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Objective

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor manifestations. Clinically, PD can be classified into early-onset PD (EOPD) and late-onset PD (LOPD), which differ in age at onset, relative contributions of genetic and environmental factors, disease progression, and long-term prognosis. Although cigarette smoking has consistently been associated with a lower incidence of PD in epidemiological studies, it remains unclear whether this inverse association differs according to age at onset. We aimed to investigate whether the association between smoking and PD incidence varies between EOPD and LOPD in a large nationwide cohort.

Materials and Methods

We conducted a nationwide population-based cohort study using the Korean National Health Insurance Service database, which includes comprehensive health screening and claims data for the entire Korean population. Individuals who underwent standardized health screening in 2012 and were free of PD at baseline were followed until December 31, 2022. Newly diagnosed PD cases during follow-up were identified and classified as EOPD (<50 years) or LOPD (≥50 years) according to age at diagnosis. Smoking status (never, former, and current) and smoking exposure, including duration and cumulative amount, were obtained from self-reported health screening questionnaires. Multivariable Cox proportional hazards regression models were used to estimate the association between smoking and early- and late-onset PD, adjusting for demographic characteristics and potential confounders.

Results

Among more than 4.5 million individuals followed for up to 10 years, 400 cases of EOPD and 17,372 cases of LOPD were identified. In individuals aged <50 years, only current smoking was significantly associated with a reduced risk of PD, whereas former smoking showed no significant association. In contrast, among individuals aged ≥50 years, both former and current smoking were significantly associated with lower PD incidence compared with never smoking (Table 1). Furthermore, a clear dose-response relationship according to smoking duration and cumulative exposure was observed in LOPD, with greater risk reduction in those with longer duration and higher cumulative smoking, whereas such exposure-response patterns were not evident in EOPD (Fig. 1).

Table 1. Cox proportional hazard regression analysis on the risk of Parkinson's disease (PD) according to smoking status stratified by age groups.

		N	PD	Person-years	Incidence rate	Model 1	Model 2	Model 3	Model 4
Age < 50	Never	1,321,885	241	9,172,529.48	0.03	1.00	1.00	1.00	1.00
	Former	321,088	72	2,127,250.02	0.03	1.30 (1.00-1.69)	0.93 (0.72-1.22)	0.962(0.739,1.253)	0.92 (0.71-1.20)
	Current	744,598	87	5,495,085.22	0.02	0.60 (0.47-0.77)	0.49 (0.38-0.62)	0.505(0.394,0.645)	0.48 (0.38-0.62)
	p for trend					0.0003	<.0001	<.0001	<.0001
Age ≥ 50	Never	1,385,042	12,599	12,608,063.48	1.00	1.00	1.00	1.00	1.00
	Former	380,753	3,151	3,412,887.74	0.92	0.93 (0.89-0.96)	0.82 (0.78-0.85)	0.84 (0.80-0.88)	0.83 (0.79-0.87)
	Current	358,955	1,622	3,190,751.73	0.51	0.51 (0.49-0.54)	0.57 (0.54-0.60)	0.59 (0.56-0.62)	0.59 (0.56-0.63)
	p for trend					<.0001	<.0001	<.0001	<.0001
p for interaction						0.0368	0.2029	0.1875	0.1407

Incidence rate is the incidence of mortality per 1000 person-years.

Model 1: unadjusted

Model 2: adjusted for age, sex, income, and residential area

Model 4: adjusted for age, sex, income, residential area, smoking, drinking, and regular exercise

Model 4: adjusted for age, sex, income, residential area, smoking, drinking, and regular exercise, body mass index, diabetes mellitus, hypertension, dyslipidemia, chronic kidney disease, and depression

Conclusion

In this large nationwide cohort, smoking was inversely associated with PD incidence; however, the magnitude and exposure-response pattern of this association differed according to age at onset. The stronger and dose-dependent inverse association observed in LOPD compared with EOPD suggests that environmental influences on PD development may vary by age group. These findings underscore the importance of considering age at onset when evaluating environmental risk factors and provide insight into potential differences in the underlying mechanisms of early- and late-onset PD.

