Smoking status at diagnosis and subsequent smoking cessation: associations with corticosteroid use and intestinal resection in Crohn's disease

Dr Christopher Alexakis MBBS BSc MRCP*

Prof. Sonia Saxena MBBS MSc MD FRCGP**

Dr Vivek Chhaya MBBS BSc MRCP MD*

Dr Elizabeth Cecil MSc PhD**

Prof. Azeem Majeed MD FRCP FRCGP FFPH**

Dr Richard Pollok FRCP PhD BSc DTM&H*

Affiliations:

*Department of Gastroenterology, St George's University Hospitals NHS Foundation Trust, London, SW17 0QT, UK *and* Institute of Infection & Immunity, St George's University of London, Cranmer Terrace, London SW17, UK

**Department of Primary Care and Public Health, Imperial College London, London W6 8RF, UK

Corresponding author:

Dr Richard Pollok - Reader and Consultant Gastroenterologist

Department of Gastroenterology, St George's University Hospitals NHS Foundation Trust, London, SW17 0QT.

Telephone: 0208 7251206, e-mail: richard.pollok@nhs.net

Running title:

Smoking and outcomes in Crohn's disease

Word count: 4373

Conflicts of interests/author declarations:

RP is supported by a Wellcome Trust Institute Strategic Support Fund (ISSF) 2017 grant. Imperial College London is grateful for support from the NW London NIHR Collaboration for Leadership in Applied Health Research & Care and the Imperial NIHR Biomedical Research Centre. This article presents independent research commissioned by the National Institute for Health Research (NIHR). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. Access to the CPRD database was funded through the Medical Research Council's license agreement with the Medicines and Healthcare products Regulatory Agency (MHRA). However, the interpretation and conclusions contained in this study are those of the authors alone. No conflicts of interest declared by other authors.

Abstract

Background: The impact of smoking at diagnosis and subsequent smoking cessation on clinical outcomes in Crohn's disease (CD)has not been evaluated in a population based cohort.

Methods: Using a nationally representative clinical research database, we identified incident cases of CD between 2005 and 2014. We compared the following outcomes: overall corticosteroid (CS) use; flares requiring CS; CS-dependency and intestinal surgery between smokers and non-smokers at time of CD diagnosis. Differences in these outcomes were also compared between persistent smokers and smokers who quit within 2 years of diagnosis.

Results: We identified 3553 patients with a new CD diagnosis over the study period of whom 1121 (32%) were smokers. Smokers at CD diagnosis had significantly higher CS-use (56% vs. 47%, p<0.0001), proportionally more CS-flares (>1 CS flare/yr: 9% vs 6%, p<0.0001), and higher CS-dependency (27% vs. 21%, p<0.0001) than non-smokers. Regression analysis identified smoking at diagnosis to be associated with a higher risk of intestinal surgery (HR 1.64, 95%CI 1.16-2.52). There was a significantly higher proportion of 'quitters' who remained steroid-free through follow-up in comparison to 'persistent smokers' (45.4% vs. 37.5% respectively, p=0.02). 'Quitters' also had lower rates of CS-dependency compared to 'persistent smokers' (24% vs 33%, p=0.008).

Conclusions: Smokers at CD diagnosis have higher CS-use, CS-dependency and higher risk of intestinal surgery. Quitting smoking appears to have beneficial effects on disease related outcomes including reducing CS-dependency highlighting the importance of offering early smoking cessation support.

Study highlights

1) What is current knowledge:

- smoking is common amongst patients with Crohn's disease (CD)
- smoking may worsen outcomes in CD but the exact association remains unclear, and much of the available data comes from secondary and tertiary care centres
- there is only limited data on the impact of smoking cessation in outcomes in CD

2) What is new here:

- patients with CD who are smokers at the time of diagnosis have higher overall corticosteroid (CS) use compared to non-smokers
- CS dependency, as defined by international guidelines, is more frequent amongst CD patients who smoke at diagnosis
- patients with CD who smoke at diagnosis are two thirds more likely to undergo intestinal surgery
- patients with CD who stop smoking within the first two years of diagnosis have lower rates of CS dependency and are more likely to be steroid-free

Introduction

Smoking is a key modifiable environmental risk factor implicated in the onset of Crohn's disease (CD).[1] Despite recent global reductions, approximately one in five British adults smoke currently.[2] Recent data from the UK indicates there may be a similar prevalence amongst patients with CD,[3] although in some CD populations smoking is much more frequent.[4,5]

Tobacco exposure impacts adversely on disease outcomes in CD. Several studies have reported increased rates of intestinal surgery amongst smokers.[6,7,8,9] Smoking may also impact upon other clinically important indices including disease flares, corticosteroid requirement and immuno-modulator use,[10,11,12] although a few small studies have found no association between tobacco exposure and poorer outcomes.[13,14,15]

The majority of previous studies examining the relationship between smoking and disease outcomes in CD have originated from secondary or tertiary care and are therefore likely to comprise of patients with a more severe phenotype. In a recent meta-analysis on the impact of smoking on disease outcomes in CD thirty-two of the 33 studies were derived from referral centres.[16] Population-based studies reporting on the relationship between smoking and disease course in CD are fewer in number,[3,13] yet may be better placed to examine the true impact of smoking on outcomes in CD as they will include a more diverse range of patient phenotypes.

Despite strong evidence that smoking is detrimental to gut health in CD, there is limited evidence that smoking cessation can improve disease outcomes.[17,18] To our knowledge, the potential benefits of smoking cessation have not previously been evaluated in a population based cohort that is free of referral centre bias.

We therefore aimed to perform a population based study to investigate both the impact of smoking status at diagnosis *and* the impact of subsequent smoking cessation after diagnosis on clinical outcomes in Crohn's disease. We hypothesised that smoking at the time of CD diagnosis is an

independent risk factor associated with adverse outcomes in CD and that smoking cessation would impact favourably.

Methods

Data source

We created a retrospective population-based incident cohort of all patients diagnosed with Crohn's disease using the Clinical Practice Research Datalink (CPRD). CPRD is one of the largest and best validated primary care research databases in the world. Importantly, it is not an administrative dataset and thus is free from the biases inherent of such data sources. It contains longitudinal, patient-level, anonymised electronic health records from 674 general practices and is representative of around 8% of the United Kingdom (UK) population.[19] 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' (UTS) 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 IBD.[20] Numerous IBD related studies have been undertaken using this data source.[21,22,23,24] Furthermore, the CPRD has been used in a number of population based studies investigating both smoking habits and the impact of tobacco consumption on outcomes in other patient populations.[25,26,27] 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 GPs in 2004.[28]

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 methodologies in defining incident cases of inflammatory bowel disease from the CPRD.[29,30,31,32,33] In brief, to separate prevalent from incident cases of CD, we

identified patients with a first Read code for CD at least one year after registering with a 'Up To Standard' practice for the period January 1st 2005 to December 31st 2014.

Patients were excluded if they had Read codes for both ulcerative colitis and CD, or indeterminate codes ('non-specific colitis', 'colitis NOS' etc). Patients who had a co-morbid condition that might require regular or prolonged steroid use, for example, chronic asthma or polymyalgia rheumatica patients, were also excluded to avoid potential confounding. Patients with previous organ transplants were also excluded because of the likely use of concurrent immunosuppressant and steroid medications in this group. Patients were followed up from date of CD diagnosis until study endpoint, de-registration, or death.

Exposure variable

Our main exposure variable was smoking status at CD diagnosis. Patients were defined as either 'smokers' or 'non-smokers' at the time of CD diagnosis based on Read codes for smoking status in the year before the first recorded CD diagnosis. 'Non-smokers' at CD diagnosis included patients who were either ex-smokers of at least one year, or 'never smokers', as defined by Read codes (see additional online material). Where patients had contradicting or multiple codes for smoking status in the preceding year, the smoking code closest to the date of CD diagnosis was used. Completeness of smoking data within our dataset was approximately 80% (Figure 1). Accuracy of smoking status recording in CPRD has been demonstrated to be within 1% of self-reported smoking habits in national surveys.[34] Since April 2004, financial incentives in primary care were introduced for GPs to offer smoking cessation advice to patients aged over 16 years via the UK Quality and Outcomes Framework (QOF) scheme. This has substantially increased completeness of recording of smoking status.[28] We therefore chose a start for the study of January 1st 2005, 9 months after implementation of this scheme.

For the secondary analysis, we identified patients with further Read codes for smoking status in the first two years after CD diagnosis. Patients were considered 'persistent smokers' if they were

smokers at CD diagnosis (as defined above) *and* had at least one further Read code indicating a smoking status within 2 years after diagnosis. Patients were labelled as 'quitters' if they were smokers at CD diagnosis, but had at least one subsequent Read code indicating they were non-smokers or ex-smokers in the two years following CD diagnosis.

Outcome measures

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

Secondly, we used a previously published methodology described by Grainge *et al*. to define the number of 'CS flares' during follow up.[35] The first 'CS-flare' was defined as the first CS prescription registered in the patient record after date of CD diagnosis. The next separate 'CS-flare' was defined where a subsequent CS prescription was recorded following a period of at least 4 months without a CS prescription. This methodology allowed for the determination of total 'CS-flares' for the entire period of follow-up for each patient. Thus, the total number of 'CS-flares' was divided by follow-up time to generate the outcome measure 'CS-flares per year'.

