Smoking, Use of Moist Snuff, and Risk of Chronic Inflammatory Diseases

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***Rationale*: Cigarette smoking is emerging as a strong risk factor in the otherwise unknown etiology of chronic inflammatory diseases. Whether the same applies also to smokeless tobacco remains unknown. Nicotine is a powerful modifier of the inflammatory response. By comparing risks associated with tobacco smoking and with smokeless tobacco, the role of nicotine in the development of chronic inflammation may be evaluated.**

***Objectives*: To assess and compare the risks of rheumatoid arthritis (RA), ulcerative colitis (UC), Crohn's disease (CD), sarcoidosis, and multiple sclerosis (MS) associated with cigarette smoking and with the use of Swedish moist snuff.**

***Methods*: We performed a cohort study of 277,777 males within a cohort of Swedish construction workers who had provided information about tobacco use in 1978–1993. Cross-linkage to the nationwide Swedish Hospital Discharge Register provided information about the occurrence of RA, UC, CD, sarcoidosis, and MS through 2004.**

***Measurements and Main Results*: Age-adjusted relative risks (RRs) associated with smoking and moist snuff, respectively, were estimated by Cox regression. Ever-smoking was associated with an increased risk for RA (RR, 2.1; 95% confidence interval [CI], 1.7–2.5), CD (RR, 1.5; 95% CI, 1.2–1.8), MS (RR, 1.9; 95% CI, 1.4–2.6), and UC (RR, 1.3; 95% CI, 1.1–1.5, confined to ex-smokers), and a decreased risk of sarcoidosis (RR, 0.5; 95% CI, 0.4–0.5). By contrast, ever-use of moist snuff, adjusted for smoking, was not associated with RA (RR, 1.0; 95% CI, 0.9–1.2), UC (RR, 1.1; 95% CI, 0.9–1.2), CD (RR, 0.9; 95% CI, 0.8–1.1), sarcoidosis (RR, 1.1; 95% CI, 0.8–1.5), or MS (RR, 1.0; 95% CI, 0.8–1.4).**

***Conclusions*: Smokeless tobacco does not increase the risk of chronic inflammatory diseases, suggesting that inhaled nonnicotinic components of cigarette smoke are more important than nicotine itself in the etiology of these diseases.**

Keywords: cohort; rheumatoid arthritis; inflammatory bowel disease; sarcoidosis; tobacco smoking

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

Cigarette smoking is a strong risk factor for chronic inflammatory diseases. Whether these risks are due to nicotine or other constituents of inhaled tobacco smoke is unclear, as are the risks for chronic inflammatory diseases with use of smokeless tobacco.

What This Study Adds to the Field

We confirm and extend the strong associations between smoking and risk of chronic inflammatory diseases, but show for the first time that smokeless tobacco does not affect the risk of these diseases. These discrepant findings suggest that the link between smoking and chronic inflammatory diseases is mediated through airway exposure to nonnicotinic components of tobacco smoke.

For several chronic autoimmune inflammatory diseases, tobacco smoke is emerging as one of the strongest of the few identified environmental risk factors. Smoking increases the risk of rheumatoid arthritis (RA), Crohn's disease (CD), and multiple sclerosis (MS). Smoking cessation may attenuate these increased risks and improve disease course (1–8). Smoking decreases the risk of ulcerative colitis (UC), whereas smoking cessation increases the risk and worsens the course of UC (4, 9–11). Smoking has also been suggested to decrease the risk of sarcoidosis (12–15), summarized in Table 1.

The underlying biology behind these strong, yet diverging, associations remains unclear. Nicotine, the major component in tobacco smoke, is a strong modifier of the inflammatory response (16, 17). As a potent agonist of the α7-nicotinic acetylcholine receptors on macrophages and other cytokine-producing cells, nicotine may exert strong antiinflammatory effects through the physiological "nicotinic antiinflammatory pathway" (18), which may be of importance in the etiology and propagation of chronic inflammation.

Besides nicotine, tobacco smoke contains more than 4,500 other chemical compounds. It may thus be that the associations between smoking and chronic inflammatory diseases are independent of nicotine, but driven by specific or unspecific host reactions to nonnicotinic inhaled components of tobacco smoke (19, 20).

