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Smoking is Associated With Extra-intestinal Manifestations in Inflammatory Bowel Disease

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Abstract

Background and aims: Smoking affects the course of disease in patients with ulcerative colitis (UC) and Crohn's disease (CD). We aimed to study the association between smoking and extra-intestinal manifestations (EIMs) in inflammatory bowel disease (IBD).

Methods: We cross-sectionally explored the association between smoking and EIMs in IBD in three cohort studies: (1) the COIN study, designed to estimate healthcare expenditures in IBD; (2) the Groningen study, focused on cigarette smoke exposure and disease behaviour in IBD; and (3) the JOINT study, evaluating joint and back manifestations in IBD.

Results: In the COIN, Groningen and JOINT cohorts, 3030, 797 and 225 patients were enrolled, of whom 16, 24 and 23.5% were current smokers, respectively. Chronic skin disorders and joint

manifestations were more prevalent in smoking IBD patients than in non-smokers (COIN, 39.1 vs 29.8%, p <0.01; Groningen, 41.7 vs 30.0%, p <0.01) in both CD and UC. In the JOINT cohort, smoking was more prevalent in IBD patients with joint manifestations than in those without (30.3 vs 13.0%, p <0.01). EIMs appeared to be more prevalent in high- than in low-exposure smokers (56.0 vs 37.1%, p = 0.10). After smoking cessation, the prevalence of EIMs in IBD patients rapidly decreased towards levels found in never smokers (lag time: COIN cohort, 1–2 years; Groningen cohort, within 1 year).

Conclusions: There is a robust dose-dependent association between active smoking and EIMs in both CD and UC patients. Smoking cessation was found to result in a rapid reduction of EIM prevalence to levels encountered in never smokers.

Key Words: Inflammatory bowel disease; extra-intestinal manifestations; smoking

1. Introduction

Inflammatory bowel disease (IBD) is a chronic intestinal disorder comprising Crohn's disease (CD) and ulcerative colitis (UC). In Europe the incidence rates are currently estimated to be 5.4 per 100 000 person-years for CD and 8.2 per 100 000 person-years for UC.[1]

IBD is frequently associated with extra-intestinal manifestations (EIMs). The most common EIMs involve the joints, the skin and the eyes.[2] The prevalence of EIMs in IBD patients ranges from 6 to 38%, and patients with CD are more prone to the development of EIMs than UC patients.[3–8]

The influence of smoking on disease activity in patients with IBD is now well established. Remarkably, smoking affects the course of disease differently in CD and UC, having a negative effect on the course of CD and a beneficial effect in UC.[8–10] The association between smoking and EIMs in IBD is currently largely undefined. As the burden of EIMs for these patients is high and its treatment remains a challenge, a better understanding of risk factors for EIMs in IBD is warranted. An increased prevalence of EIMs in smoking IBD patients was reported in two recent studies.[11,12] These studies did not correct for disease activity and were not conclusive with respect to the potential difference between CD and UC. Importantly, no studies have been performed that are solely focused on the association between smoking and EIMs in IBD.

We hypothesized that EIMs are more prevalent in smoking CD patients, as smoking may induce an inflammatory response both inside and outside the gut. Because smoking is associated with a more benign disease course in UC, EIMs might be less prevalent in smoking UC patients.

The primary aim of the current cohort study was to examine the putative association between smoking and EIMs in IBD. Our secondary aims were to detect a possible dose–response relationship between smoking and EIMs and to test whether smoking was associated with specific phenotypes of joint manifestations in IBD.

2. Methods

2.1. Study design and study population

We explored the association between smoking and EIMs in three IBD cohorts.

The COIN (Costs of Inflammatory Bowel Disease in the Netherlands) study[13] is a large multicentre cohort study initiated in 2010 to prospectively assess the quality of life and the direct and indirect IBD-related healthcare and non-healthcare costs. All patients from seven university medical centres and seven general hospitals aged 18 years or older were eligible for participation. This study is still ongoing.

The Groningen study was a prospective single-centre cohort study, mainly designed to evaluate the clinical effects of smoking on IBD.[10] The cohort population consisted of consecutive IBD patients who visited the outpatient department of the University Medical Centre Groningen between January 1995 and October 2005. Patients with a concomitant liver transplantation were excluded.

