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Original Contribution

Tobacco Use, Oral Health, and Risk of Parkinson's Disease

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Few studies have investigated the associations between use of Swedish moist snuff (snus), associated poor oral health, and risk of Parkinson's disease (PD). We followed 20,175 participants who were free of PD in 1973–1974 in Uppsala, Sweden, until the end of 2012. We used Cox proportional hazards regression models to estimate hazard ratios and corresponding 95% confidence intervals for the associations between tobacco use, oral health indicators, and PD risk. We found that tobacco use was associated with a lower risk of PD in males. Compared with males who never used any tobacco daily, pure ever tobacco smokers, pure ever snus users, and combined users had adjusted hazard ratios of 0.68 (95% confidence interval (CI): 0.49, 0.93; $n = 83$), 0.51 (95% CI: 0.27, 0.95; $n = 11$), and 0.21 (95% CI: 0.07, 0.67; $n = 3$), respectively. No association was observed for number of teeth, dental plaque, or detectable oral mucosal lesions and PD risk, although there was a suggestive association with *Candida*-related oral mucosal lesions in males (hazard ratio = 1.56, 95% CI: 0.92, 2.65; $P = 0.098$). Use of snus is associated with a lower risk of PD in males, while poor oral health seems not to be associated with PD occurrence.

cohort studies; oral health; Parkinson's disease; smoking; snus; tobacco

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; PD, Parkinson's disease.

Although the underlying mechanisms remain the subject of debate (1, 2), an inverse association between risk of Parkinson's disease (PD) and tobacco smoking is well documented (2–5). A strong inverse association between tobacco chewing and the risk of PD has also been reported in a nested case-control study (6). Given that nicotine is one of the chemicals most likely to explain the observed inverse association (7), it is plausible to hypothesize that use of Swedish moist snuff (snus), a tobacco product containing constituents of nicotine (8), may also be inversely associated with the risk of PD. To the best of our knowledge, only 2 epidemiologic studies have investigated the association between snus use and risk of PD (9, 10); both showed that snus use is inversely associated with PD incidence and mortality. However, the case-control study (9) was limited by the concerns of recall bias and potential reverse causation. The cohort study (10) identified PD cases from death certificates, which may be problematic due to the low quality or underreporting of PD as the underlying cause of death (11–13).

Systemically elevated levels of inflammatory markers have been observed in PD patients (14–18), and an animal experiment suggested that inflammation may precede neurodegeneration (19). Habitual users of snus almost invariably develop typical lesions in the mucosa corresponding to the location of the quid (20, 21), and poor oral health can cause chronic inflammation (22–24), which is associated with an increased risk of some neurodegenerative diseases (25, 26). Therefore, it is plausible that poor oral health is related to an elevated risk of PD. However, little is known about whether the inflammatory response can lead to PD occurrence. To test the hypotheses, we conducted a population-based cohort study in Uppsala, Sweden, to investigate snus use and associated poor oral health conditions (namely fewer teeth, detectable dental plaque, and presence of oral mucosal lesions) in relation to the risk of PD.

METHODS

Study population

The background of the present study has been described in detail previously (27–29). Briefly, in 1973–1974,

a population-based survey of the prevalence of oral mucosal lesions was conducted among all residents of Uppsala County, central Sweden, aged 15 years or older. Among 30,118 invited residents, 20,333 (68%) participated in an oral health examination after 2 rounds of enrollment. One of the coauthors (T.A.) performed an oral health examination of all participants. We excluded 121 participants for the following reasons: inconsistent personal identification number ($n = 98$), duplicate examinations ($n = 15$), and no readable data ($n = 8$); this left a total of 20,212 participants for the present study.

This study was first approved by the ethics committee of the medical faculty at Uppsala University. Further linkages for the present study were approved by the Regional Ethical Vetting Board in Stockholm, Sweden.

Exposure assessment

Information on sociodemographic factors, tobacco smoking, snus use, and alcohol drinking was obtained through interviews in 1973–1974. Information on tobacco smoking and snus use among participants was comprehensively ascertained, including status (never, ever, former, or current use), age (years) at initiation of use, duration of use (years), and intensity of use (g/day). Only persons who reported daily use of any tobacco (cigarette smoking or snus use) were categorized as ever tobacco users.