Thirdly, we identified patients with steroid-dependency (defined as prolonged or repeated CS exposure) adapted from the European Crohn's and Colitis Organisation guidelines criteria.[36] A patient was defined as 'CS-dependent' if they had either a prescription for CS that lasted longer than 3 months, or required a repeat CS prescription within 3 months of stopping the previous CS course. CS-dependency has been shown to be associated with poorer outcomes in patients with CD.[37]

Our secondary outcome measure was first intestinal surgery. This was defined as the first intestinal surgical procedure coded for following diagnosis of CD, and was derived using Read/OXMIS codes for intestinal surgery as previously described.[29,31]

Covariates

We included a number of covariates with known or likely associations with poorer clinical outcomes in CD. These included: age at diagnosis, body mass index, social deprivation, severity of CD, concurrent 5-aminosalicylic acid (5ASA) or thiopurine use, and co-morbid conditions. Age at diagnosis has previously been shown to be relevant to surgical outcomes in the context of smoking status.[3] Patients were sub-divided into age categories at diagnosis of CD according to the Montreal Classification (A1 - age less than 17 years, A2 - 17 years to 40 years, A3 - age greater than 40 at initial CD diagnosis). We also extracted data for Body Mass Index (BMI) at diagnosis, defined as the closest BMI recording within 1 year of CD diagnosis. Patients were defined as: underweight (BMI<18.5kg/m^2), normal weight (18.5-25kg/m^2), overweight (25-30kg/m^2) or obese (>30 kg/m^2). BMI may be associated with risk of surgery in CD.[38] 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. In the UK, people living in the areas of highest deprivation are more than twice as likely to smoke compared to the lowest.[39] We also identified patients with co-morbid irritable bowel syndrome (IBS) and depression. IBS is common in patients with IBD and may be confused with the symptoms of an IBD flare.[40] Furthermore, smoking is highly correlated with depressive illnesses.[41] We defined these co-morbidities to include any patient with a concurrent Read code for either IBS or a depressive diagnosis during the follow-up period.

We also extracted data for IBD medication usage other than CS. Patients were defined as 5-aminosalicylic acid (5ASA) users if they had one of more prescriptions during follow up. Similarly, patients were defined as thiopurine (TP) users if they had one or more prescriptions for azathioprine (AZA) or 6-mercaptopurine (6MP) during follow-up. Prescription data for anti-tumour necrosis factor (aTNF) use is not reliably recorded in CPRD.

We classified disease severity using a modification of the Beaugerie Index of severity.[42] This is a validated 4-point score calculated using three clinical variables that predict a 'disabling' disease course in CD, including a higher risk of IBD medication use, hospitalisation and surgery. The three variables are: age of CD onset < 40 years, early use of CS, defined in our population as a first CS prescription within 3 months of CD diagnosis, and lastly the presence of peri-anal disease, defined for the purpose of this study by codes for peri-anal surgery, as previously described.[32] A patient may have a score between zero (none of the variables) and 3 (all three variables). A score of 2 or more is associated with a positive predictive value of over 90% for 'disabling' disease.[42]

The 10 year study period was divided into five 2-year era to allow for assessment of the impact of era of CD 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).

Statistical analysis

We used *t*-tests to determine differences between groups of continuous data, and Chi-squared or Fisher's exact test for comparisons of categorical data. We compared the proportion of smokers versus non-smokers at CD diagnosis who had any CS exposure, the number of CS flares per year in each group, and the proportion of patients with steroid dependency.

We used Kaplan-Meier analysis to generate survival curves calculating the time to first oral CS prescription in smokers and non-smokers. For both smokers and non-smokers, we calculated cumulative oral CS exposure rates in the follow-up period. The rate of oral CS exposure was determined as a function of time, by calculating the duration between diagnosis of CD and first oral CS prescription, or end of follow-up as defined above. The risk of oral CS use at 1, 3 and 5 years after CD diagnosis was also calculated. We used the log rank test to assess for any significant differences between smokers and non-smokers. We used the same statistical methodology to calculate the 1,3 and 5 year risk of first intestinal surgery between smokers and non-smokers.

In a further analysis, we used separate Cox proportional hazards models to calculate hazard ratios (HR) for first intestinal surgery given smoking status at CD diagnosis. All available variables included in the univariate and multivariate analysis. Within this model we adjusted for sex, Montreal age category, BMI, era of CD diagnosis, IMD status (dichotomous variable - upper two IMD quintiles versus lower 3 quintiles), co-morbid depression, concurrent IBS, 5ASA and TP use, and disease severity (Beaugerie index score of greater than or equal to 2).

In the analysis comparing 'quitters' versus 'persistent smokers', we used similar outcome measures as for the primary analysis. CS flare rate, CS-dependency and IR rates were compared between these two sub-groups using student's t-test, Chi squared test, and KM survival analysis with the log rank test.

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 3553 patients with a new diagnosis of CD with 14806 person years of follow up between January 1st 2005 and December 31st 2014 (Figure 1). 1121 of 3553 patients (31.6%) were smokers at CD diagnosis. The difference in follow-up time between smokers (n=1121) and non smokers (n=2432) was not significant (4.3 years versus 4.1 years, p=0.22). The overall proportion of smokers at diagnosis across the 5 era remained constant. However, the proportion of smokers at CD diagnosis aged 17-40 (Montreal A2 category) dropped from 37.4% in years 2005-6 (era 1) to 30.5% in years 2013-14 (era 5 - Figure 2).

At baseline, there was no difference in the proportion of smokers and non-smokers aged 17-40 years (Montreal A2) and aged >40 years (Montreal A3) respectively. There were significantly more non-smokers than smokers in the youngest age cohort (Table 1).

Amongst patients with CD, smokers were more likely to be female, live in deprived areas, and have a concurrent diagnosis of depression (Table 1). No differences between smokers and non-smokers were observed in the other baseline characteristics including BMI at diagnosis, IBS prevalence or disease severity. Nor were there any significant differences in 5-ASA use (52.1% versus 54.5%) and thiopurine use (35.5% versus 32.4%) during follow-up between smokers and non-smokers respectively.

Corticosteroid use

Smokers had more overall exposure to oral CS therapy. Crude oral CS exposure was 55.8% in smokers versus 47.0% in non-smokers ($p<0.0001$). Smokers were less likely to have CS-free remission, defined as no 'CS-flares' in follow-up. Smokers also had significantly more 'CS (requiring) flares' per year when compared with non-smokers (Table 2). Similarly, a higher proportion of smokers developed CS-dependency than non-smokers (27.4% versus 20.8%, $p<0.0001$).

The cumulative risk of oral CS use at 1,3 and 5 years was 41.1%, 50.9% and 57.5% in smokers, and 34.9%, 43.0% and 49.0% in non-smokers (log rank test for trend, p=0.0001, see Figure 3).

Intestinal surgery

The crude rates for first intestinal surgery in patients with CD were 10.0% and 6.6% in smokers and non-smokers (p<0.0001). The cumulative risk of first intestinal surgery at 1, 3 and 5 years was 5.3%, 8.5% and 9.3% in smokers and 3.6%, 5.1% and 6.7% in non-smokers at CD diagnosis (log rank test for trend, p= 0.009, see figure 4). Smoking was associated with a 64% increase in risk of first intestinal surgery (HR 1.64, 95%CI 1.16-2.52 - see table 3).

Impact of smoking cessation on outcomes in CD

We identified 749 patients who were smokers at CD diagnosis who had subsequent Read codes for smoking status within the first 2 years following CD diagnosis. Of these, 334 (44%) were classified as 'quitters' and 415 were defined as 'persistent smokers'.

The proportion of female 'persistent smokers' was significantly higher than male patients (66.8% vs 33.2%, p=0.001). There was also significant differences in the proportions of 'persistent smokers' between the Montreal age groups (A2 50.1%, A3 59.8%, p=0.008). Similarly, 'persistent smokers' were more likely to have co-existent depression than 'quitters' (19.0% vs 11.6%, p=0.0001). There were no differences between 'persistent smokers' and 'quitters' with respect to BMI or IMD categories, or the proportion of patients with co-existent IBS.

'Quitters' had lower overall CS use. Crude oral CS exposure was 53.7% in 'quitters' versus 61.3 in 'persistent smokers' (p=0.03). Mean number of CS flares per year was 0.61 in 'quitters' versus 1.20 in 'persistent smokers', although this difference did not reach statistical significance. However, the proportion of 'quitters' who maintained steroid-free remission during follow-up was significantly higher than amongst 'persistent smokers' (45.4% versus 37.5%, p=0.02). Furthermore, there was a

278 significantly higher proportion of 'persistent smokers' who developed CS-dependency compared to
279 the 'quitters' (32.8% in 'persistent smokers' versus 23.9% amongst 'quitters' - see figure 5).

280 Crude IR rates were 10.2% in 'quitters' and 11.5% in 'persistent smokers (p=0.54). The 1, 3 and 5 year
281 cumulative risk of IR was 5.6%, 7.9% and 10.3% in 'quitters' and 5.5%, 10.4% and 12.1% in 'persistent
282 smokers', although the differences did not reach statistical significance (see figure 6).

283 The marked difference in co-morbid depression prevalence between 'quitters' and 'persistent
284 smokers' was explored given the potential independent effect of depression on outcomes in IBD.[43] In
285 multiple logistic regression analysis adjusting for age, sex, obesity and social deprivation, depression
286 was associated with an 84% increased odds of being a 'persistent smoker' (OR 1.84, 95% CI 1.04-
287 3.25, p=0.04). However, amongst our CD cohort, the presence of depression did not impact on the
288 key outcomes of CS-dependency and intestinal resection (IR) proportionally when comparing
289 quitters and persistent smokers with/without depression. There were no statistical differences in the
290 proportion of patients developing CS-dependency between 'persistent smokers' with or without
291 depression (35.4% vs.32.5%, p=0.56), or 'quitters' with or without depression (30.8% vs. 23.0%,
292 p=0.28). Similarly, there were no statistical differences in the proportion of CD patients who
293 underwent intestinal surgery between 'persistent smokers' with or without depression (17.7% vs.
294 10.1%, p=0.06), or 'quitters' with or without depression (2.6% vs. 11.2%, p=0.10).

