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Sources of excess steroid prescriptions and clinical adverse outcomes associated with steroid excess in patients with inflammatory bowel disease: The Leeds IBD Steroids study

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Summary

Background: Corticosteroids remain important for managing inflammatory bowel disease (IBD) flares. Steroid excess, however, may be a marker of poor care. Patients access steroid prescriptions from primary (General Practitioners [GP]) or secondary care (hospital-based). Sources of prescriptions and associated outcomes are not well described.

Methods: Patients attending IBD clinics with linked primary care information were included. We examined appropriateness and timeliness of treatment escalation and avoidability of steroid excess in relation to prescription sources.

Results: Of 2246 patients, 33% were exposed to steroids over 2 years. Primary care issued 28% of prescriptions. Secondary care prescriptions were more often of appropriate dose and duration (85% vs 41%, $p < 0.001$). Further flares occurred in 50% of patients prescribed steroids from primary care (vs 39%; $p = 0.003$).

Steroid excess was observed in 15%. Patients with steroid excess who received prescriptions from primary care that were not communicated to secondary care less often received timely treatment escalation (49% vs 66%, $p = 0.042$) and steroid excess was more often avoidable (73% vs 56%, $p = 0.022$).

Patients with steroid excess had higher risks of hospitalisation for IBD (OR = 12.33, 95% CI [8.89–17.11]), hospitalisation for infections (OR = 2.89, 95% CI [1.82–4.61]) and GP prescribed antibiotics (OR = 1.41, 95% CI [1.07–1.86]).

Conclusion: Patients commonly access steroids through primary care, but doses and durations are frequently inappropriate with patients more likely to flare. Steroid excess was associated with IBD admissions, admissions for infections and antibiotic prescriptions. Improved liaison between primary and secondary care is required to reduce steroid excess.

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1 | INTRODUCTION

Corticosteroids are considered a cornerstone in the management of disease flares of patients with inflammatory bowel disease (IBD); yet have no efficacy in the maintenance of remission.[1] Moreover, corticosteroids are well known to have significant short- and long-term side effects,[2] leading both the British Society of Gastroenterology (BSG) and the European Crohn's and Colitis Organisations (ECCO) guidelines to clearly define steroid-dependent disease and advise treatment escalation for all steroid-dependent patients.[3–5]

It has previously been demonstrated that patients with IBD may be exposed to steroids each year, with figures of around 30% reported in several studies.[6–9] Furthermore, a UK-based study suggested that 13.8% of patients with IBD are steroid dependent or receive steroid courses in excess of guideline recommendations.[7] Previously, we demonstrated that in a UK IBD cohort almost half of instances of steroid excess (49%) were potentially avoidable.[7]

IBD is a complex disease with increasing treatment options that are most often managed most appropriately in secondary care. Nevertheless, for patients living with IBD, primary care practitioners (General Practitioners [GP]) play an important contribution to their ongoing healthcare. Flares requiring the use of steroids should lead to reassessment of the overall IBD disease activity and treatment with a view to optimising maintenance treatment. Steroid prescriptions from primary care may not always be accompanied by appropriate disease reassessment or communicated to the secondary care team (hospital-based). Additionally, prescriptions for steroids may be given for inappropriate doses or durations. The interface between primary and secondary care at the time of IBD flares is therefore critical to understand but has not been robustly investigated since, to date, studies have mostly concentrated on examining primary care or secondary care only.[6,7,10]

The aim of this retrospective study is to determine steroid prescription practice comprehensively across primary and secondary care using hospital and linked community healthcare databases. We aim to identify the origins of all steroid prescription within a IBD cohort using primary and secondary care data sources and assess the proportion of primary care steroid prescriptions communicated to secondary care. Finally, we aim to assess the outcomes associated with excessive or inappropriate steroid use.

