Research Paper

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Nicotine might have a protective effect in the etiology of multiple sclerosis

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Abstract

Objective: The use of moist snuff is common in Sweden and leads to exposure to high doses of nicotine. Recent studies indicate that exposure to nicotine could modulate immune responses. The aim of this study was to investigate the influence of snuff use on the risk of developing multiple sclerosis (MS), taking smoking habits into consideration.

Methods: In two Swedish population-based, case-control studies (7883 cases, 9437 controls), subjects with different snuff use habits were compared regarding MS risk, by calculating odds ratios (ORs) with 95% confidence intervals (CIs).

Results: Snuff-takers have a decreased risk of developing MS compared with those who have never used moist snuff (OR 0.83, 95% CI 0.75–0.92), and we found clear evidence of an inverse dose-response correlation between cumulative dose of snuff use and the risk of developing the disease. We further observed that subjects who combined smoking and snuff use had a significantly lower risk for MS than smokers who had never used moist snuff, also after adjustment for amount of smoking.

Conclusions: Our results add evidence to the hypothesis that nicotine exerts anti-inflammatory and immune-modulating effects in a way that might decrease the risk of developing MS.

Keywords

Multiple sclerosis, immunology, snuff use

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Background

The use of moist snuff is common in Sweden and leads to exposure to high doses of nicotine, a major addictive component of tobacco. Recent studies indicate that exposure to nicotine could modulate immune responses within the central nervous system (CNS) and nicotine has been shown to be protective in several models of inflammatory diseases.[1] Only two studies, both from Sweden, have investigated the effect of moist snuff on the incidence of multiple sclerosis (MS) with disparate results.[2,3] The first study, which was part of the Epidemiologic Investigation of Multiple Sclerosis (EIMS) project, showed low odds ratios (ORs) for snuff users among both smokers and non-smokers.[2] In a recently published cohort study of male construction workers, no overall effect was observed with respect to use of moist snuff.[3] However, the study had a long follow-up period which means that observed relative risks may be biased towards the null value. In Sweden it is common for people who quit smoking to start using moist snuff instead. Since a large proportion of the Swedish population uses moist snuff, and since both these studies had limited numbers of cases, further studies on the subject are of interest. Using two large Swedish case-control studies, we thus aimed to investigate whether the use of moist snuff is associated with MS risk.

Methods

The report is based on data from two Swedish population-based, case-control studies; EIMS and Genes and Environment in Multiple Sclerosis (GEMS). The part of the EIMS material used in this report comprises 1798 incident MS cases, recruited from 40 clinics during the period between April 2005 and March 2012. A total of 3907 controls were randomly selected from the national population register, and these were frequency matched by age, gender,

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and residential area to the MS cases. In GEMS, prevalent cases, distinct from those in EIMS, were identified from the Swedish National MS-registry[4] and controls were randomly selected from the national population register and matched for age, gender, and residential area at the time of disease onset. The GEMS material comprises 6085 prevalent MS cases and 5530 controls recruited between November 2009 and November 2010. All cases in both studies fulfilled the McDonald criteria.[5] Ethical approval for both EIMS and GEMS were obtained from the relevant ethics committees. More details on study design and methods are given elsewhere.[6]

In both EIMS and GEMS, information on exposures and other circumstances was collected using a standardized questionnaire. Information on snuff use was obtained by asking about current and previous snuff use, including duration of snuff use and average number of snuff packets per week. One packet of snuff contains 50 g of nicotine. Questions regarding smoking were asked in a similar fashion as for snuff use. The questions regarding smoking and snuff use habits were identical in EIMS and GEMS. 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. Snuff use was considered prior to the index year in the cases and during the same period of time in the corresponding controls. Subjects who reported that they had used Swedish snuff before or during the index year were defined as snuff-takers. The subjects were then categorized into groups based on the cumulative dose (packet-years) before index. One packet-year is the equivalent of consuming one packet of snuff daily for one year. Likewise, smoking was considered prior to the index year and those who had smoked before or during the index year were defined as ever-smokers.