Baseline number of existing teeth and level of dental plaque were estimated on the basis of 6 selected teeth (teeth 16, 21, 24, 36, 41, 44) (30). The dental plaque status of each tooth was scored from 0 to 3. A score of 0 represented no detected dental plaque; 1 represented dental plaque covering not more than one-third of the tooth surface; 2 represented dental plaque covering more than one-third of the tooth surface and not more than two-thirds of the tooth surface; and 3 represented dental plaque covering more than two-thirds of the tooth surface. A dental plaque index equal to the total score divided by the number of examined teeth was calculated. The presence of oral mucosal lesions was defined as any abnormal alteration in color or surface aspect or any swelling or loss of integrity of the oral mucosa surface. Based on the previously defined criteria (27, 29), we further grouped oral mucosal lesions into 3 categories that are strongly associated with poor oral hygiene: *Candida*-related oral mucosal lesions, including the presence of pseudomembranous candidiasis, chronic candidosis, angular cheilitis, atrophic and nodular leukoplakia, the median type of atrophy of tongue papillae, or unspecified glossitis; denture-related oral mucosal lesions, comprising the presence of denture stomatitis (localized, generalized, and papillomatous), denture hyperplasia, traumatic ulcer, or flabby ridges; and tongue lesions, comprising the presence of lingua fissurata, plicated tongue, atrophy of tongue papillae, hairy tongue, coated tongue, median rhomboid glossitis, or unspecified glossitis.

Follow-up and case identification

Using each individual's unique national personal identification number (31), we followed all participants through record linkages with the National Patient Register, the Cause-of-Death Register, and the Emigration Register. All of these registers contain essentially complete data on all Swedes. Participants with PD cases were defined as those who had had 1 or more hospital contacts for PD as a primary or secondary diagnosis (11). For PD patients with more than 1 hospital contact, we defined the date of first discharge or outpatient contact for PD as the diagnosis date. After cross-linkages, we further excluded 28 participants who had had a PD diagnosis recorded before the date of enrollment and 9 participants with missing data on snus use or alcohol drinking, leaving a total of 20,175 persons (9,956 males and 10,219 females) for the final analysis.

Person-years of follow-up for each cohort member were counted from the date of enrollment onward and were censored at the date PD diagnosis, death, emigration out of Sweden, moving into a county without Inpatient Register coverage (or with incomplete coverage), or December 31, 2012, whichever occurred first. (See the Web Appendix, available at http://aje.oxfordjournals.org/, for further information.)

Statistical analyses

Age-adjusted incidence rates of PD according to baseline covariates were standardized to the distribution of person-years in the entire cohort (5-year age groups). We used Cox proportional hazards regression models with attained age as the time scale (years; continuous) to estimate hazard ratios and corresponding 95% confidence intervals for PD in association with exposure variables.

To evaluate the overall association with smoking, we initially categorized tobacco smoking status as never, former, or current daily smoking, according to the baseline questionnaire. All multivariate models included area of residence (town, rural area, or small community), marital status (married, single, divorced, or widowed), and alcohol consumption (<once a week or ≥once a week). Analyses were stratified by sex due to the low prevalence of ever daily snus use among women (only 8 women) in 1973–1974. We fitted models in which the hazard ratios associated with tobacco smoking were adjusted for snus use (never daily snus user vs. ever daily snus user) and in which hazard ratios linked to snus use were adjusted for tobacco smoking (never, former, or current daily tobacco smoker). Further, we categorized tobacco habits according to combinations of tobacco smoking and snus use. We also restricted the analysis to never smokers to exclude residual confounding by tobacco smoking. Snus use status was further categorized by duration (categorized as ≤10 years or >10 years) and intensity (categorized as ≤10 g/day or >10 g/day). We tested for linear trends with continuous variables in the models.

Because of the strong association between oral health and age, analyses of baseline oral health conditions were additionally adjusted for age at study entry and tobacco use status (never daily user of any tobacco, pure daily tobacco user, pure daily snus user, or combined user; for females, only smoking status was adjusted) (32). Number of existing teeth at baseline was estimated on the basis of number of available teeth among the 6 teeth selected for examination and was categorized as 0–1, 2–3, 4–5, or 6 of the selected teeth examined. Because evaluation of dental plaque status

is reliable only when people have at least 2 existing teeth out of the 6 teeth selected for examination, we restricted our analyses of dental plaque to those who had at least 2 existing teeth (7,963 males and 7,565 females). Unacceptable dental plaque, acceptable dental plaque, and no dental plaque were defined as an average plaque index of >1, >0–≤1, and 0, respectively. Participants without any diagnosis of *Candida*-related, denture-related, and tongue lesions were included in the reference group when examining oral lesions and PD risk. The combination group included persons with at least 2 of the above-mentioned lesions. To exclude residual confounding by tobacco use, we also performed a subgroup analysis focusing on tobacco abstainers (for females, never daily smokers). Nonproportionality of hazards was investigated using the Grambsch and Therneau test based on Schoenfeld residuals (33), and no violations were observed.