The JOINT study[14] was a single-centre prospective cohort study focused on IBD patients with and without back pain and/or peripheral joint complaints. The study population consisted of consecutive IBD patients who were systematically assessed by a multidisciplinary team of gastroenterologists and rheumatologists at the Leiden University Medical Centre between July 2009 and February 2010. All included patients were followed for 12 months.

All three studies were approved by local medical ethics committees. More details on study designs can be found in the corresponding references.[10,13,14]

2.2. Data collection

For the COIN cohort, participants were invited to fill out a baseline questionnaire followed by 3-monthly questionnaires. To control equality between the cohort population and the patients who did not respond, demographics and disease characteristics were compared between responders and non-responders.[13] For the current study, demographic data, smoking status (both current and previous, including date of smoking cessation, if applicable), EIMs and disease severity (self-reported flares) were extracted at baseline and medication use was extracted after 3 months of follow-up.

In the Groningen cohort, patients received a detailed questionnaire about their smoking behaviour. For the patients who returned the questionnaire, clinical characteristics and outcome variables were assessed by both a retrospective analysis of medical records and the collection of outcome variables during follow-up. For the current study, we focused on information on smoking behaviour (both current and previous, including number of pack-years[15] and date of smoking cessation, if applicable) and EIMs from medical records.

In the JOINT cohort, data on medical history (EIMs, family history and medication use), physical examination (palpation of the joints, entheses and digits), laboratory tests (C-reactive protein and HLA-B27) and radiological examinations of affected joints were collected from all enrolled patients. Based on these assessments, patients were categorized into two study arms: (1) patients with joint and/or back pain for ≥3 months and/or peripheral joint pain or swelling during the last year; and (2) patients without joint and/or back pain.

Peripheral arthritis was defined as the presence of both pain and swelling in one or more joints and arthralgia was defined as non-inflammatory joint pain. At baseline, demographic characteristics (including current smoking status) were collected.

2.3. Definition of extra-intestinal manifestations

In the COIN cohort, EIMs were defined as the presence of self-reported joint complaints (arthritis and chronic back pain) and/or chronic skin disorders. In the Groningen cohort, EIMs were defined as joint complaints (arthralgia, enthesitis, arthritis, sacro-iliitis and ankylosing spondylitis) and/or skin disorders (erythema nodosum, pyoderma gangrenosum, psoriasis and hidradenitis suppurativa), as extracted from medical records, confirmed by medical specialists. The JOINT study was focused on joint manifestations, which were objectified by an extensive assessment by medical specialists.

2.4. Data analysis

The association between smoking and EIMs was cross-sectionally analysed in all three cohorts separately. We compared the prevalence of EIMs between smokers, non-smokers and ex-smokers using the χ^2 test or Fisher's exact test, as appropriate. In the COIN and Groningen cohorts, we performed univariable and multivariable logistic regression analyses to test whether current smoking and ex-smoking were independent predictors of EIMs. Multivariable analysis was performed with co-variables with a p value <0.20 in the univariable analysis. Furthermore, we investigated the putative dose–response relationship between smoking and EIMs in the Groningen cohort. First, we compared the prevalence of EIMs between high (>10 pack-years) and low (≤10 pack-years) exposure smokers using the χ^2 test. Second, we compared the prevalence of EIMs between inclining levels of smoke exposure, measured by pack-years,[15,16] using one-way ANOVA with the Tukey and/or Games–Howell *post hoc* multiple comparison test for trends. Participants in the JOINT cohort were categorized based on the presence or absence of peripheral joint manifestations or back pain. Therefore, we compared the prevalence of smoking between patients with and without joint manifestations in this cohort using the χ^2 test. Moreover, we explored the association between smoking and specific phenotypes of joint manifestations by comparing the distribution of phenotypes between smokers and non-smokers using the χ^2 test. P-values < 0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 21 (Armonk, NY).

