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Association between triglyceride/high density lipoprotein ratio and incidence risk of Parkinson's disease: a population-based cohort study

Yoonkyung Chang[1,5], Ju-young Park[2,3,5] & Tae-Jin Song[4]✉

The association between insulin resistance and increased risk of Parkinson's disease (PD) has rarely been investigated. Our study aimed to investigate the association between the triglyceride/high-density lipoprotein (TG/HDL) ratio (which represents insulin resistance), and the incidence risk of PD in the general population. This study was conducted using data from the National Health Insurance Service-Health Screening Cohort Database of South Korea (2002–2019). We enrolled 310,023 participants who had no previous PD history and who had undergone more than three repeated measurements for the TG/HDL cholesterol ratio. The diagnosis of PD was determined using the International Classification of Diseases, 10th Revision code G20, specific reimbursement codes for Rare Intractable Diseases of V124, and a history of anti-PD drug prescription. During a median of 9.64 years (interquartile range 8.72–10.53), 4,587 individuals (1.47%) had an incidence of PD. Considering the multivariable time-dependent Cox proportional hazard model with repeated measures of average TG/HDL cholesterol ratio, a per unit increase in TG/HDL cholesterol ratio significantly increased the risk of PD in the entire cohort (hazard ratio (HR), 1.010; 95% confidence interval (CI), 1.001–1.020). These repeated measures of the average TG/HDL cholesterol ratio were associated with the incidence risk of PD in a J-shaped pattern for the entire diabetes mellitus (DM) and non-DM cohorts in restricted cubic spline analysis. Compared to the lowest tertiles (T1), the highest tertiles (T3) were positively associated with the incidence risk of PD (HR: 1.149, 95% CI 1.065–1.239 in the entire cohort, p for trend < 0.001; HR: 1.175, 95% CI 1.075–1.285 in the non-DM cohort, p for trend < 0.001). In contrast, the lowest (T1) and highest tertiles (T3) were not associated with the incidence risk of PD in the DM cohort (HR: 1.128, 95% CI 0.909–1.348) in fully adjusted multivariable analysis. Our study provides information that TG/HDL ratio may be positively associated with PD incidence risk in a non-DM population in longitudinal setting of the general population.

Keywords Insulin resistance, Triglyceride/high density lipoprotein ratio, Parkinson's disease, Diabetes mellitus

Parkinson's disease (PD) is the second most frequently diagnosed neurodegenerative condition[1,2]. The disease progresses over time, and is marked by the deterioration of dopaminergic neurons in the nigrostriatal pathway, leading to distinctive motor symptoms, such as rigidity, tremor, and bradykinesia. There is increasing evidence that the development of PD may start up to two decades before motor symptoms become evident[3–5]. Despite numerous compounds demonstrating neuroprotective abilities in laboratory or animal models of PD, to date, none have conclusively shown efficacy in altering disease progression in clinical trials.

Insulin resistance is a common metabolic disorder that is commonly linked with type 2 diabetes mellitus (DM)[6,7]. The implications of insulin resistance extend beyond DM, influencing a wide range of health issues[7–11].

[1]Department of Neurology, Mokdong Hospital, Ewha Womans University College of Medicine, Seoul, Republic of Korea. [2]Department of Applied Statistics, Yonsei University, Seoul 03722, South Korea. [3]Department of Statistics and Data Science, Yonsei University, Seoul 03722, South Korea. [4]Department of Neurology, Seoul Hospital, Ewha Womans University College of Medicine, 260, Gonghang-daero, Gangseo-gu, Seoul 07804, Republic of Korea. [5]Yoonkyung Chang and Ju-young Park contributed equally to this work. ✉email: knstar@ewha.ac.kr

The association between insulin and PD has been gaining attention in the field of PD research. Insulin receptors are present in brain regions such as the basal ganglia and substantia nigra[12]. Increasing 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 (TG)/high-density lipoprotein (HDL) ratio serves as a simple and practical surrogate marker for insulin resistance[14–18]. However, the association between insulin resistance and an increased risk of PD has rarely been investigated. Additionally, despite changes in insulin resistance, studies using repeatedly measured parameters in the general population are limited. We hypothesized that an increased TG/HDL cholesterol ratio would be associated with the development of PD. Our study aimed to investigate the association between the TG/HDL cholesterol ratio and the incidence risk of PD in a longitudinal setting in the general population.

Methods

Data source

This study sourced its data from the National Health Insurance Service-Health Screening Cohort (NHIS-HEALS) database, a subset of the Korean National Health Insurance Service (NHIS). The NHIS is a government program that provides health insurance to nearly 97% of the Korean population. The Medical Aid program, an affiliate of the NHIS, covers the 3% of the population not covered by the NHIS. Our study was conducted based on the NHIS-HEALS cohort database of South Korea (2002–2019)[19]. The NHIS provides a nationwide free health screening program every two years for all South Korean adults aged 40 and over.