Statistical analysis

Using logistic regression, the incidence of MS in subjects who had used moist snuff before the index year was compared with that in subjects who had never used snuff, by calculating ORs with 95% confidence intervals (CIs). The analysis was performed separately for men and women. We also carried out the analysis restricted to never-smokers. We performed matched analyses 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 significant and in close agreement with those from the matched analyses but had wider CIs (around 2000 more controls in unconditional analysis).

The analyses were adjusted for age, gender, residential area, educational level, ancestry, and when appropriate, smoking. When both studies were analyzed together, adjustment was made for study (EIMS or GEMS). Age was categorized into the following eight 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 or not, 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. Smoking was categorized into the following strata based on the amount of cigarettes smoked prior to index: 0, 1–5, 6–10, 11–15, or >15 pack years of smoking. One pack year is defined as 20 cigarettes smoked per day for one year. Educational level was categorized into those who had a university degree and those who had not.

Adjustments were also made for heredity, socioeconomic status, body mass index at age 20 and passive smoking, but these factors had a minor influence on the results and were not retained in the final analyses. All analyses were conducted using Statistical Analysis System (SAS) version 9.

Results

Our analyses of snuff use and the risk of developing MS included 7883 cases and 9437 controls matched for age, gender, and residential area. In total, 11% of the cases and 12% of the controls had used moist snuff before the index year. The mean cumulative dose was 4.4 packet-years among cases and 5.3 packet-years among controls. Characteristics for cases and controls are shown in Table 1.

Compared with subjects who had never used moist snuff, the OR of developing MS was 0.83 (95% CI 0.75–0.92) for snuff-takers. The result was almost identical for men and women (p-value for interaction 0.95). When snuff use was considered up to three years prior to index, the OR for snuff takers was 0.81 (0.68–0.97), p=0.02.

The association between cumulative dose of snuff use expressed as packet-years, and MS risk is displayed in Table 2. Significant trends that show an inverse risk of developing MS with higher dose of snuff use, were seen among both men and women. The results remained unchanged, but had a lower degree of precision, when the analysis was restricted to never-smokers (Table 3).

In smokers who had never used moist snuff, the OR for MS was 1.49 (95% CI 1.40–1.59) compared to subjects who had never used any kind of tobacco. The OR for snuff-takers who had never smoked was 0.75 (95% CI 0.63–0.90) whereas the combination of smoking and snuff use rendered an OR of 1.19 (95% CI 1.06–1.34) (Table 4). Note that subjects who combined smoking and snuff use had a significantly lower risk of MS than smokers who had never used moist snuff, also after adjustment for amount of smoking (OR 0.75, 95% CI 0.65–0.85).

Similarly, a protective effect of using snuff was observed when the analysis was restricted to past smokers, adjusted for both duration since stopping smoking and cumulative dose of smoking (OR 0.72, 95% CI 0.60–0.88).

Table 1. Characteristics of cases and controls in Epidemiologic Investigation of Multiple Sclerosis (EIMS) and Genes and Environment in Multiple Sclerosis (GEMS) studies.

EIMS	Cases	Controls
Women (%)	72	72
Men (%)	28	28
Scandinavian origin (%)	86	83
Smokers (%)	54	45
Snuff-takers (%)	17	16
Mean number of packet years (SD)	4.7 (7.1)	6.0 (5.9)
Mean age at onset (years)	34	
Mean disease duration (years)	5	
GEMS	Cases	Controls
Women (%)	73	74
Men (%)	27	26
Scandinavian origin (%)	90	91
Smokers (%)	56	47
Snuff-takers (%)	10	9
Mean number of packet years (SD)	4.2 (7.1)	4.5(5.6)
Mean age at onset (years)	33	
Mean disease duration (years)	18	

SD: standard deviation.

Discussion

Snuff-takers of both sexes have a decreased risk of developing MS compared with those who have never used moist snuff, and we found clear evidence of an inverse dose-response correlation between cumulative dose of snuff use and the risk of developing the disease. We further observed that subjects who combined smoking and snuff use had a significantly lower risk for MS than smokers who had never used moist snuff. Moist snuff contains a number of different substances apart from nicotine and any of them could theoretically be involved in the protective effect. However, nicotine stands out as the main candidate in view of numerous studies on its immunomodulatory effects.