3. Results

3.1. Study population

In the COIN cohort 3030 patients were enrolled; 16% of the patients currently smoked (CD 21.1%, UC 9.0%). There were no statistically significant differences between responders and non-responders.[13] In the Groningen cohort 797 IBD patients returned the questionnaire (97.2% response rate), of whom 24.0% were current smokers (CD 33.2%, UC 12.6%). In the JOINT cohort 255 patients (155 IBD patients with joint complaints, 100 without joint complaints) were enrolled. In this cohort 23.5% were current smokers (CD 27.4%, UC 13.0%). In the COIN cohort, ex-smoking CD and UC patients quit smoking a median of 10 years (interquartile range [IQR] 5–18) and 14 years (IQR 8–25) before inclusion. In the Groningen cohort, ex-smoking CD and UC patients quit smoking a median of 7 (IQR 2–14) and 13 (IQR 3–23) years before inclusion. In the JOINT cohort, ex-smoking CD and UC patients quit smoking a median of 10 years (IQR 3–19) and 14 years (IQR 5–27) before inclusion. Available baseline characteristics of all study participants are listed in Table 1.

3.2. Association between smoking and EIMs in IBD

The overall prevalence of EIMs in IBD was 31.3% in the COIN cohort and 32.3% in the Groningen cohort. EIMs were significantly more prevalent in the smoking IBD population than in non-smoking patients (COIN cohort, 39.1 vs 29.8%, $p < 0.01$; Groningen cohort, 41.7 vs 30.0%, $p < 0.01$) (Figure 1). EIMs were more prevalent in current smokers than in never smokers (COIN and Groningen cohort, $p < 0.01$), and in the Groningen cohort also compared with ex-smokers ($p < 0.01$) (Table 2). In the COIN cohort smoking was associated with EIMs in both CD and UC patients, although more predominantly so in CD. Joint manifestations appeared to be more strongly associated with smoking than skin disorders.

3.3. Prevalence of smoking in IBD patients with joint complaints

In the JOINT cohort, smoking was more prevalent in IBD patients with joint manifestations than in patients without joint manifestations (30.3 vs 13%, $p < 0.01$). This association was found in both CD and UC patients (CD, 33.9 vs 15.4%, $p < 0.01$; UC, 17.6 vs 8.6%, $p = 0.03$). Joint manifestations in smokers were diagnosed after a mean of 17 years of tobacco exposure (standard deviation 13 years). Smoking was not associated with a specific localization of joint manifestations (axial pain, 8.5% in smokers vs 8.3% in non-smokers, $p = 0.53$; peripheral joint manifestations, 44.7% in smokers vs 54.6% in non-smokers, $p = 0.49$). However, smoking IBD patients more often experienced a combination of both axial and peripheral joint manifestations (46.9 vs 37.0%, $p = 0.01$). Smoking was not primarily associated with peripheral arthritis, as the prevalence was not significantly higher in smoking IBD patients ($p = 0.34$). Arthralgia was found to be more prevalent in smoking IBD patients (48.3 vs 32.3% $p = 0.02$), especially in CD.

3.4. Multivariable analysis for the presence of EIMs in IBD

Adjusted for demographic data and disease severity, active smoking was associated with the presence of EIMs with an odds ratio (OR) of 1.52 in CD patients (95% confidence interval [CI] 1.15–2.01) and 1.75 in UC patients (1.07–2.84) of the COIN cohort (Supplementary Table 1). Female gender and higher age were also independently associated with the presence of EIMs in both CD and UC. The previous use of biologicals and a low level of education were found to be independent risk factors for EIMs in CD, and ex-smoking was an independent factor for EIMs in UC (OR 1.41, 95% CI 1.03–1.92). In the Groningen cohort, smoking was not an independent factor for EIMs in CD and UC (Supplementary Table 2). In this cohort, a low education level was found to be independently associated with EIMs in UC (adjusted OR 2.31, 95% CI 1.14– 4.70)

3.5. Dose–response relationship between smoking and EIMs in IBD

In the Groningen cohort, complete information on the quantity of total tobacco exposure was available for analysis in 95 currently smoking IBD patients (70 CD, 22 UC and 3 IBD unclassified). Although not statistically significant, EIMs appeared to be more prevalent in high-exposure smokers (>10 pack-years) than in low-exposure smokers (≤10 pack-years), which applied to CD but not to UC patients (IBD, 56.0 vs 37.1%, $p = 0.10$; CD, 64.7 vs 39.2%,

Table 1. Baseline characteristics.