Since the 1970s, use of oral Swedish moist snuff ("snus") has become increasingly popular. At present, approximately 20% of the adult male Swedish population are daily users of moist snuff (21). Use of moist snuff leads to exposure to similar or higher doses of nicotine than tobacco smoking, but not to airway exposure to nonnicotinic components of tobacco smoke (22). Comparisons of risks for inflammatory diseases associated with smoking and moist snuff, respectively, might therefore be used to evaluate the roles of nicotine per se and tobacco smoke, respectively, in the development of chronic inflammation. Apart from a small case-control study on the use of moist snuff versus risk of inflammatory bowel disease and a study on smoking, use of moist snuff, and the risk of MS, it is not known whether the

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TABLE 1. CURRENT UNDERSTANDING OF THE ASSOCIATION BETWEEN SMOKING AND RISK OF RHEUMATOID ARTHRITIS, ULCERATIVE COLITIS, CROHN'S DISEASE, SARCOIDOSIS, AND MULTIPLE SCLEROSIS

	Rheumatoid Arthritis	Ulcerative Colitis	Crohn's Disease	Sarcoidosis	Multiple Sclerosis
Current (or ever) smoking	Increased risk (1–3)	Decreased risk (4, 9–11)	Increased risk (4, 10, 11)	Decreased risk (12–15)	Increased risk (6–8, 24)
Smoking cessation	Attenuated increased risk (1–3)	Increased risk (4, 9–11)	Attenuated increased risk (4, 10, 11)		Attenuated increased risk (24)

marked associations between tobacco smoking and risk of inflammatory diseases apply also to smokeless tobacco (23, 24).

Using a uniquely large cohort of individuals for whom we had information about smoking and use of moist snuff, and the exceptional Swedish possibilities for linkage to national registers on morbidity and vital status, we assessed and compared the risks of RA, UC, CD, sarcoidosis, and MS associated with smoking and with the use of moist snuff.

METHODS

From 1969 through 1993 preventive health check-ups were offered to all white-collar and blue-collar workers in the Swedish construction industry by the Construction Industry's Organization for Working Environment Safety and Health, "Bygghälsan." This cohort has been described elsewhere (25). During the period 1975 to 1978 no information regarding tobacco use was collected, and therefore this study includes subjects with visits on January 1, 1978 or later (n = 300,637). Because of individual differences in number and timing of visits after the baseline visits, partly driven by self-selection, and uncertain quality of smoking data from follow-up visits, we further chose to use exposure information from the first visit counting from January 1, 1978 only.

Use of Swedish moist snuff was categorized according to user status (never, former, or current) and amount of moist snuff used per day (<22 g or ⩾22 g). Current use was defined as daily consumption of snuff. Ever–snuff use was defined as current or former use. Smoking user status was categorized in the same way as snuff use, and includes cigarette smoking, cigar smoking, and pipe smoking.

Follow-up and Occurrence of RA, UC, CD, Sarcoidosis, and MS

Using the National Registration Number, a unique number assigned to all Swedish residents, as the linkage key, the cohort was linked to the Swedish Hospital Discharge Register. Through this linkage, we identified all hospital discharge files listing a main or contributory diagnosis of RA, UC, CD, sarcoidosis, and MS from 1964 through 2004. Rheumatoid factor (RF) status was determined by the ICD (International Classification of Diseases) code used for RA in the Swedish Hospital Discharge Register. This linkage also identified individuals who had already been hospitalized with RA (n = 12), UC (n = 138), CD (n = 47), sarcoidosis (n = 11), or MS (n = 45) before their baseline visit. These individuals were excluded from further analysis.

Region of residence at the baseline visit was established by linkage to the Register of Total Population and Population Changes. If an individual was living in a county with incomplete coverage by the Swedish Hospital Discharge Register, the entry date into the cohort was reset to the date of coverage.

Censoring dates for death and emigration were obtained from the Causes of Death Register, and from the Register of Total Population and Population Changes, respectively. Each cohort member contributed person-years from the date of entry until the date of any diagnosis, death, emigration, or December 31, 2004, whichever came first. Only 5% of the cohort members were women, and because use of moist snuff among women in this cohort was less than 1%, we restricted all analyses to males.