The findings may have practical implications in counseling persons with MS who are nicotine addicts. Circumstantial evidence suggests that smoking not only increases the risk for MS, but also leads to an aggravated disease course.[7] Hence, quitting or reducing smoking through use of alternative nicotine routes may be advised.

The study was based on data from two case-control studies in which information regarding smoking habits and snuff usage was collected retrospectively. We included 1798 cases

Table 2. Odds ratio (OR) with 95% confidence interval (CI) of developing multiple sclerosis (MS) for snuff-takers compared with subjects who have never used moist snuff, by cumulative dose of snuff use.

	Packet-years	Cases/controls[a]	OR[b]	OR[c]	*p*	*p* value for trend
EIMS						
Total	0	1530/3300	1.0 (-)	1.0 (-)		
	<5	167/345	1.00 (0.82–1.23)	0.90 (0.73–1.11)	0.3	
	5–10	63/140	0.94 (0.69–1.24)	0.78 (0.63–1.11)	0.4	
	>10	38/122	0.64 (0.44–0.96)	0.62 (0.42–0.91)	0.02	0.02
GEMS						
Total	0	5565/5063	1.0 (-)	1.0 (-)		
	<5	349/297	1.00 (0.85–1.18)	0.92 (0.78–1.08)	0.3	
	5–10	118/111	0.89 (0.68–1.16)	0.82 (0.62–1.07)	0.2	
	>10	53/59	0.74 (0.51–1.09)	0.70 (0.48–1.03)	0.06	0.02
EIMS/GEMS						
Total	0	7095/8363	1.0 (-)	1.0 (-)		
	<5	516/642	0.95 (0.83–1.07)	0.85 (0.75–0.97)	0.02	
	5–10	181/251	0.84 (0.68–1.03)	0.77 (0.63–0.95)	0.01	
	>10	91/181	0.59 (0.45–0.77)	0.57 (0.44–0.74)	<0.0001	<0.0001
Women	0	5521/6644	1.0 (-)	1.0 (-)		
	<5	161/231	0.92 (0.75–1.13)	0.83 (0.68–1.04)	0.1	
	5–10	27/52	0.72 (0.45–1.15)	0.65 (0.41–1.05)	0.08	
	>10	5/18	0.37 (0.13–1.01)	0.35 (0.13–0.96)	0.04	0.003
Men	0	1574/1719	1.0 (-)	1.0 (-)		
	<5	355/411	0.97 (0.83–1.14)	0.83 (0.71–0.98)	0.03	
	5–10	154/199	0.88 (0.78–1.10)	0.78 (0.62–0.99)	0.04	
	>10	86/163	0.63 (0.48–0.85)	0.59 (0.45–0.78)	0.0004	<0.0001

EIMS: Epidemiologic Investigation of Multiple Sclerosis; GEMS: Genes and Environment in Multiple Sclerosis.
[a]Number of exposed cases and controls.
[b]Adjusted for matching variables, study, educational level, and ancestry.
[c]Adjusted for matching variables, study, educational level, ancestry, and smoking.

Table 3. Odds ratio (OR) with 95% confidence interval (CI) of developing multiple sclerosis (MS) for never-smoking snuff-takers compared with subjects who have never used any kind of tobacco, by cumulative dose of snuff use.

Packet-years	ca/co*	OR#	OR##	*p*	*p* value for trend
0	3306/4697	1.0 (-)			
<5	120/197	0.96 (0.68–1.35)		0.9	
5–10	56/86	0.87 (0.68–1.10)		0.6	
>10	27/91	0.45 (0.28–0.68)		0.001	0.01

* Number of exposed cases and controls
# Adjusted for matching variables. study, educational level, and ancestry.

Table 4. Odds ratio (OR) with 95% confidence interval (CI) for different combinations of smoking and snuff use.

