Tobacco smoking, but not Swedish snuff use, increases the risk of multiple sclerosis

Anna K. Hedström, MD
Maria Bäärnhielm, MD
Tomas Olsson, MD, PhD
Lars Alfredsson, PhD

Address correspondence and reprint requests to Dr. Anna K. Hedström, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
anna.hedstrom@ki.se

ABSTRACT

Objective: The aim of this study was to estimate the influence of tobacco smoking and Swedish snuff use on the risk of developing multiple sclerosis (MS).

Methods: A population-based case-control study was performed in Sweden, using incident cases of MS (902 cases and 1,855 controls). A case was defined as a subject from the study base who had received a diagnosis of MS, and controls were randomly selected from the study base. The incidence of MS among smokers was compared with that of never-smokers. We also investigated whether the use of Swedish snuff had an impact on the risk of developing MS.

Results: Smokers of both sexes had an increased risk of developing MS (odds ratio [OR] 1.4, 95% confidence interval [CI] 1.2–1.7 for women, and OR 1.8, 95% CI 1.3–2.5 for men). The increased risk was apparent even among subjects who had previously smoked moderately (≤5 pack-years) prior to index, and the risk increased with increasing cumulative dose ($p < 0.0001$). The increased risk for MS associated with smoking remained up to 5 years after stopping smoking. In contrast, taking Swedish snuff for more than 15 years decreased the risk of developing MS (OR 0.3, 95% CI 0.1–0.8).

Conclusions: Smokers of both sexes run an increased risk of developing multiple sclerosis (MS), and the risk increases with cumulative dose of smoking. However, the use of Swedish snuff is not associated with elevated risk for MS, which may indicate that nicotine is not the substance responsible for the increased risk of developing MS among smokers. *Neurology*® 2009;73:696–701

GLOSSARY

CI = confidence interval; **EIMS** = Epidemiologic Investigation of Multiple Sclerosis; **MS** = multiple sclerosis; **OR** = odds ratio.

Multiple sclerosis (MS) is a chronic neurologic disease with a heterogeneous pattern and a prevalence of about 1.2‰–1.6‰ in Sweden. Women are affected more commonly than men, and the incidence of MS in females has been steadily increasing. Although it seems clear that there is a genetic component, the fairly low concordance rate among identical twins indicates that environmental factors play a prominent role in influencing the risk. Smoking as a risk factor for MS has been investigated in 9 epidemiologic studies[1-9] (table 1); however, frequently, case numbers have been small and 2 of the studies were subject to methodologic limitations.[8,9] In total, 8 of the studies[1-8] observed an association between smoking and increased risk of MS. The effect of cumulative dose of smoking on the risk for MS has been investigated in only one of the studies.[4]

Previous studies have provided evidence of an association between smoking and the risk of developing MS but the effect of cumulative dose, stopping smoking, and potential sex differences requires further clarification.

The biologic basis of the potential link between smoking and MS has not yet been elucidated. One of the possibilities is that nicotine, which has been shown to increase microvascular

From the Institute of Environmental Medicine (A.K.H., L.A.) and Department of Clinical Neurosciences (M.B., T.O.), Karolinska Institutet, Stockholm, Sweden.

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Table 1 Studies on the association between smoking and multiple sclerosis

Ref.	No. of cases	Quantity smoked	OR or RR	95% CI	Study type, region, comments
1	241	Ever smoked (106)	1.4 OR	1.05–1.86	Retrospective, case-control study (Israel)
2	114	1–14/day (33)	1.2 RR	0.8–1.8	Prospective, cohort, incident cases
		≥15/day (25)	1.4 RR	0.9–2.2	All female (Oxford)
3	197	Ever smoked (138)	1.6 OR	1.0–2.4	Incident case-control; smoking in year prior to diagnosis (Montreal)
		20–40/day (71)	1.9 OR	1.2–3.2	
		>40/day (16)	5.5 OR	1.7–17.8	
4	315	Ever smoked (175), 10–24 pack-years before diagnosis (75)	1.6 RR	1.2–2.1	Prospective, incident; smoking 4 years prior to MS diagnosis; only pooled data quoted here; all female nurses (USA)
		>25 pack-years before diagnosis (57)	1.6 RR	1.2–2.4	
5	87	Smoking prior to disease onset	1.8 RR	1.1–2.9	Population based, prevalent case-control study (Norway)
		Females	1.6 RR	Not given	
		Males	2.7 RR	Not given	
6	201	Ever smoked (92)	1.3 OR	1.0–1.7	Prospective, nested case-control study (UK)
7	210	Ever smoked (114)	1.6 OR	Not given	Retrospective, case-control study (Belgrade, Serbia)

