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Dynamic Smoking Patterns and Risk of Parkinson Disease and All-Cause Mortality

A Competing Risk Analysis Approach

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Abstract

Background and Objectives

Smoking has been reported to be inversely associated with Parkinson disease (PD). However, the higher premature mortality among smokers may act as a competing risk, potentially confounding the inverse association. Because smoking behavior is dynamic, the long-term impact of changes among current smokers remains unclear. We investigated the association between longitudinal changes in smoking status and the risks of PD and all-cause mortality using a competing risk framework and an age-based time scale with left truncation.

Methods

This large-scale retrospective cohort study included current smokers aged 40 years or older who participated in all 3 examination periods of the Korean National Health Screening. Based on longitudinal changes from the initial smoking status to 2 subsequent time points, participants were categorized into 4 groups: persistent smokers, recent quitters, sustained quitters, and relapsed smokers. Cumulative incidence functions for PD were estimated, with all-cause mortality as a competing event, and subdistribution hazard ratios (sHRs) with 95% CIs were obtained using Fine-Gray models.

Results

Data were obtained from 410,489 eligible participants (mean age 51.7 ± 9.0 years; 93.5% male). During a median 9.1-year follow-up, persistent smokers exhibited the lowest risk of PD. Both recent quitters and sustained quitters had higher PD risk than persistent smokers (sHR 1.60 [1.41–1.82] and 1.61 [1.42–1.81]), whereas relapsed smokers did not differ from persistent smokers (sHR 1.05 [0.87–1.28]). For all-cause mortality, recent and sustained quitters had 3% and 17% lower risks, respectively, compared with persistent smokers, whereas relapsed smokers showed no significant difference.

Discussion

The observed pattern of PD risk was suggested to be primarily associated with current smoking status rather than cumulative smoking exposure, as relapsed smokers and recent quitters, who had the same number of smoking time points, showed distinctly different risks. Furthermore, 1 time point (~2 years) of short-term abstinence did not attenuate the protective association. Mortality was lowest in sustained quitters while recent quitters showed a marginal trend toward lower risk, supporting the benefit of early cessation. Interpretation should be cautious because smoking status was assessed at 3 time points, subsequent changes were unknown, and most participants were male.

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Glossary

ALT = alanine aminotransferase; **AST** = aspartate aminotransferase; **BMI** = body mass index; **DBP** = diastolic blood pressure; **FBG** = fasting blood glucose; **ICD-10** = International Classification of Diseases, Tenth Revision; **nAChR** = nicotinic acetylcholine receptor; **NHIS** = National Health Insurance Service; **NHSP** = National Health Screening Program; **PD** = Parkinson disease; **SBP** = systolic blood pressure; **sHR** = subdistribution hazard ratio.

Introduction

Parkinson disease (PD), the second most frequently occurring neurodegenerative disorder, is characterized by motor symptoms, including bradykinesia, rigidity, and tremor, as well as a range of nonmotor manifestations that collectively confer significant functional impairment.[1,2] The multifactorial etiology of PD involves both genetic and environmental factors that interact through shared molecular pathways, including α-synuclein aggregation, mitochondrial dysfunction, oxidative stress, and chronic neuroinflammation, culminating in dopaminergic neuronal loss.[3-5]

Among environmental factors, cigarette smoking has received considerable attention owing to its paradoxical association with the risk of PD,[6,7] which has been demonstrated as an inverse relationship,[8-10] which contrasts with the well-documented adverse health effects of smoking on other organ systems.[11-13] The proposed neuroprotective effects of smoking-related compounds such as nicotine and carbon monoxide may account for this association through mechanisms that preserve dopaminergic neurons or mitigate neuroinflammatory processes.[14-16] Nonetheless, the interpretation of this inverse association warrants caution because smokers often experience premature death, potentially leading to a competing risk that obscures the true relationship between smoking and PD.

Cigarette smoking status frequently undergoes dynamic changes over time. According to the 2015 National Health Interview Survey data from the United States, approximately 55% of adult smokers had attempted to quit smoking within the preceding year.[17] Nevertheless, most previous investigations relied on single–time point assessments or cumulative exposure measures, such as pack-years, which may not fully capture the complexities of longitudinal smoking behavior.[9,10,18] Although an inverse association between smoking and PD has been consistently reported, the long-term impact of changes in smoking status among current smokers on the risk of PD remains unclear. Given that premature death from smoking constitutes a competing event for PD and the age-related nature of PD can distort risk estimates, a detailed longitudinal analysis of dynamic smoking patterns is warranted.

In this study, we investigated the association between dynamic changes in smoking status and the risks of PD and all-cause mortality in a large-scale cohort. We tracked current smokers over multiple time points and applied a competing risk framework to account for premature death, while minimizing potential immortal time bias and age-related confounding through careful temporal alignment of exposure and follow-up periods.