The NHIS-HEALS encompasses measurements of blood pressure, body mass index, blood biochemistry, a self-administered questionnaire on medical history, and lifestyle factors including smoking habits, alcohol consumption, and physical activity. In addition, health claims data covering all hospital visits, diagnoses, surgeries, medical procedures, and participant prescriptions from 2002 to 2019 are included. The diagnoses at each hospital visit were recorded according to the International Classification of Disease, Tenth Revision (ICD-10). Demographic information such as sex, age, and household income was also included, and data regarding participants' health claims, insurance coverage maintenance, and death were available up to December 31, 2019.

Study population

We enrolled 362,285 participants from the NHIS-HEALS database aged 40 and over, who participated in the national health screening program during the baseline years of 2009–2010. Among the 362,285 participants, those with missing demographic information, lifestyle, and laboratory findings were excluded ($n = 9{,}047$). The washout period was extended from 2002 to the index date, during which time 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 exclude possible reverse causality or association, and participants with less than three repeated measurements ($n = 40{,}771$) were excluded. After applying the inclusion and exclusion criteria, the final cohort comprised 310,023 participants (Fig. 1).

Data collection and definitions

Based on the health claims data from the NHIS-HEALS, the participants' demographic information (age, sex, body mass index (BMI), waist circumference, and household income) and lifestyle (smoking status, alcohol consumption, and regular physical activity) were collected through self-reported questionnaires. BMI was calculated as the weight (kg) divided by height (m^2). Household income was categorized using the quantile of the individual's health insurance premiums, with those in the 9th decile and above considered to have a high income. Lifestyles were detailed as follows: Smoking status was categorized into never, former, and current smokers. The frequency of alcohol consumption was defined by the number of times alcohol was consumed per week, as follows: none, 1–2 times, 3–4 times, and ≥ 5 times. The frequency of regular physical activity was divided based on the number of days engaged in exercise per week: none, 1–4 days, and ≥ 5 days. Biochemical measurements, including liver enzymes, lipid panels, and fasting glucose levels, were collected from 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. Detailed definitions of these can be found in the "Supplementary methods"[20–27].

TG/HDL ratio

The TG/HDL cholesterol ratio was considered a time-dependent covariate throughout the follow-up period. For further analysis, the variable was also used as the average of repeated measures of the TG/HDL cholesterol ratio, calculated using values from at least three repeated measurements, to reduce bias in the average value.

Outcome

The diagnosis of PD was determined using the International Classification of Diseases, 10th Revision (ICD-10) code G20, and a specific reimbursement code for Rare Intractable Diseases (RIDs) V124 and prescription of PD medications such as amantadine, anticholinergics, catechol-O-methyltransferase inhibitors, dopamine agonists, carbidopa/levodopa, selegiline, and rasagiline. RIDs V124 code for PD is registered by neurologists, neurosurgeons, or specialists in rehabilitation medicine. Detailed criteria for V124 are described in "Supplementary methods". To exclude cases of secondary Parkinsonism, individuals diagnosed with both PD (G20) and Parkinsonism (ICD-10 G21–26) were not included in the incidence of PD[28]. Participants with Rare Intractable Diseases (RIDs) were required to have their diagnoses confirmed by a physician using the standard diagnostic criteria provided by the NHIS. Following the physician's evaluation, the healthcare facility examines the diagnosis before submitting it to the NHIS. This structured procedure guarantees the reliability of the data related to the RIDs. The date of diagnosis of PD was considered the first prescription of anti-PD medication

