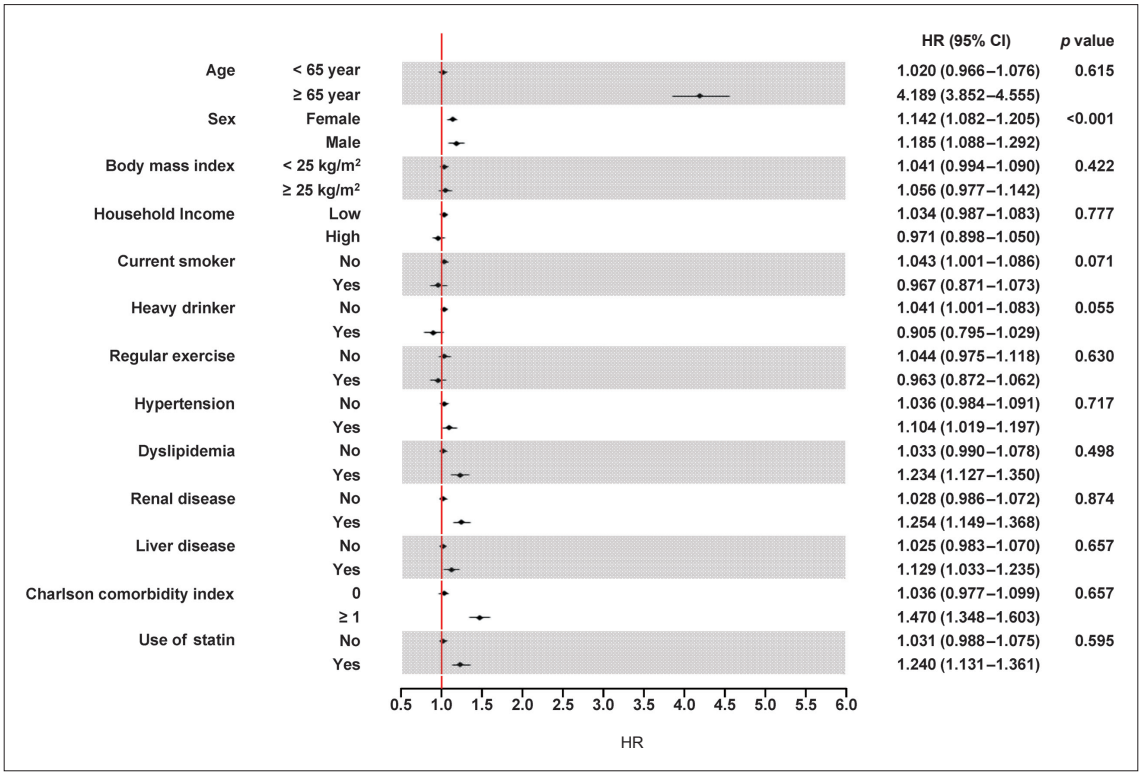


Figure 3. Forest plots of the incidence risk of PD according to demographic data and comorbidities. HR, hazard ratio; CI, confidence interval; PD, Parkinson's disease.

Table 3. Risk of Parkinson's disease based on the average TyG index tertile during the follow-up period

Average TyG index	*n*	Events	Person-years	Incidence rate (per 1,000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Total							
T1 (<9.129)	103,340	1,346	999,734	1.346	Ref	Ref	Ref
T2 (9.129–9.539)	103,340	1,627	1,000,552	1.626	1.205 (1.121–1.296)	1.106 (1.029–1.189)	1.083 (1.006–1.165)
T3 (>9.539)	103,341	1,614	998,209	1.617	1.203 (1.119–1.293)	1.153 (1.072–1.239)	1.083 (1.002–1.170)
p value for trend					<0.001	<0.001	0.044
DM							
T1 (<9.451)	19,069	447	182,361	2.451	Ref	Ref	Ref
T2 (9.451–9.870)	19,069	400	183,909	2.175	0.881 (0.769–1.008)	0.926 (0.809–1.060)	0.931 (0.813–1.067)
T3 (>9.870)	19,070	387	183,593	2.108	0.857 (0.748–1.002)	1.010 (0.881–1.158)	1.026 (0.893–1.180)
p value for trend					0.026	0.889	0.715
Non-DM							
T1 (<9.076)	84,271	1,015	816,511	1.243	Ref	Ref	Ref
T2 (9.076–9.458)	84,271	1,182	816,955	1.447	1.162 (1.069–1.264)	1.079 (0.992–1.174)	1.081 (0.993–1.177)
T3 (>9.458)	84,271	1,156	815,167	1.418	1.143 (1.051–1.244)	1.124 (1.033–1.223)	1.136 (1.042–1.239)
p value for trend					0.002	0.007	0.004

