# The impact of smoking and smoking-cessation on disease outcomes in Ulcerative Colitis: a nationwide population-based study

Running Title: Smoking and disease outcomes in ulcerative colitis

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Abstract

**Background**

Smokers are less likely to develop Ulcerative Colitis (UC) but the impact of smoking and subsequent cessation on clinical outcomes in UC is unclear.

Aims: To analyse the effect of smoking status and smoking cessation on disease outcomes.

**Methods**

Using a nationally representative clinical research database, we identified incident cases of UC during 2005-2016. Patients were grouped as never-smokers, ex-smokers and smokers, based on smoking status recorded in the two years preceding UC diagnosis. We defined subgroups of persistent smokers and smokers who quit within 2 years after diagnosis. We compared rates of overall corticosteroid use, corticosteroid-requiring flares, corticosteroid dependency, thiopurine use, hospitalization and colectomy between these groups.

**Results**

We identified 6754 patients with a new diagnosis of UC over the study period with data on smoking status, of whom 878 were smokers at diagnosis. Smokers had a similar risk of corticosteroid-requiring flares (OR 1.16, 95%CI 0.92-1.25), thiopurine use (HR 0.84, 95%CI 0.62-1.14), corticosteroid dependency (HR 0.85, 95%CI 0.60-1.11), hospitalization (HR 0.92, 95%CI 0.72-1.18), and colectomy (HR 0.78, 95%CI 0.50-1.21) in comparison with never-smokers.

Rates of flares, thiopurine use, corticosteroid dependency, hospitalization and colectomy were not significantly different between persistent smokers and those who quit smoking after a diagnosis of UC.

**Conclusions**

Smokers and never-smokers with UC have similar outcomes with respect to flares, thiopurine use, corticosteroid dependency, hospitalization and colectomy. Smoking cessation was not associated with worse disease course. The risks associated with smoking outweigh any benefits. UC patients should be counselled against smoking.

**Keywords:** Ulcerative Colitis, Outcomes Research, Epidemiology, Thiopurines, Surgery

# Introduction

Tobacco smoke exposure is associated with approximately half the risk of developing ulcerative colitis (UC)1 but the relationship between smoking status at diagnosis on the subsequent course of disease is unclear.2 Previous studies comparing overall corticosteroid use between smokers and non-smokers have conflicting findings.3–7 However, these studies have not evaluated the effect of smoking on corticosteroid dependency which is increasingly recognised as a key indicator of disease control in the management of UC*.*8,9

An early cohort study reported smokers were less likely to undergo colectomy than non-smokers (32% vs 42%, p=0.04).4 However, more recent studies have not supported this finding. 3,10–13 A 2016 meta-analysis, examining the effect of tobacco smoke on the natural history of UC, identified no significant difference between smokers and non-smokers with regard to colectomy or disease activity.14 These findings were at odds with a prior meta-analysis, using different inclusion criteria, which found smoking to be associated with reduced risk of colectomy (OR 0.55, 95% CI 0.33-0.91).15

This has led to a belief that smoking may be beneficial in UC and some patients report that they smoke to ameliorate their disease.16

The wider health benefits of smoking cessation are beyond dispute17 but its impact on clinical outcomes in UC is poorly understood. The few studies evaluating the impact of smoking cessation on disease outcomes in UC are inconsistent.3,5,11 One small study, following 32 patients who stopped smoking after being diagnosed with UC, reported that patients subsequently had more active disease, hospital admissions and use of corticosteroids and thiopurines compared with the period when they were actively smoking. Yet the same study found no difference in the rates of corticosteroid use, hospitalization or colectomy between persistent smokers and quitters.11 Data from the Sydney IBD Cohort found that long-term prescription of thiopurines and methotrexate was more frequent in patients with UC who were ex-smokers than those who were current or never-smokers.3

Almost half of UC patients, responding to a questionnaire, reported being aware of the ‘protective’ effect of tobacco smoke in UC.18 One study found that 4 out of 19 ex-smokers with UC (21%) reported resuming smoking to prevent a flare of their disease.16 Clinicians may also sometimes recommend smoking as a therapeutic approach where conventional therapies have failed.19 The ongoing belief that tobacco smoke has beneficial effects on disease outcomes in UC may be perpetuating smoking behaviour and denying patients the undisputed wider health benefits of smoking cessation. It is therefore important to evaluate the impact of smoking cessation in UC. Most previous studies exploring the relationship between tobacco use and disease outcomes in UC have been small and carried out in hospital settings. Fifteen of the sixteen studies in a recent meta-analysis originated from specialist referral centres and such studies may be prone to bias.14 Population-based studies are well suited to avoid referral centre bias but are few in number.20,21

We sought to confirm or refute the hypothesis that smoking at diagnosis amongst patients with UC is associated with a more benign disease course and that subsequent smoking cessation leads to a worse outcome. We designed a nationally representative population-based cohort study to investigate the impact of smoking status and cessation on subsequent corticosteroid use, thiopurine use, hospitalization and rates of colectomy amongst patients with UC.