2 | MATERIALS AND METHODS

2.1 | Study cohort

The study cohort consists of all patients with IBD who underwent follow-up at Leeds Teaching Hospitals, UK during the 2-year period 1 January 2016 to 31 December 2017. The diagnosis of IBD was confirmed based on international accepted criteria including endoscopy, histology and radiology.[3] Patients who were incorrectly coded to have a diagnosis of IBD were excluded from the study. Patients with a primary address outside the Leeds secondary care catchment area and those whose GP practice had not joined the combined Leeds Health care record were excluded from the study in order to ensure complete data sets were obtained for all patients (Figure 1).

2.2 | Data extraction

Patient demographics, disease and treatment characteristics, outpatient resource utilisation and steroid prescription data were all extracted from the hospital electronic health record, along with linked primary care information. Community-based prescriptions were extracted from the linked primary care information, which includes electronic capture of all prescriptions issued from primary care, and hospital-based prescriptions were extracted from computerised outpatient hospital pharmacy records as well as the clinical information in the clinic letters recorded electronically after each consultation. Steroid excess was defined based on the ECCO

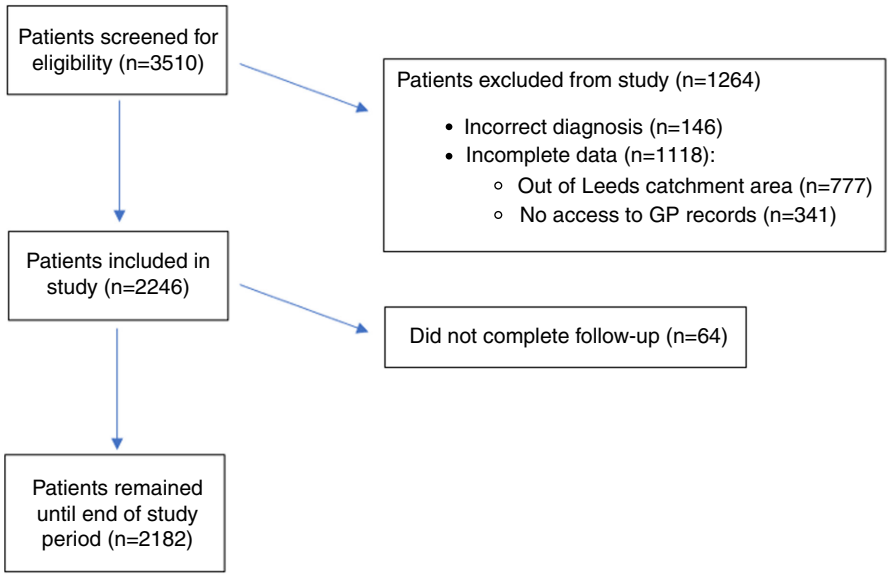

FIGURE 1 Study flow chart

guidelines as: a) more than one course of steroids in 12 months' period, b) more than two courses of steroids in 24 months' period or c) need for steroids for more than 2 consecutive months in 12 months' period. We also aimed at determining whether any steroid prescription originating from primary care was of appropriate dose and duration and communicated to secondary care (see Supplementary data for definitions).

In cases of steroid excess, the Charlson Comorbidity Index was calculated, and all records for these cases were reviewed critically to determine whether the excess was due to IBD or not, if escalation was implemented, the type of escalation, appropriateness (based on BSG and ECCO guidelines) and timeliness (escalation not considered timely if implemented >6 weeks after steroid course). Steroid excess avoidability was assessed according to previously published expert consensus definitions.[7]

2.3 | Outcomes

The primary outcome was to identify the percentage of steroid prescriptions of correct dose and duration issued from primary compared to prescriptions from secondary care.

Secondary outcomes included determining the total steroid exposure in the study cohort, the percentage of primary care steroid prescription the IBD secondary team was aware off, the percentage of patients with appropriate treatment escalation in patients with steroid excess in this cohort and the percentage of patients experiencing negative outcomes (need for additional steroids, hospitalisation, need for treatment escalation more than 3 months after steroid use, stratified by steroid excess).