Methods

Study Design and Study Population

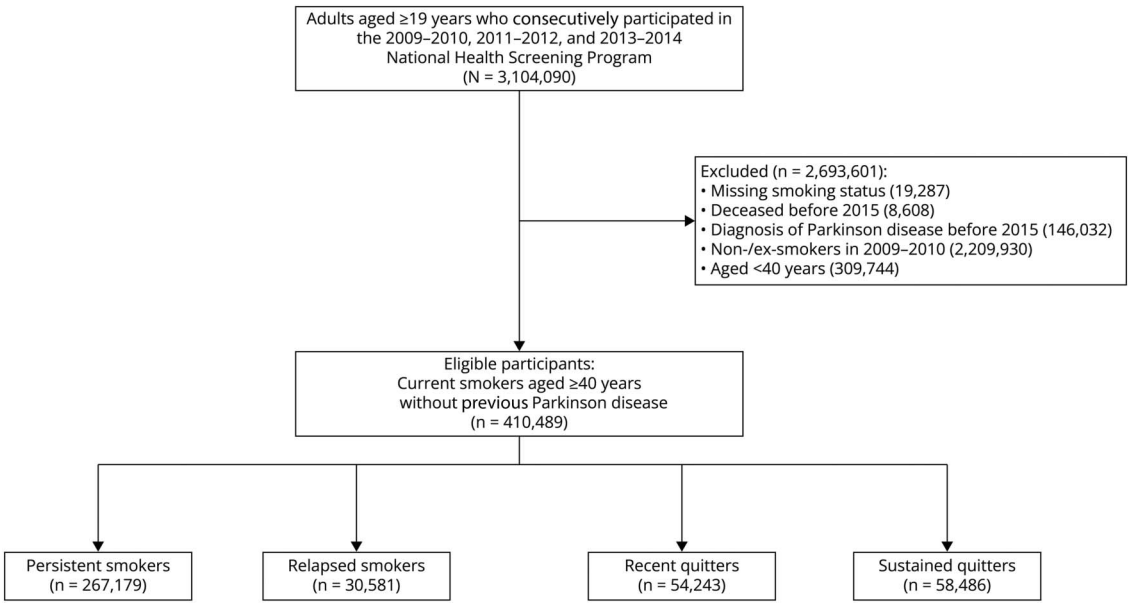
This retrospective cohort study used data from the National Health Screening Program (NHSP), provided by the Korea National Health Insurance Service (NHIS). The NHIS provides a free health-screening program biennially for Koreans under Article 52 of the National Health Insurance Act to ensure that preventive health care services facilitate early disease detection.

Figure 1 shows the flowchart of the study population. Among a total of 3,104,090 adults aged 19 years or older who participated in the 2009–2010, 2011–2012, and 2013–2014 NHSPs, we excluded individuals with the following criteria: (1) missing information on smoking status (n = 19,287); (2) death before 2015 (n = 8,608); (3) a diagnosis of PD before 2015 (n = 146,032); (4) nonsmokers or ex-smokers (n = 2,209,930); and (5) age younger than 40 years (n = 309,744). Finally, 410,489 current smokers were included in the analysis.

Assessment of Smoking Status

Participants reported their smoking status as never, former, or current. Moreover, current smokers provided information on their average daily smoking quantity and duration, which was used to calculate pack-years by multiplying the daily smoking amount by the duration (in years). Among the current smokers identified in the 2009–2010 NHSP, we assessed changes in smoking status during the 2011–2012 and 2013–2014 NHSPs. Based on these assessments, participants were classified into 4 groups: (1) persistent smokers (n = 267,179) who reported smoking at both time points; (2) relapsed smokers (n = 30,581) who had quit at the first time point but resumed smoking at the second time point; (3) recent quitters (n = 58,243) who reported smoking at the first time point and had quit by the second time point; and (4) sustained quitters (n = 58,486) who reported abstinence at both time points. Our analyses relied on the assumption that the smoking behavior observed at the final assessment was generally representative of subsequent patterns during the observation period.

Figure 1 Flowchart of the Study Population Selection



Outcome

The primary outcome was new-onset PD, which was identified using a combination of the International Classification of Diseases, Tenth Revision (ICD-10), code G20 and a national registration program with special reimbursement codes (V codes; specifically, V124). All-cause mortality was a competing risk factor. Information on the deaths was obtained from the Korean National Statistical Office. The duration was calculated from the date of the 2013–2014 NHSP to the date of diagnosis of new-onset PD, death, or December 31, 2022, for participants without recorded events.

Measurements

Height (m) and body weight (kg) were measured, and body mass index (BMI) was calculated by dividing the body weight by the square of height (kg/m^2). Systolic and diastolic blood pressures (SBP and DBP, respectively) were measured in the sitting position after at least 5 minutes of rest. Laboratory tests were conducted after at least 8 hours of fasting, and fasting blood glucose (FBG), serum aspartate aminotransferase (AST), alanine aminotransferase (ALT), and total cholesterol levels were measured. Alcohol consumption was categorized as current or nondrinking. Physical activity was assessed, and regular exercisers were defined as individuals who engaged in moderate-intensity or vigorous-intensity activities for at least 5 or 3 days per week, respectively. Individuals with low income were defined as those receiving Medical Aid or belonging to the lowest income quintile based on NHIS premiums. Hypertension was defined as having (1) ICD-10 codes I10–I13 or I15 while taking antihypertensive medication; (2) an SBP ≥140 mm Hg; or (3) a DBP of ≥90 mm Hg.[19] Type 2 diabetes mellitus was defined as having (1) ICD-10 codes E11–E14 while taking antidiabetic medication or insulin therapy or (2) an FBG level ≥126 mg/dL.[20] Dyslipidemia was defined as having (1) the ICD-10 code E78 while taking lipid-lowering medication or (2) a serum total cholesterol level ≥240 mg/dL.[21]

Statistical Analysis

Data are presented as mean ± SD or median (25th and 75th) for continuous variables and number (%) for categorical variables.

To account for the age-dependent risk of PD, analyses were performed using attained age as the underlying time scale with left truncation at baseline age, which appropriately handled delayed entry and minimized bias due to differential entry times. Cumulative incidence functions for PD and all-cause mortality were estimated across smoking trajectory groups within a competing risk framework based on the Fine-Gray method, treating death or PD as the respective competing events. Pointwise 95% CIs were calculated from nonparametric variance estimates.