Statistics

For each of the outcomes, incidence rates per 100,000 person-years standardized to the age distribution (5-yr age categories) in the entire cohort were calculated. Relative risks for the association between tobacco use and the inflammatory diseases were estimated using Cox proportional hazards models taking age into account, with adjustment for region of residence. Two sets of models were performed; First, ever-smoking (yes/no) and ever-snuff use (yes/no) were entered into a bivariable model. Thereafter, and because smoking and use of Swedish moist snuff are correlated, we categorized each cohort member into either of the following mutually exclusive exposure categories of tobacco exposure: (*1*) former, current, and ever, respectively, smokers who were never-users of moist snuff, (*2*) former, current, and ever, respectively, users of moist snuff who were never-smokers, (*3*) ever-smokers who were also ever-users of moist snuff, and (*4*) never-users of tobacco, that is, never-smokers who were never-users of moist snuff. Separate models were subsequently fitted for each of these exposure categories 1 to 3, all using nontobacco users (category 4) as reference.

The assumption of proportional hazards for smoking, snuff use, and covariates was examined by the method of Shoenfeld's partial residuals (26). The results indicated that the proportional assumption was satisfied for all models. All analyses were conducted with SAS statistical software, version 9.1 (Cary, NC). The study was approved by the Ethics Committee at Karolinska Institute (Stockholm, Sweden).

RESULTS

The final cohort consisted of 277,777 men (Figure 1). Mean age at entry into the cohort was 36 years, and mean follow-up time was 20 years, resulting in a total follow-up of more than 5 million person-years. For smoking- and snuff-use characteristics in the cohort, *see* Table 2. The average number of cigarettes smoked per day among smokers who were never-users of moist snuff was 12, and the average amount of Swedish moist snuff used among never-smokers at entry was 22.2 g/day.

During follow-up, 797 cases of RA were identified, corresponding to an incidence rate (IR) of 14 per 100,000 person-

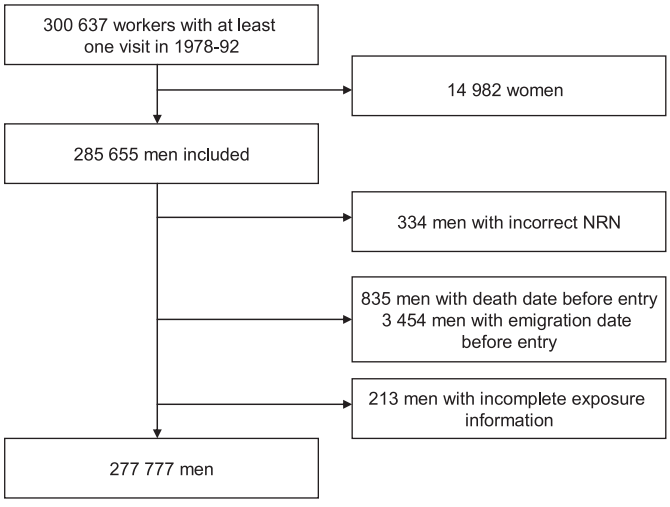

Figure 1. Flow chart describing the assembly of the study population. NRN = National Registration Number.

TABLE 2. CHARACTERISTICS OF TOBACCO USE IN THE SWEDISH CONSTRUCTION WORKERS COHORT

			Ever-users of Moist Snuff among Never-smokers		Ever-smokers among Never-users of Moist Snuff		Ever-users of Moist Snuff and Smoking		
	Total Number	No Tobacco Use Number (%)	Number (%)	Mean Snuff Use (g/d)	Number (%)	Mean Cigarette Use (cig/d)	Number (%)	Mean Snuff Use (g/d)	Mean Cigarette Use (cig/d)
Age at entry									
<24 yr	78,377	33,508 (43)	21,282 (27)	23	15,044 (19)	10	8,543 (11)	19	8
25–34 yr	72,289	20,371 (28)	10,200 (14)	23	27,804 (39)	12	13,914 (19)	17	10
35–44 yr	59,025	15,048 (25)	3,529 (6)	21	29,355 (50)	13	11,093 (19)	16	11
45–54 yr	37,404	10,462 (28)	1,313 (3)	19	20,028 (54)	11	5,601 (15)	14	10
⩾55 yr	30,684	8,361 (27)	1,135 (4)	15	16,909 (55)	10	4,274 (14)	12	8
Total	277,777	87,750 (32)	37,459 (13)	22	109,143 (39)	12	43,425 (16)	16	9
Person-time of follow-up	5,401,749	1,699,100	679,808		2,162,271		860,570		