We conducted a number of sensitivity analyses. First, because there is a long preclinical period before PD diagnosis (34, 35), we reanalyzed the data by starting follow-up 8 years after the date of enrollment. Second, we limited the study cohort to participants who were aged 40 years or more at baseline to reduce misclassification of the exposures and covariate measurements. Third, because tobacco use could be affected by tremor, we conducted an analysis by setting the diagnosis date of PD 5 years before the date of discharge or outpatient contact. Fourth, given the potential uncertainty of case ascertainment for persons with only 1 diagnosis of PD recorded in the Patient Register, alternatively we defined PD cases as participants with at least 2 entries in the Patient Register or a primary diagnosis of PD.

Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, North Carolina). All statistical tests were 2-sided, and P values less than 0.05 were considered statistically significant.

RESULTS

Baseline characteristics

Baseline characteristics are shown in Table 1. The median age at interview for PD cases was 54.1 years (interquartile range (IQR), 44.5–67.3) in males and 56.7 years (IQR, 45.7–66.9) in females; for non-PD subjects, it was 41.6 years (IQR, 28.8–57.6) in males and 40.8 years (IQR, 28.1–57.4) in females. During an average of 27.9 years (standard deviation, 13.7) of follow-up, we identified 307 incident PD cases. The crude incidence rate of PD was 54.6 per 100,000 person-years.

Tobacco use

For males, we confirmed that current tobacco smoking was inversely associated with PD risk (Table 2). The adjusted hazard ratios for PD in former smokers and current smokers were 0.70 (95% confidence interval (CI): 0.47, 1.04) and 0.62 (95% CI: 0.44, 0.90), respectively, as compared with never daily tobacco smoking. In analyses of snus use, we found that the adjusted hazard ratio for PD among ever daily snus users versus never users was 0.45 (95% CI: 0.26, 0.77), based on 14 observed cases. In addition, we examined the joint contribution of tobacco smoking and snus use to PD risk. Compared with never daily use of any tobacco, pure current tobacco smokers had a lower risk of PD (hazard ratio (HR) = 0.64, 95% CI: 0.44, 0.93). The relative risk was even lower for pure snus users (n = 11; HR = 0.51, 95% CI: 0.27, 0.95) and was lowest among combined users (n = 3; HR = 0.21, 95% CI: 0.07, 0.67). In analyses restricted to never daily tobacco smokers (n = 3,968), there was no obvious dose-response relationship with increasing duration (HR = 0.54 (95% CI: 0.20, 1.49) and HR = 0.50 (95% CI: 0.23, 1.10) for ≤10 years and >10 years, respectively; $P_{\text{trend}} = 0.11$) or intensity (HR = 0.33 (95% CI: 0.12, 0.91) and HR = 0.76 (95% CI: 0.35, 1.66) for ≤10 g/day and >10 g/day, respectively; $P_{\text{trend}} = 0.16$) of snus use.

Ever smoking was not significantly associated with PD risk in females. Compared with females who never smoked daily, the adjusted hazard ratios for PD in former smokers and current smokers were 1.42 (95% CI: 0.81, 2.48) and 0.77 (95% CI: 0.46, 1.30), respectively. Snus use in females was too uncommon (only 8 users, with no PD cases) for us to estimate the association between snus use and PD risk among females.

Oral hygiene

Overall, we observed no associations between fewer teeth or more dental plaque and PD risk (Table 3). For specific types of oral mucosal lesions, we observed a marginally significant excess risk of PD associated with *Candida*-related lesion in males (HR = 1.56, 95% CI: 0.92, 2.65; $P = 0.098$), compared with persons without any of the 3 types of oral mucosa lesions at baseline. Analysis limited to persons who were never daily users of any tobacco revealed similar results, except that the magnitude of the associations with number of teeth was stronger among males. Compared with those with 6 existing teeth, the hazard ratios for persons with 4–5, 2–3, and 0–1 existing teeth (out of the 6 selected teeth examined) were 1.79 (95% CI: 1.00, 3.20), 1.89 (95% CI: 0.93, 3.84), and 1.35 (95% CI: 0.60, 3.01), respectively (Web Table 1). No significant association was detected between dental plaque or detectable oral mucosal lesions and PD risk in either males or females.

Sensitivity analysis

Results from sensitivity analyses are presented in Web Tables 2–6, including analyses excluding the first 8 years of follow-up, analyses limiting the study cohort to participants aged 40 years or more at baseline, analyses setting the diagnosis date of PD 5 years before the discharge or outpatient contact date, and analyses using definitions of PD cases as those with at least 2 entries in the Patient Register or a primary diagnosis of PD. Different sensitivity analyses showed results comparable to those of the main analyses in both males and females.