Fine and Gray[22] competing risk regression was used to estimate subdistribution hazard ratios (sHRs) and 95% CIs for incident PD, treating all-cause mortality as a competing event. The age-based time scale with left truncation at baseline was used to account for delayed entry. Covariates were adjusted sequentially across 3 models: model 1 included sex; model 2 further adjusted for BMI, low income, smoking pack-years, alcohol consumption, and physical activity, representing demographic and lifestyle factors; and model 3 further incorporated hypertension, type 2 diabetes mellitus, and dyslipidemia to account for major cardiometabolic comorbidities that may influence both smoking behaviors and mortality risk, thereby providing a more conservative estimate of the association with PD. These variables were included only

in model 3 to avoid potential overadjustment in earlier models and to evaluate the robustness of the association under a fully adjusted framework.

The proportional hazards assumption was assessed using Schoenfeld residual–based tests and time-varying interaction terms between age and smoking trajectory. No significant violations were observed (global $p = 0.382$ for the cause-specific Cox model and $p = 0.461$ for the Fine-Gray model; eTable 1).

All statistical analyses were performed using R (version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria) and SAS Enterprise Guide version 7.1 (SAS Institute, Cary, NC). Statistical significance was set at 2-sided $p < 0.05$.

Standard Protocol Approvals, Registrations, and Patient Consents

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Nowon Eulji Medical Center (2023-09-009). Informed consent was waived by the Institutional Review Board of Nowon Eulji Medical Center due to the anonymity of the data provided by the NHIS, and all personal information was encrypted.

Data Availability

The authors do not have the authority to share the data because it was derived from public data provided by the Korean NHIS.

Results

Clinical Characteristics of the Study Population

Table 1 summarizes the baseline characteristics of the study population according to smoking trajectory groups. Among 410,489 adults aged 40 years or older, men accounted for 93.5% of the total population and the mean age was 51.7 ± 9.0 years. Persistent smokers were predominantly male (95.6%) and showed the greatest lifetime tobacco exposure (median 20 pack-years) and highest prevalence of alcohol drinking (75.1%). Relapsed smokers had a slightly higher mean waist circumference (83.6 cm) and included the largest proportion of individuals with low income (13.3%). Recent quitters showed intermediate characteristics across most variables, including a mean age of 53.0 years and BMI of 23.9 kg/m^2. Sustained quitters were older (mean 53.6 years) and had the highest proportions of regular exercisers (29.7%) and those with hypertension (28.6%). Mean FBG, serum AST, ALT, and total cholesterol levels were similar across groups, and the prevalence of type 2 diabetes mellitus and dyslipidemia was approximately 12% and 14%, respectively.

Risk of New-Onset PD and All-Cause Mortality Across Changes in Smoking Status

During a median follow-up of 9.1 years encompassing 3,589,925 person-years, 1,794 new-onset PD cases (0.44%) and 31,203 deaths (7.60%) were identified.

Figure 2 shows the cumulative incidence of PD by smoking trajectory groups. The incidence increased progressively with age in all groups, diverging in mid-adulthood. Sustained quitters and recent quitters had the highest cumulative incidence of PD, whereas persistent smokers showed the lowest risk throughout follow-up. Figure 3 illustrates the cumulative incidence of all-cause mortality, which rose steadily with age in all groups. Persistent and relapsed smokers had higher mortality than recent and sustained quitters, with trajectories converging at older ages. Because attained age was used as the underlying time scale, the cumulative incidence curves represent age-specific risk rather than a direct function of follow-up duration. Corresponding cumulative incidence values at 5-year intervals are summarized in eTables 2 and 3, showing that the cumulative incidence of PD reached approximately 0.24% in persistent smokers and 0.47% in sustained quitters by age 100, whereas the cumulative incidence of death reached approximately 5.2% and 4.5%, respectively.

Table 2 summarizes the sHRs for new-onset PD and all-cause mortality across smoking trajectory groups, estimated from Fine-Gray competing risk regression models using attained age as the underlying time scale. Persistent smokers served as the reference group in all analyses. In the unadjusted model, both recent and sustained quitters showed higher risks of PD (sHR 1.64 [95% CI 1.46–1.86] and 1.65 [1.47–1.85], respectively), whereas relapsed smokers did not differ significantly (sHR 1.06 [0.88–1.28]). In model 3, the risk of PD remained elevated in recent (sHR 1.60 [1.41–1.82]) and sustained (sHR 1.61 [1.42–1.81]) quitters, but not in relapsed smokers (sHR 1.05 [0.87–1.28]). For all-cause mortality, unadjusted sHRs were 0.93 (0.89–0.97) for relapsed smokers, 0.93 (0.90–0.96) for recent quitters, and 0.76 (0.74–0.79) for sustained quitters. After adjustment in model 3, sustained quitters maintained a significantly lower mortality risk (sHR 0.83 [0.80–0.86]), while recent quitters showed a marginally lower risk (sHR 0.97 [0.94–1.00], $p = 0.038$). Relapsed smokers no longer differed significantly from persistent smokers (sHR 0.97 [0.93–1.02]).

Discussion

In this large-scale cohort study, smoking cessation was significantly associated with an increased risk of PD, even after accounting for all-cause mortality as a competing risk. Both recent and sustained quitters showed a higher risk of PD compared with persistent smokers, whereas relapsed smokers exhibited a risk comparable to that of persistent smokers. From a mortality perspective, recent quitters showed marginal reduction in mortality risk and sustained quitters demonstrated a significant reduction in death risk compared with persistent smokers. This trend highlights that early and sustained cessation remains the sole behavior associated with improved survival within the framework of dynamic smoking patterns.

