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# Nicotine from cigarette smoking and diet and Parkinson disease: a review

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## Abstract

Evidence from epidemiological studies suggest a relationship between cigarette smoking and low risk of Parkinson disease (PD). As a major component of tobacco smoke, nicotine has been proposed to be a substance for preventing against PD risk, with a key role in regulating striatal activity and behaviors mediated through the dopaminergic system. Animal studies also showed that nicotine could modulate dopamine transmission and reduce levodopa-induced dyskinesias. However, previous clinical trials yield controversial results regarding nicotine treatment. In this review, we updated epidemiological, preclinical and clinical data, and studies on nicotine from diet. We also reviewed interactions between genetic factors and cigarette smoking. As a small amount of nicotine can saturate a substantial portion of nicotine receptors in the brain, nicotine from other sources, such as diet, could be a promising therapeutic substance for protection against PD.

**Keywords:** Nicotine, Smoking, Diet, Gene-environment interactions, Parkinson disease

## Background

Parkinson disease (PD) is an age-related neurodegenerative disorder, with a prevalence of 1–2% among adults aged 55 years and older [1]. It is characterized by a progressive degeneration of dopaminergic neurons in the substantia nigra pars compacta that results in tremor, rigidity, bradykinesia, and possibly dementia [2]. The current evidence related to the pathogenesis of PD includes defective handling of proteins, mitochondrial dysfunction, oxidative stress, and inflammation [3–6]. There is no cure for the disease and only symptomatic relief is available. Especially in the early stages of the disease, dopamine replacement therapies provide effective control of the motor symptoms with L-dopa as the gold standard. However, chronic L-dopa use does not adequately manage the non-motor deficits and additionally induces a variety of motor and psychiatric side effects that limits its effectiveness [7, 8]. These shortcomings strengthen the importance of identifying alternate treatment strategies that delay or halt disease progression, or ideally restore function in PD. Previous reviews reported the association between nicotine and PD risk, but the sources were limited to cigarette smoking and medical use. We thus updated epidemiological, preclinical and clinical data, and studies on nicotine from other sources. We also reviewed interactions between genetic factors and cigarette smoking to broaden the understanding of the potential protective role of nicotine on PD.

### Tobacco and PD

Previous epidemiologic studies have consistently shown that cigarette smoking [9–12] and smokeless tobacco use [13, 14] are associated with a lower risk of PD. Environmental tobacco smoke exposure is also associated with a significantly lower PD risk among never active smokers [15, 16]. Population-based studies have shown that smoking was associated with approximately 40–50% reduced risk of developing PD. [10, 11] This inverse relationship between smoking and PD was dose-dependent: age-adjusted relative risks (RRs) of PD were 0.8, 0.6, 0.5, and 0.4, for 1-9, 10-24, 25-44, and 45+ pack-years, relative to never-smokers, as shown in a large prospective cohort study [9]. There is also a temporal relationship between cigarette smoking and PD risk [9, 17]. Individuals with more years of smoking, older age at quitting smoking, and fewer years since quitting smoking had lower PD risk. Researchers prospectively observed a significantly lower

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risk of PD for smoking as early as 15 to 24 years before symptom onset, but not for smoking 25+ years before onset ($n$ = 143,325) [17].

For smokeless tobacco use, such as tobacco chewing and snus use, three epidemiology studies have investigated their association with PD. [13, 14] One case-control study with 196 cases, have shown that tobacco use, including tobacco chewing or snuff use, is inversely associated with risk of PD. [13] In a cohort study with 9 years of follow-up, men who were current users of smokeless tobacco at enrollment had a significant lower risk of PD mortality (age-adjusted RR = 0.22, 95% confidence interval (CI), 0.07 to 0.67) [14]. Another prospective cohort study with 307 PD cases also had a similar inverse association between snus use and PD in men [18]. Consistently, in a case-control study based on 154 PD cases from Washington State, environmental tobacco smoke exposure was associated with 64% lower risk of PD. [15] Among persons with passive smoking as the only tobacco smoke exposure, risk was inversely associated with years exposed [15]. One cohort study using parental smoking as the tobacco exposure, has also shown the dose-response inverse association with PD incidence [16].