years. In bivariable models, ever-smoking was associated with an increased risk of RA (relative risk [RR], 2.1; 95% confidence interval [CI], 1.7–2.5), whereas use of moist snuff was not (RR, 1.0; 95% CI, 0.9–1.2) (Table 3). When modeled separately and compared with nontobacco users, the relative risk among current smokers (who were never-users of moist snuff) was 2.6 (95% CI, 2.1–3.2) and the relative risk among former smokers (who were never-users of moist snuff) was 1.5 (95% CI, 1.2–2.0) (Table 4). Ever-use of moist snuff (among never-smokers) was not associated with risk of RA (RR, 1.2; 95% CI, 0.8–1.8) irrespective of the amount of moist snuff used (data not shown). Combined tobacco use, that is, ever-smoking and ever-use of moist snuff, was associated with an increased risk of RA (RR, 2.0; 95% CI, 1.6–2.6), similar to that of smokers who did not use moist snuff (Table 5).

Sensitivity analysis according to RF status suggested that the overall association with smoking was confined to RF-positive RA (RR, 2.2; 95% CI, 1.6–3.2) rather than RF-negative RA (RR, 1.1; 95% CI, 0.7–1.8). No such difference was noted for ever-use of moist snuff (RR for RF-positive RA, 1.2; 95% CI, 0.6–2.7 and RR for RF-negative RA, 1.3; 95% CI, 0.6–2.8), but was based on only eight exposed cases in each group.

During follow-up, 1,014 cases of UC were identified, corresponding to an incidence of 18 per 100,000 person years. In bivariable models, the relative risk associated with ever-smoking was 1.3 (95% CI, 1.1–1.5) and the relative risk associated with ever-use of moist snuff was 1.1 (95% CI, 0.9–1.2) (Table 3). When modeled separately and compared with nontobacco users, the relative risk among current smokers (who were never-users of moist snuff) was 1.1 (95% CI, 1.0–1.4) and the relative risk among former smokers (who were never-users of moist snuff) was 1.5 (95% CI, 1.2–1.8) (Table 4). Ever-use of moist snuff (among never-smokers) was not associated with risk of UC (RR, 1.0; 95% CI, 0.8–1.2), and no dose–response association was observed (data not shown). Combined tobacco use, that is, ever-smoking and ever-use of moist snuff, was associated with an increased risk of UC (RR, 1.4; 95% CI, 1.1–1.6) similar to that of former smokers (Table 5).

During follow-up, 628 cases of CD were identified, corresponding to an incidence of 11 per 100,000 person-years. In bivariable models, the relative risk associated with ever-smoking was 1.5 (95% CI, 1.2–1.8) and the relative risk associated with ever-use of moist snuff was 0.9 (95% CI, 0.8–1.1) (Table 3). When modeled separately and compared with nontobacco users, the relative risk among current smokers (who were never-users of moist snuff) was 1.6 (95% CI, 1.3–2.0) and the relative risk among former smokers (who were never-users of moist snuff) was 1.3 (95% CI, 1.0–1.8). Ever-use of moist snuff (among never-smokers) was not associated with risk of CD (RR, 1.0; 95% CI, 0.8–1.4), and no dose–response association was noted (data not shown). Combined tobacco use, that is, ever-smoking and ever-use of moist snuff, was associated with an increased risk of CD (RR, 1.4; 95% CI, 1.1–1.8), similar to that for smokers who did not use moist snuff.

During follow-up, 342 cases of sarcoidosis were identified, corresponding to an incidence of 7 per 100,000 person-years. In bivariable models, the relative risk associated with ever-smoking was 0.5 (95% CI, 0.4–0.5) and the relative risk associated with ever-use of moist snuff was 1.1 (95% CI, 0.9–1.4) (Table 3). Compared with nontobacco users, the relative risk among current smokers (who were never-users of moist snuff) was 0.5 (95% CI, 0.4–0.6) and the relative risk among former smokers (who were never-users of moist snuff) was 0.5 (95% CI, 0.4–0.8). Ever-use of moist snuff (among never-smokers) was not associated with a decreased risk of sarcoidosis (RR, 1.1; 95% CI, 0.8–1.5). Combined tobacco use, that is, ever-smoking and ever-use of moist snuff, was associated with a decreased risk of sarcoidosis (RR, 0.5; 95% CI, 0.4–0.8), similar to that among current or former smokers who did not use moist snuff.