Table 1 Baseline Characteristics of the Study Population

Variables	Persistent smokers (n = 267,179)	Relapsed smokers (n = 30,581)	Recent quitters (n = 54,243)	Sustained quitters (n = 58,486)
Men, n (%)	255,443 (95.6)	27,816 (91.0)	49,622 (91.5)	51,056 (87.3)
Age, y	50.9 ± 8.7	52.3 ± 9.2	53.0 ± 9.4	53.6 ± 9.6
BMI, kg/m^2	23.9 ± 3.0	24.0 ± 2.9	23.9 ± 2.9	24.0 ± 2.9
WC, cm	83.5 ± 7.8	83.6 ± 7.8	83.5 ± 7.8	83.4 ± 7.9
SBP, mm Hg	124.2 ± 14.6	124 ± 14.8	124.2 ± 14.7	124.1 ± 14.8
DBP, mm Hg	78.1 ± 10.0	77.8 ± 10.0	77.8 ± 10.0	77.7 ± 10.0
Low income, n (%)	34,642 (13.1)	4,018 (13.3)	6,890 (12.9)	7,322 (12.7)
Smoking pack-year	20.0 (13; 30.0)	19.0 (10.0; 30.0)	19.0 (10.0; 30.0)	15.0 (6.0; 25.0)
Alcohol drink, n (%)	198,347 (75.1)	21,993 (72.9)	38,759 (72.4)	40,102 (69.6)
Regular exercise, n (%)	70,956 (26.7)	8,843 (29.1)	15,240 (28.3)	17,236 (29.7)
FBG, mg/dL	101.9 ± 28.1	101.8 ± 28.3	101.4 ± 27.1	101.3 ± 26.1
AST, U/L	24.0 (20.0; 30.0)	24.0 (20.0; 30.0)	24.0 (20.0; 30.0)	24.0 (20.0; 29.0)
ALT, U/L	24.0 (17.0; 34.0)	23.0 (17.0; 33.0)	23.0 (17.0; 32.0)	23.0 (17.0; 32.0)
Total cholesterol, mg/dL	199.1 ± 36.8	198.4 ± 37.1	198.4 ± 36.6	198.6 ± 36.7
Hypertension, n (%)	69,083 (25.9)	8,287 (27.1)	14,859 (27.4)	16,723 (28.6)
Type 2 diabetes mellitus, n (%)	31,828 (11.9)	3,687 (12.1)	6,336 (11.7)	6,789 (11.6)
Dyslipidemia, n (%)	38,294 (14.3)	4,389 (14.4)	7,698 (14.2)	8,432 (14.4)

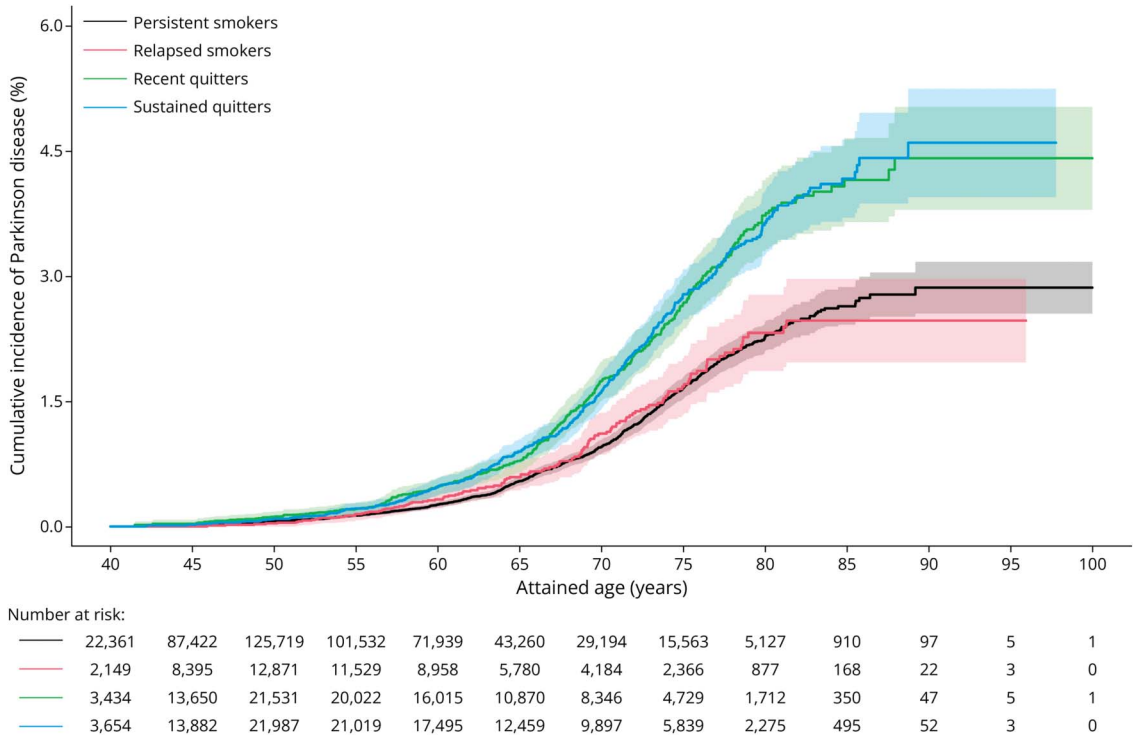
Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; FBG = fasting blood glucose; SBP = systolic blood pressure; WC = waist circumference.