# Methods

## Data source

Using the Clinical Practice Research Datalink (CPRD) we identified a retrospective population-based incident cohort of patients diagnosed with UC. CPRD is one of the largest validated primary care research databases in the world. It contains longitudinal, patient-level, anonymised electronic health records from 674 general practices (around 8% of the country’s total) and is broadly representative of the United Kingdom (UK) population. The median prospective follow-up for patients registered on CPRD is 9.4 years, meaning study of long-term disease outcomes is possible.22 Primary care physicians use Read codes to record symptoms, signs, diagnoses, prescriptions, referrals and procedures including surgical operations. Data are rigorously audited to ensure a high level of accuracy and completeness. Participating practices need to achieve and maintain 'Up to standard' status to continue contributing to the dataset. The database's primary purpose is for epidemiological research and the coding system has been previously validated for use in Inflammatory Bowel Disease (IBD).23 Numerous IBD related studies have been undertaken using it.24,25 CPRD has also been used in a number of population based studies investigating both smoking habits and the impact of tobacco consumption on outcomes in other patient groups.26,27,28 CPRD is well suited for this purpose and subsequent accuracy of recording of smoking status has been of high quality since its assessment became a key performance indicator for General Practitioners (GP) in 2004.29 The Hospital Episode Statistics (HES) database contains data on all admissions and outpatient appointments in National Health Service hospitals in England. Using an established method, the CPRD dataset were linked to the Hospital Episodes Statistics database to obtain additional data on hospitalization and surgery.30

We obtained ethical and scientific approval for the use of CPRD for our study from the Independent Scientific Advisory Committee (ISAC Protocol number: 15\_018R).

## Incident case definition and cohort construction

We have previously published detailed methods in defining incident cases of IBD from the CPRD.9,31–33 In brief, to separate prevalent from incident cases of UC, we identified patients with a first code for UC at least one year after registering with an 'Up To Standard' practice for the period January 1st 2005 to April 30th 2016.

Patients were excluded if they had codes for both UC *and* CD, or indeterminate codes ('non-specific colitis', 'colitis NOS' etc). Patients who had a co-morbid condition that might require regular or prolonged corticosteroid use, for example, chronic asthma, polymyalgia rheumatic and organ transplants, were also excluded to avoid potential confounding. Patients were followed up from date of UC diagnosis until study endpoint, de-registration, or death.

## Exposure variable

Smoking status at the time of UC diagnosis was the primary exposure variable. Patients were defined as either 'never-smokers', ‘ex-smokers’ or 'smokers' at UC diagnosis based on codes for smoking status in the two years before the first record of UC diagnosis. Using our published methodology, subsequent codes for smoking status were analysed to determine any change in smoking status after diagnosis (Figure 1).33 Smoking status was recorded in approximately 70% of patients within our dataset. Accuracy of data on current smoking status in CPRD is within 1% of self-reported smoking habits in national surveys.34 Since April 2004, the UK Quality and Outcomes Framework (QOF) scheme has provided a financial incentive for GPs to offer smoking cessation advice to patients. As a result, the completeness of smoking data has markedly improved.29 Therefore we began our study period on January 1st 2005, 9 months after introduction of this scheme.

## Outcome measures

Our primary outcome measure was oral corticosteroid use as a proxy measure of a corticosteroid-requiring disease flare-up ('corticosteroid-flare') indicative of an exacerbation of UC. We derived 3 measures of corticosteroid use. We calculated the proportion of patients 'ever exposed' or 'never exposed' to oral corticosteroids. Patients were identified as 'ever exposed' if they had at least one prescription for oral corticosteroids during follow-up.

Secondly, we used a previously published method described by Grainge *et al*. to define the number of 'corticosteroid-flares' during follow-up.36 The first 'corticosteroid-flare' was defined as the first corticosteroid prescription registered in the patient record after date of UC diagnosis. The next separate 'corticosteroid-flare' was defined where a subsequent corticosteroid prescription was recorded following a period of at least 4 months without a corticosteroid prescription. This methodology allowed for the determination of total 'corticosteroid-flares' for the entire period of follow-up for each patient. Thus, the total number of 'corticosteroid-flares' was divided by follow-up time to generate the outcome measure 'corticosteroid-flares per person-year'.

We identified patients with corticosteroid-dependency (defined as prolonged or repeated corticosteroid exposure), adapted from the European Crohn's and Colitis Organisation guidelines criteria.37 A patient was defined as 'corticosteroid-dependent' if they had either a prescription for corticosteroid that lasted longer than 3 months or required a repeat corticosteroid prescription within 3 months of stopping the previous corticosteroid course.

First thiopurine use was defined as the first prescription of either azathioprine or mercaptopurine following diagnosis of UC.

We used a previously published list of ICD-10 codes to identify hospital admissions where IBD was the primary reason for admission.38 We identified admissions lasting more than one day as a proxy measure of UC disease activity severe enough to warrant hospital admission overnight. We excluded day case activity and “zero day admissions” which are not reliable markers of UC disease activity as they may represent routine care such as endoscopic surveillance. We calculated the time to the first IBD-related hospital admission following diagnosis of UC.

Colectomy was defined as any colectomy procedure and stoma formation coded for in either the CPRD or HES databases following diagnosis of UC.38,39

## Covariates

We included a number of covariates with known or likely associations with clinical outcomes in UC and smoking status. These included: sex, age at diagnosis, social deprivation, concurrent oral 5-aminosalicylic acid (5-ASA) use, and era of diagnosis . Age at diagnosis has previously been shown to be relevant to surgical outcomes in the context of smoking status.20 Patients were sub-divided into age categories at diagnosis of UC (<17, 17-40 and >40). In the UK, people living in the areas of highest deprivation are more than twice as likely to smoke compared with the lowest.40 We used a surrogate marker for postcode-linked social deprivation, the Index of Multiple Deprivation (IMD), to stratify patients by socio-economic status. Patients were categorised into IMD quintiles, where IMD category 1 represents the least deprived, and IMD category 5 represents the most socio-economically deprived.

We also extracted data for IBD medication usage. Patients were defined as oral 5-aminosalicylic acid (5-ASA) users if they had one or more prescriptions during follow-up. Prescription data for anti-tumour necrosis factor (aTNF) use is not reliably recorded in CPRD.