Because smoke has always been shown as a cause of adverse health outcomes, the inverse association between smoking and the risk of PD was counterintuitive. Some researchers believed that this relation resulted from a true biological protective effect of cigarette smoking. However, some researchers proposed that the reverse association might result from bias. For example, the association between smoking and lower PD risk could be explained by a still-unknown third factor that increases the risk of PD and also causes an aversion to smoking behavior [19]. A recent study reported that patients with PD were able to quit smoking more easily than controls [19]. This study suggests that the ease of smoking cessation is an early manifestation of pre-motor PD related to the loss of nicotinic rewards. In this case, quitting smoking could be just a pre-clinical marker rather than a risk factor [20]. However, in a case-control study in France, with 247 cases and 676 controls, when smoking was defined as cigarette smoking 18 years before PD onset, the same inverse association was still present [21].

Further, one of disadvantages of case-control studies is incidence-prevalence bias. This type of bias could be due to higher smoking-related mortality among incident cases than among controls, leading to a lower proportion of smokers among prevalent PD cases than among controls. However, the results of prospective cohort studies are in agreement with the results of case-control studies, which could minimize this type of bias. In addition, in a prospective study in the Health Professional Follow-up Study with 288 incident PD cases, smoking was not associated with a higher relative risk of death among PD patients than among non-PD patients [22]. An alternative hypothesis that genetic polymorphisms that influence tolerance to tobacco smoke may also increase the risk of PD might account this inverse association. Twin studies are usually used to test this type of hypothesis as a gold standard. An inverse relationship between smoking and PD was observed among monozygotic twins, suggesting that genetic factors is unlikely to confound this relationship [23, 24].

### Smoking and prodromal PD

REM sleep behavior disorder (RBD) is a parasomnia characterized by symptoms of dream-enacting behaviors and a loss of muscle atonia throughout a REM period as confirmed by polysomnography [25, 26]. A large proportion of individuals (>75%) with RBD developed neurodegenerative synucleinopathy based on prospective cohort studies [27–31]. However, in a hospital-based case-control study, RBD cases were more likely to smoke (adjusted OR = 1.43, $p$ = 0.028), although nonsmoking status has been consistently linked with risk of PD. [32] In addition, two recent community-based cross-sectional studies [33, 34] showed that smoking was not a significant risk factor for probable RBD. For example, in our previous study based on 12,784 Chinese participants of the Kailuan study, the adjusted ORs for probable RBD was 0.91(95% CI: 0.74-1.1) for current smoking and 1.17 (95% CI: 0.85–1.6) for past smoking, compared with non-smokers [33]. In this context, it is possible that some RBD have different pathogenesis.

Both population-based studies [35, 36] and those performed in at-risk populations [37–40] showed that impaired olfactory function was associated with higher PD risk, and could predate development of PD [35]. With regard to the association between smoking and olfactory function, previous studies (all cross-sectional design) generated mixed results: some [41, 42], but not all [43–47], reported that smokers were more likely to have olfactory dysfunction. It remains unclear whether this is due to a true biological effect of smoking on olfaction or a reverse causality – individuals with olfactory dysfunction may quit smoking.

Constipation and higher risk of developing PD was observed in six population-based studies [48–53]. A cross-sectional study with 516 functional constipation cases reported an association between smoking and higher likelihoods of several functional gastrointestinal symptoms, including functional constipation [54]. Researchers observed that smoking delayed gastric emptying of solids, rather than liquids, and nicotine was not responsible for the effect [55], while acute cigarette smoking in habitual smokers delayed mouth–cecum transit time, an effect most likely due to nicotine [56]. After use of transdermal nicotine application in nonsmokers, a dose-dependent, significant decrease of total colon transit