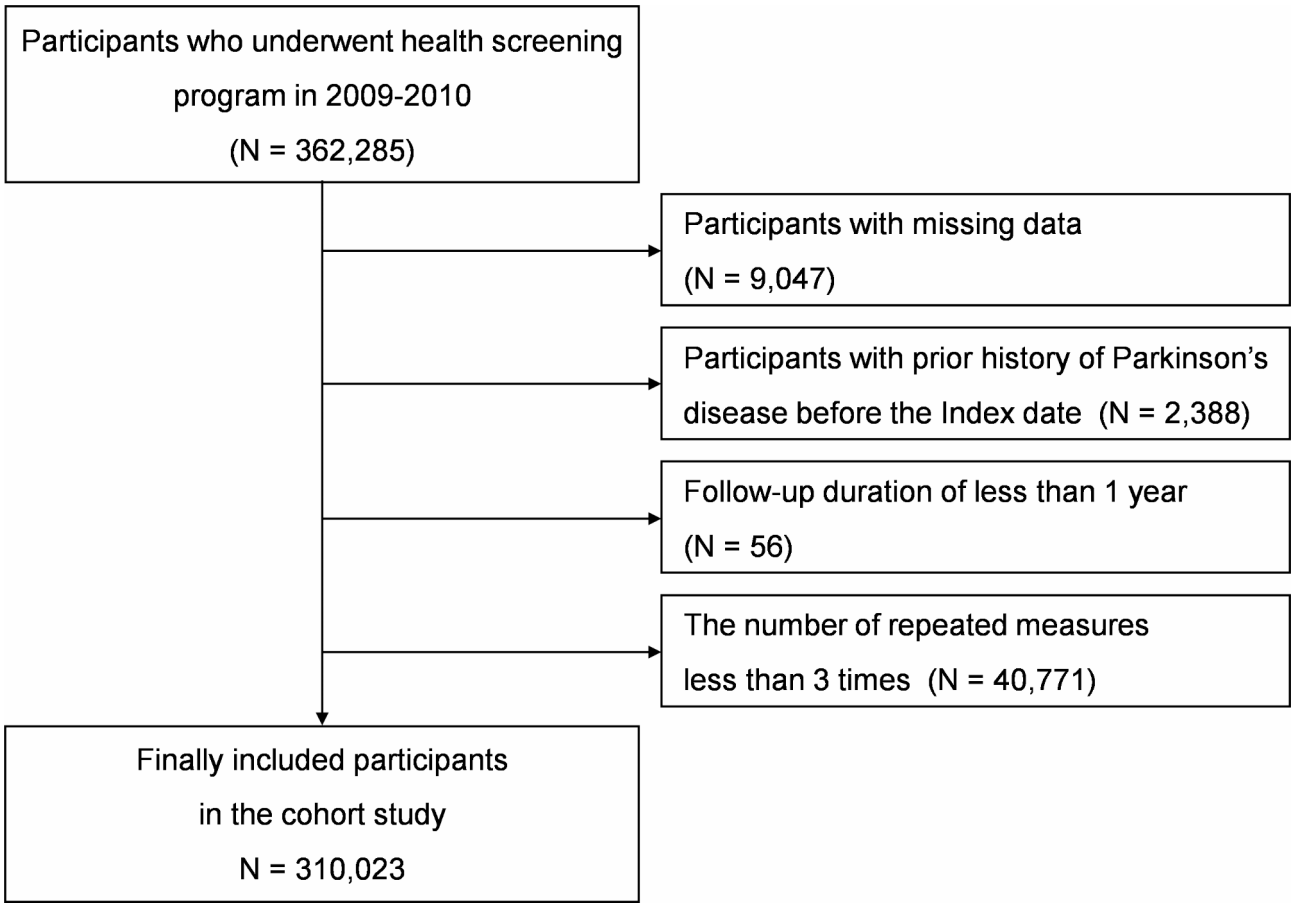

Fig. 1. Flow chart of the inclusion and exclusion criteria.

based on relevant ICD-10 codes in the claim records. Follow-up was performed until December 31, 2019, death or the first occurrence of PD.

Statistical analysis

Comparisons between groups based on quartiles of the TG/HDL cholesterol ratio were made using one-way ANOVA (Analysis of Variance) for continuous variables and the chi-squared test (or Fisher's exact test) for categorical variables. The survival curves for the time-to-event outcomes were plotted as Kaplan-Meier curves, and the log-rank test was used to compare the survival curves across the TG/HDL cholesterol ratio groups. Restricted cubic splines were used to explore the linear relationship between the TG/HDL cholesterol ratio per standard deviation (x-axis) and the incidence of PD (y-axis). The optimal change-point in the spline curve analysis was estimated using a regression model with piecewise linear relationships.

To evaluate the incidence risk of PD in relation to the repeatedly measured TG/HDL cholesterol ratio during the follow-up period, a time-dependent Cox proportional hazards model was applied. Furthermore, participants were divided into three groups based on the tertiles (T, as follows: T1, T2, and T3) of the average TG/HDL cholesterol ratio during the follow-up period. The conventional Cox proportional hazard model was used to ascertain the risk of PD according to quartile groups. The proportionality of the hazard assumption was evaluated using the Grambsch–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 (HR) and 95% confidence intervals (CI) for the 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 + BMI, household income, smoking status, alcohol consumption, regular physical activity, hypertension, DM, renal disease, liver disease, and CCI. Blood biomarkers, such as aspartate aminotransferase (AST), alanine aminotransferase (ALT), and liver disease, were not additionally adjusted for in multivariable model 2 due to multicollinearity. Considering covariates, in cases where participants underwent multiple health checkups from 2009 to 2019, data from their latest examinations were utilized for statistical analysis. For subgroup analysis, we performed further analyses according to the presence of DM. Sensitivity analyses of the association between the TG/HDL cholesterol ratio and PD were performed according to demographics, lifestyle, and covariates, suggesting a p-value for interaction. All statistical analysis were conducted using SAS version 9.4 (SAS Inc., Cary, NC, USA) and R software, version 4.2.1 (R Foundation for Statistical Computing, Vienna, Austria), with statistical significance defined as a two-sided p-value < 0.05.

Ethics declarations

were obtained according to the guidelines of the Declaration of Helsinki. This study was approved by Ewha Womans University Seoul Hospital Institutional Review Board (EUMC-2022-02-018). Given that the data were accessible to the public through the NHIS database, the need for ethical approval and informed consent was waived by Ewha Womans University Seoul Hospital Institutional Review Board.

Results

Baseline characteristics of the study participants

The number of measurements repeated during the follow-up period is described in Supplementary Tables 1, and the characteristics of the variables for each year are described in Supplementary Table 2. Table 1 presents the baseline characteristics of the entire cohort divided into four groups based on the tertiles of the average TG/HDL cholesterol ratio (T1 (< 1.820), T2 (1.820–2.959); and T3 (> 2.959). Patients in the T2 group were older than those in the other groups. The T3 group had a higher predominance of men and obese individuals. Additionally, the T3 group had more frequent current smokers and alcohol consumption, while the number of exercise (≥ 5 days/week) sessions was lower. Laboratory findings, including liver enzyme, total cholesterol, triglyceride, and fasting blood glucose, were higher than those in the other groups (T1 and T2), and the proportions of comorbidities, including hypertension, DM, dyslipidemia, renal disease, and liver disease were statistically higher in the T3 group (Table 1).