2.4 | Statistical analysis

Descriptive statistics are reported as median or proportions. Categorical data were compared between groups using the chi-squared test, whereas the independent samples *t*-test or Mann–Whitney *U* test was used for continuous variables. Odds ratios were calculated for hospital admissions for IBD and infections as well as courses of antibiotics prescribed by GP for patients with steroid exposure and steroid excess. *p*-values were adjusted for multiplicity using the Benjamini–Hochberg approach with false discovery rate set to 5%. Differences were considered statistically significant if $p < 0.05$. IBM SPSS version 25 (IBM Corp.) was used for statistical analysis.

3 | RESULTS

3.1 | Overall cohort

Our study cohort consisted of 2246 patients (Table 1). Median age at study entry was 46 years, ranging from 16 to 94 years. Forty-eight per cent of patients were male and 97% of patients remained in the cohort until the end of the study period.

Baseline characteristics, medications and resource utilisation of the study cohort are shown in Table 1. During the study period, 19%

TABLE 1 Overall cohort

Age (median, IQR)	46 y	33-61 y
Gender (*N*, %)		
Male	1068/2246	48
Female	1178/2246	52
Diagnosis (*N*, %)		
UC	1051/2246	47
CD	1042/2246	46
IBD-U	153/2246	7
UC distribution (*N*, %)		
E1	270/1051	26
E2	456/1051	44
E3	310/1051	30
CD distribution (*N*, %)		
L1	305/1042	29
L2	332/1042	32
L3	397/1042	38
+Perianal	165/1042	16
CD behaviour (*N*, %)		
Inflammatory	581/1042	56
Stricturing	272/1042	26
Penetrating	180/1042	18
Medications (*N*, %)	UC	CD
5-ASA	806/1051, 79	209/1042, 20
Thiopurines	225/1051, 21	376/1042, 36
Infliximab	29/1051, 3	125/1042, 12
Adalimumab	19/1051, 2	138/1042, 13
Vedolizumab	10/1051, 1	9/1042, 1
Change in medication	202/1051, 19	258/1042, 25
Service utilisation (Median, IQR)		
Contacts with IBD clinic	3	2–5
Contacts with IBD Helpline	0	0–1
Contacts with GP	7	3–12
Hospital admissions for IBD	0	0–0
Hospital admissions for infections	0	0–0
Courses of antibiotics prescribed by GP	0	0–2
Investigations (Median, IQR)		
Colonoscopies	0	0–0
Surveillance colonoscopies	0	0–0
Sigmoidoscopies	0	0–0
CT scans	0	0–0
MRI scans	0	0–0

of all patients with ulcerative colitis (UC) and one quarter of patients with Crohn's disease (CD) had changes in their medication.

3.2 | Patients with steroid exposure

During the study period, 33% of patients were exposed to steroids, compared to 67% who did not have any courses of steroids (Table 2). Among the patients who had steroids, 51% had only one course, with a median of 1 (range 1–15).

Prednisolone was prescribed in 88% of all steroid courses with the percentage being 11 and 1 for Budesonide and Budesonide MMX respectively. Twenty-eight per cent of prescriptions with an IBD indication originated from primary care, with the rest issued by secondary dare (see Table 2).

There was a statistically significant difference observed among the proportion of prescriptions issued for IBD with appropriate dose and duration when comparing prescriptions originating from primary care to prescriptions from secondary care; 85% of prescriptions from secondary care were of appropriate dose and duration (definitions displayed in Supplementary material) compared to 41% of prescriptions from primary care, $p < 0.001$. Among prescriptions issued by primary care for IBD, the secondary care team was made aware within 6 weeks of steroid initiation in 60% of instances. Thirty-three per cent of steroid courses originating in primary care were not communicated to secondary care at all, and 7% only later than 6 weeks from initiation. Finally, a statistically significant difference was observed in the proportion of patients who flared within 3 months of a steroid course with 50% of patients flaring after being prescribed steroids for their IBD from primary care, compared to 39% of those prescribed from secondary care ($p = 0.003$).