The estimated HR (95% CI) was derived from the conventional Cox regression model. Model 1 was adjusted for age and sex. Model 2 was adjusted for age, sex, body mass index, household income, smoking status, alcohol consumption, regular physical activity, hypertension, DM, dyslipidemia, renal disease, liver disease, and Charlson comorbidity index.
TyG, triglyceride-glucose; HR, hazard ratio; CI, confidence interval; ref, reference; DM, diabetes mellitus.

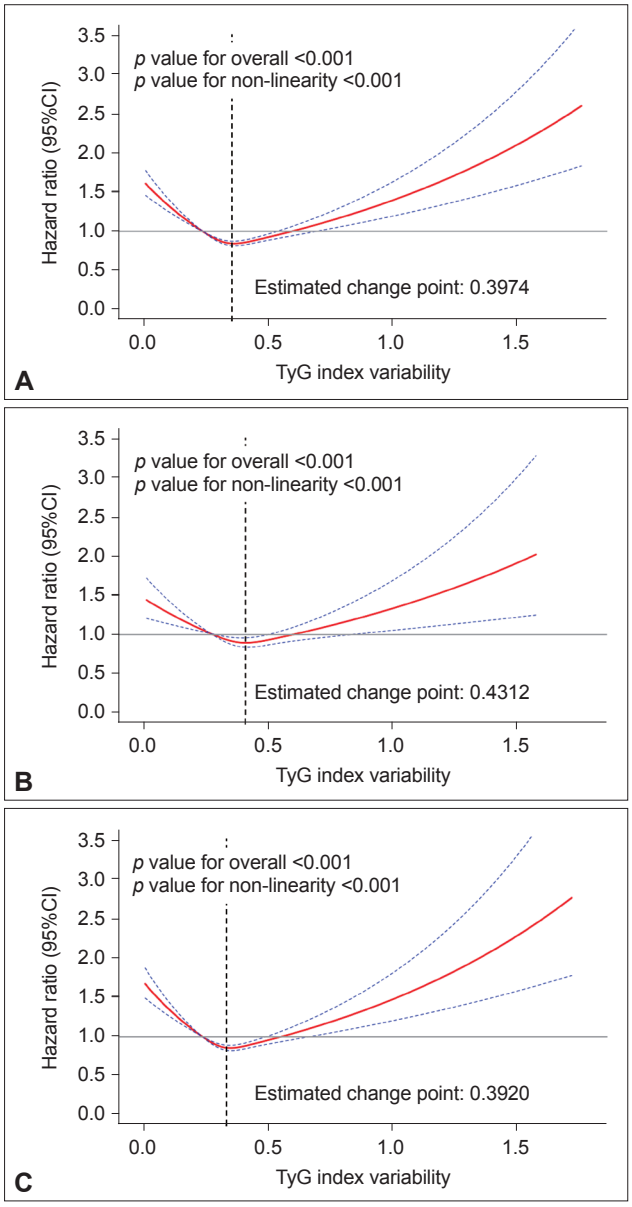


Figure 4. Spline curve for the incidence risk of PD according to average TyG index scores. A: Total cohort. B: Diabetes mellitus cohort. C: Non-diabetes mellitus cohort. CI, confidence interval; TyG, triglyceride-glucose; PD, Parkinson's disease.

events. For example, increased TyG index scores are correlated with a heightened incidence of coronary artery disease, cerebrovascular disease, and peripheral arterial disease.[24] Elevated TyG index scores can predict the progression of coronary artery atherosclerosis and calcification.[15] Moreover, a previous study established a significant association between the TyG index and all-cause and cardiovascular mortality, particularly in young and middle-aged patients.[25] Our study presents additional information regarding the association between the TyG index as an indicator of insulin resistance and the incidence risk of PD in a general population, given the large sample size and longitudinal setting.