Relationship of TG/HDL ratio with incidence risk for PD

During a median of 9.64 years (interquartile range 8.72–10.53), 4,587 individuals (1.47%) had an incidence of PD. The survival curves depicting the incidence of PD across the tertiles of the average TG/HDL cholesterol ratio are presented in Fig. 2. The incidence of PD was dependent on the TG/HDL cholesterol ratio tertiles in the entire cohort (log-rank test, $P < 0.001$) and non-DM cohorts ($P < 0.001$). In contrast, the incidence of PD was not dependent on the tertiles of the TG/HDL cholesterol ratio in the DM cohort ($p = 0.266$).

Considering the multivariable time-dependent Cox proportional hazard model with repeated measures of average TG/HDL cholesterol ratio, a per unit increase in TG/HDL cholesterol ratio significantly increased the risk of PD in the entire cohort (Model 2, HR: 1.010, 95% CI 1.001–1.020, Table 2). The repeated measures of the average TG/HDL cholesterol ratio were associated with an increased risk of PD in the non-DM cohort (Model 2, HR: 1.013, 95% CI 1.004–1.021), but not in the DM cohort (Model 2, HR: 0.996, 95% CI 0.974–1.118) (Table 2 and Supplementary Table 3).

Moreover, there was no statistical interaction for the association of repeated measures of the average TG/HDL cholesterol ratio with the incidence risk of PD, regardless of the demographic data and covariates (Fig. 3). In subgroup analysis for aged less than 60 years or 65 years, TG/HDL ratio was not associated with new-onset PD (Supplementary Tables 6, 7, 8, 9).

The results of the multivariate Cox proportional model for the average TG/HDL cholesterol ratio tertiles during follow-up are detailed in Tables 3 and Supplementary Table 4. Compared to the lowest tertile (T1), the highest tertile (T3) was positively associated with the incidence risk of PD (HR: 1.149, 95% CI 1.065–1.239 in the entire cohort, p for trend < 0.001; HR: 1.175, 95% CI 1.075–1.285 in the non-DM cohort, p for trend < 0.001). In contrast, the lowest (T1) and highest tertiles (T3) were not associated with the incidence risk of PD in the DM cohort (HR: 1.128, 95% CI 0.909–1.348) in the fully adjusted multivariable analysis.

Considering the association of the average TG/HDL cholesterol ratio with the incidence risk of PD, in visual inspection, restricted cubic spline analysis (Supplementary Fig. 1) displayed a pattern of J-shaped association of the TG/HDL cholesterol ratio per one standard deviation with the incidence risk of PD for the entire, DM, and non-DM cohorts.

Discussion

The key finding of our study was that the TG/HDL ratio was associated with the incidence risk of PD in the general population, even though the time-dependent analysis of the TG/HDL ratio and conventional Cox regression analysis repeatedly measured the average value of the TG/HDL ratio. Furthermore, this association was demonstrated in the entire cohort and the non-DM cohort, but not in the DM cohort.

The TG/HDL cholesterol ratio is linked to several health conditions, including disease presence, progression, and adverse events. For example, increased TG/HDL ratio has been correlated with a heightened incidence of metabolic syndrome, cerebrovascular disease, coronary artery disease, and peripheral arterial disease[29]. Notably, in patients infected with coronavirus disease 2019, an elevated TG/HDL ratio levels was associated with more severe illness and increased mortality rates[30]. Moreover, a previous study showed a significant association between TG/HDL ratio and long-term all-cause mortality in patients with coronary artery disease[31]. Our study is meaningful in that it presents additional information regarding the association between TG/HDL ratio, representing insulin resistance, and the incidence risk of PD in the general population with a large sample size and longitudinal setting.

Our study revealed that compared to the lowest tertile, the highest tertile of the TG/HDL cholesterol ratio were 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 of PD is controversial. Prospective studies have previously indicated a weak association between type 2 DM and the risk of PD[32,33]. Additionally, case-control studies conducted in Asian or European populations suggest that type 2 DM is associated with an increased risk of PD[34,35]. While most research supports this connection, it is important to acknowledge that several studies have either found no link between the presence of DM and PD[36,37], or showed an inverse relationship between