295

Discussion

Main findings

This is the is the first population based study to report on the impact of smoking cessation on clinical outcomes in Crohn's disease. Smoking at diagnosis was associated with both an increase in CS-requiring flares, the development of CS dependency and risk of intestinal resection. Smoking cessation within the first 2 years of diagnosis was associated with a reduction in CS-dependency by almost a quarter compared to persistent smokers. The proportion of quitters in steroid-free remission during follow-up was almost a fifth higher than in persistent smokers. Rates of intestinal surgery amongst quitters were reduced but did not reach statistical significance.

Findings in relationship to other studies

This study is the first to demonstrate the benefit of smoking cessation in a population based cohort on the key clinical outcome of CS-dependency. In a landmark study by Cosnes et *al*., CD patients from a tertiary centre who continued to smoke, when compared to those who had quit or had never smoked, had higher rates of disease flares, steroid use and immunosuppressant use, although surgical rates remained unaffected.[17] More recently, a prospective observational study by Nunes et *al.* including 573 patients with CD from 14 IBD referral centres in Spain reported similar findings.[18]

Our study is the first to address the impact of smoking on CS-dependency as specifically defined by ECCO guidelines.[44] Reducing CS-dependency is an important goal in IBD management given the long term clinical side effects and adverse outcomes associated with CS dependency in IBD.[45] Our findings are in keeping with other referral centre studies that have demonstrated that smoking is associated with increased corticosteroid use,[10,11,12] increased disease activity or disease flares,[6,13] and progression from an inflammatory to a stricturing or penetrating disease pattern that often requires surgery.[46] A recent meta-analysis that included nine studies of patients with CD, found a 56% increased risk of disease flare in patients who smoked (pooled odds ratio 1.56, 95%CI 1.21-2.01).[16]

We did not find any statistical difference in risk of TP exposure in between smokers and non-smokers, although the results approached statistical significance (35.5% vs. 32.4% in smokers and non-smokers respectively, p=0.06) Similar findings have also been reported in a study by Seksik *et al*, in which immuno-modulator (IM) use did not vary between non-smokers, light smokers and heavy smokers.[6] By contrast, other studies have demonstrated increased IM use amongst smokers with CD.[10,11,12] Interestingly, in a retrospective analysis of steroid-dependent IBD patients, including 103 CD patients treated with thiopurines, there was no difference in steroid-free remission between smokers and non-smokers.[47]

We found a significantly higher risk of first intestinal surgery amongst CD patients who smoked at diagnosis (HR 1.64, 95%CI 1.06-2.52). Our findings add to the body of evidence base that suggest an increased risk of intestinal surgery amongst smokers.[6,9,48] The majority of studies in this field have been derived from data collected in secondary care. One previous study by Frolkis *et al.* reported population-based data on the impact of smoking on risk of surgery in CD using The Health Improvement Network (THIN), although did not evaluate the impact of smoking cessation in this cohort. THIN is a UK primary care database that shares information from some practices within CPRD and also includes patient data from practices that do not contribute to CPRD, although is smaller in size than CPRD. This study included 1500 CD patients and reported that current smoking at time of CD diagnosis was associated with a threefold increase in risk of intestinal surgery (HR 2.99, 95%CI 1.52-5.92), although this increased risk was only apparent in patients diagnosed with CD over the age of 40 years (Montreal A3).[3] This contrasts with our own larger study that found no age-related differences in multi-variate analysis, which may reflect the size of our cohort, differences in adjusting for confounding, and minor variations in the definitions of smoking at CD diagnosis.

Smoking rates in the UK as in many developed countries have fallen since legislation banning smoking in public spaces were introduced and our cohorts show similar trends in smoking prevalence. Data from the Global Burden of Disease (GBD) tobacco collaborators study reported an

annual percentage drop in smoking prevalence of 0.9-1.2 between 2005-15.[2] During our 10 year study period, there was a sustained and significant decrease in proportion of patients aged 17-40 years (Montreal A2) who were smokers at diagnosis from 37.4% to 30.5%, or a drop of approximately 0.7%/year. Research on smoking cessation in the UK general population has also shown a differential rate of smoking cessation, with the highest quit rates amongst 21-30 year olds.[49] This is against a background of an overall drop in smoking prevalence in UK adults from 46% in 1974 to 19% in 2014.[50] The drop in smokers at diagnosis may also reflect changing smoking habits in the wake of the UK smoking ban that was introduced in July 2007,[51] in addition to the introduction of Quality and Outcome Framework (QOF) targets in UK general practices.[28] In a sensitivity analysis of our own data, we found the proportion of CD patients aged 17-40 years (Montreal A2) who smoked at diagnosis dropped significantly from 37% in the pre-smoking ban era to 30% in the post-smoking ban era, whereas there were no changes in the other age categories.

That smoking worsens, and conversely cessation improves disease course in CD, can be explained by a host of biological, clinical and social factors. Tobacco smoke is postulated to cause inflammation and damage to the gastrointestinal tract via a number of mechanisms.[52] Smoking may lead to alterations in the intestinal flora in patients with IBD manifest as decreased species diversity and reduced anti-inflammatory phyla, for example *Firmicutes*.[53] Smoking in CD may also increase potentially pro-inflammatory *Bacteioroides* species.[54] Constituents of tobacco smoke may inhibit anti-inflammatory pathways, dysregulate monocyte function and alter small bowel permeability.[55,56,57]

Smoking may also impact on the efficacy of CD-specific medication. Smokers are more likely to discontinue thiopurine therapy because of side effects.[47] Smoking has also been suggested to reduce the effectiveness of biologic therapies, but this association remains unconfirmed.[58] Furthermore, reports from some non-IBD populations indicate medication adherence amongst smokers may be worse.[59]

Strengths and limitations

This is the first population-based study investigating the impact of smoking cessation on disease outcomes in patients with Crohn's disease. Data were drawn from a large nationally representative validated research database free of referral centre bias. CPRD has previously been validated as a tool to study IBD, including smoking exposure.[20,60] Completeness for the recording of smoking status is reported at over 98% in some patient populations.[28] In our regression model we have accounted for multiple demographic and clinical covariates that add strength to our findings.

We acknowledge certain limitations to our study. A potential limitation is that longitudinal data with regard to smoking continuation and cessation was incomplete and reduced the size of the cohort available for analysis of the impact of smoking cessation. However to date this is the only population based study to evaluate the impact of smoking cessation in CD. Furthermore, our measure of smoking status may have been subject to recall bias by patients or a failure of clinicians to inquire about and record status acurately.[4] This could potentially result in an underestimation of any effect. Furthermore, our study did not account for smoking intensity or alternative types of tobacco exposure.

With respect to the smoking cessation analysis, we evaluated the impact of cessation with in the first 2 years of diagnosis. We classified the status of quitting or smoking persistence based on changes in smoking codes within the first two years after CD diagnosis. Our methodology defines cessation based on an event documented and coded for by the primary care physician and not the actual date the patient stopped smoking. It is possible therefore that CS use and IR may have occurred before the actual 'quit date'. Reassuringly in this respect we found in a sensitivity analysis that mean time to a change in smoking code (227 days from CD diagnosis) was significantly shorter than the mean time to either CS dependency (1112 days) or intestinal surgery (395 days) This suggests smoking cessation usually preceded CS use or IR in our analysis .

We also acknowledge CPRD contains limited information about disease phenotype, activity, severity and endoscopic data, but emphasize that this database has been validated for use in IBD-related research.[20] We have however attempted to adjust for some of these restrictions including developing surrogate markers for disease activity to generate 'CS-flare' data using a previously published methodology.[35] We also recognise the potential limitations of using CS prescription data to define disease activity rather than objective markers. Nevertheless this does often reflect 'real world' clinical practice. Our methodology will also fail to capture patients who choose against taking steroids for a flare, although postulate this would be a small proportion of patients.

We were however able to control for disease severity using the validated Beaugerie index.[42] Additionally, we used a previously described comprehensive list of Read codes to determine whether a patient had had intestinal surgery.[29] We accept some patients, in particular those in the older (A3) age group, may have undergone surgery for indications other than CD, such as cancer. The associated impact of smoking status on IBD-specific hospitalisation would also have been of interest but CPRD does not code for this parameter.

CPRD contains limited data on anti-tumour necrosis factor (aTNF) medications, since these treatments are usually prescribed in secondary care and thus is a potential confounder. It is noteworthy that in 2006, only an estimated 3% of the British CD population was on biologic therapy,[61] but has steadily risen since.[62] In our multivariate analysis we have shown that era of diagnosis was not a significant covariate implying that changes in biologic use between the era did not impact significantly on the measured outcomes. This is also consistent with a recent Spanish registry study, which reported that smoking was associated with a more deleterious disease course irrespective of increased biologic use.[11]

Implications

Our results support the hypothesis that intestinal inflammation is exacerbated by tobacco exposure in Crohn's disease and worsens subsequent clinical outcomes, notably steroid use and requirement

for intestinal surgery. Importantly it supports the notion that smoking cessation has a favourable impact.

Smoking is the only truly modifiable risk factor in disease course in CD and our findings underscore the importance of assessing smoking status at first presentation, and counselling patients who smoke that continued tobacco use is likely to be associated with detrimental outcomes, but that quitting smoking will improve their disease course. This is particularly pertinent given patient knowledge as to the potentially negative impact of smoking on outcomes in IBD may be lacking.[63,64] We recommend that smoking cessation strategies should be prioritised in systematic shared care protocols bridging primary and secondary care since there is good evidence, that when clinicians support patients, about a third will quit,[65] with resultant improvement in clinical outcomes in those that achieve this goal.[18] There may be added value in focusing this effort on certain target populations including younger patients or light smokers who are more likely to succeed with complete cessation.[66] There may also be considerable economic benefits to healthcare services employing cessation programs in CD.[67]

Further work is needed to quantify the effect of smoking exposure ideally using objective markers that are not subject to recall bias such as salivary cotinine.[68] Additionally, future prospective studies that quantify smoking exposure by accurately recording smoking intensity (number of cigarettes smoked per day), could be used to investigate the potential of a tobacco 'dose effect'.