OR = odds ratio; RR = rate ratio; CI = confidence interval.

blood flow,[10] causes leakage in the blood–brain barrier. It has also been assumed that nicotine may be an immunotoxic component in cigarette smoke since it may impair antigen-mediated signaling in T-cells.[11,12]

To investigate the influence of environmental factors on the risk of developing MS, and the interaction of these factors with genotype, we started an extensive case-control study—the Epidemiologic Investigation of Multiple Sclerosis (EIMS). In this report from EIMS, we investigated aspects of the association between smoking and the risk of developing MS that have previously been investigated only to a limited extent. We also aimed to clarify the role of nicotine by estimating the possible impact of snuff use on the risk of developing the disease.

METHODS

Study design. This study was designed as a population-based case-control study using incident cases of MS, with a study group comprising the population aged 16–70 years in defined areas of Sweden. The study period for this report was April 2005 to October 2008.

Study group. The study sought to identify incident cases in the study base as soon as possible after disease onset. In Sweden, patients with MS are cared for by neurologists. There is equal access to publicly sponsored health care, including inpatient care, for all residents. Potential cases were recruited via hospital-based neurology units as well as privately run neurology units in Sweden (which are few). All university hospitals participated in the study, and in total, 32 study centers reported cases of MS to the study. All cases were examined and diagnosed by a neurologist located at the unit in which the case was entered. Cases that did not fulfill the McDonald criteria at the time of this report were excluded.

For each potential case, 2 controls were randomly selected from the national population register, taking into consideration the case's sex, age (5-year age group), and residential area (county). If information could not be obtained from the control selected, then another control was chosen using the same principles.

Data collection. Information on exposures and other circumstances was collected using a standardized questionnaire given to the cases shortly after they had received their diagnosis and was sent by mail to the controls. All questionnaires were supposed to be answered at home. Incompletely answered questionnaires were completed by mail or by telephone. Completed questionnaires were obtained from 961 potential cases and 1,855 controls, the response proportion being 92% for the case group and 70% for the controls. Of those 961 cases, 59 were excluded as they did not satisfy the McDonald criteria. The present study thus comprises 902 cases (648 women, 253 men) and 1,855 controls (1,343 women, 513 men).

Definition of smoking habits and snuff use. The extensive questionnaire contained questions about demographic and reproductive factors, heredity, previous health, body weight and height, lifestyle factors, occupational exposures, and socioeconomic circumstances. Information on smoking was obtained by asking about current and previous smoking including duration of smoking, average number of cigarettes smoked per day, and type of cigarettes.

For each case, the time at the initial appearance of symptoms indicative of MS was used as an estimate of the disease onset, and the year in which this occurred was defined as the index year. Tobacco smoking was considered prior to the index year in the cases and during the same period of time in the corresponding controls. Subjects who had smoked during the index year were defined as current smokers, those who had stopped smoking prior to the index year were defined as ex-smokers, and people who had never smoked before or during the index year were defined as never-smokers.

In order to analyze the influence of cumulative dose of smoking on the risk of developing the disease, we categorized the smokers into groups based on the amount of cigarettes smoked (pack-years) prior to index. One pack-year is defined as 20 cigarettes smoked per day for 1 year.

With respect to the use of snuff, questions were asked in a similar fashion as for smoking. Subjects who reported that they had used Swedish snuff before or during the index year were defined as snuff-takers. The subjects were categorized into groups based on the duration of snuff use (years) and the cumulative dose (packet-years) before index. One packet-year is the equivalent of consuming one packet of snuff daily for 1 year.

Statistical analysis. Using logistic regression, the incidence of MS in subjects with different smoking habits was compared with that in never-smokers by calculating odds ratios (OR) with 95% confidence intervals (CI). We compared the incidence of MS in snuff-takers who had never smoked with that in subjects who had never used any kind of tobacco. Analyses were also performed including all snuff-takers with adjustment for smoking.