TABLE 3. RELATIVE RISKS WITH 95% CONFIDENCE INTERVALS OF RHEUMATOID ARTHRITIS, ULCERATIVE COLITIS, CROHN'S DISEASE, SARCOIDOSIS, AND MULTIPLE SCLEROSIS AMONG EVER-SMOKERS AND EVER–SNUFF USERS IN MODELS CONTAINING BOTH EXPOSURES

	Rheumatoid Arthritis: RR (95% CI); n = cases	Ulcerative Colitis: RR (95% CI); n = cases	Crohn's Disease: RR (95% CI); n = cases	Sarcoidosis: RR (95% CI); n = cases	Multiple Sclerosis: RR (95% CI); n = cases
Never-users of tobacco	1.0 (reference); n = 129	1.0 (reference); n = 284	1.0 (reference); n = 157	1.0 (reference); n = 145	1.0 (reference); n = 37
Ever-smoker	2.1 (1.7–2.5); n = 641	1.3 (1.1–1.5); n = 616	1.5 (1.2–1.8); n = 405	0.5 (0.4–0.5); n = 135	1.9 (1.4–2.6); n = 150
Ever-user of moist snuff	1.0 (0.9–1.2); n = 168	1.1 (0.9–1.2;) n = 305	0.9 (0.8–1.1); n = 174	1.1 (0.9–1.4); n = 103	1.0 (0.8–1.4); n = 64

Definition of abbreviations: CI = confidence interval; RR = relative risk.

TABLE 4. RELATIVE RISKS WITH 95% CONFIDENCE INTERVALS AND INCIDENCE RATES OF RHEUMATOID ARTHRITIS, ULCERATIVE COLITIS, CROHN'S DISEASE, SARCOIDOSIS, AND MULTIPLE SCLEROSIS AMONG EVER-SMOKERS NEVER USING SNUFF, EVER–SNUFF USERS WHO WERE NEVER-SMOKERS, AND AMONG EVER-SMOKERS AND SNUFF USERS IN COMBINATION

	Rheumatoid Arthritis		Ulcerative Colitis		Crohn's Disease		Sarcoidosis		Multiple Sclerosis	
	RR (95% CI)	IR	RR (95% CI)	IR	RR (95% CI)	IR	RR (95% C)	IR	RR (95% C)	IR
Never-user of tobacco	1.0 (reference); n = 129	8	1.0 (reference); n = 284	16	1.0 (reference); n = 157	9	1.0 (reference); n = 145	9	1.0 (reference); n = 37	2
Ever-smoker, never-use of moist snuff	2.3 (1.9–2.7); n = 500	21	1.2 (1.1–1.4); n = 425	19	1.5 (1.3–1.9); n = 297	13	0.5 (0.4–0.6); n = 94	4	2.5 (1.7–3.6); n = 113	6
Ever-use of moist snuff, never-smoker	1.2 (0.8–1.8); n = 27	7	1.0 (0.8–1.2); n = 114	15	1.0 (0.8–1.4); n = 66	9	1.1 (0.8–1.5); n = 62	10	1.8 (1.1–2.9); n = 27	4
Ever-smoker and ever-user of moist snuff	2.0 (1.6–2.6); n = 141	17	1.4 (1.1–1.6); n = 191	22	1.4 (1.1–1.8); n = 108	12	0.5 (0.4–0.8); n = 41	5	1.9 (1.2–3.1); n = 37	4

Definition of abbreviations: CI = confidence interval; IR = incidence rate per 100,000 person-years standardized to age distribution of person-years experienced by all workers, using 5-year age categories; RR = relative risk.

During follow-up, 214 cases of MS were identified, corresponding to an incidence of 4 per 100,000 person years. In bivariable models, the relative risk associated with ever-smoking was 1.9 (95% CI, 1.4–2.6) and the relative risk associated with ever-use of moist snuff was 1.0 (95% CI, 0.8–1.4) (Table 3). Compared with nontobacco users the relative risk among current smokers (who were never-users of moist snuff) was 2.8 (95% CI, 1.9–4.1) and the relative risk among former smokers (who were never-users of moist snuff) was 1.6 (95% CI, 0.9–2.8). Ever-use of moist snuff (among never-smokers) was associated with an increased risk of MS of borderline statistical significance (RR, 1.8; 95% CI, 1.1–2.9) without any apparent dose–response relationship (data not shown). Combined tobacco use, that is, ever-smoking and use of moist snuff, was associated with an increased risk of MS (RR, 1.9; 95% CI, 1.2–3.1), which was somewhat lower than that among smokers who did not use moist snuff (Table 4).