Our study revealed that the TyG index was associated with an increased risk of PD in the entire population and the non-DM population but not in the DM population. Although DM is a representative disease accompanied by insulin resistance, the relationship between the presence of DM and the incidence risk of PD remains controversial. Prospective studies indicate that the link between DM and PD may be less strong, with type 2 DM patients showing an approximately 40% greater likelihood of developing PD.[26,27] Additionally, case-control studies conducted in Scandinavian and Asian populations suggest that type 2 DM is associated with an increased risk of PD.[28,29] While most research supports this connection, several studies have reported either no link[30,31] or an inverse relationship between type 2 DM and PD.[32] Our study revealed no association between TyG index scores and the incidence risk of PD in the DM population. These inconsistencies may be the result of differences in research methods and residual confounding factors, such as how PD diagnoses are obtained, the use of other medications, and the presence of additional medical conditions that are common among people with DM. For the non-DM population, even in those without DM, PD patients with dementia were significantly more likely to exhibit insulin resistance than PD patients without dementia were.[33] In contrast, previous research based on the Nurses' Health Study and Health Professionals Follow-up Study revealed that plasma levels of insulin resistance–related metabolites did not contribute to the risk of PD.[34] Our study, which was conducted in a longitudinal setting of a general population, suggests that insulin resistance is positively associated with the incidence risk of PD in a non-DM population.

Our study revealed evidence of a nonlinear association (a J-shaped trend) between the TyG index and the incidence risk of PD. This relationship was not uniform across all the ranges. In a previous study, the association between the TyG index and the incidence of atrial fibrillation in a general population without known cardiovascular disease showed U- or J-shaped trends.[35] In a nationwide cohort study, the TyG index was found to have a U- or J-shaped relationship with all-cause and cardiovascular mortality in patients with DM.[36] The results of these previous studies can also be applied to our findings regarding the incidence risk of PD. In other words, because the TyG index is composed of both TG and FBG levels, it is difficult to rule out the possibility that if the TyG index score is very low, it may be associated with a relatively poor health condition. Specifically, low TyG index scores may signify optimal metabolic health, characterized by robust insulin sensitivity and reduced lipid levels. However, excessively low TyG index scores could signal an underlying health issue, such as malnutrition or a genetic predispo-

sition, which could paradoxically increase cardiovascular risk. In support of these hypotheses, lower TG levels are associated with increased motor performance in PD patients.[37] According to a meta-analysis, high TG levels are protective factors for the pathogenesis of PD.[38] The J-shaped trends in our study therefore support the findings of previous studies.

The relationship between antidiabetic medications and PD has been of increasing interest in recent years. A population-based cohort study with diabetic patients revealed that the use of DPP-4 inhibitors and/or GLP-1 mimetics was associated with a lower risk of PD.[39] In another large population-based study, thiazolidinediones, meglitinides, GLP-1 analogs, DPP-4 inhibitors, and SGLT2 inhibitors were associated with a lower risk of PD than metformin was.[40] The possible mechanisms are anti-inflammatory effects and neuroprotective effects of antidiabetic drugs.[12,39-41] In our study, in the group of patients with diabetes, the use of diabetes medications—alpha-glucosidase inhibitors, sulfonylurea or meglitinide, DPP-4 inhibitors, or GLP-1 agonists, or SGLT2 inhibitors, biguanides, and insulin—did not affect the risk of PD compared with the risk in the group not taking diabetes medications. On the other hand, insulin was associated with an increased risk of PD compared with sulfonylurea. However, evaluating the association of diabetes medication with PD may have limited the design of this study.