Table 2 Odds ratio (OR) with 95% confidence interval (CI) of developing multiple sclerosis for different categories of cigarette smokers compared with never-smokers

	Exposed cases	Exposed controls	OR*	OR†	95% CI
Never-smoker	385	967	1.0‡	1.0‡	—
Ever-smoker	517	888	1.5	1.5	1.3–1.8
Ex-smoker	195	358	1.4	1.4	1.1–1.8
<5 y since stopping	74	107	1.5	1.5	1.1–2.0
≥5 y since stopping	120	251	1.0	1.0	0.8–1.3
Current smoker	322	530	1.6	1.6	1.3–1.9
Women					
Never-smoker	287	699	1.0‡	1.0‡	—
Ever-smoker	362	643	1.4	1.4	1.2–1.7
Ex-smoker	133	262	1.3	1.3	1.0–1.7
Current smoker	229	381	1.5	1.5	1.2–1.8
Men					
Never-smoker	98	268	1.0‡	1.0‡	—
Ever-smoker	155	245	1.8	1.8	1.3–2.5
Ex-smoker	62	96	1.8	1.8	1.2–2.8
Current smoker	93	149	1.8	1.8	1.2–2.5

Information on smoking cessation was missing for one of the cases who had stopped smoking. Thirteen cases had stopped smoking during the index year.
*Crude data.
†Adjusted for age, ancestry, residential area, and for gender when women and men were analyzed together.
‡Reference category.

We performed matched analyses based on all available case-control triplets, as well as unmatched analyses of the data based on all available cases and controls. Only the results from the unmatched analyses are presented in this report since these were in close agreement with those from the matched analyses but had a higher degree of precision.

All analyses were adjusted for age, sex, residential area (according to study design), and ancestry.

In the analysis, age was categorized into the following 8 strata: 16–19, 20–24, 25–29, 30–34, 35–39, 40–45, 45–49, and 50–70 years of age. Assessment of ancestry was based on whether the subject was born in Sweden and whether either of the subject's parents had immigrated to Sweden. A subject who was born in Sweden, whose parents had not immigrated, was classified as Swedish. Adjustments were also done for educational level (university degree or not), body mass index (<19 vs >19 kg/m^2), parity (yes/no), and oral contraceptive use (ever/never), but these factors had minor influence on the results of the study and were not retained in the final analyses.

When women and men were analyzed together, the results were also adjusted for potential confounding by sex. All analyses were conducted using Statistical Analysis System (SAS) version 9.

Standard protocol approvals, registrations, and patient consents. All patients and controls consented to participate in the study after receiving written information. All aspects of the study were approved by the Regional Ethical Review Board at Karolinska Institutet.

RESULTS Our analyses of tobacco smoking and the risk of developing MS included 902 cases and 1,855 controls matched for age, sex, and residential area. All cases had clinically proven or laboratory-confirmed MS according to the McDonald criteria. Ninety-eight percent of the diagnoses were supported by a positive result on MRI.

Among the cases, 649 (72%) were women and 253 (28%) were men. The mean age at onset was 34 years and the mean duration from the initial appearance of symptoms indicative of MS to the diagnosis was 3.8 years.

Overall, the proportion of ever-smokers before the index year was 57% among cases (517/902) and 48% among controls (888/1,855).

Compared with never smoking before the index year, the OR (95% CI) for MS was 1.5 (1.3–1.8) for ever smokers, 1.6 (1.3–1.9) for current smokers, and 1.4 (1.1–1.8) for past smokers. When separate analyses were made for women and men, female ever-smokers had an OR for MS of 1.4 (1.2–1.7) compared with never-smokers. The corresponding result for men was 1.8 (1.3–2.5) (table 2).

The increased risk for MS associated with smoking remained up to 5 years after stopping smoking (table 2). The association between cumulative dose of smoking, expressed as pack-years, and MS risk is displayed in table 3. Significant trends that show higher risk of developing MS with higher dose of smoking were seen among both women and men.