DISCUSSION

The results of our large cohort study based on prospectively recorded data confirm, and extend, respectively, previous observations from various study designs that smoking is a risk factor for (seropositive) RA, CD, and MS; that these risks are reduced among former smokers; that former smokers have an increased risk for UC; and that smoking reduces the risk of sarcoidosis (1–15). In sharp contrast, no evidence of any significant association was noted between use of moist snuff and the risk for any of these chronic inflammatory diseases with the exception of a borderline increased risk for MS with snuff use among never-smokers.

Major health hazards of tobacco smoke are well known, but the specific role of nicotine in the risk of chronic inflammation remains debated. Animal studies suggest that nicotine may exert several immune-modulatory effects through its capacity to inhibit both the innate and the adaptive immune response, partly mediated through the potent "nicotinic antiinflammatory pathway" (summarized in References 16, 17, and 27), although its impact on the development of chronic inflammation is little known.

With respect to RA, our results (a higher risk for RF-positive than RF-negative RA, a lower risk among former smokers) are well in line with previous studies of smoking (28), (reviewed in References 29 and 30), although RF status in our study was assessed on the basis of incomplete data. Data on risk of RA in relation to use of moist snuff is largely lacking. Our finding that use of moist snuff was not associated with risk of RA would suggest that the role of cigarette smoking in RA is mediated through other mechanisms than nicotine, and thus that the role of smoking might be parallel to that of other inhaled non-nicotine–containing irritants such as silica and charcoal, both of which have been identified as risk factors for RA (31).

We noted an increased risk of CD in smokers, but did not observe the previously reported reduced risk of UC in current smokers (4, 9). One possible explanation is the fact that we did not have information on changes in smoking habits during follow-up. Some of the current smokers at the baseline visit might have stopped smoking during follow-up, and because former smokers are at increased risk of UC (4, 10), any true protecting effect of current smoking in our study would be underestimated.

Although not unequivocally, transdermal nicotine has in some studies been shown to be beneficial in active UC (32). Despite extensive animal and human studies the opposite effect of smoking in CD and UC is still debated. Nicotine has been suggested to be the protective agent in UC whereas the negative

TABLE 5. RELATIVE RISKS WITH 95% CONFIDENCE INTERVALS OF RHEUMATOID ARTHRITIS, ULCERATIVE COLITIS, CROHN'S DISEASE, SARCOIDOSIS, AND MULTIPLE SCLEROSIS AMONG CURRENT AND FORMER SMOKERS WHO WERE NEVER-USERS OF MOIST SNUFF

	Rheumatoid Arthritis		Ulcerative Colitis		Crohn's Disease		Multiple Sclerosis		Sarcoidosis	
	RR (95% CI)	IR	RR (95% CI)	IR	RR (95% CI)	IR	RR (95% CI)	IR	RR (95% CI)	IR
Never-user of tobacco	1.0 (reference); n = 129	8	1.0 (reference); n = 284	16	1.0 (reference); n = 157	9	1.0 (reference); n = 37	2	1.0 (reference); n = 145	9
Current smoker	2.6 (2.1–3.2); n = 641	18	1.1 (1.0–1.4.); n = 616	18	1.6 (1.3–2.0); n = 405	14	2.8 (1.9–4.2); n = 150	6	0.5 (0.4–0.6); n = 135	4
Former smoker	1.5 (1.2–2.0); n = 144	12	1.5 (1.2–1.8); n = 143	24	1.3 (1.0–1.8); n = 71	10	1.6 (0.9–2.8); n = 20	4	0.5 (0.4–0.8); n = 28	4

Definition of abbreviations: CI = confidence interval; IR = incidence rate per 100,000 person-years standardized to age distribution of person-years experienced by all workers, using 5-year age categories; RR = relative risk.

effect of smoking on CD might be mediated through mechanisms independent of nicotine (17, 27, 33–35). One earlier case-control study on smoking and use of moist snuff as risk factors for UC and CD did not show any association between use of moist snuff among nonsmokers and risk of UC or CD, but did show increased risks associated with snuff use among ever-smokers (23), based on 15 and 11 exposed cases. In our study we did not detect any effect of moist snuff, irrespective of dose, on the risk of IBD.