Numerous studies have investigated the relationship between smoking and PD, reporting a consistent inverse association across diverse populations. When categorized by current smoking status, several large-scale cohort studies have shown that PD risk is substantially lower among current smokers than among former or never smokers.[9,23-25] A previous meta-analysis[24] reported a 41% reduction in PD risk among smokers. Furthermore, cumulative smoking exposure has been shown to play a key role, with a clear dose-response relationship being particularly emphasized. Chen et al.[9] demonstrated that the inverse association with PD was driven more by smoking duration than by daily cigarette intensity. However, in a 65-year cohort of 30,000 British doctors, the inverse association between smoking and PD strengthened with both greater cumulative exposure duration and higher daily consumption, although the association attenuated as time since cessation increased.[25]

Although PD risk has been suggested to relate to both current smoking status and cumulative exposure during the enrollment period, our findings indicate that it is primarily determined by the current smoking status at the beginning of follow-up. The difference between persistent smokers and sustained quitters, who differed by 2 additional time points of smoking exposure, may reflect cumulative effects, but the marked contrast between relapsed smokers and recent quitters with the same number of smoking time points underscores the predominant influence of recent smoking status on PD risk. Notably, the comparable 2-year gap in exposure between relapsed and persistent smokers, and between recent and sustained quitters, did not result in substantial differences in PD risk. This pattern indicates that short-term abstinence of approximately 1 time point did not attenuate the protective association with PD risk. Collectively, these findings indicate that the protective association with PD is primarily governed by current smoking status, followed by the cumulative effects of previous exposure, and is not reversed by temporary abstinence. These speculations, however, are based on the assumption that the dynamic smoking pattern observed during the enrollment period might have persisted throughout the observation period and thus should be interpreted with caution. Future studies are warranted to incorporate cumulative exposure after the enrollment period, which remains an unobserved exposure window in the present analysis.

This inverse association may be explained through multiple behavioral and biological mechanisms. The prodromal symptoms of PD, such as olfactory dysfunction and reduced

Figure 2 Cumulative Incidence of Parkinson Disease Across Smoking Trajectory Groups

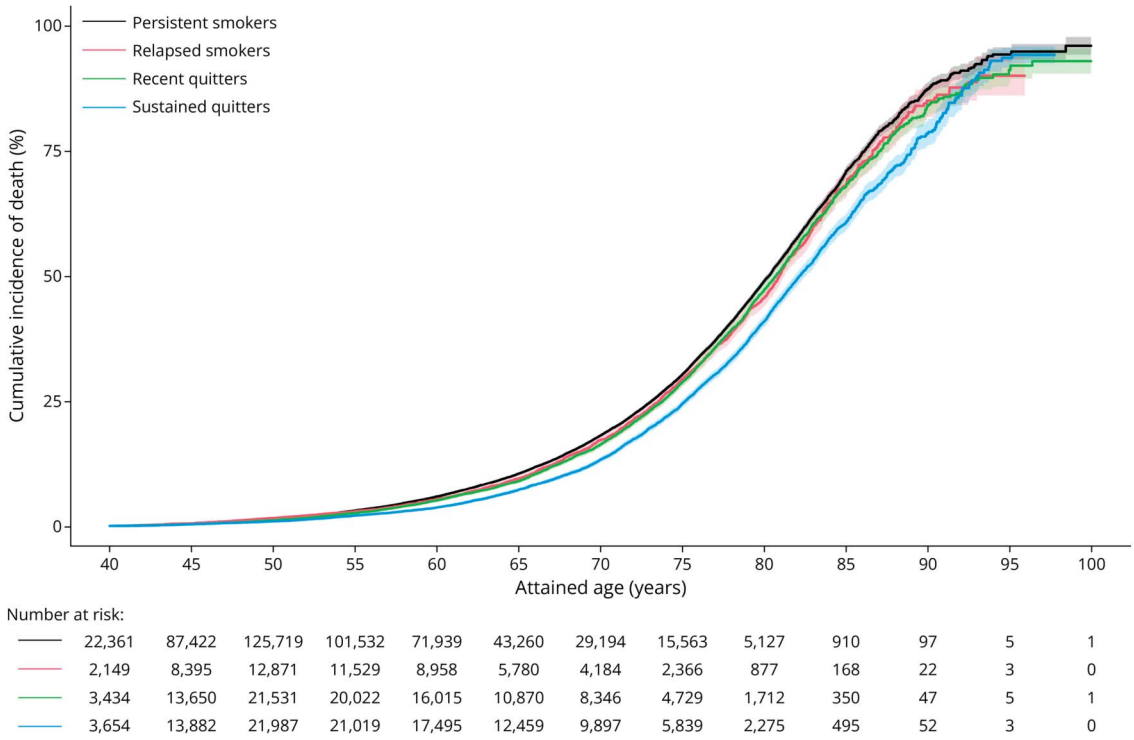


Curves are based on Fine-Gray competing risk models using attained age as the underlying time scale, with death treated as a competing event. Numbers at risk by attained age are shown below the figure. Group sizes were as follows: persistent smokers (n = 267,179), relapsed smokers (n = 30,581), recent quitters (n = 54,243), and sustained quitters (n = 58,486).

reward-seeking behavior, may lead individuals to quit smoking.[26] Recent longitudinal analyses suggest that the inverse relationship between smoking and PD risk intensifies as the prodromal phase shortens, showing a gradual linear pattern.[27] These findings suggest that neurodegenerative changes may begin to alter smoking behavior well before the clinical onset of PD. Therefore, the finding that sustained quitters exhibited the highest PD incidence despite their lowest mortality may not be fully attributed to a loss of the protective effect of smoking, as reverse causation due to prodromal behavioral changes may still have influenced these associations. Several Mendelian randomization studies have sought to disentangle this reverse causation hypothesis, but their results remain inconsistent.[3,28,29] Although the exposure assessment and event accrual periods were separated to minimize potential temporal overlap in our study, this structural approach cannot completely eliminate reverse causation. Further large-scale analyses with adequate statistical power are required to clarify the causal direction of this association.