Variables	Total	TG/HDL ratio tertile			
		T1 (< 1.820)	T2 (1.820–2.959)	T3 (≥ 2.959)	
		Mean ± SD, N(%)	Mean ± SD, N(%)	Mean ± SD, N(%)	p-value
Number	310,023	103,341	103,341	103,341	
Age, years					< 0.001
< 65	246,240 (79.4)	84,204 (81.5)	80,049 (77.5)	81,987 (79.3)	
≥ 65	63,783 (20.6)	19,137 (18.5)	23,292 (22.5)	21,354 (20.7)	
Sex					< 0.001
Female	142,741 (46.0)	57,544 (55.7)	48,855 (47.3)	36,342 (35.2)	
Male	167,282 (54.0)	45,797 (44.3)	54,486 (52.7)	66,999 (64.8)	
Body mass index (kg/m^2)					< 0.001
< 25	201,855 (65.1)	79,987 (77.4)	65,897 (63.8)	55,971 (54.2)	
≥ 25	108,168 (34.9)	23,354 (22.6)	37,444 (36.2)	47,370 (45.8)	
Waist circumference (cm)					< 0.001
Male < 90, female < 85	249,267 (80.4)	91,843 (88.9)	82,358 (79.7)	75,066 (72.6)	
Male ≥ 90, female ≥ 85	60,756 (19.6)	11,498 (11.1)	20,983 (20.3)	28,275 (27.4)	
Household income					0.043
Low	197,766 (63.8)	65,794 (63.7)	66,237 (64.1)	65,735 (63.6)	
High	112,257 (36.2)	37,547 (36.3)	37,104 (35.9)	37,606 (36.4)	
Smoking status					< 0.001
Never	199,496 (64.3)	75,852 (73.4)	67,548 (65.4)	56,096 (54.3)	
Former	58,782 (19.0)	16,820 (16.3)	19,604 (19.0)	22,358 (21.6)	
Current	51,745 (16.7)	10,669 (10.3)	16,189 (15.6)	24,887 (24.1)	
Alcohol consumption (days/week)					< 0.001
None	185,044 (59.7)	65,341 (63.2)	63,369 (61.3)	56,334 (54.5)	
1–2 times	82,203 (26.5)	25,665 (24.8)	26,563 (25.7)	29,975 (29.0)	
3–4 times	28,072 (9.1)	7,905 (7.6)	8,799 (8.5)	11,368 (11.0)	
≥ 5 times	14,704 (4.7)	4,430 (4.4)	4,610 (4.5)	5,664 (5.5)	
Regular physical activity (days/week)					< 0.001
None	76,287 (24.6)	24,139 (23.4)	25,935 (25.1)	26,213 (25.4)	
1–4 days	138,580 (44.7)	45,184 (43.7)	45,745 (44.3)	47,651 (46.1)	
≥ 5 days	95,156 (30.7)	34,018 (32.9)	31,661 (30.6)	29,477 (28.5)	
Laboratory findings					
AST (U/L)	26.2 ± 16.2	25.3 ± 15.3	25.9 ± 15.9	27.5 ± 17.1	< 0.001
ALT (U/L)	25.1 ± 18.7	22.0 ± 17.1	24.8 ± 18.4	28.6 ± 20.0	< 0.001
Total-C (mg/dL)	200.1 ± 37.1	195.9 ± 35.1	200.6 ± 37.0	203.9 ± 38.8	< 0.001
HDL-C (mg/dL)	54.7 ± 23.7	63.6 ± 29.1	53.9 ± 20.7	46.6 ± 16.3	< 0.001
LDL-C (mg/dL)	118.8 ± 35.8	116.9 ± 33.2	122.6 ± 35.3	117.0 ± 38.5	< 0.001
Triglyceride (mg/dL)	137.3 ± 83.4	83.1 ± 35.2	124.3 ± 47.0	204.5 ± 99.1	< 0.001
FBG (mg/dL)	100.6 ± 24.2	96.6 ± 19.6	100.3 ± 23.0	104.7 ± 28.3	< 0.001
Comorbidities					
Hypertension	94,511 (30.5)	24,337 (23.6)	32,861 (31.8)	37,313 (36.1)	< 0.001
Diabetes mellitus	38,194 (12.3)	8,009 (7.8)	12,612 (12.2)	17,573 (17.0)	< 0.001
Dyslipidemia	50,141 (16.2)	13,074 (12.7)	17,153 (16.6)	19,914 (19.3)	< 0.001
Renal disease	40,929 (13.2)	12,135 (11.7)	13,603 (13.2)	15,191 (14.7)	< 0.001
Liver disease	52,229 (16.8)	15,652 (15.1)	17,368 (16.8)	19,209 (18.6)	< 0.001
Charlson comorbidity index					< 0.001
0	160,824 (51.9)	55,937 (54.1)	52,809 (51.1)	52,078 (50.4)	
1	128,525 (41.5)	40,949 (39.6)	43,733 (42.3)	43,843 (42.4)	
2 or more	20,674 (6.6)	6,455 (6.3)	6,799 (6.6)	7,420 (7.2)	
Use of statin	42,172 (13.6)	10,809 (10.5)	14,715 (14.2)	16,648 (16.1)	< 0.001

Table 1. Baseline characteristics of study participants. TG, triglyceride; HDL, high-density lipoprotein; T, tertile; SD, standard deviation; N, number; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Total-C, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; FBS, fasting blood glucose.