	COIN cohort	Groningen cohort	JOINT cohort
Number of patients	3030	797	255
Demographics			
Male gender, *n* (%)	1325 (43.7)	326 (40.9)	97 (38.0)
Type of IBD, *n* (%)			
Crohn's disease	1558 (51.4)	428 (53.7)	186 (72.9)
Ulcerative colitis	1054 (34.8)	307 (38.5)	69 (27.1)
Unspecified	418 (13.8)	62 (7.8)	0 (0.0)
Age, years, mean (SD)	51.6 (13.7)	41.0 (14.5)	43.1 (13.5)
Low education level, *n* (%)	1898 (62.6)	468 (58.7)	135 (52.9)
Currently employed, *n* (%)	1557 (51.4)	470 (59.0)	157 (61.6)
Smoking status, *n* (%), IBD, CD, UC			
Current	486 (16.0), 329 (21.1), 95 (9.0)	188 (24.0), 139 (33.2), 38 (12.6)	60 (23.5), 51 (27.4), 9 (13.0)
Never	1605 (53.0), 781 (50.1), 603 (57.1)	304 (38.9), 133 (31.7), 142 (47.0)	98 (38.4), 61 (32.8), 37 (53.6)
Ex	939 (31.0), 448 (28.8), 358 (33.9)	290 (37.1), 147 (35.1), 122 (40.4)	97 (38.0), 74 (39.8), 23 (33.3)
Disease characteristics, Montreal classification, *n* (%)			
Location, *n* (%)			
L1, ileal	–	99 (33.9)	46 (24.7)
L2, colonic	–	62 (21.2)	40 (21.5)
L3, ileocolonic	–	105 (36.0)	83 (44.6)
L4, upper	–	4 (1.4)	2 (1.1)
L1–3 + L4	–	22 (7.5)	15 (8.1)
Behaviour of CD			
B1, non-stricturing/penetrating	–	130 (42.2)	109 (58.6)
B2, stricturing	–	46 (14.9)	38 (20.4)
B3, penetrating + perianal disease	–	132 (42.9)	39 (21.0), 55 (30.0)
Extension of UC, *n* (%)			
E1, ulcerative proctitis	–	33 (15.7)	7 (10.1)
E2, left-sided UC	–	63 (30.0)	23 (33.3)
E3, extensive UC (pancolitis)	–	114 (54.3)	39 (56.5)
UC severity, *n* (%)			
S1, clinical remission	–	22 (7.2)	–
S2, mild	–	64 (20.8)	–
S3, moderate	–	64 (20.8)	–
S4, severe	–	61 (19.8)	–
Unknown	–	96 (31.3)	–
Disease location, *n* (%)			
Small bowel	306 (19.6)	–	–
Large bowel	431 (27.7)	–	–
Small and large bowel	768 (49.3)	–	–
Penetrating disease in CD, *n* (%)	814 (52.2)		
Disease in remission, *n* (%)	2549 (84.2)	–	152 (59.6)
Stoma, *n* (%)	300 (9.9)	102 (12.8)	20 (7.8)
Pouch *n* (%)	167 (5.5)	9 (1.1)	13 (5.1)
Abdominal surgery in the past, *n* (%)	1143 (37.7)	250 (45.2)	107 (42.0)
Medication use, *n* (%), CD, UC*			
5-ASA	307 (23.5), 596 (65.2)	27 (6.3), 144 (46.9)	18 (9.7), 33 (47.8)
Steroids	134 (10.2), 70 (7.6)	63 (14.7), 30 (9.8)	9 (4.8), 5 (7.2)
Immunosuppressive drugs, (Aza + 6MP +MTX)	463 (35.4), 203 (22.2)	155 (36.2), 65 (21.1)	43 (23.1), 12 (17.4)
Anti-TNF	299 (22.9), 35 (3.8)	114 (26.6), 11 (3.6)	66 (35.5), 6 (8.7)
None	337 (25.8), 198 (21.7)	57 (13.3), 44 (14.3)	50 (26.9), 13 (18.8)

IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; ASA, aminosalicylic acid; Aza, azathioprine; 6MP, 6-mercaptopurine; MTX, methotrexate; TNF, tumour necrosis factor.

*At 3 months of follow-up.

$p = 0.07$; UC, 20.0 vs 33.3%, $p = 0.57$). Based on a subdivision of smoking patients into light smokers (0.1–20.0 pack-years), moderate smokers (20.1–40.0 pack-years) and heavy smokers (>40 pack-years), the prevalence of EIMs appeared to increase with higher levels of smoke exposure (IBD, 37.8, 50.0 and 60.0%, respectively; CD, 41.7, 50.0 and 100.0%). Meaningful statistical analysis in UC could not be performed due to the low number of cases. For the total IBD population, no statistical significant trend was found, but for CD a statistical significant difference in prevalence of EIMs between light smokers and heavy smokers was found ($p < 0.05$).