Conclusions

Amongst patients with CD, smoking status at diagnosis impacts on key clinical outcomes within the first five years of the disease course. CD patients who are smokers at diagnosis are a third more likely to be steroid dependent, have more steroid flares during follow-up, and are two thirds more likely to undergo intestinal surgery. Patients who stopped smoking within the first 2 years following CD diagnosis had reduced rates of CS-dependency, a key clinical outcome in this cohort. These

findings underpin the importance of early targeted smoking cessation programmes within this patient group.

Author contributions

CA will act as the guarantor for the article. All authors contributed to the concept and design of the study. CA wrote the paper and all authors contributed and approved the final manuscript.

References

1. Parkes GC, Whelan K, Lindsay JO. Smoking in inflammatory bowel disease: Impact on disease course and insights into the aetiology of its effect. *J Crohn's Colitis*. 2014;8(8):717-725. doi:10.1016/j.crohns.2014.02.002.

2. Collaborators GB of D 2015 T. Smoking prevalence and attributable disease burden in 195 countries and territories, 1990-2015: A systematic analysis from the Global Burden of Disease Study 2015. *Lancet*. 2017;13;389(100:1885-1906. doi:10.1016/S0140-6736(17)30819-X.

3. Frolkis AD, de Bruyn J, Jette N, et al. The Association of Smoking and Surgery in Inflammatory Bowel Disease is Modified by Age at Diagnosis. *Clin Transl Gastroenterol*. 2016;7(4):e165. doi:10.1038/ctg.2016.21.

4. Hwang SW, Seo H, Kim G, et al. Underestimation of Smoking Rates in an East Asian Population with Crohn ' s Disease. 2016:1-6.

5. Biedermann L, Fournier N, Misselwitz B, et al. High Rates of Smoking Especially in Female Crohn's Disease Patients and Low Use of Supportive Measures to Achieve Smoking Cessation--Data from the Swiss IBD Cohort Study. *J Crohns Colitis*. 2015;9(10):819-829. doi:10.1093/ecco-jcc/jjv113.

6. Seksik P, Nion-Larmurier I, Sokol H, Beaugerie L, Cosnes J. Effects of light smoking consumption on the clinical course of Crohn's disease. *Inflamm Bowel Dis*. 2009;15(5):734-741. doi:10.1002/ibd.20828.

7. Sands BE, Arsenault JE, Rosen MJ, et al. Risk of early surgery for Crohn's disease: implications for early treatment strategies. *Am J Gastroenterol*. 2003;98(12):2712-2718. doi:10.1111/j.1572-0241.2003.08674.x.

8. Song X, Gao X, Li M, et al. Clinical features and risk factors for primary surgery in 205 patients with Crohn's disease: analysis of a South China cohort. *Dis Colon Rectum*. 2011;54(9):1147-1154. doi:10.1097/DCR.0b013e318222ddc3.

9. Lunney PC, Kariyawasam VC, Wang RR, et al. Smoking prevalence and its influence on disease course and surgery in Crohn's disease and ulcerative colitis. *Aliment Pharmacol Ther*. 2015;42(1):61-70. doi:10.1111/apt.13239.

10. Cosnes J, Carbonnel F, Beaugerie L, Le Quintrec Y, Gendre J. Effects of cigarette smoking on the long-term course of Crohn's disease. *Gastroenterology*. 1996;110(2):424-431. doi:10.1053/gast.1996.v110.pm8566589.

11. Nunes T, Etchevers MJ, Domènech E, et al. Smoking does influence disease behaviour and impacts the need for therapy in Crohn's disease in the biologic era. *Aliment Pharmacol Ther*. 2013;38(7):752-760. doi:10.1111/apt.12440.

12. Lakatos PL, Vegh Z, Lovasz BD, et al. Is current smoking still an important environmental factor in inflammatory bowel diseases? Results from a population-based incident cohort. *Inflamm Bowel Dis*. 2013;19(5):1010-1017. doi:10.1097/MIB.0b013e3182802b3e.

13. Bernstein CN, Singh S, Graff L a, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol*. 2010;105(9):1994-2002. doi:10.1038/ajg.2010.140.

14. Solberg IC, Vatn MH, Høie O, et al. Clinical Course in Crohn's Disease: Results of a Norwegian Population-Based Ten-Year Follow-Up Study. *Clin Gastroenterol Hepatol*. 2007;5(12):1430-1438. doi:10.1016/j.cgh.2007.09.002.

15. Zabana Y, Garcia-Planella E, Van Domselaar M, et al. Does active smoking really influence the course of Crohn's disease? A retrospective observational study. *J Crohn's Colitis*. 2013;7(4):280-285. doi:10.1016/j.crohns.2012.03.020.

16. To N, Gracie DJ, Ford a C. Systematic review with meta-analysis: the adverse effect of tobacco smoking on the natural history of Crohn's disease. *Aliment Pharmacol Ther*. 2016:549-561. doi:10.1111/apt.13511.

17. Cosnes J, Beaugerie L, Carbonnel F, Gendre JP. Smoking cessation and the course of Crohn's disease: an intervention study. *Gastroenterology*. 2001;120(5):1093-1099. doi:10.1053/gast.2001.23231.

18. Nunes T, Etchevers MJ, García-Sánchez V, et al. Impact of Smoking Cessation on the Clinical Course of Crohn's Disease Under Current Therapeutic Algorithms: A Multicenter Prospective Study. *Am J Gastroenterol*. 2016;(November 2015):1-9. doi:10.1038/ajg.2015.401.

19. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015;44(3):827-836. doi:10.1093/ije/dyv098.

20. Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. *Pharmacoepidemiol Drug Saf*. 2002;11(3):211-218. doi:10.1002/pds.698.

21. Lewis JD, Bilker WB, Brensinger C, Deren JJ, Vaughn DJ, Strom BL. Inflammatory bowel disease is not associated with an increased risk of lymphoma. *Gastroenterology*. 2001;121(5):1080-1087. doi:10.1053/gast.2001.28703.

22. Lewis JD, Aberra FN, Lichtenstein GR, Bilker WB, Brensinger C, Strom BL. Seasonal Variation in Flares of Inflammatory Bowel Disease. *Gastroenterology*. 2004;126(3):665-673. doi:10.1053/j.gastro.2003.12.003.

23. Van Staal TP, Card T, Logan RF, et al. 5-Aminosalicylate use and colorectal cancer risk in inflammatory bowel disease: a large epidemiological study. *Gut*. 2005;54(11):1573-1578. doi:10.1136/gut.2005.070896.

24. Armstrong RG, West J, Card TR. Risk of cancer in inflammatory bowel disease treated with azathioprine: a UK population-based case-control study. *Am J Gastroenterol*. 2010;105(7):1604-1609. doi:10.1038/ajg.2009.745.

25. Boggon R, Timmis A, Hemingway H, Raju S, Malvestiti F, Van Staa T. Smoking cessation interventions following acute coronary syndrome: A missed opportunity? *Eur J Prev Cardiol*. 2014;21(6):767-773. doi:10.1177/2047487312460517.Smoking.

524 26. Dhalwani NN, Tata LJ, Coleman T, Fleming KM, Szatkowski L. Completeness of Maternal
525 Smoking Status Recording during Pregnancy in United Kingdom Primary Care Data. *PLoS One*.
526 2013;8(9). doi:10.1371/journal.pone.0072218.

527 27. Alonso A, Logroscino G, Jick SS, Hernán M a. Association of smoking with amyotrophic lateral
528 sclerosis risk and survival in men and women: a prospective study. *BMC Neurol*. 2010;10(1):6.
529 doi:10.1186/1471-2377-10-6.

530 28. Millett C, Gray J, Saxena S, Netuveli G, Majeed A. Impact of a pay-for-performance incentive
531 on support for smoking cessation and on smoking prevalence among people with diabetes.
532 *CMAJ*. 2007;176(12):1705-1710. doi:10.1503/cmaj.061556.

533 29. Chatu S, Saxena S, Subramanian V, et al. The Impact of Timing and Duration of Thiopurine
534 Treatment on First Intestinal Resection in Crohn's Disease: National UK Population-Based
535 Study 1989-2010. *Am J Gastroenterol*. 2014;109(3):409-416. doi:10.1038/ajg.2013.462.

536 30. Chhaya V, Saxena S, Cecil E, et al. The impact of timing and duration of thiopurine treatment
537 on colectomy in ulcerative colitis: a national population-based study of incident cases
538 between 1989-2009. *Aliment Pharmacol Ther*. 2015;41(1):87-98. doi:10.1111/apt.13017.

539 31. Chhaya V, Pollok RCG, Cecil E, et al. Impact of early thiopurines on surgery in 2770 children
540 and young people diagnosed with inflammatory bowel disease: a national population-based
541 study. *Aliment Pharmacol Ther*. 2015;42(8):990-999. doi:10.1111/apt.13361.

542 32. Chhaya V, Saxena S, Cecil E, et al. Impact of Timing and Duration of Thiopurine Treatment on
543 First Perianal Surgery in Crohn's Disease. *Inflamm Bowel Dis*. 2015;21(0):385-391.
544 doi:10.1097/MIB.0000000000000290.

545 33. Chhaya V, Saxena S, Cecil E, et al. Steroid dependency and trends in prescribing for
546 inflammatory bowel disease: a 20-year national population-based study. *Aliment Pharmacol*
547 *Ther*. 2016;44(5):482-494. doi:10.1111/apt.13700.

548 34. Booth H, Prevost A, Gulliford M. Validity of smoking prevalence estimates from primary care
549 electronic health records compared with national population survey data for England, 2007
550 to 2011. *Pharmacoepidemiol Drug Saf Dec;22(12)*. 2013;22(12):1357-1361.