Although our study was not mechanistic, several plausible hypotheses can be made regarding the association between the TyG index and the incidence risk of PD. Age is a primary risk factor for PD, and aging typically involves a reduction in the sensitivity of insulin receptors outside of the brain. Research has shown that the mRNA levels of insulin receptors in the brain, specifically in the hypothalamus, cortex, and hippocampus, also decrease with age. This reduction contributes to a condition known as chronic secondary hyperinsulinemia.[42] However, a natural decline in insulin signaling with age may be more pronounced in individuals with PD. Research has revealed a significant reduction in insulin receptor mRNA in the substantia nigra pars compacta of PD patients, along with greater insulin resistance, than in individuals of the same age without PD.[43] Alpha-synuclein may contribute to impaired insulin signaling in PD by improperly activating the PI3K/AKT/mTORC1 pathway and triggering the activation of c-Jun N-terminal kinase. This mechanism is compounded by a weakening of normal responses to insulin and insulin-like growth factor 1 (insulin resistance), leading to disrupted AKT homeostasis and diminished protective effects from FoxO activation and glycogen synthase kinase-3B inactivation.[12] As a result, insulin resistance may be associated with intensification of alpha-synuclein pathology and the loss of dopaminergic neurons. Other studies indicate that alpha-synuclein–induced insulin resistance can promote further aggregation of alpha-synuclein, creating a vicious cycle of worsening pathology that is also observed in Alzheimer's disease models with amyloid-beta and tau proteins.[12]

We acknowledge several limitations of our study. First, our findings may not be generalizable to different ethnic groups, as the study exclusively involved a Korean population. Second, despite multiple assessments of the TyG index to enhance reliability, the retrospective nature of the study limits the establishment of a causal relationship. Third, participants without at least three TyG index measurements during the follow-up period were excluded, which could bias the study results. Further analysis including patients with one or two TyG index measures also revealed an association between the TyG index and PD risk, with a slightly greater HR than when only participants with three or more measures were analyzed. We cannot explain why this difference occurred in this study, but it may be due to differences in the population. Fourth, the reliance on health screening data from a general population means that key PD-related imaging biomarkers, such as the results of a beta-CIT–PET study, were not included. Fifth, hemoglobin A1C and homeostatic model assessment of insulin resistance data were not available for our study cohort. Sixth, the accuracy of blood-based measurements of triglycerides and glucose in this cohort may be inaccurate because of a lack of standardization among laboratories. Additionally, long-term dietary or nutritional status can also impact these tests. Finally, because this cohort was constructed between 2002 and 2019 and the median follow-up was 9.64 years, recent antidiabetic medications, including DPP-4 inhibitors, GLP-1 agonists or SGLT2 inhibitors, were not commonly used in the baseline dataset.

Conclusion

Our study demonstrated that increased TyG index scores were nonlinearly associated with the incidence risk of PD in the general population. Future research with direct measurement of insulin resistance combined with nutritional data in a large population longitudinal study would be helpful to further investigate the impact of insulin resistance on the occurrence of PD.

Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.24131.

Conflicts of Interest

The authors have no financial conflicts of interest.