DISCUSSION

To our knowledge, this is the first prospective cohort study to have investigated the associations between snus

Table 1. Baseline Characteristics of Participants in a Study of Tobacco Use and Associated Poor Oral Health and the Risk of Parkinson's Disease, Uppsala, Sweden, 1973–2012

	Males						Females					
	PD Cases		Non-PD Subjects		Total		PD Cases		Non-PD Subjects		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age at study entry, years[a]	54.7 (14.1)		43.6 (18.0)		43.8 (18.0)		56.5 (13.6)		43.3 (18.2)		43.5 (18.2)	
Duration of follow-up, years[a]	21.3 (11.5)		27.1 (13.9)		27.0 (13.9)		19.4 (11.6)		28.8 (13.4)		28.7 (13.4)	
Age at study exit, years[a]	75.9 (8.2)		70.7 (15.4)		70.8 (15.3)		75.9 (7.8)		72.1 (16.6)		72.2 (16.5)	
Age group at study entry, years												
14–24	1	0.6	1,430	14.6	1,431	14.4	1	0.8	1,555	15.4	1,556	15.2
25–34	15	8.6	2,207	22.6	2,222	22.3	4	3.0	2,311	22.9	2,315	22.6
35–44	24	13.7	1,634	16.7	1,658	16.6	22	16.7	1,658	16.4	1,680	16.4
45–54	47	26.9	1,512	15.5	1,559	15.7	30	22.7	1,537	15.2	1,567	15.3
55–64	37	21.1	1,464	15.0	1,501	15.1	34	25.8	1,367	13.6	1,401	13.7
65–74	36	20.6	986	10.1	1,022	10.3	26	19.7	1,048	10.4	1,074	10.5
≥75	15	8.6	548	5.6	563	5.6	15	11.4	611	6.1	626	6.1
Area of residence												
Town	22	12.6	1,480	15.1	1,502	15.1	13	9.8	1,595	15.8	1,608	15.7
Rural area	71	40.6	3,494	35.7	3,565	35.8	53	40.2	3,338	33.1	3,391	33.2
Small community	82	46.8	4,807	49.2	4,889	49.1	66	50.0	5,154	51.1	5,220	51.1
Marital status												
Single	29	16.6	2,752	28.1	2,781	27.9	13	9.8	2,176	21.6	2,189	21.4
Married	134	76.6	6,469	66.1	6,603	66.3	95	72.0	6,691	66.3	6,786	66.4
Divorced	4	2.3	236	2.4	240	2.4	8	6.1	355	3.5	363	3.6
Widowed	8	4.6	324	3.3	332	3.3	16	12.1	865	8.6	881	8.6
Alcohol consumption, times/week												
<1	37	21.1	1,432	14.6	1,469	14.7	49	37.1	3,029	30.0	3,078	30.1
≥1	138	78.6	8,349	85.4	8,487	85.3	83	62.9	7,058	70.0	7,141	69.9

Abbreviation: PD, Parkinson's disease.
[a] Values are expressed as mean (standard deviation).

use, associated oral health conditions, and the risk of PD incidence. We found that both tobacco smoking and snus use were associated with a lower risk of PD in males; the inverse associations tended to be stronger for the latter. Poor oral health did not appear to be associated with an increased risk of PD, although we observed a suggestive association with *Candida*-related mucosal lesions in males.

The inverse association between snus use and the risk of PD is consistent with the findings of 2 previous studies. Benedetti et al. (9) reported that the odds ratio for PD in association with ever tobacco chewing or snus use was 0.18 (95% CI: 0.04, 0.82). O'Reilly et al. (10) reported that current snus use was associated with a decreased risk of PD mortality (HR = 0.24, 95% CI: 0.08, 0.75) among never-smoking males. The association is biologically plausible. Nicotine and hydroquinone, compounds of cigarette smoke, can stabilize soluble oligomeric forms of α-synuclein (7). In the present study, snus users were even less likely to develop PD than tobacco smokers, which supports the notion that nicotine is one of the chemicals most likely to explain the observed reduced risk of PD. Experimental data showed that snus can cause the same peak nicotine concentrations in blood as tobacco smoke does, and that the high nicotine levels tend to persist and to decline more slowly than those from tobacco smoking (8, 36). This hypothesis, unfortunately, could not be directly tested in the present study. Chen et al. (37) and Kenborg et al. (38) reported that longer duration of tobacco smoking is more likely to be associated with a lower risk of PD. The lack of a positive dose-response trend with duration of snus use could be due to a small number of cases in each group; alternatively, it could be explained by exposure misclassification resulting from a lack of updated information during follow-up or a lack of detailed information on persons who had used snus less often than daily. Because we also lacked information on smoking intensity for participants who smoked but did not smoke daily, we could not examine the association with smoking in detail when studying the dose-response trend with snus use.