Tobacco use	Cases/controls[a]	OR[b]	*p*
None	3286/4679	1.0 (-)	
Ever smoking (no snuff use)	3704/3600	1.49 (1.40–1.59)	<0.0001
Current smoking (no snuff use)	2313/2161	1.56 (1.45–1.67)	<0.0001
Past smoking (no snuff use)	1391/1439	1.35 (1.24–1.47)	<0.0001
Snuff use (no smoking)	223/392	0.75 (0.63–0.90)	0.002
Snuff use and ever smoking	668/765	1.19 (1.06–1.34)	<0.0001
Current smoking and snuff use	359/344	1.42 (1.21–1.65)	<0.0001
Past smoking and snuff use	309/421	1.03 (0.88–1.20)	0.7

[a]Number of exposed cases and controls.
[b]Adjusted for matching variables, study, educational level, and ancestry.

and 3907 controls from EIMS, recruited between April 2005 and March 2012. Our previous study was based on subjects recruited between April 2005 and October 2008 (902 cases and 1855 controls). In EIMS, we predominantly included cases who had received their diagnosis within the past year whereas GEMS was based on prevalent cases of MS. Memory or recall bias may thus be a concern. However, we took great care to obtain information in an identical way for the cases and the controls. The questionnaire contained a wide range of questions regarding many potential environmental risk factors and no section in the questionnaire was given prime focus. Moreover, since the relationship between snuff use and MS risk had not been investigated until recently, the quality of the reported information on snuff use would probably not differ between cases and controls.

The recruitment of cases and controls may introduce selection bias. Some cases, such as those who were diagnosed in private clinics, may have been unidentified in our study. However, the Swedish health care system provides free of charge access to all Swedish residents and almost all cases of MS are referred to hospital-based neurological units. In total, 40 study centers reported cases of MS to the study, including all university hospitals. Furthermore, incident cases unidentified in EIMS would instead be identified in GEMS. It is thus unlikely that the relatively few unidentified cases would cause a substantial bias. The proportion of responders with regard to participation in the study was 91% for cases and 69% for controls. A potential selection bias may result from the relatively high proportion of non-responders among the controls. However, this bias is probably modest since the prevalence of smoking and snuff use among the controls was consistent with that expected for the general population.[8]

Our analyses were adjusted for a broad range of possible confounding factors including socioeconomic status and educational level. Quitting smoking and starting using snuff may be associated with higher socioeconomic status which in turn is associated with, for example, dietary habits, including a higher intake of vitamin D. Thus, if not taken into consideration, differences in socioeconomic position could potentially explain an observed inverse association between snuff use and MS risk among previous smokers. However, adjustments for socioeconomic status and educational level had a minor influence on the results, both among smokers as well as among previous smokers.

Tobacco smoke contains thousands of compounds which comprise human carcinogens and toxic agents such as carbon monoxide, ammonia and nitrogen oxides. Although the net effect of smoking is pro-inflammatory, there is increasing evidence that smokers have a lower incidence of several inflammatory diseases, such as ulcerative colitis and sarcoidosis.[9] The protective effect has been attributed to the ability of nicotine to dampen inflammation.[10]

Recent studies demonstrate that the immune system can be significantly regulated by the vagus nerve via the peripheral release of acetylcholine. The neurotransmitter also functions as an immune cytokine that inhibits the release of pro-inflammatory cytokines from immune cells, such as macrophages, through a mechanism dependent on the

alpha7 nicotinic receptor. Nicotine, a more selective cholinergic agonist, is more efficient than acetylcholine at attenuating the production of pro-inflammatory cytokines.[11]

Nicotine has been shown to be protective in several models of inflammatory diseases, including experimental autoimmune encephalomyelitis.[1] Nicotine treatment is associated with reduced T cell reactivity and decreased production of Th1 and Th17 cytokines.[12] The anti-inflammatory effects exerted by nicotine on macrophages are counteracted by selective alpha7 antagonists.