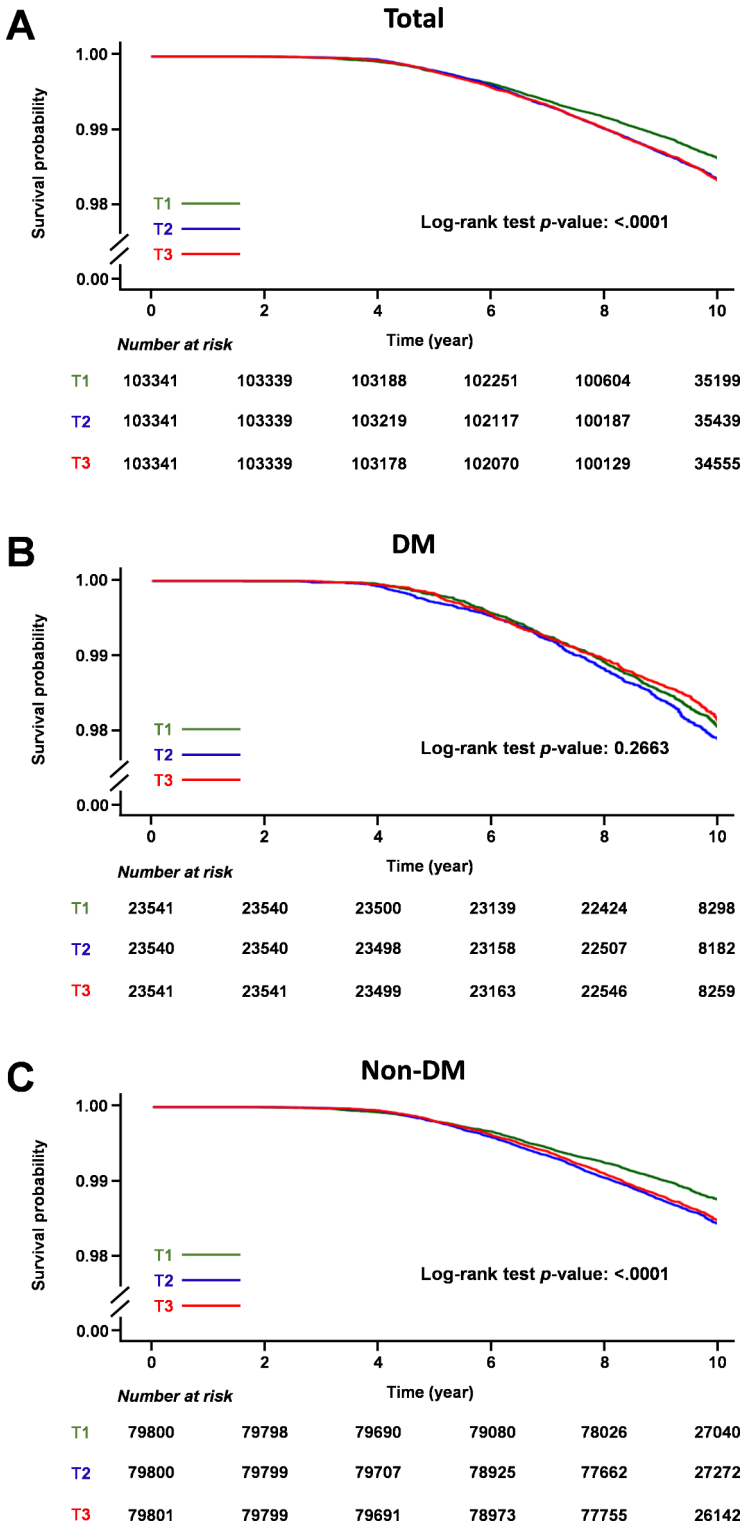

Fig. 2. Kaplan-Meier survival curves for the incidence risk of PD according to TG/HDL ratio tertile. (**A**) Total cohort, (**B**) Diabetic mellitus cohort, (**C**) Non-diabetic mellitus cohort.

type 2 DM and PD[38,39]. Nevertheless, our findings support previous findings that there is a lack of association between insulin resistance and the incidence risk of PD in the DM population. These inconsistencies could potentially be explained by variations in research methods and residual confounding factors, such as how PD diagnoses were obtained, the use of various medications, and the presence of additional medical comorbidities common among the population with DM. Considering non-DM population, even in without DM, PD patients with dementia were significantly more likely to have insulin resistance than PD patients without dementia[40]. In

Groups	*N*	Events	Person-years	Incidence rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Total	310,023	4,587	2,998,513	1.530	1.011 (1.002, 1.020)	1.013 (1.004, 1.021)	1.010 (1.001, 1.020)
DM	70,622	1,312	681,051	1.926	0.986 (0.965, 1.007)	0.996 (0.975, 1.018)	0.996 (0.974, 1.018)
Non-DM	239,401	3,275	2,317,463	1.413	1.012 (1.003, 1.022)	1.014 (1.005, 1.022)	1.013 (1.004, 1.022)

Table 2. Results of risk of Parkinson's disease considering the TG/HDL ratio as a time-dependent covariate. TG, triglyceride; HDL, high-density lipoprotein; N, number; HR, hazard ratio; CI, confidence interval; DM, diabetes mellitus. The estimated HR (95% CI) was calculated using a 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 use of statin.