551 35. Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission
552 in inflammatory bowel disease: a cohort study. *Lancet*. 2010;375(9715):657-663.
553 doi:10.1016/S0140-6736(09)61963-2.

554 36. Van Assche G, Dignass A, Reinisch W, et al. The second European evidence-based Consensus
555 on the diagnosis and management of Crohn's disease: Definitions and diagnosis. *J Crohn's*
556 *Colitis*. 2010;4(1):63-101. doi:10.1016/j.crohns.2009.09.009.

557 37. Gelbmann CM, Rogler G, Gross V, et al. Prior bowel resections, perianal disease, and a high
558 initial Crohn's Disease Activity Index are associated with corticosteroid resistance in active
559 Crohn's disease. *Am J Gastroenterol*. 2002;97(6):1438-1445. doi:10.1016/S0002-
560 9270(02)04041-8.

38. Brown P, Clark T, Dowson G, et al. Relationship of Body Mass Index to Clinical Outcomes after Infliximab Therapy in Patients with Crohn's Disease. *J Crohns Colitis*. 2016;10(10):1144-1150. doi:10.1093/ecco-jcc/jjw079. Epub 2016 Mar 19.

39. Do smoking rates vary between more and less advantaged areas? *Off Natl Stat*. www.ons.gov.uk/ons/rel/disability-and-health-measurement/do-smoking-rates-vary-between-more-and-less-advantaged-areas-/2012/sty-smoking-rates.html. Accessed February 28, 2017.

40. Teruel C, Garrido E, Mesonero F. Diagnosis and management of functional symptoms in inflammatory bowel disease in remission. *World J Gastrointest Pharmacol Ther*. 2016;Feb 6;7(1):78-90. doi:10.4292/wjgpt.v7.i1.78.

41. Audrain-McGovern J, Leventhal A, Strong D. The Role of Depression in the Uptake and Maintenance of Cigarette Smoking. *Int Rev Neurobiol*. 2015;124:209-243. doi:10.1016/bs.irn.2015.07.004.

42. Beaugerie L, Seksik P, Nion-Larmurier I, Gendre JP, Cosnes J. Predictors of crohn's disease. *Gastroenterology*. 2006;130(3):650-656. doi:10.1053/j.gastro.2005.12.019.

43. Alexakis C, Kumar S, Saxena S, Pollok R. Systematic review and meta-analysis: the impact of a depressive state on disease course in adult inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;(January):1-11. doi:10.1111/apt.14171.

44. Gomollón F, Dignass A, Annese V, et al. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management on behalf of ECCO. *J Crohn's Colitis*. 2016:1-23. doi:10.1093/ecco-jcc/jjw168.

45. Rutgeerts PJ. Review article : the limitations of corticosteroid therapy in Crohn ' s disease. *Ailm Pharmacol Ther*. 2001;15:1515-1525.

46. Lakatos PL, Czegledi Z, Szamosi T, et al. Perianal disease, small bowel disease, smoking, prior steroid or early azathioprine/biological therapy are predictors of disease behavior change in patients with Crohn's disease. *World J Gastroenterol*. 2009;15(28):3504-3510. doi:10.3748/wjg.15.3504.

47. Domènech E, Carrión S, Garcia-Planella E, et al. Smoking status and response to thiopurines in steroid-dependent inflammatory bowel disease. *Inflamm Bowel Dis*. 2011;17(4):971-975. doi:10.1002/ibd.21456.

48. Moon CM, Park DI, Kim ER, et al. Clinical features and predictors of clinical outcomes in Korean patients with Crohn's disease: a Korean association for the study of intestinal diseases multicenter study. *J Gastroenterol Hepatol*. 2014;29:74-82. doi:10.1111/jgh.12369 [doi].

49. Fidler J, Ferguson SG, Brown J, Stapleton J, West R. How does rate of smoking cessation vary by age, gender and social grade? Findings from a population survey in England. *Addiction*. 2013;108(9):1680-1685. doi:10.1111/add.12241.

50. Public Health England. Smoking prevalence in adults: Opinions and lifestyle survey 2014. 2014. http://content.digital.nhs.uk/catalogue/PUB20781/stat-smok-eng-2016-rep.pdf. Accessed May 17, 2017.

51. Elton P, Campbell P. Smoking prevalence in a north-west town following the introduction of Smoke-free England. *J Public Heal (Oxf) 2008 Dec;30(4)415-20*. 2008;30(415-20).

52. Ananthakrishnan AN. Environmental risk factors for inflammatory bowel disease. *Gastroenterol Hepatol (N Y)*. 2013;9(6):367-374. http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=3736793&tool=pmcentrez&rendertype=abstract.

53. Van den Elsen LW, Poyntz HC, Weyrich LS, Young W, Forbes-Blom EE. Embracing the gut microbiota: the new frontier for inflammatory and infectious diseases. *Clin Transl Immunol*. 2017;6(1):e125. doi:10.1038/cti.2016.91.

54. Benjamin JL, Hedin CRH, Koutsoumpas A, et al. Smokers with active Crohn's disease have a clinically relevant dysbiosis of the gastrointestinal microbiota. *Inflamm Bowel Dis*. 2012;18(6):1092-1100. doi:10.1002/ibd.21864.

55. Eliakim R, Fan QX, Babyatsky MW. Chronic nicotine administration differentially alters jejunal and colonic inflammation in interleukin-10 deficient mice. *Eur J Gastroenterol Hepatol*. 2002;14(6):607-614. doi:10.1097/00042737-200206000-00005.

56. Bergeron V, Grondin V, Rajca S, et al. Current smoking differentially affects blood mononuclear cells from patients with Crohn's disease and ulcerative colitis: relevance to its adverse role in the disease. *Inflamm Bowel Dis*. 2012;18(6):1101-1111. doi:10.1002/ibd.21889.

57. Zuo L, Li Y, Wang H, et al. Cigarette smoking is associated with intestinal barrier dysfunction in the small intestine but not in the large intestine of mice. *J Crohn's Colitis*. 2014;8(12):1710-1722. doi:10.1016/j.crohns.2014.08.008.

58. Narula N, Fedorak RN. Does smoking reduce infliximab's effectiveness against Crohn's disease? *Can J Gastroenterol*. 2009;23(2):121-125.

59. Warren J, Falster M, Fox D, Jorm L. Factors influencing adherence in long-term use of statins. *Pharmacoepidemiol Drug Saf*. 2013;22(12):1298-1307.

60. Lewis JD, Brensinger C. Agreement between GPRD smoking data: A survey of general practitioners and a population-based survey. *Pharmacoepidemiol Drug Saf*. 2004;13(7):437-441. doi:10.1002/pds.902.

61. Bardhan KD, Simmonds N, Royston C, Dhar a., Edwards CM. A United Kingdom inflammatory bowel disease database: Making the effort worthwhile. *J Crohn's Colitis*. 2010;4(4):405-412. doi:10.1016/j.crohns.2010.01.003.

62. Royal College of Physicians. National clinical audit of biological therapies - UK Inflammatory Bowel Disease (IBD) audit. 2015;(September). https://www.rcplondon.ac.uk/projects/outputs/national-clinical-audit-report-biological-therapies-adult-report-2015. Accessed March 3, 2017.

63. De Bie C, Ballet V, Hendriks N, et al. Smoking behaviour and knowledge of the health effects of smoking in patients with inflammatory bowel disease. *Aliment Pharmacol Ther*. 2015;42(11-12):1294-1302. doi:10.1111/apt.13423.

64. Ducharme-Bénard S, Côté-Daigneault J, Lemoyne M, et al. Patients With Inflammatory Bowel Disease Are Unaware of the Impact of Smoking on Their Disease. *J Clin Gastroenterol*. 2016;50(6):490-497. doi:26196475.

65. Nunes T, Etchevers MJ, Merino O, et al. High smoking cessation rate in Crohn's disease patients after physician advice - The TABACROHN Study. *J Crohn's Colitis*. 2013;7(3):202-207. doi:10.1016/j.crohns.2012.04.011.

66. Song E, Kim G, Seo M, et al. Assessment of factors associated with smoking cessation at diagnosis or during follow-up of Crohn's disease. *J Gastroenterol Hepatol*. 2017;5(26).

67. Coward S, Heitman S, Clement F, et al. Funding a smoking cessation program for Crohn's disease: an economic evaluation. *Am J Gastroenterol 2015 Mar;110(3)368-77*. 2015;110(3):368-377.

68. Bernert JJ, McGuffey J, Morrison M, Pirkle J. Comparison of serum and salivary cotinine measurements by a sensitive high-performance liquid chromatography-tandem mass spectrometry method as an indicator of exposure to tobacco smoke among smokers and nonsmokers. *J Anal Toxicol*. 2000;24(5):333-339.

Table and figure legends

Figure 1:

IBD - inflammatory bowel disease

CPRD - Clinical Practice Research Datalink

UTS - Up to Standard

QOF - UK Quality Outcomes and Framework introduced to GPs in 2004

UC - Ulcerative Colitis

CD - Crohn's disease

Figure 2:

Bar height indicate % of smokers at CD diagnosis by each age category. Actual number of smokers in each group displayed in base of individual bars.

* p=0.02 for across era comparison for proportion of smokers at CD diagnosis in Montreal A2 category. No significant differences in A1 or A3 categories across era. Note in Era 1 and Era 5, there were no smokers in the A1 group.