In current snuff-takers who had never smoked, the incidence of MS was 0.8 (95% CI 0.4–1.3) compared to subjects who had never used any kind of tobacco. The longer the period of snuff use before the index year, the lower was the risk of developing MS. However, the only significant result was for subjects who had taken Swedish snuff for more than 15 years prior to the disease onset (OR = 0.3, 95% CI 0.1–0.8, $p = 0.02$).

Analyses based on all snuff-takers, adjusted for smoking, showed similar results. A decreased risk of developing MS was more obvious among current snuff-takers than among ever snuff-takers, and the association between decreased MS incidence and snuff use was significant for those who had taken Swedish snuff for 5 years or more prior to the disease onset (table 4).

DISCUSSION According to our observations, tobacco smokers of both sexes run an increased risk of developing MS compared with never-smokers, and we found clear evidence of a dose-response correlation between cumulative dose of smoking with the risk of developing the disease. From a clinical point of view, these results support the view that abstinence from smoking should be recommended to those at risk of developing MS, such as children of patients with MS. We further observed that the increased risk

Table 3 Odds ratio (OR) with 95% confidence interval (CI) of developing multiple sclerosis for ever-smokers compared with never-smokers by cumulative dose of smoking

No. of pack-years	Exposed cases	Exposed controls	OR*	OR†	95% CI	*p* Value for trend
Total						
0	385	967	1.0	1.0	—	
≤5	250	463	1.4	1.3	1.0–1.6	
6–10	101	176	1.5	1.5	1.1–2.0	
11–15	59	93	1.7	1.7	1.2–2.4	
16+	99	145	1.9	1.9	1.4–2.6	<0.0001
Women						
0	287	699	1.0	1.0	—	
≤5	180	328	1.3	1.3	1.1–1.7	
6–10	73	132	1.4	1.4	1.0–1.9	
11–15	41	71	1.5	1.5	1.0–2.3	
16+	62	104	1.6	1.6	1.1–2.3	0.002
Men						
0	98	268	1.0	1.0	—	
≤5	70	135	1.4	1.4	1.0–2.0	
6–10	28	44	1.9	1.8	1.1–3.1	
11–15	18	22	2.5	2.4	1.2–4.8	
16+	37	41	2.9	2.9	1.7–5.1	<0.0001

Information on cumulative dose was missing for 19 ever-smokers (8 cases and 11 controls).
*Crude data.
†Adjusted for age, ancestry, residential area, and for gender when women and men were analyzed together.

of developing MS due to smoking abates a few years after smoking cessation. The use of Swedish snuff was not associated with an increased risk of developing MS. In current snuff-takers who had taken Swedish snuff for 5 or more years, the incidence rate was significantly lower compared to those who had never taken Swedish snuff, even after smoking had been taken into consideration.

Table 4 Odds ratio (OR) with 95% confidence interval (CI) of developing multiple sclerosis for current snuff-takers compared with never snuff-takers among never smokers and ever smokers

No. of pack-years	Exposed cases	Exposed controls	OR*	OR	95% CI	*p* Value for trend
Never smokers						
0	366	903	1.0	1.0†	—	
<5	10	26	0.4	0.4†	0.01–13	
≥5	9	38	0.4	0.4†	0.01–18	
Ever smokers						
0	430	702	1.0	1.0‡	—	
<5	57	102	0.5	0.5‡	0.2–1.3	
≥5	30	84	0.3	0.3‡	0.1–0.9	0.02

*Crude data.
†Adjusted for age, sex, ancestry, and residential area.
‡Adjusted for age, sex, ancestry, residential area, and smoking.

The study was designed as a case-control study with incident cases, in which information regarding smoking habits and snuff use was collected retrospectively. There could be a potential recall bias in this case-control design, introducing systematic error in the calculation of the association between smoking and MS. In order to minimize such recall bias, we primarily included incident cases of MS who had received the diagnosis within the past year. We also took great effort to obtain the information on smoking in an identical way for the cases and the controls. Moreover, the questionnaire contained a wide range of questions regarding many potential environmental risk factors and no section in the questionnaire was given prime focus. Therefore, the potential recall bias is likely to be small in this study. Another potential methodical problem is that the recruitment of cases and controls may introduce selection bias. Some cases may have been unidentified in our study; for example, those who were diagnosed in private clinics not participating in our study. Considering the structure of the public Swedish health care system, which provides equal free of charge access to medical services for all Swedish citizens, we believe almost all cases of MS are referred to neurologic units and it is therefore not likely that the relatively few unidentified cases would cause a substantial bias in our calculations. The proportion of responders with regard to participation in the study was 92% for cases and 70% for controls. A potential selection bias may result from the relatively high proportion of nonresponders among the controls. However, this bias is probably modest because the prevalence of smoking among the controls was consistent with that expected for the general population in similar ages.[13]