The 12 year study period was divided into six eras to allow for assessment of the impact of era of UC diagnosis on outcome measures (era 1: 1/1/05 to 31/12/06, era 2: 01/1/07 to 31/12/08, era 3: 01/1/09 to 31/12/10, era 4: 01/1/11 to 31/1/12, era 5: 01/1/13 to 31/12/14, era 6 1/1/15 to 30/4/16).

## Statistical analysis

We used *t*-tests and the one-way analysis of variance (ANOVA) to determine differences between groups of continuous data, and Chi-squared for comparisons of categorical data. We compared the proportion of never-smokers, ex-smokers and smokers at UC diagnosis who had any corticosteroid exposure and the proportion of patients with corticosteroid dependency. Simple and multiple Cox regression was used to calculate hazard ratios (HR) for corticosteroid dependency given smoking status.

We categorised patients according to the number of corticosteroid-flares they experienced per year (i.e. no flares, less than 1 flare per year, and more than 1 flare per year). Simple and multiple ordered logistic regression was used to identify risk factors for a corticosteroid-flare.

We used Kaplan-Meier analysis to generate survival curves calculating the time to first oral corticosteroid prescription according to smoking status. We calculated cumulative oral corticosteroid exposure rates in the follow-up period according to smoking status. The rate of oral corticosteroid exposure was determined as a function of time, by calculating the duration between diagnosis of UC and first oral corticosteroid prescription, or end of follow-up as defined above. The risk of oral corticosteroid use at 1, 3 and 5 years after UC diagnosis was also calculated. We used the log rank test to assess for any significant differences dependent on smoking status. We used the same statistical methodology to calculate the 1, 3 and 5 year risk of thiopurine use, hospitalization and also colectomy.

In a further analysis, we used separate Cox proportional hazards models to calculate hazard ratios (HR) for thiopurine use, hospitalization and colectomy given smoking status. Within all the multiple regression models we adjusted for sex, age at diagnosis, era of UC diagnosis, IMD status and oral 5-ASA use.

We identified patients with codes for smoking status after UC diagnosis. Patients were considered 'persistent smokers' if they were smokers at UC diagnosis (as defined above) and had at least one further code after UC diagnosis to indicate active smoking *and* they did not have any code during the follow-up period to indicate they had quit smoking after diagnosis. Patients were labelled as 'quitters' if they were smokers at UC diagnosis, but had at least one subsequent code indicating they were non-smokers or ex-smokers in the first two years of follow-up after UC diagnosis.

The same outcome measures as for the primary analysis were compared between 'persistent smokers' and 'quitters' using student's t-test, Chi squared test, and KM survival analysis with the log rank test. Quitters were excluded from the analysis of colectomy rates if the date of their colectomy preceded the date of quitting smoking.

To determine whether there was a dose-response relationship between smoking and UC outcomes we performed a further analysis examining the impact of smoking intensity as defined by number of cigarettes smoked per day. We identified patients with codes indicating smoking intensity in the two years leading up to UC diagnosis. Smokers were classified as `light smokers’ (<10 cigarettes per day), `moderate smokers’ (10-19 cigarettes per day) and `heavy smokers’ (≥20 cigarettes per day) or `unknown’. These groups were compared with never smokers using the same outcome measures as in the primary analysis.

A p-value of less than or equal to 0.05 was considered statistically significant. All analyses were performed using STATA 12 (Statacorp LP, College Station, TX, USA).

# Results

We identified 9616 patients with a new diagnosis of UC between January 1st 2005 and April 30th 2016. Of these 6754 had data on smoking status at UC diagnosis, with a cumulative 41,024person years of follow-up. 2698 (39.9%) were never-smokers, 3178 (47.1%) were ex-smokers and 878 patients (13%) were smokers at UC diagnosis (Figure 1). The follow-up time was longer for never-smokers compared with ex-smokers and smokers (5.2 years, 4.9 years & 4.8 years,p<0.05).

During the 12 year study period, there was no significant reduction in the proportion of patients who were smokers at diagnosis (13.7% in 2005/2006 vs 13.6% in 2015/2016, p=0.93). Data on smoking status before *and* after the diagnosis of UC was available in three quarters of our cohort (n=5127). 46% of patients who were smokers at the time of UC diagnosis continued to smoke (n=325). Just 2% of never-smokers at the time of UC diagnosis took up smoking for the first time after UC was diagnosed (n=40). Overall, 378 patients quit smoking after UC was diagnosed while 286 patients either returned to smoking or took it up for the first time (see figure 1).

At baseline, the proportion of patients who were smokers was highest among those diagnosed between the ages of 17-40 years followed by those diagnosed after the age of forty (18% vs 11%, p<0.001). No patients in the youngest age cohort (<17 years) were smokers at the time of their diagnosis. Amongst patients with UC, smokers and ex-smokers were more likely to be male while never-smokers were more likely to be female (p<0.001 table 1). Smokers were also more likely to live in deprived areas than never-smokers and ex-smokers (37.6% vs 30.7% vs 29.8%, p=0.004). Oral 5-ASA use was lower among smokers than never-smokers and ex-smokers (60.1% vs 64% 65.6%, p=0.009).

## Impact of smoking status at time of UC diagnosis on disease outcomes of UC

The cumulative risk of oral corticosteroid use at 1,3 and 5 years was 27.9%, 34.8% and 37.1% in never-smokers was comparable to that in smokers and ex-smokers (log rank test for trend, p=0.53, figure 2). The risk of a 'corticosteroid-flare' was similar among smokers (Ordered Logistic Regression: OR 1.16, 95% CI 0.92-1.46, p=0.21) and ex-smokers (Ordered Logistic Regression: OR 1.07, 95% CI 0.92-1.25, p=0.36) compared with never-smokers. A lower proportion of smokers developed corticosteroid dependency than ex-smokers and never-smokers (12.0% vs 13.9% vs 15.7% respectively, p=0.013). However, in the adjusted Cox regression the risk of corticosteroid dependency was similar in smokers (HR 0.85, 95% CI 0.60-1.11, p=0.11) and ex-smokers (HR 0.82, 95% CI 0.70-1.03, p=0.20) compared with never-smokers (Table 2).