Selective agonists for the alpha7 nicotinic receptor could represent a pharmacological strategy to control a variety of pro-inflammatory cytokines, and may prove beneficial in several inflammatory and neurodegenerative disorders.[13] However, the development of nicotine as a therapeutic tool has potential disadvantages such as toxicity related side effects and lack of pharmacological specificity. Nicotine may also have pro-inflammatory effects independent of acetylcholine receptor activation, and its long-term effects on human health are unknown.[1]

In conclusion, we found clear evidence of an inverse dose-response correlation between cumulative dose of snuff use and the risk of developing MS. Nicotine, by targeting alpha7 nicotinic receptors, exerts anti-inflammatory and immune-modulating effects in a way that might decrease the risk of developing MS.

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TO and LA supervised the EIMS project, JH supervised the GEMS project, AKH conducted the statistical analyses and prepared the manuscript. TO and LA commented on the manuscript. All authors approved the final version of the manuscript to be published.

Conflict of interest

Dr Hedström receives research support from the Swedish Association for Persons with Neurological Disabilities.

Dr. Hillert received honoraria for serving on advisory boards for BiogenIdec, Merck-Serono and Novartis and for speaker's fees from BiogenIdec, Merck-Serono, Bayer-Schering, Teva and Sanofi-Aventis. He has served as P.I. for and received projects supported by BiogenIdec, Merck-Serono, and Bayer-Schering. His MS research is funded by the Swedish Research Council, Bibbi and Nils Jensens Foundation and the European Commission.

Dr. Olsson served on scientific advisory boards for Merck-Serono, Biogen Idec, and SanofiAventis; served as Co-editor of Current Opinion in Immunology; received speaker honoraria from Novartis and Biogen; and receives research support from Bayer Schering, Sanofi-Aventis, Biogen Idec, the Swedish Research Council, EU fp6 Neuropromise, EURATools, the Söderberg Foundation, Bibbi and Nils Jensens Foundation, the Montel Williams Foundation, and the Swedish Brain Foundation.

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References

1. Filippini P, Cesario A, Fini M, et al. The yin and yang of non-neuronal alpha7 nicotinic receptors in inflammation and autoimmunity. *Curr Drug Targets* 2012; 5: 644–655.
2. Hedström AK, Bäärnhielm M, Olsson T, et al. Tobacco smoking, but not Swedish snuff usage, increases the risk of multiple sclerosis. *Neurology* 2009; 73: 696–701.
3. Carlens C, Hergens MP, Grunewald J, et al. Smoking, use of moist snuff, and risk of chronic inflammatory diseases. *Am J Respir Crit Care Med* 2010; 181: 1217–1222.
4. SMSreg. Välkommen till Svenska MS-registret, www.msreg.net (accessed 30 October 2012).
5. Thompson AJ, Montalban X, Barkhof F, et al. Diagnostic criteria for primary progressive multiple sclerosis: A position paper. *Ann Neurol* 2000; 47: 831–835.
6. Hedström AK, Åkerstedt T, Hillert J, et al. Shift work at young age is associated with increased risk for multiple sclerosis. *Ann Neurol* 2011; 67; 110–117.
7. Wingerchuk DM. Smoking: Effects on multiple sclerosis susceptibility and disease progression. *Ther Adv Neurol Disord* 2012; 5: 13–22.
8. Cnattingius S, Galanti R, Grafström R, et al. Statens folkhälsoinstitut. Hälsorisker med svenskt snus. (available at http://www.fhi.se/PageFiles/3094/a200515snusrapport0512yy.pdf).
9. Sopori M. Effects of cigarette smoke on the immune system. *Nat Rev Immunol* 2002; 2: 372–377.
10. Piao WH, Campagnolo D, Dayao C, et al. Nicotine and inflammatory neurological disorders. 2009; 30: 715–722.
11. Ulloa L. The vagus nerve and the nicotinic anti-inflammatory pathway. *Nat Rev Drug Discov* 2005; 4: 673–684.
12. Nizri E, Irony-Tur-Sinai M, Lory O, et al. Activation of the cholinergic anti-inflammatory system by nicotine attenuates neuroinflammation via suppression of Th1 and Th17 responses. *J Immunol* 2009; 183: 6681–6688.
13. De Jonge WJ and Ulloa L. The alpha7 nicotinic acetylcholine receptor as a pharmacological target for inflammation. *Br J Pharmacol* 2007; 151: 915–929.