It has been argued that the inverse association between smoking and PD risk may be explained by various types of

Table 2. Association Between Tobacco Use Status and Risk of Parkinson's Disease Among Males, Uppsala, Sweden, 1973–2012[a]

Smoking Status	No. of Participants	%	No. of PD Cases	IR[b]	HR	95% CI
Smoking[c]						
Never daily smoker	3,968	39.9	89	85.4	1.00	Referent
Ever daily smoker						
Former smoker	1,763	17.7	37	61.8	0.70	0.47, 1.04
Current smoker	4,225	42.4	49	55.0	0.62	0.44, 0.90
Snus use[c]						
Never daily use	8,401	84.4	161	75.0	1.00	Referent
Ever daily use	1,555	15.6	14	36.9	0.45	0.26, 0.77
Tobacco use status						
Never daily user of any tobacco	3,103	31.2	78	95.5	1.00	Referent
Ever daily user of any tobacco	6,853	68.8	97	56.9	0.61	0.45, 0.83
Pure ever smoker	5,298	53.2	83	62.5	0.68	0.49, 0.93
Former smoker	1,635	16.4	37	64.9	0.73	0.49, 1.09
Current smoker	3,663	36.8	46	59.3	0.64	0.44, 0.93
Pure snus user	865	8.7	11	48.7	0.51	0.27, 0.95
Combined user	690	6.9	3	21.7	0.21	0.07, 0.67

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate; PD, Parkinson's disease.

[a] HRs and 95% CIs were estimated from Cox proportional hazards regression models with attained age as the time scale and were adjusted for baseline variables, including area of residence, marital status, and alcohol consumption.

[b] Incidence rate per 100,000 person-years, standardized to the age distribution of person-years experienced by all participants using 5-year age categories.

[c] We fitted models in which the HRs associated with smoking were adjusted for snus use (ever vs. never) and in which the HRs associated with snus use were adjusted for smoking (former vs. never, current vs. never).

bias (39–44). First, smoking might only delay age at onset of PD. However, our results showed that the hazard ratios associated with tobacco use were consistent by attained age during follow-up. Second, the prospective study design precluded the possibility of reverse causation in which PD patients might be less prone to smoking or more prone to quit smoking, and it also precluded the possibility that this association was only related to higher mortality among smoking PD patients than among nonsmoking PD patients. Third, twin studies (45) and studies focusing on exposure to passive smoking (46) have also confirmed an inverse association between smoking and the risk of PD, which suggests that the association is unlikely to be confounded by genetic factors.

Our results did not support any associations between indicators of poor oral health—namely fewer teeth, higher levels of dental plaque, and the presence of oral mucosal lesions—and the risk of PD in either males or females. Poor oral health is associated with systematic inflammation (22–24) and an increased risk of several other neurodegenerative diseases (25, 26). Poor oral health thus might also be associated with a higher risk of PD. However, we did not verify that hypothesis in the present study. To evaluate the association with poor oral health more precisely and comprehensively, information on other indicators such as the presence of periodontal diseases and dental caries would also need to be collected. In addition, tobacco use is associated with poor oral health. Therefore, tobacco use may negatively confound the association between poor oral health and PD. Although we found no changes in the hazard ratio estimates before and after adjusting crudely for tobacco use status, we observed a stronger magnitude of association with number of teeth among persons who never used any tobacco daily. This suggests that some associations may have been attenuated by residual confounding by tobacco use history, and the association with oral health, if any, may be complex. Misclassification bias cannot be ruled out, because we only had information on participants' oral health in 1973–1974, which was up to 39 years prior to the PD occurrence. This misclassification of oral health conditions is likely to have been nondifferential and hence may have biased our findings towards the null. Further, we only used oral health as an indirect indicator, rather than direct serological evidence of systematic inflammation and infection.

Strengths of the present study include its prospective population-based design and the use of high-quality Swedish health and demographic registers for outcome ascertainment and censoring of follow-up. Information on oral health conditions was collected by 1 professional dentist; therefore, misclassification of exposure information at baseline has been largely excluded. However, our results should be interpreted in light of several methodological limitations. First, tobacco use habits might change over time, but the

Table 3. Association Between Oral Health Indicators and Risk of Parkinson's Disease in Uppsala, Sweden, 1973–2012[a]