Crude thiopurine exposure was lower among smokers than ex-smokers and never-smokers (12.0% vs 15.1% vs 16.8%, p=0.02). In an adjusted analysis the risk of thiopurine use did not differ significantly according to smoking status at diagnosis (Table 3).

3916 patients (58%) had linkage to the HES database, providing data on hospitalization. Ex-smokers were less likely to ever have an IBD-related hospital admission than smokers and never-smokers (22.6% vs 27.8% vs 25.8% respectively, p=0.017). The multiple Cox regression did not find smoking status to be associated with the risk of hospitalization. However, low socioeconomic status was a strong predictor of hospitalization (HR 1.38, 95% CI 1.18-1.62, p<0.001, see Table 4).

The crude rates for colectomy in patients with UC were 9.3%, 9.7% and 6.6% in never-smokers, ex-smokers and smokers respectively (p=0.02). The cumulative risk of colectomy at 1, 3 and 5 years was 5.2%, 7.2% and 8.2% in never-smokers, 5.7%, 7.7% and 8.7% in ex-smokers, and 4.6%, 5.6% and 6.4% in smokers at UC diagnosis (log rank test for trend, p= 0.24, see figure 3). Multiple Cox regression demonstrated the risk of colectomy was similar in smokers (HR 0.78, 95% CI 0.50-1.21, p=0.26) and ex-smokers (HR 1.03, 95% CI 0.79-1.34, p=0.82) compared with never-smokers (Table 5).

## Impact of smoking cessation

We identified 703 patients who were smokers at UC diagnosis and who had subsequent codes for smoking status following UC diagnosis. Of these, 233 (33%), gave up smoking in the first 2 years of diagnosis and were classified as 'quitters'. 325 patients (46%) were defined as 'persistent smokers'. Persistent smokers had a shorter follow-up period than those who quit smoking (4.6 years vs 5.6 years, P=0.002). There were no differences between persistent smokers and quitters with respect to sex, age at diagnosis, IMD categories, use of oral 5-ASA.

Crude oral corticosteroid use was 35.7% in persistent smokers versus 45.9% in quitters (p=0.02). The risk of corticosteroid-flares was similar in quitters compared with persistent smokers (OR 1.13, 95% CI 0.66-1.94, p=0.66). There was no significant difference in the rates of corticosteroid dependence between persistent smokers and quitters (12.3% vs 15.9%, p=0.48) and the multiple Cox regression confirmed this (HR 1.03, 95% CI 0.52-2.04, p=0.93, Figure 2). The crude rate of thiopurine use was lower among persistent smokers versus quitters, (8.6% vs 19.3%, p>0.001). However, in the adjusted multiple Cox regression this did not reach significance (HR 1.93, 95% CI 0.96-3.91, p=0.07). 28.8% of quitters and 26.1% of persistent smokers had an IBD-related hospital admission (p=0.61). 7 quitters (3.3%) and 14 persistent smokers (4.3%) underwent colectomy (p=0.55, Figure 3).

## Impact of smoking intensity

Amongst smokers (n=878) we identified 517 smokers with data on the number of cigarettes smoked per day. There were 240 light smokers (<10 cigarettes per day), 141 moderate smokers (10-19 cigarettes per day), 136 heavy smokers (≥20 cigarettes per day) and 361 smokers of unknown smoking intensity (SUSI).

A greater proportion of heavy smokers were male compared with moderate, light and never-smokers, and SUSIs (61.8% vs 50.4% vs 52.5% vs 46.2% vs 50.2% respectively, p=0.001). Heavy and moderate smokers were also more likely to be diagnosed after the age of 40 than light and never-smokers, and SUSIs (72.1% vs 66.7% vs 48.8% vs 60.5%, 57.8% p<0.001). 54.9% of heavy smokers were in the bottom two IMD quintiles compared with 36.6% of moderate smokers, 34.1% of SUSIs, 31% of light smokers and 30.7% of never-smokers (p<0.001). There were no significant differences between the groups with respect to the era of diagnosis.

The proportion of patients using thiopurines was highest among never-smokers (16.8%) then light smokers (14.2%), SUSIs (13.4%) and moderate smokers (9.9%) and lowest among heavy smokers (8.1%) (p=0.007). However, after adjusting for covariates in a Cox regression we found no association between smoking intensity and the risk of using a thiopurine.

Rates of crude corticosteroid use and the risk of corticosteroid flares were similar between all groups. The proportion of patients developing corticosteroid dependence was highest among never-smokers (15.7%), then SUSIs (13.8%), followed by light (13.3%) and moderate smokers (12.1%) and finally lowest among heavy smokers (7.4%) (p=0.034). A multiple Cox regression found heavy smokers to have a trend towards lower risk of developing corticosteroid dependence compared with never-smokers but this did not reach significance (HR 0.25, 95% CI 0.06-1.03, p=0.055).

The risk of hospitalization was similar between never-smokers and smokers, regardless of smoking intensity. Rates of colectomy were similar between all groups (p=0.09) and a multiple Cox regression analysis found no association between smoking intensity and risk of colectomy.

# Discussion

## Main findings

To our knowledge, this is the largest nationally representative cohort study to evaluate the impact of smoking and its cessation on clinical outcomes in UC. The study population comprised 6754 incident cases of UC, with a cumulative 41,024person years of follow-up, and demonstrated no difference in the risk of corticosteroid-flares, corticosteroid dependency, thiopurine use, hospitalization or colectomy between never-smokers, ex-smokers and smokers.