TABLE 2 Patients with steroid exposure

Steroid exposure (%)		
Yes	33	
No	67	
Steroid prescribed (%)		
Prednisolone	88	
Budesonide	11	
Cortiment®	1	
Steroid courses (Median, range)	1, 1–15	
Prescriptions of appropriate dose and duration (%)		
From primary care	41	$p < 0.001$
From secondary care	85	
Flared within 3 months (%)		
Prescription from primary care	50	$p = 0.003$
Prescription from secondary care	39	
Issued for IBD (%)		
Yes	77	
No	22	
Originating from (%)		
Primary care	28	
IBD clinic	48	
IBD Helpline	6	
After admission	18	
Steroids prescribed by primary care, IBD aware (%)		
Within 6 weeks	60	
Later than 6 weeks	7	
Not aware	33	

3.3 | Comparison of patients with steroid exposure to patients without steroid exposure

Groups of patients with and without steroid exposure differed significantly in age and disease distribution (Table 3), with patients exposed to steroids tending to be older and with more limited disease. Patients with exposure to steroids were more likely to undergo medication adjustment (UC: 37% of steroid exposed vs 11% of not exposed, $p < 0.001$; CD: 43% of steroid exposed vs 16% of not exposed, $p < 0.001$).

Patients with steroid exposure had significantly more contacts with the IBD Clinic (Median: 5 vs 3, $p < 0.001$), the IBD Helpline (Median: 1 vs 0, $p < 0.001$) and the GP (Median: 10 vs 6, $p < 0.001$) when compared to patients without steroid exposure. Moreover, there was a significant difference in the odds of requiring one or more admissions for IBD (OR = 6.14, 95% CI [4.73–7.98]), one or more admissions for infections (OR = 2.48, 95% CI [1.76–3.51]) and one or more courses of antibiotics prescribed by their GP (OR = 1.71, 95% CI [1.43–2.05]) when comparing patients with steroid exposure to the steroid naïve group. Finally, patients in the steroid exposed group had statistically more investigations compared to those not exposed to steroids, apart from surveillance colonoscopies and MRI scans where a difference was not observed (Table 4).

3.4 | Patients with steroid excess

Overall, steroid excess was observed in 15% of patients (Table 5) with a median Charlson Comorbidity Index of 0 (range 0–8). Steroid excess was related to reasons other than IBD in around one quarter of patients (24%), whereas steroid excess was related to IBD in 76% of patients in the study cohort.

When examining the subset of patients with steroid excess due to their IBD, we found that excess was acted upon in 83% of patients. Escalation decisions were considered appropriate on review in the majority of patients (99%). However, escalation was timely (definition in Supplementary material) in less than two thirds of patients (62%). Moreover, the analysis of data stratified according to

TABLE 3 Not steroid exposed, steroid exposed and steroid excess due to IBD group characteristics

	Not steroid exposed	Steroid exposed	Adj. *p*-values	Steroid excess due to IBD	Adj. *p*-values
Age (Median, y)	47	42	0.002	37	0.002
Diagnosis (%)					
UC	47	46	0.82	46	0.838
CD	47	45	0.505	45	0.693
IBD-U	6	9	0.031	9	0.136
UC extent (%)					
E1	30	16	$p < 0.001$	11	$p < 0.001$
E2	40	50		53	
E3	30	34		36	
CD distribution (%)					
L1	29	30	$p = 0.869$	29	$p = 0.703$
L2	32	32		36	
L3	39	38		35	
+perianal	16	17	0.769	23	0.079
CD behaviour (%)					
Inflammatory	55	58	$p = 0.01$	59	$p = 0.022$
Stricturing	25	30		32	
Penetrating	20	12		9	
Medications UC (%)					
5-ASA	76	79	0.34	77	0.855
Thiopurines	18	29	0.007	30	0.004
Infliximab	1	7	0.006	13	0.003
Adalimumab	1	4	0.007	4	0.007
Vedolizumab	0	2	0.005	4	0.003
Change in medication	11	37	0.005	55	0.004
Medications CD (%)					
5-ASA	20	19	0.77	20	0.992
Thiopurines	38	32	0.12	38	0.955
Infliximab	14	9	0.027	7	0.097
Adalimumab	14	12	0.528	13	0.83
Vedolizumab	0	2	0.04	4	0.004
Change in medication	16	43	0.003	58	0.004