Oral Health Indicator	Males						Females					
	No. of Participants	%	No. of Cases	IR[b]	HR	95% CI	No. of Participants	%	No. of Cases	IR[b]	HR	95% CI
No. of existing teeth (out of 6 selected teeth examined at baseline)												
6	4,936	49.6	50	66.0	1.00	Referent	4,593	44.9	24	31.5	1.00	Referent
4–5	1,883	18.9	42	67.2	1.10	0.71, 1.69	1,874	18.3	32	44.4	1.10	0.63, 1.91
2–3	1,144	11.5	34	77.0	1.29	0.80, 2.08	1,098	10.7	24	49.2	1.05	0.57, 1.96
0–1	1,993	20.0	49	72.8	1.23	0.75, 2.00	2,654	26.0	52	49.6	0.90	0.49, 1.65
Dental plaque status[c]												
No dental plaque	1,080	13.5	15	58.2	1.00	Referent	2,143	28.3	26	45.4	1.00	Referent
Acceptable	4,959	62.3	78	71.4	1.21	0.70, 2.11	4,697	62.1	47	41.3	0.90	0.55, 1.45
Unacceptable	1,924	24.2	33	69.6	1.25	0.67, 2.33	725	9.6	7	34.9	0.74	0.31, 1.73
Oral mucosal lesions[d]												
None	6,928	69.6	110	69.8	1.00	Referent	6,654	65.1	68	40.9	1.00	Referent
Candida-related	538	5.4	17	105.7	1.56	0.92, 2.65	650	6.4	13	58.9	1.18	0.63, 2.22
Denture-related	1,755	17.6	41	65.8	0.96	0.66, 1.41	2,521	24.7	51	48.5	1.04	0.70, 1.55
Tongue	1,578	15.9	31	68.5	0.96	0.64, 1.43	1,490	14.6	24	47.4	1.05	0.65, 1.70
Combination	707	7.1	19	79.7	1.19	0.71, 1.97	901	8.8	18	61.1	1.13	0.64, 1.97

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate.

[a] HRs and 95% CIs were estimated from Cox proportional hazards regression models with attained age as the time scale and were adjusted for baseline variables, including age at study entry, area of residence, marital status, tobacco use status (for females, only smoking status was adjusted), and alcohol consumption.

[b] Incidence rate per 100,000 person-years, standardized to the age distribution of person-years experienced by all participants using 5-year age categories.

[c] Only among participants who had at least 2 existing teeth out of the 6 selected teeth examined (7,963 males, 7,565 females).

[d] The reference group included persons without any evidence of *Candida*-related, denture-related, or tongue lesions. The combination group included subjects with at least 2 of the above lesions.

information was not updated after baseline. It is possible that the inverse association between snus use and PD risk was due to changed habits from snus use to tobacco smoking. However, several Swedish studies showed that snus use is a habit which tends to be stable over time (47–49). Estimates of the hazard ratios were very similar to those from the analysis using the full cohort when we restricted analysis to persons aged 40 years or more at study entry. Our previous results in a subcohort comprising 252 males with retrievable information on tobacco use habits in 1973–1974 and 1993–1995 showed that none of 60 exclusively snus users in 1973–1974 had changed to tobacco smoking and only 1 man out of 22 who were never users of any tobacco in 1973–1974 had taken up daily snus use. Taken together, it is unlikely that the observed reduced risk among snus users would be explained by changed habits to tobacco smoking. Second, PD is a slowly progressing disease with symptoms arising several years prior to diagnosis (50); therefore, we cannot entirely rule out the possibility that the observed association was from reverse causation due to preclinical PD at baseline. However, the inverse association between snus use and PD risk was consistent in a number of sensitivity analyses, such as analyses excluding the first 8 years of follow-up and analyses using a diagnosis date set to 5 years before the discharge date, which showed the robustness of our findings. Third, misclassification of PD might have occurred because we identified PD cases from the Swedish Patient Register (11). It might be possible that snus-using PD patients are more likely to be recorded in the Patient Register than snus-abstaining PD patients; however, we observed an inverse association between snus use and PD risk. Differential misclassification of PD outcome, again, could have led to underestimation of a true inverse association. In addition, the majority of PD patients are not hospitalized, and outpatient register data were not available before 2001. Therefore, this may have led to both uncertainty regarding true age at PD onset and underdiagnosis of PD cases. It is difficult to predict exactly how misdiagnosis might have affected the results, but most likely, risk estimates would have been attenuated due to nondifferential misclassification. Fourth, we lacked information on other potential confounders such as body mass index, dietary pattern, and physical activity. The estimated associations may have been confounded by socioeconomic status. Although we controlled for residential area and marital status, residual confounding by socioeconomic status may still have occurred. Last, although we had enough statistical power to detect a significant inverse association between snus use

and PD risk, interpretation of these findings should be cautious given the small number of exposed cases observed. A chance finding cannot be ruled out.

In conclusion, tobacco use, including use of Scandinavian moist snuff, was associated with a reduced risk of PD in males, while poor oral health, as indicated by fewer teeth, more dental plaque, and the presence of oral mucosal lesions, was not associated with the risk of PD. Further studies with larger sample sizes, comprehensive oral health examination, and measurement of biomarkers of systemic inflammation are needed to more deeply investigate the question of whether snus use and poor oral health are associated with the risk of PD.