Among smokers who quit within the first two years of being diagnosed with UC the risk of corticosteroid-requiring flares, thiopurine use, corticosteroid dependency, hospitalization and colectomy was not significantly different compared with persistent smokers.

We explored the possibility of a dose-response relationship between smoking intensity and disease outcomes in UC. There was a non-significant trend towards a lower risk of corticosteroid dependency among heavy smokers compared with never smokers (HR 0.25, 95% CI 0.06-1.03, p=0.055) but in all other respects smokers, regardless of smoking intensity, had similar disease outcomes compared with never-smokers.

## Findings in relation to previous studies

Previous studies provide conflicting evidence for an association of smoking at diagnosis with corticosteroid use.4,5,7,41,42 Our study is the largest study to examine this relationship and found that smoking status at diagnosis did not impact on the likelihood of corticosteroid exposure. We also examined the number of courses of corticosteroid prescribed per year and found that this was the same in both smokers and non-smokers. These findings are consistent with a recent meta-analysis that found no difference in flares of disease activity according to smoking status.14 Our study is the first to address the impact of smoking on corticosteroid-dependency as defined by ECCO guidelines.43 Reducing corticosteroid-dependency is an important goal in IBD management given the long term clinical side effects and adverse outcomes associated with corticosteroid dependency in IBD.44 In a multivariable analysis we found no difference in corticosteroid-dependency between never-smokers, smokers and ex-smokers. Our findings contrast with those of a previous study that reported smokers had reduced requirements for “long-term” corticosteroids compared to non-smokers but the number of smokers included was small (n=59), there was no data on smoking intensity and it differed in its definition of long-term corticosteroid use.41

Previous studies regarding the impact of smoking in UC on the requirement for thiopurines are inconsistent.4,7,11,41,42 In a multivariable analysis, we found no difference in thiopurine use according to smoking status. Previous studies have found similar rates of hospitalization among smokers and non-smokers with UC, although one study found patients who quit smoking went on to have more hospital admissions.11,41 By contrast, our study found smoking status did not alter the risk of hospitalization.

We found no difference in rates of colectomy according to smoking status. An early study previously reported smokers to have lower rates of colectomy than non-smokers (32% versus 42%, p=0.04). However, rates of colectomy reported in this previous study were high, likely as a result of tertiary centre referral bias and the era in which the study was conducted.4,45 In 2015, Dias *et al.* published a meta-analysis examining the impact of smoking on colectomy rates in UC.46 They found that smoking reduced the risk of colectomy (OR 0.55, CI 0.33-0.91, p=0.02). By contrast, and in keeping with our findings, a more recent systematic review and meta-analysis on this topic reported that the odds of colectomy, derived from 4 studies, were unaffected by smoking (OR 1.00, CI 0.63-1.59)14 10–12,14,41

Few previous studies have evaluated the impact of smoking cessation on clinical outcomes in UC.3,5,11 Smoking cessation has previously been linked to a detrimental effect on the disease course of UC, including increased use of immunomodulation and corticosteroids, and rates of hospitalization.3,5,11 The current study is the largest study to examine the effects of smoking cessation after diagnosis of UC. While our study found higher crude corticosteroid and thiopurine use among quitters compared to persistent smokers these differences were not sustained in the multiple Cox regression. It is reassuring that smoking cessation had no negative impact on rates of corticosteroid-flares, corticosteroid dependency or hospitalization. The risk of colectomy was similar among persistent smokers compared with quitters.

We explored the possibility of a dose-response relationship between smoking intensity and outcomes in UC. We found that heavy smokers (≥20 cigarettes per day) had lower unadjusted rates of thiopurine use and corticosteroid dependency than moderate, light and never smokers. However almost three quarters of heavy smokers were diagnosed after the age of 40, which is associated with a more mild disease course,47 and in the adjusted Cox regression heavy smokers had a similar risk of thiopurine use compared with never-smokers. Interestingly, in the adjusted Cox regression for corticosteroid dependence there was a non-significant trend suggesting a reduced risk of corticosteroid dependence in heavy smokers compared with never-smokers (HR 0.25, 95% CI 0.06-1.03, p=0.055); however, there was no such trend for light and moderate smokers. Even if this finding had reached statistical significance to suggest there is a dose-response, to derive any potential benefit, patients would have to smoke heavily, incurring the significant added risks of high-intensity smoking such as higher rates of lung cancer, bladder cancer, diabetes and cardiovascular disease.48–51 There was no benefit from smoking, regardless of intensity, with respect to corticosteroid-flares, thiopurine use, hospitalization or colectomy. There are anecdotal reports from patients that smoking appears to improve their UC and this has been supported by evidence from trials which found transdermal nicotine patches were superior to placebo in the induction of remission in UC.52 Even so the magnitude of any benefit from smoking is likely to be very small and was not detected in this study.

Smoking prevalence in UK adults has steadily fallen from 24% in 2005 to 19% in 2015. However, our cohort did not reflect this trend.53,54 During the 12 year study period, there was no significant reduction in the proportion of UC patients who were smokers at diagnosis (13.7% in 2005/2006 vs 13.6% in 2015/2016, p=0.93). The stable proportion of smokers at diagnosis, in the context of falling smoking prevalence in the general population, may reflect the protective effect of smoking against the development of UC and the lower prevalence of smoking among UC patients compared with the general population.1,55

In 2015, the Office for National Statistics reported that 56.7% of all adults in Great Britain who had previously smoked have now quit.54 This is similar to the 54% of smokers in our study who quit following diagnosis with UC. Even so, the proportion of patients who smoked only fell from 13% before diagnosis to 12% after diagnosis, largely as a result of ex-smokers resuming smoking. There is limited data on how a diagnosis of UC influences patients’ behaviour with respect to smoking, however a small study found 21% of ex-smokers with UC (n=19) resumed smoking with the intention of preventing flares of their disease. In our study a lower proportion of 9.7% of ex-smokers at the time of UC diagnosis resumed smoking during the follow-up period but we are unable to determine their reasons for doing so.