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REFERENCES

1. GBD 2021 Nervous System Disorders Collaborators. Global, regional, and national burden of disorders affecting the nervous system, 1990-2021: a systematic analysis for the global burden of disease study 2021. Lancet Neurol 2024;23:344-381.
2. Kang S, Eum S, Chang Y, Koyanagi A, Jacob L, Smith L, et al. Burden of neurological diseases in Asia from 1990 to 2019: a systematic analysis using the global burden of disease study data. BMJ Open 2022;12:e059548.
3. Tolosa E, Gaig C, Santamaría J, Compta Y. Diagnosis and the premotor phase of Parkinson disease. Neurology 2009;72(7 Suppl):S12-S20.
4. Lee J, Kim JJ, Lyoo CH, Kim YJ. Mitochondrial-membrane-protein-associated neurodegeneration in longitudinal magnetic resonance imaging over 11 years of follow-up. J Clin Neurol 2024;20:220-222.
5. Schapira AH, Olanow CW, Greenamyre JT, Bezard E. Slowing of neurodegeneration in Parkinson's disease and Huntington's disease: future therapeutic perspectives. Lancet 2014;384:545-555.
6. Lebovitz HE. Insulin resistance: definition and consequences. Exp Clin Endocrinol Diabetes 2001;109(Suppl 2):S135-S148.
7. Singh B, Saxena A. Surrogate markers of insulin resistance: a review. World J Diabetes 2010;1:36-47.
8. Bugianesi E, McCullough AJ, Marchesini G. Insulin resistance: a metabolic pathway to chronic liver disease. Hepatology 2005;42:987-1000.
9. Chang Y, Jeon J, Song TJ, Kim J. Association of triglyceride-glucose index with prognosis of COVID-19: a population-based study. J Infect Public Health 2022;15:837-844.
10. Wang T, Li M, Zeng T, Hu R, Xu Y, Xu M, et al. Association between insulin resistance and cardiovascular disease risk varies according to glucose tolerance status: a nationwide prospective cohort study. Diabetes Care 2022;45:1863-1872.
11. Ormazabal V, Nair S, Elfeky O, Aguayo C, Salomon C, Zuñiga FA. Association between insulin resistance and the development of cardiovascular disease. Cardiovasc Diabetol 2018;17:122.
12. Athauda D, Foltynie T. Insulin resistance and Parkinson's disease: a new target for disease modification? Prog Neurobiol 2016;145-146:98-120.
13. Bassil F, Delamarre A, Canron MH, Dutheil N, Vital A, Négrier-Leibreich ML, et al. Impaired brain insulin signalling in Parkinson's disease. Neuropathol Appl Neurobiol 2022;48:e12760.
14. Lee SB, Ahn CW, Lee BK, Kang S, Nam JS, You JH, et al. Association between triglyceride glucose index and arterial stiffness in Korean adults. Cardiovasc Diabetol 2018;17:41.
15. Park K, Ahn CW, Lee SB, Kang S, Nam JS, Lee BK, et al. Elevated TyG index predicts progression of coronary artery calcification. Diabetes Care 2019;42:1569-1573.
16. Seong SC, Kim YY, Park SK, Khang YH, Kim HC, Park JH, et al. Cohort profile: the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) in Korea. BMJ Open 2017;7:e016640.
17. Lee K, Lee JS, Kim J, Lee H, Chang Y, Woo HG, et al. Oral health and gastrointestinal cancer: a nationwide cohort study. J Clin Periodontol 2020;47:796-808.
18. Kim J, Kim HJ, Jeon J, Song TJ. Association between oral health and cardiovascular outcomes in patients with hypertension: a nationwide cohort study. J Hypertens 2022;40:374-381.
19. Song TJ, Chang Y, Jeon J, Kim J. Oral health and longitudinal changes in fasting glucose levels: a nationwide cohort study. PLoS One 2021;16:e0253769.
20. Charlson ME, Carrozzino D, Guidi J, Patierno C. Charlson comorbidity index: a critical review of clinimetric properties. Psychother Psychosom 2022;91:8-35.
21. Chang Y, Lee JS, Lee KJ, Woo HG, Song TJ. Improved oral hygiene is associated with decreased risk of new-onset diabetes: a nationwide population-based cohort study. Diabetologia 2020;63:924-933.
22. Simental-Mendía LE, Rodríguez-Morán M, Guerrero-Romero F. The product of fasting glucose and triglycerides as surrogate for identifying insulin resistance in apparently healthy subjects. Metab Syndr Relat Disord 2008;6:299-304.
23. Park JH, Kim DH, Kwon DY, Choi M, Kim S, Jung JH, et al. Trends in the incidence and prevalence of Parkinson's disease in Korea: a nationwide, population-based study. BMC Geriatr 2019;19:320.
24. Sánchez-Íñigo L, Navarro-González D, Fernández-Montero A, Pastrana-Delgado J, Martínez JA. The TyG index may predict the development of cardiovascular events. Eur J Clin Invest 2016;46:189-197.
25. Chen J, Wu K, Lin Y, Huang M, Xie S. Association of triglyceride glucose index with all-cause and cardiovascular mortality in the general population. Cardiovasc Diabetol 2023;22:320.
26. Driver JA, Smith A, Buring JE, Gaziano JM, Kurth T, Logroscino G. Prospective cohort study of type 2 diabetes and the risk of Parkinson's disease. Diabetes Care 2008;31:2003-2005.
27. Hu G, Jousilahti P, Bidel S, Antikainen R, Tuomilehto J. Type 2 diabetes and the risk of Parkinson's disease. Diabetes Care 2007;30:842-847.
28. Schernhammer E, Hansen J, Rugbjerg K, Wermuth L, Ritz B. Diabetes and the risk of developing Parkinson's disease in Denmark. Diabetes Care 2011;34:1102-1108.
29. Wahlqvist ML, Lee MS, Hsu CC, Chuang SY, Lee JT, Tsai HN. Metformin-inclusive sulfonylurea therapy reduces the risk of Parkinson's disease occurring with type 2 diabetes in a Taiwanese population cohort. Parkinsonism Relat Disord 2012;18:753-758.
30. Palacios N, Gao X, McCullough ML, Jacobs EJ, Patel AV, Mayo T, et al. Obesity, diabetes, and risk of Parkinson's disease. Mov Disord 2011;26:2253-2259.
31. Savica R, Grossardt BR, Ahlskog JE, Rocca WA. Metabolic markers or conditions preceding Parkinson's disease: a case-control study. Mov Disord 2012;27:974-979.
32. Lu 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.
33. Bosco D, Plastino M, Cristiano D, Colica C, Ermio C, De Bartolo M, et al. Dementia is associated with insulin resistance in patients with Parkinson's disease. J Neurol Sci 2012;315:39-43.