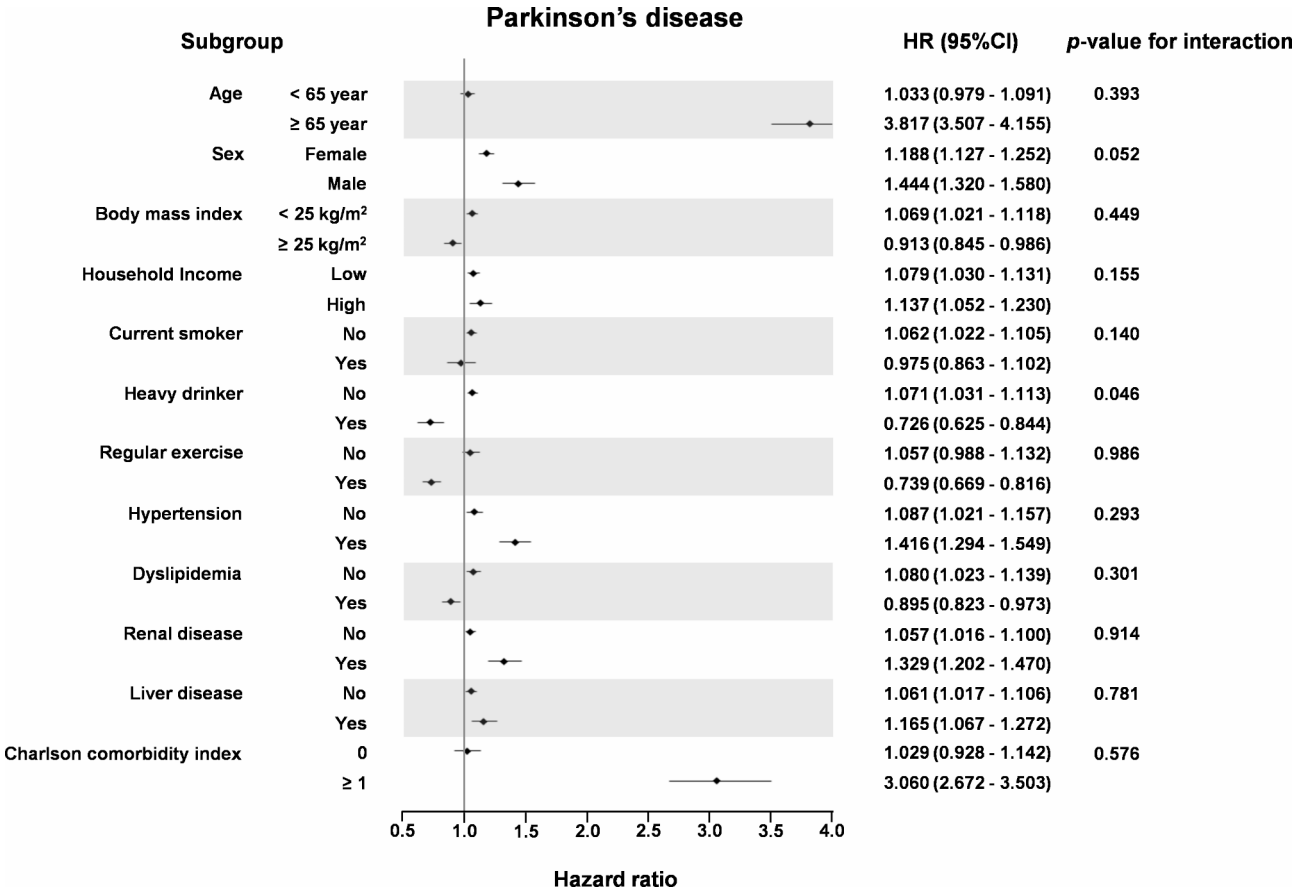

Fig. 3. Forest plots of incidence risk of PD according to the demographic data and comorbidities.

contrast, previous research based on Nurses' Health Study and Health Professionals Follow-up Study showed that plasma levels of insulin resistance-related metabolites were not predictive of the risk of PD[41]. Our study provides information that insulin resistance is positively associated with PD incidence risk in a non-DM population in longitudinal setting of general population.

Few studies have investigated the relationship between TG/HDL ratio and Parkinson's disease. Previous studies for association between PD and lipid profiles and found that a low blood lipid level is associated with PD[42]. There are also studies that show that elevated TG, LDL and TC have a protective effect on PD[43]. The association and mechanisms of insulin resistance and PD development are not clearly concluded[12,44–46]. However, neuronal death, amyloid aggregation, neuroinflammation, autophagy, and mitochondrial dysfunction may be a common denominator in the development of insulin resistance and PD[47]. On the other hand, a recent study of GBA1 mutation-associated PD and insulin resistance using midbrain organoids have shown that local insulin signaling dysfunction influences PD development and that pioglitazone has shown protective effect[48].