Almost a half of UC patients believe smoking to have protective properties in relation to UC.18 Data from the Swiss IBD Cohort found that only 2.6% of smokers with UC received any support to cease smoking, suggesting clinicians may be hesitant to recommend smoking cessation to patients with UC. Indeed, there is evidence that some clinicians have recommended smoking as a therapeutic approach where conventional treatments have failed.19 Our study found no evidence to substantiate these perceived benefits of smoking and does not support this controversial approach.

## Strengths and limitations

To our knowledge, this is the largest population-based study to investigate the impact of tobacco exposure on disease outcomes in patients with UC. Data were drawn from a large nationally representative validated research database, free of referral centre bias. CPRD has been specifically validated as a tool to study UC, as well as having high quality data on smoking.23,29,56 Smoking is associated with lower socioeconomic status which has been linked to worse outcomes in IBD57 and we adjusted for this potential bias in our analyses. We evaluated objective clinical endpoints, including thiopurine use, corticosteroid dependency, hospitalization and colectomy, key clinical measures that could be determined in a standardized fashion, derived from prospectively collected data and therefore not subject to recall bias.

Some limitations should be noted. We used a cross-sectional marker of smoking status at diagnosis to evaluate its impact on long-term clinical outcomes. This was recorded prospectively and we also looked at all previous records to establish if any patients were ex-smokers. However, our measure of smoking status does not take into account alternative types of tobacco exposure or the use of transdermal nicotine patches.

During the study period, 30% of UC patients did not have data on their smoking status in the two years before diagnosis. These patients were not included in the complete case analysis and there is a possibility this may have introduced bias, if for example the reason for the missing data was because such patients had less severe UC and were therefore less likely to visit their GP. We therefore conducted a sensitivity analysis, imputing patients with missing data on smoking status randomly as never or ex-smokers, as previous research found patients with missing data are very unlikely to be current smokers.58 Reassuringly this did not alter any of our findings.

CPRD data does not include information on endoscopic or inflammatory markers of disease activity. Instead we evaluated corticosteroid use and corticosteroid dependency as surrogate markers of disease activity. We were unable to capture data on corticosteroids prescribed in a hospital outpatient setting, meaning the rates of corticosteroid use in this study are likely to be underestimates. Even so, this is likely to be non-differential, as it is not expected to differ according to smoking status. We used previously described comprehensive lists of codes from both CPRD and HES to determine whether a patient had undergone a colectomy.38,39 We acknowledge that patients, in particular those in the older age group, may have undergone surgery for indications other than UC, such as cancer. We did not have data regarding disease extent and therefore we were unable to adjust for this. As more extensive disease has been associated with higher risk of colectomy and poorer response to anti-tumour necrosis therapies (aTNF) this could have affected our findings.10,59,60 CPRD contains limited data on aTNF, since these treatments are generally prescribed in hospital inpatient and outpatient settings, and this is a potential confounder. We also accept we have no data on Vedolizumab prescription, though this was only approved for use in UC in the final year of our twelve year study period and is unlikely to significantly alter our findings.

## Implications

Our findings, taken together with those of others, support the view that smoking is not associated with a beneficial impact in on disease outcomes in UC. Furthermore we found no evidence that smoking cessation impacts adversely on subsequent clinical outcomes. These are important observations since evidence suggest that some patients believe smoking has a beneficial effect on the disease course of UC.16,18 Studies in non-IBD populations have found that smoking initiation is more likely when there is a perceived short-term benefit, despite acceptance of short and long-term risks.61,62 Our findings should therefore embolden clinicians to advise against smoking and reassure patients who already smoke that they can benefit from the many advantages of smoking cessation without risk of worsening their UC.

## Conclusions

Smoking is not associated with reduced corticosteroid use, corticosteroid dependency, thiopurine use, hospitalization or colectomy in patients with UC, and smoking cessation does not worsen disease course. The risks associated with smoking outweigh any benefits. Newly diagnosed patients with UC should be counselled against smoking and smokers encouraged to quit.

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# Tables

**Table 1: baseline characteristics of cohort**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **Never-Smoker at UC diagnosis****(n=2,698)** | **Ex-Smoker at UC diagnosis****(n=3,178)** | **Smoker at UC diagnosis****(n=878)** | **p-value** |
| **Sex** % male | 46.2 | 57.7 | 53.3 | **<0.001** |
| **Age at diagnosis** **(%)** A1 A2 A3 | 1.737.860.5 | 0.120.879.2 | 042.957.1 | **<0.001** |
| **BMI category at diagnosis**a **(%)** Underweight Normal Overweight Obese | 3.543.835.517.2 | 1.234.044.220.7 | 4.244.836.214.7 | **<0.001** |
| **Social deprivation**b **(%)** IMD 1 IMD 2 IMD 3 IMD 4 IMD 5 | 26.525.117.719.111.6 | 25.824.919.517.911.8 | 18.923.819.820.617.0 | **0.006** |
|  |  |  |  |  |

a - BMI (Body Mass index) - calculated as the closest BMI recording within one year of UC diagnosis. Data available for 88% of patients

b - IMD (Index of Multiple Deprivation). Data available for 58% of patients.