At the molecular level, nicotine, a key component of tobacco, activates nicotinic acetylcholine receptors (nAChRs), particularly the α7 subtype.[30] This activation increases dopamine release, reduces oxidative stress, and mitigates α-synuclein aggregation, which is a hallmark of PD pathology.[31,32] While the reversibility of nicotinic receptor upregulation offers a plausible explanation for the attenuation of the protective association after prolonged abstinence, our findings indicate that short-term cessation within 2 years did not substantially alter PD risk. This suggests that the neuroprotective effect may not dissipate immediately after quitting, but rather decline gradually over time. Given that previous long-term cohort studies have reported diminished protection in analyses using broad cessation categories such as <10 years,[25,33] further research is warranted to delineate the temporal threshold at which the inverse association begins to wane. Although receptor-based mechanisms may adequately explain the short-term and cessation-related patterns, they cannot fully account for the cumulative dose-response relationship consistently observed across studies.[9,10,24,25] Additional long-term neuroadaptive or epigenetic processes may underlie this chronic exposure effect, which requires further experimental validation. Similarly, inhibition of monoamine oxidase B, an enzyme involved in dopamine metabolism,[34] produces a reversible and short-lived reduction in dopamine breakdown and the formation of neurotoxic byproducts such as hydrogen peroxide, thereby limiting oxidative stress and supporting dopaminergic neuron survival.[35] Recently, Rose et al.[14] demonstrated that low doses of carbon monoxide improved mitochondrial function, prevented dopaminergic neuronal loss, and reduced protein aggregation that contributes to the pathology of PD. These findings suggest that carbon monoxide may represent a novel neuroprotective mechanism.

Figure 3 Cumulative Incidence of All-Cause Mortality Across Smoking Trajectory Groups



Curves were estimated using Fine-Gray competing risk models with attained age as the time scale and Parkinson disease treated as a competing event. Numbers at risk by attained age are shown below the figure. Group sizes were as follows: persistent smokers (n = 267,179), relapsed smokers (n = 30,581), recent quitters (n = 54,243), and sustained quitters (n = 58,486).

Despite evidence of the neuroprotective effects of smoking, its severe health risks cannot be overlooked. Smoking remains a leading cause of preventable death worldwide and contributes to cardiovascular diseases, cancer, and chronic respiratory disorders.[36-38] Therefore, the observed inverse association between smoking and the risk of PD must not be interpreted as an endorsement of smoking. These findings highlight the urgent need to develop safe and targeted therapies that replicate the neuroprotective mechanisms of smoking without harmful health consequences. Potential strategies include nicotine replacement therapies, synthetic α7 nAChR agonists, and low-dose carbon monoxide treatments. For example, previous studies[39,40] proposed that selective nAChR agonists and dietary nicotine analogs are promising therapeutic candidates, and these interventions represent important opportunities for future research and clinical applications that offer pathways to address PD prevention and treatment without exacerbating public health challenges.

This study has several strengths that enhance the validity of its findings. The use of a large cohort provides substantial statistical power, whereas a longitudinal design allows for a detailed examination of temporal changes in smoking behavior and their relationship with PD risk and mortality. Furthermore, comprehensive adjustments were made to minimize potential biases, including the competing risk of smoking-related mortality, the possibility of immortal time bias arising from cohort entry, the age dependency of PD incidence, and major confounders such as age, sex, BMI, and alcohol consumption.

However, this study had some limitations that must be considered. First, the reliance on self-reported smoking data introduces the potential for recall bias. Second, smoking patterns were defined based on 3 assessments during the enrollment period, and subsequent behavioral changes could not be verified, possibly limiting the accuracy of cumulative exposure estimation. Third, because this study design focused mainly on dynamic smoking patterns rather than quantitative exposure levels, detailed measures of cigarette consumption were incorporated only as adjustment variables. In addition, as an observational study, potential residual confounding and reverse causation cannot be fully excluded because unmeasured lifestyle or environmental factors and prodromal behavioral changes may have influenced both smoking behavior and disease risk. Finally, because most of the participants ultimately included in our analysis were Korean men, caution is warranted when generalizing these results to women or to other ethnic and cultural groups.

In conclusion, competing risk analyses incorporating dynamic smoking patterns revealed that PD risk was primarily determined by current smoking status rather than cumulative exposure, and that short-term abstinence did not attenuate the protective association. Although sustained smoking

Table 2 Competing Risk Analysis for the Risk of PD and All-Cause Mortality

	Persistent smokers	Relapsed smokers		Recent quitters		Sustained quitters	
Total cases, n	267,179	30,581		54,243		58,486	
Median follow-up, years	9.1 (8.4–9.5)	9.1 (8.4–9.5)		9.0 (8.3–9.4)		9.1 (8.4–9.5)	
Incident PD cases, n	890	125		364		415	
Risk of PD	sHR	sHR (95% CI)	*p* Value	sHR (95% CI)	*p* Value	sHR (95% CI)	*p* Value
Unadjusted	1 (reference)	1.06 (0.88–1.28)	0.517	1.64 (1.46–1.86)	<0.001	1.65 (1.47–1.85)	<0.001
Model 1	1 (reference)	1.07 (0.89–1.29)	0.487	1.65 (1.46–1.87)	<0.001	1.66 (1.47–1.87)	<0.001
Model 2	1 (reference)	1.05 (0.87–1.28)	0.602	1.60 (1.41–1.81)	<0.001	1.60 (1.42–1.81)	<0.001
Model 3	1 (reference)	1.05 (0.87–1.28)	0.603	1.60 (1.41–1.82)	<0.001	1.61 (1.42–1.81)	<0.001
Death cases, n	19,347	2,475		4,754		4,627	
Risk of death	sHR	sHR (95% CI)	*p* Value	sHR (95% CI)	*p* Value	sHR (95% CI)	*p* Value
Unadjusted	1 (reference)	0.93 (0.89–0.97)	<0.001	0.93 (0.90–0.96)	<0.001	0.76 (0.74–0.79)	<0.001
Model 1	1 (reference)	0.95 (0.91–0.99)	0.011	0.94 (0.91–0.97)	<0.001	0.78 (0.76–0.81)	<0.001
Model 2	1 (reference)	0.97 (0.93–1.01)	0.183	0.96 (0.93–0.99)	0.021	0.83 (0.80–0.85)	<0.001
Model 3	1 (reference)	0.97 (0.93–1.02)	0.217	0.97 (0.94–1.00)	0.038	0.83 (0.80–0.86)	<0.001