Our study showed a nonlinear association, similar to the J-shaped relationship between the TG/HDL cholesterol ratio and incidence risk of PD. This J-shaped relationship suggests that the risk of PD associated with

Average TG/HDL ratio	*N*	Events	Person-years	Incidence rate (per 1000 person-years)	Unadjusted HR (95% CI)	Model 1 HR (95% CI)	Model 2 HR (95% CI)
Total							
T1 (< 1.820)	103,341	1,339	1,000,010	1.339	Ref	Ref	Ref
T2 (1.820–2.959)	103,341	1,625	1,000,049	1.625	1.212 (1.128, 1.303)	1.165 (1.084, 1.253)	1.129 (1.049, 1.214)
T3 (≥ 2.959)	103,341	1,623	998,454	1.626	1.216 (1.131, 1.307)	1.201 (1.117, 1.292)	1.149 (1.065, 1.239)
p-value for trend					< 0.001	< 0.001	< 0.001
DM							
T1 (< 2.263)	23,541	427	226,861	1.882	Ref	Ref	Ref
T2 (2.263–3.602)	23,540	471	227,145	2.074	1.101 (0.966, 1.255)	1.121 (0.983, 1.278)	1.110 (0.973, 1.266)
T3 (≥ 3.602)	23,541	414	227,045	1.823	0.969 (0.846, 1.109)	1.052 (0.918, 1.205)	1.045 (0.910, 1.199)
p-value for trend					0.648	0.465	0.536
Non-DM							
T1 (< 1.718)	79,800	943	772,953	1.220	Ref	Ref	Ref
T2 (1.718–2.769)	79,800	1,186	772,830	1.535	1.257 (1.154, 1.369)	1.208 (1.109, 1.316)	1.182 (1.084, 1.288)
T3 (≥ 2.769)	79,801	1,146	771,680	1.485	1.219 (1.119, 1.329)	1.199 (1.099, 1.307)	1.175 (1.075, 1.285)
p-value for trend					< 0.001	< 0.001	< 0.001

Table 3. Risk of Parkinson's disease based on the average TG/HDL ratio tertile during the follow-up period. TG, triglyceride; HDL, high-density lipoprotein; N, number; HR, hazard ratio; CI, confidence interval; T, tertile; DM, diabetes mellitus. 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, diabetes mellitus, dyslipidemia, renal disease, liver disease, and use of statin.

the TG/HDL cholesterol ratio is not uniform across all ranges. In one prior study, the association between insulin resistance biomarker and incidence of atrial fibrillation in a general population without known cardiovascular disease showed U or J-shape phenominon[49]. In a nation-wide cohort study in Japanese, the TG/HDL ratio was found to have a U shaped relationship with the incidence risk of DM[50]. The results of these previous studies can also be applied to our study in terms of the incidence risk of PD. In other words, because the TG/HDL cholesterol ratio is composed of TG and HDL cholesterol levels, it is difficult to rule out the possibility that a very low TG level is associated with relatively poor health. Specifically, low TG levels may be associated with mortality in stroke and coronary artery disease patients[51,52]. Supporting these hypotheses, lower triglyceride levels were associated with more progressive motor performance in PD patients[53]. In one meta-analysis, high triglyceride levels were further identified as a protective factor in the pathogenesis of PD[43]. Therefore, the J-shaped phenomenon in the present study supports this previous study.

We acknowledge the limitations of this study. First, although the large cohort allows for statistically significant differences to be found, interpretation of the actual clinical difference needs to be cautious due to small difference in HR. It is also possible that the absolute value of the TG/HDL ratio itself is small. Based on this, further study to determine clinical significance may be needed. Second, our findings may not be generalizable to different ethnic groups as they exclusively involved the Korean population. Third, despite multiple assessments of TG/HDL cholesterol ratio to enhance reliability, the retrospective nature of the study limited the establishment of a causal relationship. Fourth, the reliance on health screening data from the general population means that key PD-related imaging biomarkers, such as the results of the beta-CIT-PET study, were not included. Although we have used ICD-10 code and RIDs code and anti PD medications for PD diagnosis, there is a possibility that atypical parkinsonism such as MSA-P and PSP-P were included in the study. In the early stages of Parkinson's disease, non-pharmacological treatments may be used, which are not available in the claim data. Therefore, it is possible that Parkinson's disease actually occurred earlier than our defined index date. We could not assess genetic status in this study. Lastly, measurement of insulin resistance is indirect, and factors modifying HDL and TG might influence the ratio.

In conclusion, our study provides information that TG/HDL ratio may be positively associated with PD incidence risk in a non-DM population in longitudinal setting of the general population.

Data availability

The data used in this study are available from the National Health Insurance Service-National Health Screening Cohort (NHIS-HEALS) database. However, restrictions apply to the public availability of the data used under license for the current study. Requests for access to NHIS data can be made through the National Health Insurance Sharing Service homepage (http://nhiss.nhis.or.kr/bd/ab/bdaba021eng.do). To access the database, a completed application form, research proposal, and application for approval from the Institutional Review Board should be submitted to the Inquiry Committee of Research Support at the NHIS for review.

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Author contributions
Tae-Jin Song designed this study. Yoonkyung Chang and Ju-young Park extracted, collected, and analyzed the data. Ju-Young Park and Tae-Jin Song prepared the tables and figures. Song, Chang, and Park reviewed the results and interpreted the data. Tae-Jin Song and Yoonkyung Chang prepared the manuscript. All authors have approved the submission of the manuscript.

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Declarations

Competing interests
The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to T.-J.S.