communication of steroid prescriptions from primary to secondary care demonstrated that patients in whom one or more prescriptions from primary care were not communicated to secondary care were more likely not to have timely escalation of their medication compared to patients where secondary care team was aware of all steroid courses (49% vs 66%, $p = 0.042$). Finally, steroid excess was unavoidable in less than half of the patients (48%), whereas in 27% it could probably be avoided and in 25% of patients excess was preventable. More interestingly, on reviewing patients with steroid excess, the excess in patients with one or more courses of steroids not known to the secondary care team was more likely to be considered preventable or probably preventable, compared to patients where all steroid courses prescribed prom primary care were communicated timely to secondary care (73% vs 56%, $p = 0.022$).

3.5 | Comparison of patients with steroid excess due to IBD to patients without steroid exposure

Patients with steroid excess due to their IBD were more likely to be younger than steroid naïve patients and, with regard to UC, have more extensive disease (Table 3). Moreover, a higher percentage of patients with steroid excess had change in treatment during the study period (UC: 55% in the steroid excess group vs 11% in the

TABLE 4 Contacts with the service, admissions, antibiotic courses, investigations

	Not steroid exposed	Steroid exposed	Adj. *p*-values	Steroid excess due to IBD	Adj. *p*-values
Contacts with IBD Clinic (Median, Range)	3 (0–20)	5 (0–21)	0.003	6 (1–21)	0.006
Contacts with IBD Helpline (Median, Range)	0 (0–16)	1 (0–21)	0.003	2 (0–18)	0.008
Contacts with GP (Median, Range)	6 (0–75)	10 (0–48)	0.003	10 (0–48)	0.01
≥1 Hospital admissions for IBD (OR, 95% CI)		6.14, [4.73–7.98]		12.33, [8.89–17.11]	
≥1 Hospital admissions for infections (OR, 95% CI)		2.48, [1.76–3.51]		2.89, [1.82–4.61]	
≥1 Courses of antibiotics prescribed by GP (OR, 95% CI)		1.71, [1.43–2.05]		1.41, [1.07–1.86]	
Investigations					
Colonoscopy (Median, Range)	0 (0–3)	0 (0–4)	0.002	0 (0–4)	0.013
Surveillance Colonoscopy (Median, Range)	0 (0–4)	0 (0–3)	0.128	0 (0–2)	0.525
Sigmoidoscopy (Median, Range)	0 (0–3)	0 (0–3)	0.002	1 (0–3)	0.017
CT scan (Median, Range)	0 (0–4)	0 (0–5)	0.002	0 (0–5)	0.025
MRI scan (Median, Range)	0 (0–4)	0 (0–3)	0.05	0 (0–3)	0.002

steroid naïve, $p < 0.001$; CD: 58% in the steroid excess group vs 16% in the steroid naïve $p < 0.001$).

Patients with steroid excess were more often in contact with the IBD Clinic (Median: 6 vs 3, $p < 0.001$) as well as the IBD Helpline (Median: 2 vs 0, $p < 0.001$) and the GP (Median: 10 vs 6, $p < 0.001$) compared to patients not exposed to steroids. More importantly, steroid excess patients had significantly higher odds of requiring one or more admissions for their IBD (OR = 12.33, 95% CI [8.89–17.11]), one or more admissions for infections (OR = 2.89, 95% CI [1.82–4.61]) and one or more courses of antibiotics prescribed by their GP during the study period (OR = 1.41, 95% CI [1.07–1.86]) compared to patients without steroid exposure. Lastly, steroid excess patients underwent significantly more investigations during the study period, apart from surveillance colonoscopies (Table 4).