3.6. EIMs in ex-smoking IBD patients

The prevalence of EIMs in ex-smoking IBD patients and in patients who never smoked was comparable to that in the Groningen cohort

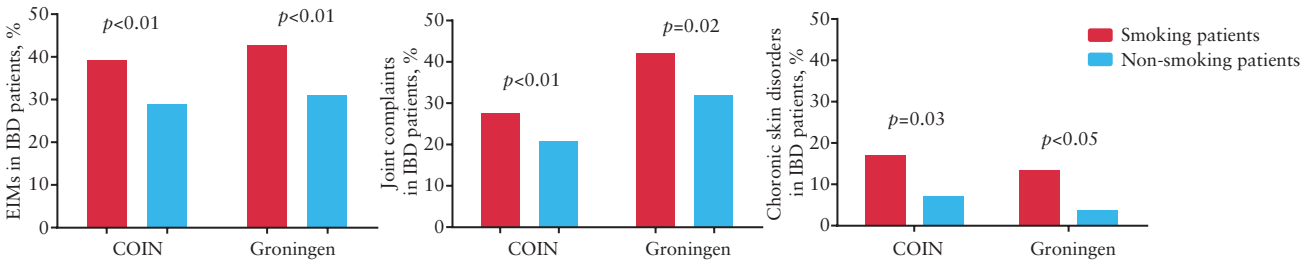

Figure 1. Prevalence of extra-intestinal manifestations in smoking versus non-smoking inflammatory bowel disease patients.

Table 2. Association between smoking and extra-intestinal manifestations in inflammatory bowel disease.

	Study	Smoking patients (1)	Never-smoking patients (2)	Ex-smoking patients (3)	*p*-value, smoking vs non-smoking	*p*-value, (1 vs 2)	*p*-value, (1 vs 3)
Inflammatory bowel disease							
Total EIMs	COIN	190 (39.1)	432 (26.9)	325 (34.6)	<0.01	<0.01	0.10
	Groningen	75 (41.7)	87 (29.3)	86 (30.5)	<0.01	<0.01	0.01
Joint complaints	COIN	134 (27.6)	290 (18.1)	241 (25.7)	< 0.01	<0.01	0.44
	Groningen	69 (42.3)	84 (31.6)	84 (32.4)	0.02	0.02	0.04
Chronic skin disorders	COIN	82 (16.9)	207 (12.9)	128 (13.6)	0.03	0.03	0.10
	Groningen	12 (6.8)	8 (2.7)	11 (4.0)	<0.05	0.04	0.19
Crohn's disease							
Total EIMs	COIN	140 (42.6)	235 (30.1)	167 (37.3)	<0.01	<0.01	0.14
	Groningen	64 (47.1)	51 (38.6)	58 (39.5)	0.12	0.16	0.20
Joint complaints	COIN	101 (30.7)	155 (19.8)	117 (26.1)	<0.01	<0.01	0.16
	Groningen	58 (46.4)	49 (39.5)	58 (41.4)	0.26	0.27	0.42
Chronic skin disorders	COIN	60 (18.2)	117 (15.0)	76 (17.0)	0.27	0.18	0.65
	Groningen	12 (9.0)	6 (4.6)	8 (5.6)	0.13	0.15	0.27
Ulcerative colitis							
Total EIMs	COIN	32 (33.7)	136 (22.6)	115 (32.1)	0.11	0.02	0.77
	Groningen	9 (25.7)	27 (19.6)	26 (22.8)	0.56	0.42	0.72
Joint complaints	COIN	24 (25.3)	92 (15.3)	86 (24.0)	0.11	0.02	0.80
	Groningen	9 (31.0)	26 (21.7)	24 (24.0)	0.34	0.29	0.45
Chronic skin disorders	COIN	12 (12.6)	63 (10.3)	38 (10.6)	0.50	0.49	0.58
	Groningen	0 (0.0)	2 (1.5)	3 (2.7)	0.39	1.00	1.00

IBD, inflammatory bowel disease; EIMs, extra-intestinal manifestations.