Era 1: 2005-06 (inclusive), Era 2: 2007-08, Era 3: 2009-10, Era 4: 2001-12, Era 5: 2013-14

A1 - age at diagnosis <17 years

A2 - age at diagnosis 17-40 years

A3 - age at diagnosis >40 years

Figure 3:

CS - corticosteroid **IBD** - inflammatory bowel disease **CD** - Crohn's disease

Figure 4:

IBD - inflammatory bowel disease **CD** - Crohn's disease

Table 1:

a - Age at diagnosis categories as per Montreal classification (A1 <17 years, A2 17-40, A3 >40 years)

b - BMI (Body Mass index) - calculated as the closest BMI recording within one year of Crohn's diagnosis. Data available for 58% of patients

c - IMD (Index of Multiple Deprivation)

d - IBS (Irritable Bowel Syndrome) - co-diagnosis considered as any patient with a defined Read code for IBS in records

e - Co-diagnosis of depression considered if patient had any Read code for depressive illness in CPRD record

f - BI (Beaugerie index) - BI score of 2 or more associated with disabling disease course. Please see methodology for detailed description of the indices

Table 2:

* a steroid flare was considered as the first steroid prescription (after a Crohn's diagnosis) and any other prescription for oral steroids following a 4 month time free of steroid prescription

** 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 months

Table 3:

Multivariate analysis includes all covariates of univariate analysis. Only significant hazard ratios shown for multivariate analysis

HR - Hazard ratio **CI** - Confidence Interval **IBD** - Inflammatory Bowel Disease **BMI** - Body Mass Index **IMD** - index of multiple depravity **IBS** - irritable bowel syndrome **5-ASA** - 5-aminosalicylates **TP** - Thiopurine **BI** - Beaugerie Index

a - smoker at diagnosis defined as any patient with Read codes for active smoking within the year preceding IBD diagnosis

b - Age categories as per Montreal classification (A1 <17 years, A2 17-40, A3 >40 years)

c - Era 1: 2005-06 (inclusive), Era 2: 2007-08, Era 3: 2009-10, Era 4: 2011-12, Era 5: 2013-14

d - calculated as the closest recorded BMI to date of IBD diagnosis, one year either side of IBD diagnosis

e - IMD upper includes IMD categories 1 and 2 (versus IMD category 3,4 and 5)

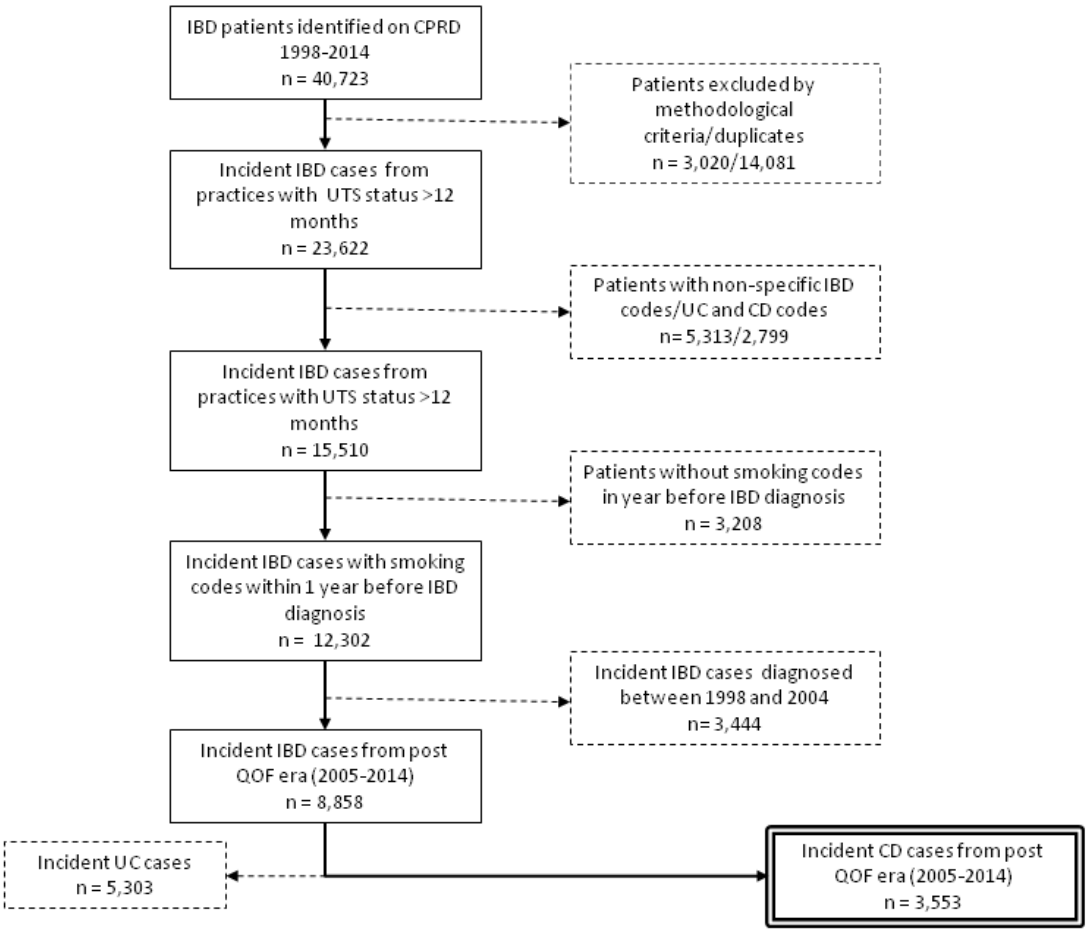
f - IBS co-diagnosis defined as any patient with a Read code for IBS before or after IBD diagnosis. Depression defined as any patient with a Read code for depression before or after IBD diagnosis

g - exposure of 5-ASA or TP medications defined as any patients with at least one or more prescription for either 5-ASA of TP after IBD diagnosis

h - BI 2+ - Beaugerie Index score of 2+ - please refer to methodology for exact details of these definitions

Figures

Figure 1: schematic of cohort construction for incident cases of Crohn's disease



IBD - inflammatory bowel disease

CPRD - Clinical Practice Research Datalink

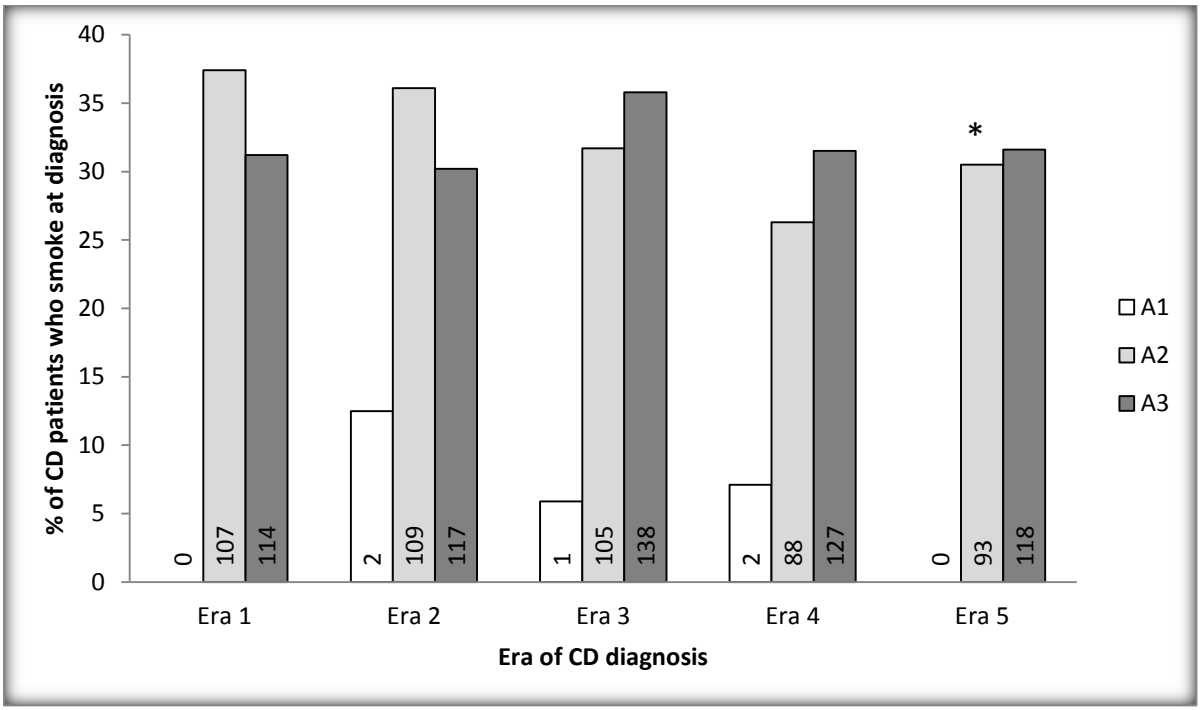
UTS - Up to Standard

QOF - UK Quality Outcomes and Framework introduced to GPs in 2004

UC - Ulcerative Colitis

CD - Crohn's disease

Figure 2: Smoking prevalence at diagnosis of CD patients by Montreal age category and year of CD diagnosis



Bar height indicate % of smokers at CD diagnosis by each age category. Actual number of smokers in each group displayed in base of individual bars.

* p=0.02 for across era comparison for proportion of smokers at CD diagnosis in Montreal A2 category. No significant differences in A1 or A3 categories across era.. Note in Era 1 and Era 5, there were no smokers in the A1 group.