Abbreviations: BMI = body mass index; PD = Parkinson disease; sHR = subdistribution hazard ratio.
sHRs and 95% CIs were estimated using Fine-Gray competing risk regression models, with attained age as the underlying time scale and death treated as a competing event for PD.
Model 1 was adjusted for sex. Model 2: adjusted for sex, BMI, low income, smoking pack-years, alcohol consumption, and physical activity. Model 3: adjusted for sex, BMI, low income, smoking pack-years, alcohol consumption, physical activity, hypertension, type 2 diabetes mellitus, and dyslipidemia.

cessation was associated with a 61% increase in the risk of PD, it was associated with a 17% reduction in all-cause mortality. Therefore, despite the apparent paradox, promoting early and sustained smoking cessation remains vital for public health because of its extensive benefits in reducing preventable deaths and improving the quality of life.

Author Contributions

S.-H. Ahn: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. D.H. Kim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; analysis or interpretation of data. J. Park: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Yoon: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. J.-H. Lee: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data.

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References

1. Ben-Shlomo Y, Darweesh S, Llibre-Guerra J, Marras C, San Luciano M, Tanner C. The epidemiology of Parkinson's disease. *Lancet*. 2024;403(10423):283-292. doi:10.1016/S0140-6736(23)01419-8
2. Jankovic J. Parkinson's disease: clinical features and diagnosis. *J Neurol Neurosurg Psychiatry*. 2008;79(4):368-376. doi:10.1136/jnnp.2007.131045
3. Domenighetti C, Sugier PE, Sreelatha AAK, et al. Mendelian randomisation study of smoking, alcohol, and coffee drinking in relation to Parkinson's disease. *J Parkinsons Dis*. 2022;12(1):267-282. doi:10.3233/JPD-212851
4. Nalls MA, Pankratz N, Lill CM, et al. Large-scale meta-analysis of genome-wide association data identifies six new risk loci for Parkinson's disease. *Nat Genet*. 2014;46(9):989-993. doi:10.1038/ng.3043
5. Morris HR, Spillantini MG, Sue CM, Williams-Gray CH. The pathogenesis of Parkinson's disease. *Lancet*. 2024;403(10423):293-304. doi:10.1016/S0140-6736(23)01478-2
6. Ascherio A, Schwarzschild MA. The epidemiology of Parkinson's disease: risk factors and prevention. *Lancet Neurol*. 2016;15(12):1257-1272. doi:10.1016/S1474-4422(16)30230-7
7. Lee PC, Ahmed I, Loriot MA, et al. Smoking and Parkinson disease: evidence for gene-by-smoking interactions. *Neurology*. 2018;90(7):e583-e592. doi:10.1212/WNL.0000000000004953
8. Allam MF, Campbell MJ, Hofman A, Del Castillo AS, Fernández-Crehuet Navajas R. Smoking and Parkinson's disease: systematic review of prospective studies. *Mov Disord*. 2004;19(6):614-621. doi:10.1002/mds.20029
9. Chen H, Huang X, Guo X, et al. Smoking duration, intensity, and risk of Parkinson disease. *Neurology*. 2010;74(11):878-884. doi:10.1212/WNL.0b013e3181d55f38
10. Thacker E, O'reilly E, Weisskopf M, et al. Temporal relationship between cigarette smoking and risk of Parkinson disease. *Neurology*. 2007;68(10):764-768. doi:10.1212/01.wnl.0000256374.50227.4b
11. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol*. 2004;43(10):1731-1737. doi:10.1016/j.jacc.2003.12.047
12. Gritz ER, Vidrine DJ, Fingeret MC. Smoking cessation: a critical component of medical management in chronic disease populations. *Am J Prevent Med*. 2007;33(6 suppl):S414-S422. doi:10.1016/j.amepre.2007.09.013