(30.5 vs 29.3%, $p = 0.95$), which applied to both CD and UC. In the COIN cohort, the prevalence of EIMs was higher in ex-smoking patients than in never smokers (34.6 vs 26.9%, $p < 0.01$), which also applied to both CD and UC. However, when comparing the prevalence of EIMs between patients who recently quitted smoking and patients who quitted longer ago, we observed a rapid decline in prevalence towards levels encountered in never smokers in both cohorts. In the Groningen cohort, IBD patients who quitted smoking >3 months ago appeared to have EIMs less often than patients who stopped smoking <3 months before inclusion (33.0 [$n = 60$] vs 57.1% [$n = 7$], $p = 0.07$). In the COIN cohort, the prevalence of EIMs in the ex-smoking IBD population appeared to decline if smoking was stopped for >1 year, since the prevalence of EIMs was 42.9% ($n = 3$) in patients who quitted smoking <1 year before inclusion compared with 30.9% ($n = 17$) in patients who quitted between 1 and 2 years before inclusion, although the difference was not statistically significant ($p = 0.52$).

4. Discussion

This study, encompassing results from three different cohorts, has demonstrated a strong association between smoking and EIMs in IBD, and indicates a dose–response relationship, as EIMs appear to be more prevalent in heavy-smoking patients. Interestingly, the prevalence rates of EIMs rapidly declined to levels encountered in never-smoking patients when patients quit smoking.

We found a higher prevalence of joint manifestations and chronic skin disorders in smoking CD and UC patients. Moreover, we found smoking to be significantly more common in both CD and UC patients with joint manifestations. Current data on the association of smoking and EIMs are inconclusive. While some studies on risk factors for EIMs found smoking to be associated with EIMs in CD but not in UC patients,[11,17] other studies found an increased prevalence of ocular EIMs,[18] spondylarthropathy and cutaneous complications[18] in smoking UC patients. Two studies reported no association between smoking and EIMs in CD.[19,20] The strength of the present study is that we were able to focus on smoking and EIMs in IBD in three different cohorts, encompassing more than 4000 patients. This cohort corroborated previous results and provided further insight into several aspects of this association. For the first time, a dose–response relationship was suggested. We could not clearly identify an association with specific phenotypes of joint manifestations, however. Furthermore, our data allowed us to correct for possible confounders, such as disease severity and the previous use of biologicals or immunosuppressive drugs, which had not been evaluated before.

The diverse effects of smoking on the clinical course in CD and UC are well established in the literature,[9,10,21] but the underlying mechanisms are incompletely understood. In the multivariable analyses of the COIN data, smoking was an independent factor for the presence of EIMs in both CD and UC, irrespective of disease severity. Based on a predefined statistical significance level of $p < 0.05$, the analyses in the Groningen cohort could not confirm these results, probably due to a smaller number of patients.[22] The molecular mechanisms through which the association between smoking and EIMs are established in UC and CD might be based on different pathways. It has been postulated that the opposing effects of smoking on the alimentary tract can be explained by differential effects on dendritic cells.[23] Furthermore, in mice smoking is associated with intestinal barrier dysfunction in the small intestine, but not in the large intestine, indicating different responses in ileal and colonic epithelial cells.[24]

Apart from smoking, female gender, greater age and a low level of education were also associated with EIMs. Female gender and greater age were previously identified as risk factors for EIMs in IBD.[20] As for low educational level, this association has not been described before. It can be speculated that worse control of disease and/or other environmental factors are involved in these patients. Of note, smoking was associated with EIMs independently of educational level.

Smoking has been identified as one of the most important extrinsic factors for the development and severity of rheumatoid arthritis (RA).[25–27] The pathophysiology of RA in smokers is believed to include oxidative stress, systemic inflammation, autoantibody formation and epigenetic changes, such as DNA methylation.[28] Moreover, smoking has been reported to be the main predictor of severe extra-articular manifestations in RA, such as rheumatoid vasculitis, polyneuropathy and pleuritis.[29–32] Both in CD and in RA, smoking has been associated with a poor response to anti-tumour necrosis factor (TNF) treatment.[33–35] Smoking has also been linked to a more severe disease course in psoriasis,[36,37] which is thought to be caused by smoking-induced oxidative damage along with insufficient capacity of antioxidant mechanisms.[38] Similar pathways might underlie the association of smoking with EIMs in IBD, although at present this assumption cannot be substantiated.