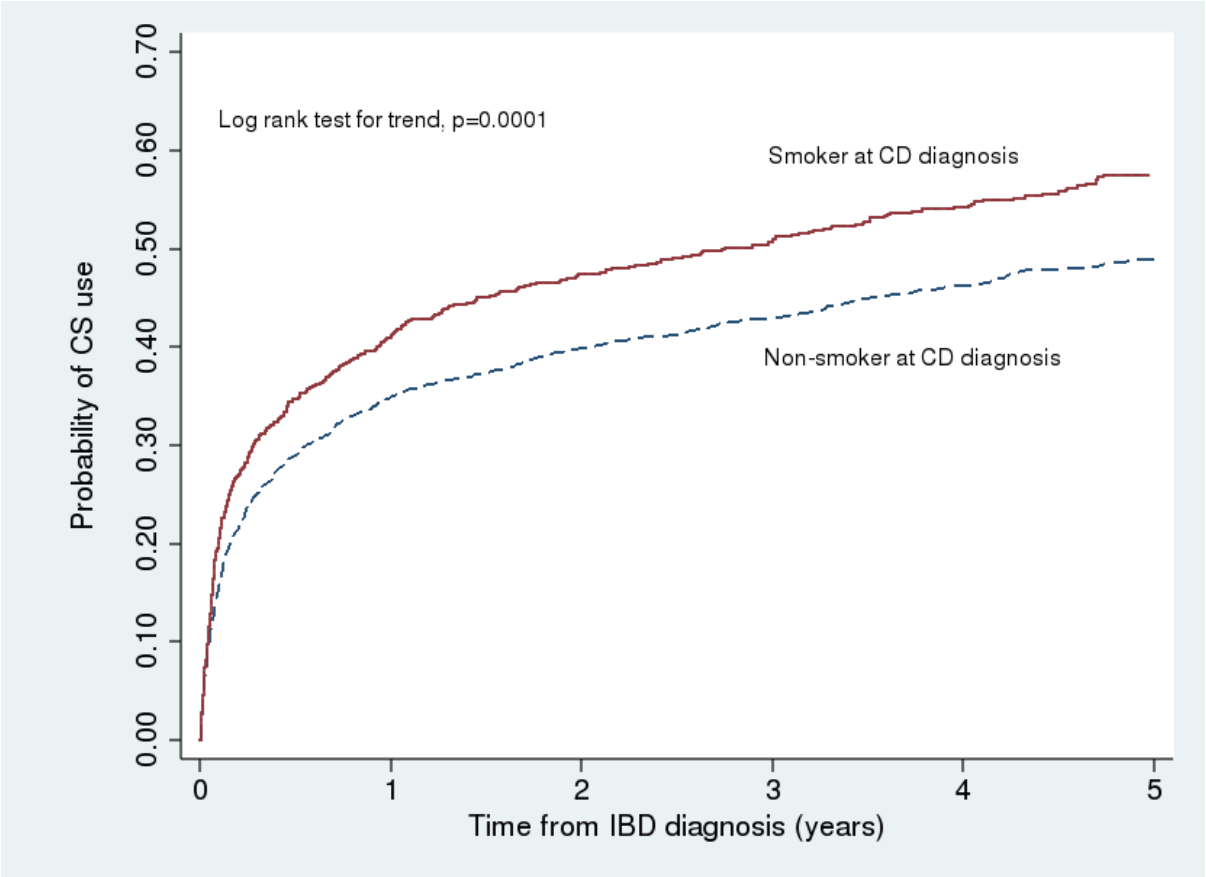
Era 1: 2005-06 (inclusive), Era 2: 2007-08, Era 3: 2009-10, Era 4: 2001-12, Era 5: 2013-14

A1 - age at diagnosis <17 years

A2 - age at diagnosis 17-40 years

A3 - age at diagnosis >40 years

736 **Figure 3: KM curves showing probability of oral CS exposure in patients with Crohn's disease given**
737 **diagnosis smoking status**

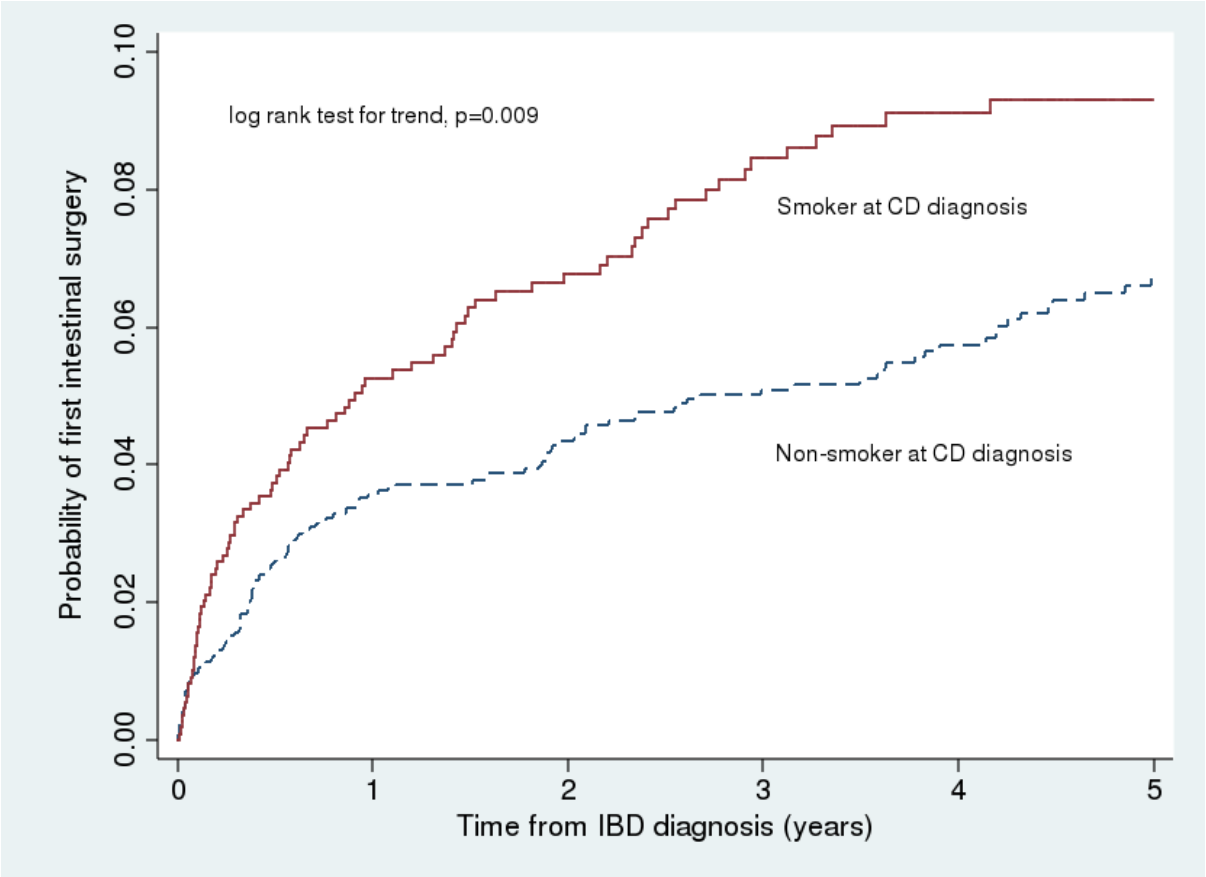


738

739 **CS** - corticosteroid **IBD** - inflammatory bowel disease **CD** - Crohn's disease

740

741 **Figure 4: KM curves showing probability of first intestinal surgery in patients with Crohn's disease**
742 **given diagnosis smoking status**

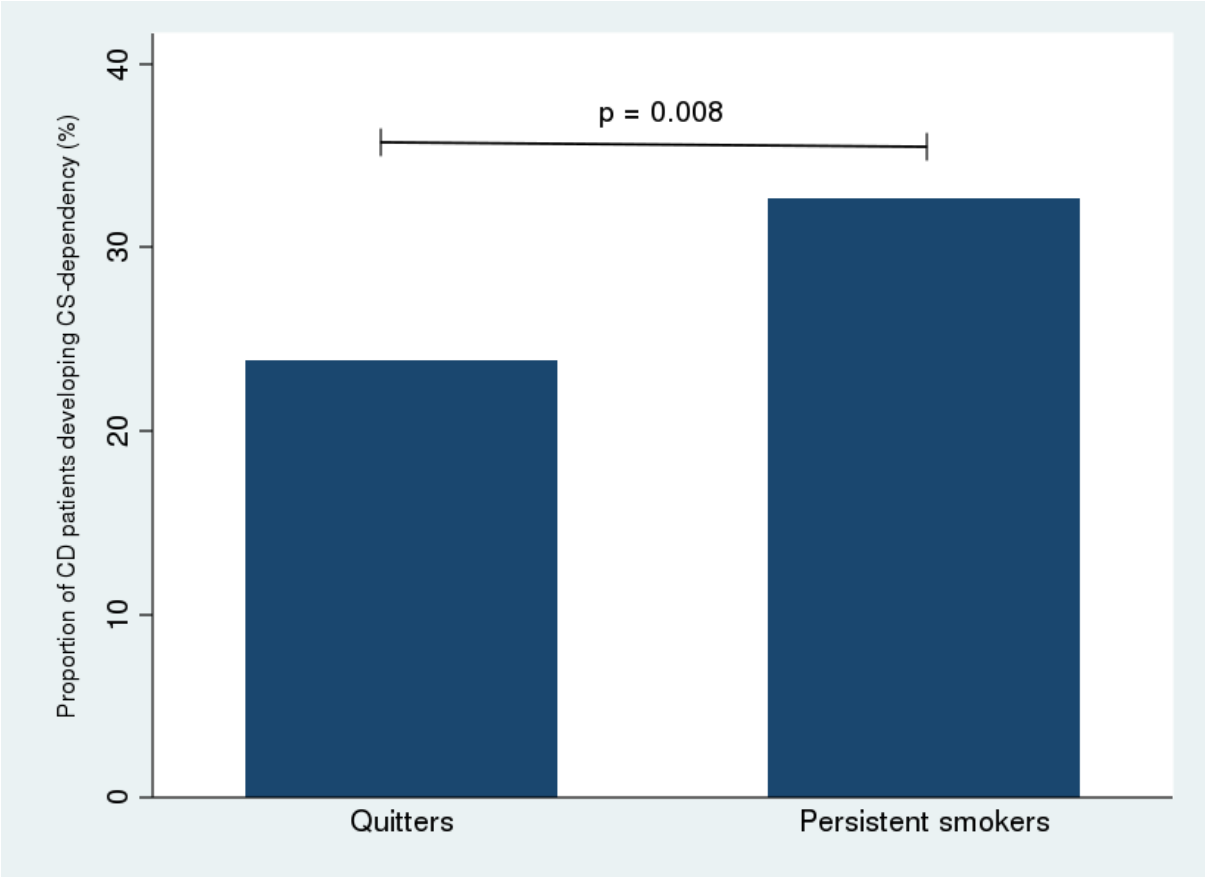


743

744 **IBD** - inflammatory bowel disease **CD** - Crohn's disease

745

Figure 5: Bar chart comparing CS-dependency between quitters and persistent smokers amongst patients with CD