**Table 2: Simple and multiple cox regression analysis for risk of corticosteroid dependency\* in patients with Ulcerative Colitis**

|  |  |  |
| --- | --- | --- |
|  | **simple cox regression****n=6714** | **multiple cox regression****n=3,894** |
| **OR** | **95% CI** | **p value** | **OR** | **95% CI** | **p value** |
| **Smoking status at diagnosis** Never-Smoker Ex-Smoker Smoker | 10.890.75 | -0.78-1.020.60-0.93 | -0.10**0.009** | 10.820.85 | -0.70-1.030.60-1.11 | -0.200.11 |
| **Sex** (ref to female) | 1.15 | 1.01-1.31 | **0.033** | 1.40 | 1.16-1.68 | **<0.001** |
| **Age at UCdiagnosis**<17 17-40 >40 | 3.40 10.77 | 2.12-5.47-0.67-0.88 | **<0.001-<0.001** | 2.9910.87 | 1.51-5.92-0.71-1.05 | **0.002**-0.16 |
| **Era of IBD diagnosis**aEra 1 Era 2 Era 3 Era 4 Era 5 Era 6 | 11.060.950.960.870.84 | -0.87-1.290.78-1.170.78-1.200.69-1.090.62-1.14 | -0.570.630.740.230.26 | 10.970.840.840.940.76 | -0.74-1.260.64-1.110.62-1.140.69-1.290.47-1.23 | -0.800.230.270.700.26 |
|  |  |  |  |  |  |  |
| **Social deprivation**b IMD lower | 0.96 | 0.79-1.17 | 0.68 | 0.94 | 0.77-1.14 | 0.52 |
|  |  |  |  |  |  |  |
| **Oral 5-ASAc** | 6.95 | 5.47-8.83 | **<0.001** | 6.56 | 4.74-9.08 | **<0.001** |

Multiple regression includes all covariates of simple regression. Significant odds ratios shown in bold.

**OR** – Odds Ratio **CI** - Confidence Interval **IBD** - Inflammatory Bowel Disease **IMD** - index of multiple deprivation **5-ASA** - 5-aminosalicylates

a - Era 1: 2005-06, Era 2: 2007-08, Era 3: 2009-10, Era 4: 2011-12, Era 5: 2013-14, Era 6: 2015-04/2016

b – IMD upper includes IMD categories 1 and 2 (versus IMD category 3,4 and 5), data available for 58% of patients

c – exposure of oral 5-ASA defined as any patients with at least one or more prescription for oral 5-ASA after IBD diagnosis

\* steroid dependency calculated as any patient with a repeat steroid prescription within 3 months of the end of a previous steroid prescription or patients with steroid prescriptions for greater than 3 consecutive months

**Table 3: Simple and multiple Cox regression analysis for risk of thiopurine use in patients with Ulcerative Colitis**

|  |  |  |
| --- | --- | --- |
|  | **simple Cox regression****n=6714** | **multiple Cox regression****n=3882** |
| **HR** | **95% CI** | **p value** | **HR** | **95% CI** | **p value** |
| **Smoking status at diagnosis** Never-Smoker Ex-Smoker Smoker | 10.920.90 | -0.80-1.050.60-0.93 | -0.22**0.009** | 10.970.84 | -0.80-1.170.62-1.14 | -0.740.26 |
| **Sex** (ref to female) | 1.16 | 1.02-1.32 | **0.023** | 1.38 | 1.15-1.65 | **0.001** |
| **Age at IBD diagnosis** <17 17-40 >40 | 2.4010.49 | 1.48-3.90-0.43-0.56 | **<0.001****-****<0.001** | 1.4810.52 | 0.72-3.03-0.43-0.62 | 0.28-**>0.001** |
| **Era of IBD diagnosis**a Era 1 Era 2 Era 3 Era 4 Era 5 Era 6 | 11.121.171.431.331.34 | -0.91-1.390.95-1.451.15-1.781.06-1.681.01-1.79 | -0.280.14**0.001****0.014****0.044** | 10.960.901.191.201.21 | -0.73-1.270.67-1.200.88-1.600.88-1.640.79-1.86 | -0.770.460.250.250.37 |
|  |  |  |  |  |  |  |
| **Social deprivation**b IMD lower | 1.14 | 0.95-1.38 | 0.15 | 1.13 | 0.94-1.37 | 0.20 |
|  |  |  |  |  |  |  |
| **IBD medication**c Oral 5-ASA | 13.96 | 10.13-19.23 | **<0.001** | 12.80 | 8.26-19.82 | **<0.001** |
|  |  |  |  |  |  |  |

Multiple regression includes all covariates of simple regression. Significant hazard ratios shown in bold.

**HR** – Hazard Ratio **CI** - Confidence Interval **IBD** - Inflammatory Bowel Disease **IMD** - index of multiple deprivation **5-ASA** - 5-aminosalicylates

a – Era 1: 2005-06, Era 2: 2007-08, Era 3: 2009-10, Era 4: 2011-12, Era 5: 2013-14, Era 6: 2015-04/2016

b – IMD lower includes IMD categories 4 and 5 (versus IMD category 1, 2 and 3), data available for 58% of patients

c – exposure of oral 5-ASA defined as any patients with at least one or more prescription for oral 5-ASA after IBD diagnosis