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REFERENCES

1. Ritz B, Lee PC, Lassen CF, et al. Parkinson disease and smoking revisited: ease of quitting is an early sign of the disease. *Neurology*. 2014;83(16):1396–1402.
2. Wirdefeldt K, Adami HO, Cole P, et al. Epidemiology and etiology of Parkinson's disease: a review of the evidence. *Eur J Epidemiol*. 2011;26(suppl 1):S1–S58.
3. Hernán MA, Takkouche B, Caamaño-Isorna F, et al. A meta-analysis of coffee drinking, cigarette smoking, and the risk of Parkinson's disease. *Ann Neurol*. 2002;52(3):276–284.
4. Allam MF, Campbell MJ, Hofman A, et al. Smoking and Parkinson's disease: systematic review of prospective studies. *Mov Disord*. 2004;19(6):614–621.
5. Ritz B, Ascherio A, Checkoway H, et al. Pooled analysis of tobacco use and risk of Parkinson disease. *Arch Neurol*. 2007; 64(7):990–997.
6. Das SK, Misra AK, Ray BK, et al. Epidemiology of Parkinson disease in the city of Kolkata, India: a community-based study. *Neurology*. 2010;75(15):1362–1369.
7. Hong DP, Fink AL, Uversky VN. Smoking and Parkinson's disease: does nicotine affect alpha-synuclein fibrillation? *Biochim Biophys Acta*. 2009;1794(2):282–290.
8. Benowitz NL. Drug therapy. Pharmacologic aspects of cigarette smoking and nicotine addition. *N Eng J Med*. 1988; 319(20):1318–1330.
9. Benedetti MD, Bower JH, Maraganore DM, et al. Smoking, alcohol, and coffee consumption preceding Parkinson's disease: a case-control study. *Neurology*. 2000;55(9): 1350–1358.
10. O'Reilly EJ, McCullough ML, Chao A, et al. Smokeless tobacco use and the risk of Parkinson's disease mortality. *Mov Disord*. 2005;20(10):1383–1384.
11. Feldman AL, Johansson AL, Gatz M, et al. Accuracy and sensitivity of Parkinsonian disorder diagnoses in two Swedish national health registers. *Neuroepidemiology*. 2012;38(3): 186–193.
12. Beyer MK, Herlofson K, Arsland D, et al. Causes of death in a community-based study of Parkinson's disease. *Acta Neurol Scand*. 2001;103(1):7–11.
13. Fall PA, Saleh A, Fredrickson M, et al. Survival time, mortality, and cause of death in elderly patients with Parkinson's disease: a 9-year follow-up. *Mov Disord*. 2003; 18(11):1312–1316.
14. Reale M, Iarlori C, Thomas A, et al. Peripheral cytokines profile in Parkinson's disease. *Brain Behav Immun*. 2009; 23(1):55–63.
15. Lindqvist D, Kaufman E, Brundin L, et al. Non-motor symptoms in patients with Parkinson's disease—correlations with inflammatory cytokines in serum. *PLoS One*. 2012;7(10): e47387.
16. Stypuła G, Kunert-Radek J, Stepień H, et al. Evaluation of interleukins, ACTH, cortisol and prolactin concentrations in the blood of patients with Parkinson's disease. *Neuroimmunomodulation*. 1996;3(2-3):131–134.
17. Dobbs RJ, Charlett A, Purkiss AG, et al. Association of circulating TNF-alpha and IL-6 with ageing and parkinsonism. *Acta Neurol Scand*. 1999;100(1):34–41.
18. Chen H, O'Reilly EJ, Schwarzschild MA, et al. Peripheral inflammatory biomarkers and risk of Parkinson's disease. *Am J Epidemiol*. 2008;167(1):90–95.
19. Gao HM, Jiang J, Wilson B, et al. Microglial activation-mediated delayed and progressive degeneration of rat nigral dopaminergic neurons: relevance to Parkinson's disease. *J Neurochem*. 2002; 81(6):1285–1297.
20. Roosaar A, Johansson AL, Sandborgh-Englund G, et al. A long-term follow-up study on the natural course of snus-induced lesions among Swedish snus users. *Int J Cancer*. 2006;119(2): 392–397.
21. Axéll T, Mörnstad H, Sundström B. The relation of the clinical picture to the histopathology of snuff dipper's lesions in a Swedish population. *J Oral Pathol*. 1976;5(4):229–236.
22. Kowolik MJ, Dowsett SA, Rodriguez J, et al. Systemic neutrophil response resulting from dental plaque accumulation. *J Periodontol*. 2001;72(2):146–151.
23. Noack B, Genco RJ, Trevisan M, et al. Periodontal infections contribute to elevated systemic C-reactive protein level. *J Periodontol*. 2001;72(9):1221–1227.
24. Margolis KL, Manson JE, Greenland P, et al. Leukocyte count as a predictor of cardiovascular events and mortality in postmenopausal women: the Women's Health Initiative Observational Study. *Arch Intern Med*. 2005;165(5):500–508.
25. Noble JM, Scarmeas N, Papapanou PN. Poor oral health as a chronic, potentially modifiable dementia risk factor: review of the literature. *Curr Neurol Neurosci Rep*. 2013;13(10): 384.
26. Kisely S, Baghaie H, Lalloo R, et al. A systematic review and meta-analysis of the association between poor oral health and severe mental illness. *Psychosom Med*. 2015; 77(1):83–92.
27. Axéll T. A prevalence study of oral mucosal lesions in an adult Swedish population. *Odontol Revy Suppl*. 1976;36:1–103.
28. Roosaar A, Johansson AL, Sandborgh-Englund G, et al. Cancer and mortality among users and nonusers of snus. *Int J Cancer*. 2008;123(1):168–173.