In a large study on environmental risk factors for sarcoidosis, tobacco smoking was inversely associated with risk of the disease (14). The potential mechanism behind this possible association is not understood. In experimental studies, nicotine has been shown to reduce the bronchoalveolar lavage (BAL) cellular response, the production of inflammatory cytokines, and the extent of inflammation as analyzed in biopsy samples (36). An influence of smoke on BAL cellular composition has been noted also in humans (15). These immune-modulatory effects by nicotine have been suggested to underlie the reduced frequency of pulmonary granulomatous disease among smokers (37). It is therefore interesting to note that use of moist snuff, leading to similar exposure levels of nicotine as in smokers, did not seem to influence the risk of sarcoidosis. Our results would argue against nicotine as an important protective agent against sarcoidosis, but indicate other constituents in cigarette smoke as responsible for the protective effect.

Several studies have shown an increased risk for MS among smokers (5–7), and a faster transmission from a relapsing–remitting clinical course to a secondary progressive course has been indicated (38, 39). Potential mechanisms include the effect of nitric oxide, chronic cyanide intoxication, the effect of nicotine on the blood–brain barrier, and smoking-mediated increased frequency and persistency of infections, but the relevance of these must be established (*see* discussion in References 5 and 6). With respect to use of moist snuff, we observed no overall effect but increased risks among never-smokers (and a tendency toward lower risks for the combination of smoking and snuff use than with smoking alone) in analyses stratified by smoking status. The explanation for this is currently unknown, but include a chance finding, that the pattern of use of moist snuff is different in smokers and nonsmokers, that other characteristics of smokers who use, and do not use, respectively, moist snuff, are different, as well as a true biological effect of combination use (40, 41). In contrast, another study showed no overall association between use of moist snuff and MS (24).

Our study has several strengths and limitations. The use of prospectively registered data minimized the risk of recall and information bias. The size of the cohort, the relatively high prevalence of exposure, and the long and complete follow-up contributed to a high power. Because data on both smoking and moist snuff were available we could adjust and stratify assessment of each adjusted for the other, although we had sparse information about other risk factors for these diseases. Because all analyses were performed within the cohort of construction workers, confounding by socioeconomic factors may be limited. On the other hand, other exposures in this cohort (such as other inhaled agents), and selection into the cohort ("healthy worker effect") may limit the generalizability of our results, as does the fact that all subjects were male.

Outcome was defined on the basis of hospitalization, why selection of more severe cases is possible. The diagnostic validity of RA, UC, and CD in the Swedish Hospital Discharge Register has been shown to be high (42, 43), but we lack information about the validity of the other diagnoses. The observed incidences in our study are, however, in broad accordance with those previously reported for males in the age groups under study (43–51). It may, however, be that the true onset of disease predated the recorded date of outcome in our study.

Because we only used information from one visit, we did not have information about changes in smoking habits and snuff use during follow-up. For the same reason, we could not assess the effect of duration of tobacco use, nor did we have information about actual tobacco use at the time of the outcome. Finally, snuff use was used as an interesting model for noninhaled exposure to nicotine; the lack of association between use of moist snuff and risk of chronic inflammatory diseases does not preclude that moist snuff has other detrimental health effects. Smokeless tobacco use has been associated with an increased risk of oropharyngeal and pancreatic cancer (52). Thus, our results cannot be used as argument to advocate its use.

In conclusion, the discrepant pattern of risks associated with tobacco smoking and with use of moist snuff, respectively, for chronic inflammatory diseases points to the importance of airway exposure to (nonnicotinic components of) tobacco smoke in the etiology of chronic inflammatory diseases.

Conflict of Interest Statement: The authors declare that they have no conflicts of interest. C.C. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. M.-P.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.G. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. A.E.'s dependent received up to $1,000 from Centicort and up to $1,000 from Schering Plough in advisory board fees, and up to $1,000 from AstraZeneca in lecture fees. C.O.H. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript. J.A. does not have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.

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