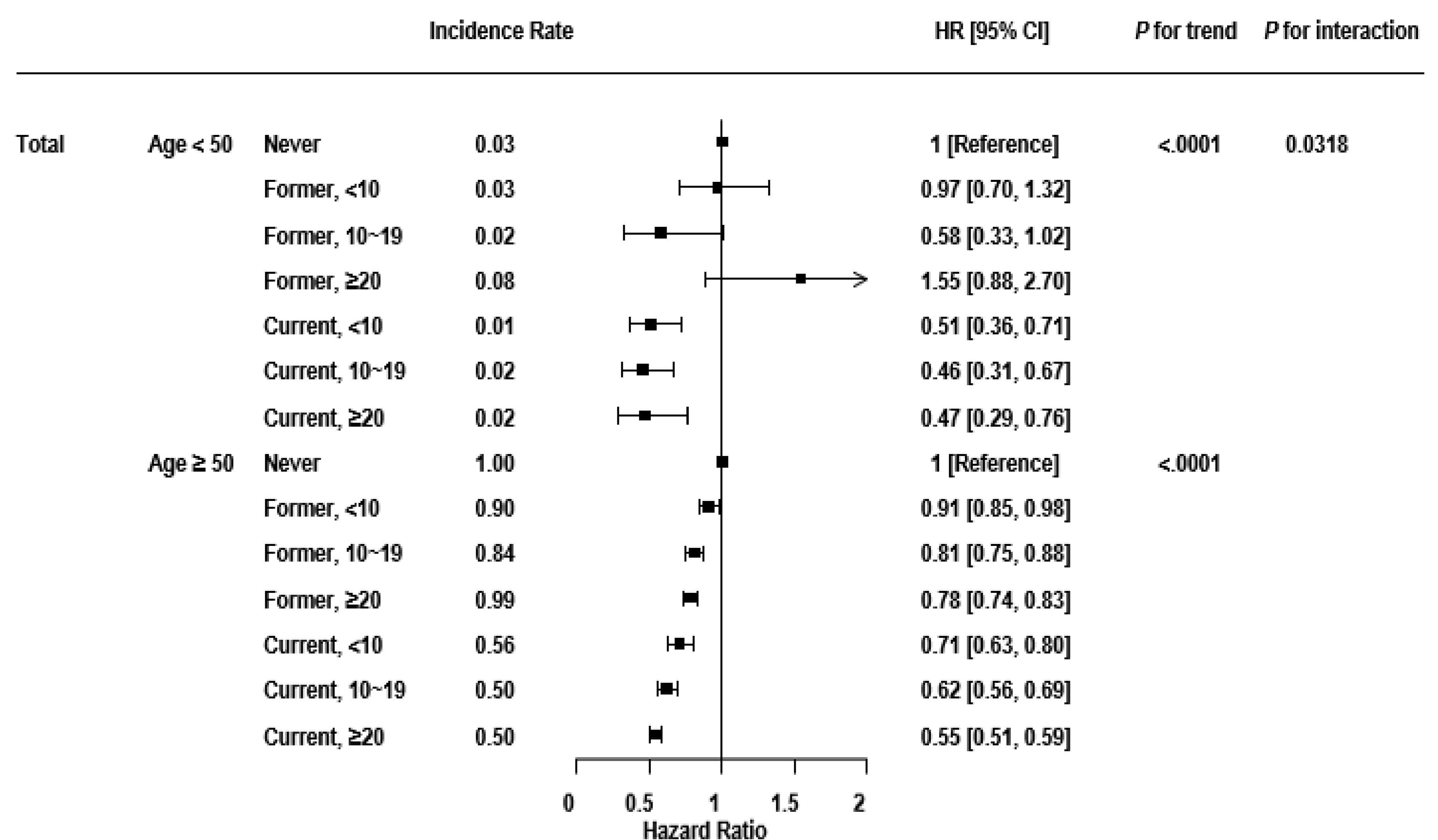


Fig. 1. Cox proportional hazard regression analysis on the risk of Parkinson's disease according to the amount of smoking