29. Huang J, Roosaar A, Axéll T, et al. A prospective cohort study on poor oral hygiene and pancreatic cancer risk. *Int J Cancer*. 2016;138(2):340–347.
30. Ramfjord SP. The Periodontal Disease Index (PDI). *J Periodontol*. 1967;38(6)602–610.
31. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24(11):659–667.
32. Pencina MJ, Larson MG, D'Agostino RB. Choice of time scale and its effect on significance of predictors in longitudinal studies. *Stat Med*. 2007;26(6):1343–1359.
33. Grambsch PM, Therneau TM. Proportional hazards tests and diagnostics based on weighted residuals. *Biometrika*. 1994; 81(3):515–526.
34. Yang F, Trolle Lagerros Y, Bellocco R, et al. Physical activity and risk of Parkinson's disease in the Swedish National March Cohort. *Brain*. 2015;138(2):269–275.
35. Hawkes CH. The prodromal phase of sporadic Parkinson's disease: does it exist and if so how long is it? *Mov Disord*. 2008;23(13):1799–1807.
36. Holm H, Jarvis MJ, Russell MA, et al. Nicotine intake and dependence in Swedish snuff takers. *Psychopharmacology (Berl)*. 1992;108(4):507–511.
37. Chen H, Huang X, Guo X, et al. Smoking duration, intensity, and risk of Parkinson disease. *Neurology*. 2010;74(11):878–884.
38. Kenborg L, Lassen CF, Ritz B, et al. Lifestyle, family history, and risk of idiopathic Parkinson disease: a large Danish case-control study. *Am J Epidemiol*. 2015;181(10):808–816.
39. Golbe LI, Cody RA, Duvoisin RC. Smoking and Parkinson's disease. Search for a dose-response relationship. *Arch Neurol*. 1986;43(8):774–778.
40. Shahi GS, Moochhala SM. Smoking and Parkinson's disease—a new perspective. *Rev Environ Health*. 1991;9(3):123–136.
41. Riggs JE. Cigarette smoking and Parkinson disease: the illusion of a neuroprotective effect. *Clin Neuropharmacol*. 1992;15(2):88–99.
42. Morens DM, Grandinetti A, Reed D, et al. Cigarette smoking and protection from Parkinson's disease: false association or etiologic clue? *Neurology*. 1995;45(6):1041–1051.
43. Fratiglioni L, Wang HX. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. *Behav Brain Res*. 2000;113(1-2):117–120.
44. Hershey LA, Perlmutter JS. Smoking and Parkinson disease: where there is smoke there may not be fire. *Neurology*. 2014; 83(16):1392–1393.
45. Wirdefeldt K, Gatz M, Pawitan Y, et al. Risk and protective factors for Parkinson's disease: a study in Swedish twins. *Ann Neurol*. 2005;57(1):27–33.
46. Mellick GD, Gartner CE, Silburn PA, et al. Passive smoking and Parkinson disease. *Neurology*. 2006;67(1):179–180.
47. Rodu B, Stegmayr B, Nasic S, et al. Evolving patterns of tobacco use in northern Sweden. *J Intern Med*. 2003;253(6): 660–665.
48. Furberg H, Lichtenstein P, Pedersen NL, et al. Cigarettes and oral snuff use in Sweden: prevalence and transitions. *Addiction*. 2006;101(10):1509–1515.
49. Lundqvist G, Sandström H, Ohman A, et al. Patterns of tobacco use: a 10-year follow-up study of smoking and snus habits in a middle-aged Swedish population. *Scand J Public Health*. 2009;37(2):161–167.
50. Schrag A, Horsfall L, Walters K, et al. Prediagnostic presentations of Parkinson's disease in primary care: a case-control study. *Lancet Neurol*. 2015;14(1):57–64.