**Table 4: Simple and multiple Cox regression analysis for risk of first hospitalization in patients with Ulcerative Colitis**

|  |  |  |
| --- | --- | --- |
|  | **simple Cox regression** **n=3633** | **multiple Cox regression****n=3630** |
| **HR** | **95% CI** | **p value** | **HR** | **95% CI** | **p value** |
| **Smoking status at diagnosis**Never-Smoker Ex-Smoker Smoker | 10.820.91 | -0.70-0.970.71-1.17 | -**0.017**0.46 | 10.850.92 | -0.72-1.010.72-1.18 | -0.0520.53 |
| **Sex**  (ref to female) | 0.91 | 0.78-1.06 | 0.23 | 0.96 | 0.83-1.12 | 0.62 |
| **Age at IBD diagnosis**a<17 17-40 >40 | 2.3610.72 | 1.12-5.02-0.61-0.84 | **>0.001-0.025** | 2.1710.80 | 1.02-4.64-0.68-0.94 | **0.045**-**0.007** |
| **Era of IBD diagnosis**a Era 1 Era 2 Era 3 Era 4 Era 5 Era 6 | 11.131.121.171.371.44 | -0.90-1.420.88-1.430.89-1.521.04-1.810.99-2.11 | -0.300.360.26**0.026**0.058 | 11.151.121.161.341.57 | -0.91-1.440.88-1.430.89-1.521.01-1.781.07-2.30 | -0.250.360.27**0.039****0.020** |
|  |  |  |  |  |  |  |
| **Social deprivation**b IMD lower | 1.38 | 1.18-1.62 | **<0.001** | 1.38 | 1.18-1.62 | **<0.001** |
|  |  |  |  |  |  |  |
| **IBD medication**cOral 5-ASA  | 1.96 | 1.64-2.35 | **0.006** | 1.94 | 1.62-2.32 | **<0.001** |
|  |  |  |  |  |  |  |

Multiple regression includes all covariates of simple regression. Significant hazard ratios shown in bold.

**HR** – Hazard Ratio **CI** - Confidence Interval **IBD** - Inflammatory Bowel Disease **IMD** - index of multiple deprivation **5-ASA** - 5-aminosalicylates

a – Era 1: 2005-06, Era 2: 2007-08, Era 3: 2009-10, Era 4: 2011-12, Era 5: 2013-14, Era 6: 2015-04/2016

b – IMD lower includes IMD categories 4 and 5 (versus IMD category 1, 2 and 3), data available for 58% of patients

c – exposure of oral 5-ASA defined as any patients with at least one or more prescription for oral 5-ASA after IBD diagnosis

**Table 5: Simple and multiple Cox regression analysis for risk of colectomy in patients with Ulcerative Colitis**

|  |  |  |
| --- | --- | --- |
|  | **simple Cox regression****n=6553** | **multiple Cox regression****n=3813** |
| **HR** | **95% CI** | **p value** | **HR** | **95% CI** | **p value** |
| **Smoking status at diagnosis**Never-Smoker Ex-Smoker Smoker | 11.120.76 | -0.91-1.370.53-1.07 | -0.290.12 | 11.030.78 | -0.79-1.340.50-1.21 | -0.820.26 |
| **Sex**  (ref to female) | 1.12 | 0.92-1.36 | 0.25 | 1.29 | 1.01-1.66 | **0.043** |
| **Age at IBD diagnosis**<17 17-40 >40 | 2.1810.82 | 0.96-4.94-0.67-1.01 | 0.061**-**0.062 | 3.2010.84 | 1.28-8.02-0.64-1.10 | **0.013-**0.21 |
| **Era of IBD diagnosis**a Era 1 Era 2 Era 3 Era 4 Era 5 Era 6 | 11.060.910.960.890.80 | -0.80-1.400.67-1.230.70-1.340.60-1.230.48-1.32 | -0.710.550.850.410.37 | 11.010.871.080.830.59 | -0.71-1.440.60-1.280.72-1.630.51-1.320.27-1.31 | -0.950.490.700.430.20 |
|  |  |  |  |  |  |  |
| **Social deprivation**b IMD lower | 1.02 | 0.78-1.33 | 0.90 | 1.00 | 0.76-1.31 | 0.99 |
|  |  |  |  |  |  |  |
| **IBD medication**cOral 5-ASA | 1.36 | 1.09-1.69 | **0.006** | 1.22 | 0.93-1.61 | 0.14 |
|  |  |  |  |  |  |  |

Multiple regression includes all covariates of simple regression. Significant hazard ratios shown in bold.

**HR** – Hazard Ratio **CI** - Confidence Interval **IBD** - Inflammatory Bowel Disease **IMD** - index of multiple deprivation **5-ASA** - 5-aminosalicylates

a – Era 1: 2005-06, Era 2: 2007-08, Era 3: 2009-10, Era 4: 2011-12, Era 5: 2013-14, Era 6: 2015-04/2016

b – IMD lower includes IMD categories 4 and 5 (versus IMD category 1, 2 and 3), data available for 58% of patients

c – exposure of oral 5-ASA defined as any patients with at least one or more prescription for oral 5-ASA after IBD diagnosis

# Figures

**Figure 1: Smoking status at and following the time of Ulcerative Colitis diagnosis.**

**UC** – Ulcerative Colitis

**QOF** – UK Quality Outcomes and Framework introduced to GPs in 2004

**IBD** – Inflammatory Bowel Disease

**Figure 2: KM curves showing probability of corticosteroid dependence in persistent smokers and quitters with Ulcerative Colitis**

**UC** – Ulcerative Colitis

**Persistent Smoker -** UC patients who were smokers at diagnosis with codes to indicate they continued to smoke following diagnosis

**Quitter** – UC patients who were smokers at the time of UC diagnosis with Read codes indicating they quit smoking within two years after UC diagnosis

**Figure 3: KM curves showing probability colectomy in persistent smokers and quitters with Ulcerative Colitis**

**UC** – Ulcerative Colitis

**Persistent Smoker** – UC patients who were smokers at diagnosis with Read codes to indicate they continued to smoke following diagnosis

**Quitter** – UC patients who were smokers at the time of UC diagnosis with Read codes indicating they quit smoking within two years after UC diagnosis