34. Molsberry S, Bjornevik K, Hughes KC, Zhang ZJ, Jeanfavre S, Clish C, et al. Plasma metabolomic markers of insulin resistance and diabetes and rate of incident Parkinson's disease. J Parkinsons Dis 2020;10:1011-1021.
35. Liu X, Abudukeremu A, Jiang Y, Cao Z, Wu M, Ma J, et al. U-shaped association between the triglyceride-glucose index and atrial fibrillation incidence in a general population without known cardiovascular disease. Cardiovasc Diabetol 2023;22:118.
36. Zhao M, Xiao M, Tan Q, Lu F. Triglyceride glucose index as a predictor of mortality in middle-aged and elderly patients with type 2 diabetes in the US. Sci Rep 2023;13:16478.
37. Zhang M, Chen H, Liu G, Wang X, Wang Z, Feng T, et al. Lower serum triglyceride levels linked to more severe motor performance in Parkinson's disease. Neurol Sci 2022;43:5343-5353.
38. Fu X, Wang Y, He X, Li H, Liu H, Zhang X. A systematic review and meta-analysis of serum cholesterol and triglyceride levels in patients with Parkinson's disease. Lipids Health Dis 2020;19:97.
39. Brauer R, Wei L, Ma T, Athauda D, Girges C, Vijiaratnam N, et al. Diabetes medications and risk of Parkinson's disease: a cohort study of patients with diabetes. Brain 2020;143:3067-3076.
40. Rozani V, Bezimianski MG, Azuri J, Bitan M, Peretz C. Anti-diabetic drug use and reduced risk of Parkinson's disease: a community-based cohort study. Parkinsonism Relat Disord 2024;128:107132.
41. Yun SP, Kam TI, Panicker N, Kim S, Oh Y, Park JS, et al. Block of A1 astrocyte conversion by microglia is neuroprotective in models of Parkinson's disease. Nat Med 2018;24:931-938.
42. Kushner JA. The role of aging upon β cell turnover. J Clin Invest 2013;123:990-995.
43. Morris JK, Vidoni ED, Perea RD, Rada R, Johnson DK, Lyons K, et al. Insulin resistance and gray matter volume in neurodegenerative disease. Neuroscience 2014;270:139-147.