The possibility that the association between smoking and increased risk of developing MS is due to some factor that affects both smoking behavior and MS risk cannot be excluded. In order to differentiate between smoking and smoking-associated behavior, we initially adjusted our analyses for educational level, parity, and body weight. However, these adjustments had only a minor influence on the results. Another factor of potential importance is passive smoking, but the data so far have been conflicting.[14,15]

Smoking as a risk factor for MS has previously been evaluated in 9 epidemiologic studies (table 1). We conducted a pooled analysis of these studies (OR 1.5, 95% CI 1.3–1.7), and the result was in accordance with our findings. None of the previous studies have evaluated the effect of stopping smoking or the impact of snuff use on the risk of developing MS.

Although there is strong evidence that tobacco smoking influences the risk of developing MS, this does not contribute to an explanation of the geo-

graphic variations in MS incidence, the female-to-male ratio, or the increasing incidence of MS among females. Available data accommodate more than one type of environmental effect.[16] Apart from smoking, vitamin D status and infection with Epstein-Barr virus have been consistently associated with increased risk of developing MS and may better explain the geographic variations in MS incidence.

Although migration studies suggest the existence of influential risk factors operating early in life, Australian data indicate that there are harmful factors also acting later in life,[17] which supports the action of more than one environmental factor.

The molecular pathways responsible for the observed association between smoking and MS are not yet known, but a variety of mechanisms have been suggested to explain the association. Cigarette smoke elevates peripheral blood leukocyte counts[18] and is associated with important markers of inflammation in autoimmune disease such as C-reactive protein and interleukin-6.[19] Abnormalities in T-cell function[20] and impairment of both humoral and cell-mediated immunity have been observed in smokers.[21]

Nicotine has been shown to increase microvascular blood flow[10] and increase blood–brain barrier permeability.[22] Leakage of the blood–brain barrier has been suggested as an initiating event in the development of MS.[23] It has also been assumed that nicotine may be immunotoxic since it may impair antigen-mediated signaling in T-cells.[11,12] However, our findings indicate that the association between MS and smoking is not a result of the influence of nicotine.

Other hypothesized mechanisms relating smoking and MS include chronic cyanide intoxication leading to widespread demyelination.[24,25] Serum concentrations of cyanide are strongly correlated with the level of tobacco consumption.[26,27] Some experimental evidence points to a potential role of the free radical nitric oxide. Exposure of nitric oxide has been shown to cause axonal degeneration or block axonal conduction, especially in axons that are physiologically active or demyelinated.[28,29] Furthermore, elevated levels of nitric oxide metabolites in the CSF are associated with the clinical progression of MS.[30] Finally, smoking may increase the risk of MS by increasing the frequency and persistence of respiratory infections.

Tobacco smoking is not associated with increased risk of all inflammatory diseases. It is protective against ulcerative colitis.[31] Furthermore, a decreased risk of Parkinson disease has consistently been demonstrated among tobacco users.[32] These findings have been attributed to the ability of nicotine to act as a neuroprotective agent. Nicotine may exert systemic effects on the immune system by inhibiting the production of proinflammatory cytokines from immune cells, such as macrophages, via the alpha7 subunit of the acetylcholine nicotinic receptor.[33,34] Since MS is most likely driven by systemic immune responses targeted at the CNS, nicotine may also be involved in this disease, consistent with the apparent lower incidence in long-term snuff-takers.

The molecular mechanisms establishing the association between smoking and MS are still unclear and warrant further investigation. A possible interaction between smoking and genotype will be investigated within EIMS. This line of research may provide a better understanding of the pathogenesis of MS and new insights into the potential prevention of the development of the disease.

AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Anna K. Hedström, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden.

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