Smoking cessation may be beneficial in IBD patients with EIMs, as in both the COIN cohort and the Groningen cohort we observed a rapid decrease in prevalence rates of EIMs after smoking cessation towards levels seen in never smokers. The beneficial effect of smoking cessation on the clinical course of disease in CD patients has been reported previously,[39] but its effect on EIMs has never been demonstrated before. Whether the relationship between smoking cessation and a decline of EIMs is causal cannot be deduced from our data.

Some aspects of our findings need consideration. The results of the COIN study are based on self-reported data, which could have led to over- or underreporting of actual EIMs. However, the internal validity of this study seems to be robust[13] and the accuracy of responses to health-related questionnaires from patients with IBD is generally high.[40] Moreover, the prevalences of EIMs in the COIN and Groningen cohorts were very similar (31.3% and 32.3% respectively), and our observations are in line with those described in the literature.[3–7,41] The JOINT cohort was designed to study different aspects of joint complaints in IBD. Therefore, selection bias might have occurred in this cohort. For this reason, we analysed the results of this study separately and refrained from comparing the presence of skin disorders or eye diseases between smokers and non-smokers. Recall bias may be present for the number of pack-years per patient in the Groningen cohort. Self-reported smoking behaviour, however, has been rated as reliable in the literature, although in some studies a trend towards underestimation of total smoke exposure has been found.[42,43] A relatively small number (95) of currently smoking patients adequately reported their exact total smoke exposure. In a larger cohort, a dose–response relationship regarding smoking and EIMs might have reached statistical significance, but for now only a statistically significant trend could be detected in CD patients. Finally, the three examined studies differed in their baseline characteristics and definitions of EIMs. For example, the number of currently smoking CD patients was highest in the Groningen cohort, the mean age of all patients was highest in the COIN cohort, and the JOINT cohort had a relatively high number of anti-TNFα users. EIMs were collected by self-report in the COIN study, extracted from medical records in the Groningen study and objectified by an extensive medical assessment in the JOINT study. However, regardless of the differences between the cohorts, the analyses of all cohorts separately led to the same conclusion with respect to the association between smoking and EIMs in IBD.

In conclusion, we have demonstrated a positive association between smoking and EIMs in IBD in three different cohorts, in both CD and UC patients. Our data suggest a dose–response relationship regarding smoking behaviour. Most importantly, the prevalence of EIMs rapidly decreases towards levels found in never-smoking patients after smoking cessation. As EIMs frequently complicate the clinical course of IBD, clinicians should be aware that smoking cessation might reduce the burden of EIMs in these patients.

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Conflict of Interest

AAvB has acted as a consultant for Abbvie, Ferring, MSD-Merck and Tramedico and received payments for lectures from AbbVie, Ferring, Pfizer and Takeda. HHF has acted as a consultant for AbbVie. DdJ has acted as a consultant for Synthon Netherlands and received payments for lectures from AbbVie, Ferring and MSD. GD participated in an advisory board for Mundipharma. CJvdW has acted as a consultant for AbbVie, Ferring, Shire and MSD and received payment for lectures from AbbVie, Falk Pharma and MSD. JMJ (Jeroen M Jansen) has acted as a consultant for AbbVie, MSD, Ferring and Falk and received payments for lectures for AbbVie and MSD. PCvdM received payments for lectures for Falk. CYP has acted as a consultant for AbbVie and received payments for lectures from Ferring and MSD. MJP has acted as a consultant for MSD and received payments for lectures from MSD, Falk Pharma, AbbVie and Ferring. AEvdMdJ has acted as consultant for AbbVie, MSD, Ferring and Falk and received payments for lectures from AbbVie and MSD. BO has acted as a consultant for AbbVie, Takeda and MSD and received payment for lectures from Ferring, MSD and AbbVie. All other authors have no competing interest to declare.

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Author Contributions

Cohort concept and design: MS, BO. Acquisition of data: MS, BO, SJHvE, GD, MEvdV. Analysis and interpretation of data: MS, BO, MJJM. Drafting of the manuscript: MS. Critical revision of the manuscript for important intellectual content: All authors. Final approval of the submitted manuscript: all authors.

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