4 | DISCUSSION

Despite the effectiveness of corticosteroids in induction of remission in IBD, the fact that they are not effective in maintaining remission,[11,12] as well as their numerous documented side effects, has led IBD societies to advocate early initiation of steroid-sparing medications.[3–5]

Previous studies have assessed steroid prescription rates either in primary care or predominantly in secondary care settings,[8,10,13] but our study is the first large study to identify sources by comprehensive examination of steroid prescriptions by using hospital and linked community healthcare databases. We demonstrated that primary care steroid prescribing is common, accounting for 28% of all steroids prescribed with an IBD indication. However, more than half of these prescriptions (59%) were of inappropriate dose or length, and close to 40% were either not communicated to secondary care at all (33%), or only later than 6 weeks from initiation (7%). It is important to note that we do not want to blame any clinicians in primary or secondary care and accuse them of inappropriate prescribing habits. Care of IBD patients is becoming increasingly complex with more biologics and small molecule choices.[14,15] Many GPs will only have a handful of IBD cases under their care. Integrated primary and secondary care system should therefore have robust pathways and rapid access to specialist advice in order to facilitate better IBD care.

More importantly, our study demonstrated that patients prescribed steroids by their GP flare after the end of the steroid course

TABLE 5 Patients with steroid excess

Overall excess (%)	15
Charlson Comorbidity Index (Median, Range)	0, (0–8)
Steroid excess (%)	
Due to IBD	76
Due to non-IBD	24
≥1 course within 12 months (%)	14
≥2 courses within 24 months (%)	6
≥2 consecutive months on steroids (%)	8
Treatment escalation (%)	
Yes	77
Not considered	18
Offered by patient refused	5
Appropriate escalation (%)	
Yes	99
No	1
Timely escalation (%)	
Yes	62
No	38
Steroid excess unavoidable (%)	
Yes	48
Probably	27
No	25
Escalation options (%)	
5-ASA new or dose increase	11
Thiopurines/ MTX	40
Anti-TNF, or switch in class	35
Vedolizumab	7
Ustekinumab	1
Surgery	4

more often than patients prescribed steroids by secondary care. Therefore, any steroid course originating from primary care needs to be communicated timely to secondary care services to allow for prompt treatment escalation where required. Indeed, patients with steroid excess with prescriptions initiated in secondary care or in primary care but where the secondary care team was informed, compare to those with steroid prescriptions initiated in primary care that were not conveyed onwards, were more likely to have timely escalation of their medication. Moreover, in those cases, steroid excess was less often unavoidable, highlighting the need for effective communication between primary and secondary care. Previous experience of steroid effectiveness, and positive and negative steroid side effects influence the patient's view regarding future steroid therapy significantly.[16] IBD clinicians should communicate these effects and side effects and the contemporary role of steroids for IBD proactively with patients. The observed rate of primary care steroid prescription points towards access problem or lack of familiarity with the IBD Helpline. The hospital-based IBD service should highlight the helpline to patients and GPs with every written communication and provide local pathways for primary care on how to best access specialist IBD advice and services.