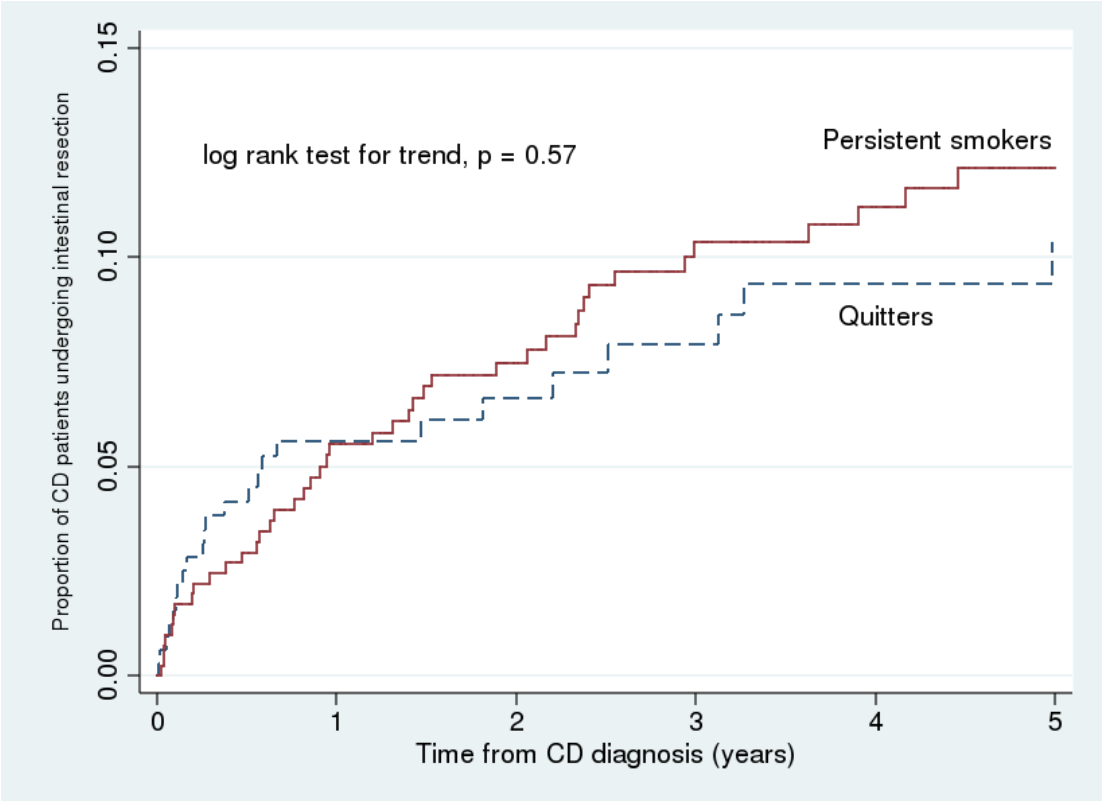


legend:

Quitters - CD patients who were smokers at diagnosis but had subsequent Read codes in the two years following diagnosis indicating they were ex or non-smokers

Persistent smokers - CD patients who were smokers at diagnosis and had subsequent Read codes in the two years following diagnosis indicating they were still smokers

Figure 6: KM curves showing probability of first intestinal surgery in patients with Crohn's disease: 'quitters' versus 'persistent smokers'



legend:

Quitters - CD patients who were smokers at diagnosis but had subsequent Read codes in the two years following diagnosis indicating they were ex or non-smokers

Persistent smokers - CD patients who were smokers at diagnosis and had subsequent Read codes in the two years following diagnosis indicating they were still smokers

Tables

Table 1: baseline characteristics of cohort

	Smoker at Crohn's diagnosis (n=1121)	Non-smoker at Crohn's diagnosis (n=2432)	p-value
Sex			
% male	42.5	47.0	**0.01**
Age at diagnosis[a] (%)			
A1	0.5	3.2	**<0.0001**
A2	44.8	43.4	0.45
A3	54.8	53.4	0.44
BMI category at diagnosis[b] (%)			
Underweight	7.2	7.3	0.93
Normal	45.8	44.5	0.57
Overweight	29.5	29.0	0.80
Obese	17.4	19.2	0.33
Social deprivation[c] (%)			
IMD 1	13.6	25.3	**<0.0001**
IMD 2	21.2	23.2	0.34
IMD 3	21.8	19.5	0.22
IMD 4	23.8	18.2	**0.003**
IMD 5	19.5	13.7	**0.001**
Comorbidities (%)			
IBS[d]	19.4	18.4	0.51
Depression[e]	11.3	7.1	**<0.0001**
Severity indices[f] (%)			
BI score 0	37.7	39.4	
1	42.7	43.9	0.27
2	19.3	16.6	
3	0.3	0.2	

a - Age at diagnosis categories as per Montreal classification (A1 <17 years, A2 17-40, A3 >40 years)

b - BMI (Body Mass index) - calculated as the closest BMI recording within one year of Crohn's diagnosis. Data available for 58% of patients

c - IMD (Index of Multiple Deprivation)

d - IBS (Irritable Bowel Syndrome) - co-diagnosis considered as any patient with a defined Read code for IBS in records

e - Co-diagnosis of depression considered if patient had any Read code for depressive illness in CPRD record

f - BI (Beaugerie index) - BI score of 2 or more associated with disabling disease course. Please see methodology for detailed description of the indices

Table 2: Steroid flares and steroid dependency in patients with Crohn's disease by smoking status at diagnosis

	smoker at diagnosis	non-smoker at diagnosis	p-value
flares/year*(%)			
0	42.9	51.4	**<0.0001**
0-1	47.8	42.7	**0.004**
>1	9.3	6.0	**<0.0001**
steroid dependency(%)**	27.4	20.8	**<0.0001**

* a steroid flare was considered as the first steroid prescription (after a Crohn's diagnosis) and any other prescription for oral steroids following a 4 month time free of steroid prescription

** 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 months

Table 3: Univariate and multivariate Cox regression analysis for risk of intestinal surgery in patients with Crohn's disease

	univariate analysis n=3553			multivariate analysis n=3553		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
Smoking status at diagnosis[a]						
Smoker	1.42	1.09-1.86	**0.01**	1.64	1.06-2.52	**0.02**
Sex						
(ref to female)	0.78	0.59-1.01	0.07	-	-	-
Age at IBD diagnosis[b]						
A1	1	-	**-**	-	-	-
A2	0.56	0.30-1.03	0.06	-	-	-
A3	0.34	0.18-0.64	**0.001**	-	-	-
Era of IBD diagnosis[c]						
Era 1	1	-	-	-	-	-
Era 2	1.18	0.82-1.71	0.37	-	-	-
Era 3	0.88	0.59-1.32	0.54	-	-	-
Era 4	0.98	0.65-1.48	0.91	-	-	-
Era 5	0.70	0.40-1.21	0.23	-	-	-
BMI category[d]						
Underweight	0.99	0.54-1.81	0.97	-	-	-
Normal	1	-	-	-	-	-
Overweight	0.67	0.45-1.00	0.06	-	-	-
Obese	0.70	0.44-1.11	0.13	-	-	-
Social deprivation[e]						
IMD upper	0.91	0.64-1.28	0.57	-	-	-
Co-morbidities[f]						
IBS	1.13	0.82-1.55	0.47	-	-	-
Depression	0.98	0.60-1.59	0.93	-	-	-
IBD medication[g]						
5-ASA	0.95	0.73-1.2	0.68	-	-	-
TP	2.64	2.03-3.44	**<0.0001**	2.72	1.73-4.29	**<0.0001**
Severity Indices[h]						
MBI 2+	1.94	1.45-2.59	**<0.0001**	-	-	-

Multivariate analysis includes all covariates of univariate analysis. Only significant hazard ratios shown for multivariate analysis

HR - Hazard ratio **CI** - Confidence Interval **IBD** - Inflammatory Bowel Disease **BMI** - Body Mass Index **IMD** - index of multiple depravity **IBS** - irritable bowel syndrome **5-ASA** - 5-aminosalicylates **TP** - Thiopurine **BI** - Beaugerie Index

a - smoker at diagnosis defined as any patient with Read codes for active smoking within the year preceding IBD diagnosis

b - Age categories as per Montreal classification (A1 <17 years, A2 17-40, A3 >40 years)

c - Era 1: 2005-06 (inclusive), Era 2: 2007-08, Era 3: 2009-10, Era 4: 2011-12, Era 5: 2013-14

d - calculated as the closest recorded BMI to date of IBD diagnosis, one year either side of IBD diagnosis

e - IMD upper includes IMD categories 1 and 2 (versus IMD category 3,4 and 5)

f - IBS co-diagnosis defined as any patient with a Read code for IBS before or after IBD diagnosis. Depression defined as any patient with a Read code for depression before or after IBD diagnosis

g - exposure of 5-ASA or TP medications defined as any patients with at least one or more prescription for either 5-ASA of TP after IBD diagnosis

h - BI 2+ - Beaugerie Index score of 2+ - please refer to methodology for exact details of these definitions