13. Carter BD, Abnet CC, Feskanich D, et al. Smoking and mortality: beyond established causes. *N Engl J Med*. 2015;372(7):631-640. doi:10.1056/NEJMsa1407211
14. Rose K, Zorlu M, Fassini A, et al. Neuroprotection of low dose carbon monoxide in Parkinson's disease models commensurate with the reduced risk of Parkinson's among smokers. *NPJ Parkinsons Dis*. 2024;10(1):152. doi:10.1038/s41531-024-00763-6
15. Villafane G, Thiriez C, Audureau E, et al. High-dose transdermal nicotine in Parkinson's disease patients: a randomized, open-label, blinded-endpoint evaluation phase 2 study. *Eur J Neurol*. 2018;25(1):120-127. doi:10.1111/ene.13474
16. Wang C, Zhou C, Guo T, Huang P, Xu X, Zhang M. Association between cigarette smoking and Parkinson's disease: a neuroimaging study. *Ther Adv Neurol Disord*. 2022;15:17562864221092566. doi:10.1177/17562864221092566
17. Babb S, Malarcher A, Schauer G, Asman K, Jamal A. Quitting smoking among adults: United States, 2000-2015. *MMWR Morb Mortal Wkly Rep*. 2017;65(52):1457-1464. doi:10.15585/mmwr.mm6552a1
18. Kim R, Yoo D, Jung YJ, Han K, Lee JY. Sex differences in smoking, alcohol consumption, and risk of Parkinson's disease: a nationwide cohort study. *Parkinsonism Relat Disord*. 2020;71:60-65. doi:10.1016/j.parkreldis.2019.12.006
19. Chobanian AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. *Hypertension*. 2003;42(6):1206-1252. doi:10.1161/01.HYP.0000107251.49515.c2
20. American Diabetes Association Professional Practice Committee. 2. Diagnosis and classification of diabetes: standards of care in diabetes: 2024. *Diabetes Care*. 2024;47(suppl 1):S20-S42. doi:10.2337/dc24-S002
21. Rhee EJ, Kim HC, Kim JH, et al. 2018 Guidelines for the management of dyslipidemia. *Korean J Int Med*. 2019;34(4):723-771. doi:10.3904/kjim.2019.188
22. Fine JP, Gray RJ. A proportional hazards model for the subdistribution of a competing risk. *J Am Stat Assoc*. 1999;94(446):496-509. doi:10.1080/01621459.1999.10474144
23. Rose KN, Schwarzschild MA, Gomperts SN. Clearing the smoke: what protects smokers from Parkinson's disease? *Mov Disord*. 2024;39(2):267-272. doi:10.1002/mds.29707
24. Li X, Li W, Liu G, Shen X, Tang Y. Association between cigarette smoking and Parkinson's disease: a meta-analysis. *Arch Gerontol Geriatr*. 2015;61(3):510-516. doi:10.1016/j.archger.2015.08.004
25. Mappin-Kasirer B, Pan H, Lewington S, et al. Tobacco smoking and the risk of Parkinson disease: a 65-year follow-up of 30,000 male British doctors. *Neurology*. 2020;94(20):e2132-e2138. doi:10.1212/WNL.0000000000009437
26. Ritz B, Lee PC, Lassen CF, Arah OA. Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease. *Neurology*. 2014;83(16):1396-1402. doi:10.1212/WNL.0000000000000879
27. Bouhadoun S, Zolfaghari S, Delva A, Pelletier A, Kouchache T, Postuma R. Smoking and Parkinson's disease: insights from the UK Biobank Dataset (P8-3.017). *Neurology*. 2024;102(7 suppl 1):3912. doi:10.1212/wnl.0000000000205459
28. Zhang X, Zhu Z, Zhu L, et al. Integrating Mendelian randomization with single-cell sequencing data reveals the causal effect and related mechanisms of smoking on Parkinson's disease. *Nicotine Tob Res*. 2025;27(5):884-892. doi:10.1093/ntr/ntae180
29. Noyce AJ, Bandres-Ciga S, Kim J, et al. The Parkinson's disease Mendelian randomization research portal. *Mov Disord*. 2019;34(12):1864-1872. doi:10.1002/mds.27873
30. De Simone R, Ajmone-Cat MA, Carnevale D, Minghetti L. Activation of alpha7 nicotinic acetylcholine receptor by nicotine selectively up-regulates cyclooxygenase-2 and prostaglandin E2 in rat microglial cultures. *J Neuroinflammation*. 2005;2(1):4. doi:10.1186/1742-2094-2-4
31. Nozaki S, Hijioka M, Wen X, et al. Galantamine suppresses α-synuclein aggregation by inducing autophagy via the activation of α(7) nicotinic acetylcholine receptors. *J Pharmacol Sci*. 2024;156(2):102-114. doi:10.1016/j.jphs.2024.07.008
32. Quik M, Perez XA, Bordia T. Nicotine as a potential neuroprotective agent for Parkinson's disease. *Mov Disord*. 2012;27(8):947-957. doi:10.1002/mds.25028
33. Hernán MA, Zhang SM, Rueda-deCastro AM, Colditz GA, Speizer FE, Ascherio A. Cigarette smoking and the incidence of Parkinson's disease in two prospective studies. *Ann Neurol*. 2001;50(6):780-786. doi:10.1002/ana.10028
34. Fowler JS, Volkow ND, Wang GJ, et al. Inhibition of monoamine oxidase B in the brains of smokers. *Nature*. 1996;379(6567):733-736. doi:10.1038/379733a0
35. Soares AR, Picciotto MR. Nicotinic regulation of microglia: potential contributions to addiction. *J Neural Transm (Vienna)*. 2024;131(5):425-435. doi:10.1007/s00702-023-02703-9
36. McBride PE. The health consequences of smoking. Cardiovascular diseases. *Med Clin North Am*. 1992;76(2):333-353. doi:10.1016/s0025-7125(16)30356-x
37. Gandini S, Botteri E, Iodice S, et al. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer*. 2008;122(1):155-164. doi:10.1002/ijc.23033
38. Forey BA, Thornton AJ, Lee PN. Systematic review with meta-analysis of the epidemiological evidence relating smoking to COPD, chronic bronchitis and emphysema. *BMC Pulm Med*. 2011;11:36. doi:10.1186/1471-2466-11-36
39. Quik M, Zhang D, McGregor M, Bordia T. Alpha7 nicotinic receptors as therapeutic targets for Parkinson's disease. *Biochem Pharmacol*. 2015;97(4):399-407. doi:10.1016/j.bcp.2015.06.014
40. Crooks PA, Bardo MT, Dwoskin LP. Nicotinic receptor antagonists as treatments for nicotine abuse. *Adv Pharmacol*. 2014;69:513-551. doi:10.1016/B978-0-12-420118-7.00013-5