Overall steroid exposure reached 33% of patients, whereas steroid excess was observed in 15% of patients. These findings are similar to previous publications examining steroid exposure over 1-year period.[6,7] This confirms that the cohort of IBD patients exposed to steroid and steroid excess is stable over time. Moreover, when critically reviewing patients with steroid excess because of their IBD, we found that steroid excess was unavoidable in less than half of the patients (48%), which would again be in line with studies.[7] We have previously identified a number of service-related factors that are associated with steroid excess and offer potential targets for quality improvement programs (QIP). A multidisciplinary IBD team, the provision of a joint IBD surgical clinic and treatment with an anti-TNF for CD were associated with reduced risk of steroid excess. Interestingly UC is associated with higher risk of steroid access and no protective effect of anti-TNF could be demonstrated in our previous studies. While not directly examined previously, timely responses from an IBD flare line and timely access to IBD clinic flare slots are important to allow appropriate IBD management. Initiatives using QIP methodology on a health system wide approach are needed to drive service improvements[17] and the introduction of key performance indicators including steroid excess will allow individual IBD centres to benchmark their performance.[17] It is vitally important that steroids prescriptions from primary care are included in these efforts. Steroid exposure is currently included in the quality markers in the UK IBD standards.[17] Moreover, it has been previously demonstrated that in UK centres participating in a quality improvement project, implementing interventions can result in reduction in steroid exposure and excess.[6] Given that primary care steroid prescribing is not only often, but also many times inappropriate, offering education for primary care physicians in steroid prescribing can potentially result in improving the management of IBD patients. Apart from that, our study has demonstrated that there is often lack of communication between primary and secondary care. Better communication of steroid courses can lead to more timely escalation of medications by secondary care physicians, thus reducing steroid excess. The Royal College of General Practitioners has recently published a tool kit to improve the management of IBD in primary care.[18]

In this study, we have also demonstrated that both steroid exposure and excess can be associated with negative consequences. Patients with steroid exposure or excess had more IBD admissions, as well as more admissions for infections and more antibiotics prescribed by primary care. Waljee et al. have shown that among patients with corticosteroid exposure, the rate of infections increased in the year after corticosteroid exposure compared to the year prior to diagnosis.[8] Our study has clearly shown that steroid excess is associated with negative IBD and infectious outcomes for patients highlighting the need for timely treatment escalation after steroid exposure to better control IBD inflammation and to avoid steroid excess.

The major strength of this study is the large number of patients included in the cohort, as well as the use of linked primary and secondary

care data. However, there are limitations to our study. This was a single centre study. While rates for overall steroid exposure and excess were similar to those reported in previous multicentre studies, we cannot assume that the findings are applicable UK-wide, or in countries with a different healthcare system although evolving international data demonstrate similar rates of steroid exposure.[9,13] While we were able to account for steroid prescriptions during the study period, patient-initiated steroid use from previously kept stocks or steroid prescriptions obtained from outside our hospital and primary care system may potentially have been missed. Similarly, we could only examine steroid prescription, but had no access to information on whether these prescriptions were filled. It would have been interesting to examine the effects of comorbidity on steroid exposure and excess compared to those not exposed but these data were only collected for patients with steroid exposure. Exact data on the level of disease activity and what drove patients to request a steroid prescription were not consistently available and could therefore not be analysed.

In conclusion, our study has shown that a substantial amount of steroid prescriptions originates from primary care and these can often be inappropriate in dose and duration, or not communicated to secondary care. Moreover, steroid exposure and excess can have a significant negative impact on IBD patients. The interface between primary care and secondary care needs to be critically re-evaluated in the light of these findings if we are to improve overall outcomes for patients living with IBD.

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AUTHOR CONTRIBUTIONS

Konstantina Rosiou: Formal analysis (equal); investigation (equal); writing – original draft (equal). **Jenelyn Carbonell:** Data curation (equal); investigation (equal); project administration (equal); writing – review and editing (supporting). **Vivien Dolby:** Data curation (equal); investigation (equal); writing – review and editing (supporting). **Niloufar Monfared:** Data curation (equal); investigation (equal); writing – review and editing (supporting). **Tim Raine:** Formal analysis (supporting); methodology (equal); writing – review and editing (equal). **Christian P Selinger:** Conceptualization (equal); formal analysis (equal); funding acquisition (lead); investigation (supporting); methodology (equal); project administration (equal); resources (equal); supervision (equal); writing – review and editing (lead).

AUTHORSHIP

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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