BMJ Open Gastroenterology

Risk of common infections in people with inflammatory bowel disease in primary care: a population-based cohort study

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To cite: Irving PM, de Lusignan S, Tang D, *et al*. Risk of common infections in people with inflammatory bowel disease in primary care: a population-based cohort study. *BMJ Open Gastro* 2021;**8**:e000573. doi:10.1136/bmjgast-2020-000573

► Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/bmjgast-2020-000573).

Received 12 November 2020
Revised 20 January 2021
Accepted 31 January 2021

Check for updates

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ABSTRACT

Objective To evaluate the risk of common infections in individuals with inflammatory bowel disease (IBD) [ulcerative colitis and Crohn's disease] compared with matched controls in a contemporary UK primary care population.

Design Matched cohort analysis (2014–2019) using the Royal College of General Practitioners Research and Surveillance Centre primary care database. Risk of common infections, viral infections and gastrointestinal infections (including a subset of culture-confirmed infections), and predictors of common infections, were evaluated using multivariable Cox proportional hazards models.

Results 18 829 people with IBD were matched to 73 316 controls. People with IBD were more likely to present to primary care with a common infection over the study period (46% vs 37% of controls). Risks of common infections, viral infections and gastrointestinal infections (including stool culture-confirmed infections) were increased for people with ulcerative colitis and Crohn's disease compared with matched controls (HR range 1.12–1.83, all p<0.001). Treatment with oral glucocorticoid therapy, immunotherapies and biologic therapy, but not with aminosalicylates, was associated with increased infection risk in people with IBD. Despite mild lymphopenia and neutropenia being more common in people with IBD (18.4% and 1.9%, respectively) than in controls (6.5% and 1.5%, respectively), these factors were not associated with significantly increased infection risk in people with IBD.

Conclusion People with IBD are more likely to present with a wide range of common infections. Health professionals and people with IBD should remain vigilant for infections, particularly when using systemic corticosteroids, immunotherapies or biologic agents.

Trial registration number Clinicaltrials.gov (NCT03836612).

Summary box

What is already known about this subject?

- ► Although people with inflammatory bowel disease (IBD) are known to be at increased risk of infection, the burden of common infections among people with IBD in primary care has not been clearly established.

What are the new findings?

- ► Using the UK primary care infectious disease sentinel network, we demonstrate people with IBD are at increased risk of common infections including gastrointestinal and viral infections, and that risk is highest in those managed with systemic corticosteroids, immunotherapies and biologic therapy.

How might it impact on clinical practice in the foreseeable future?

- ► Clinicians should be aware of the higher risk of common infections in people with IBD in primary care, particularly in the context of the ongoing COVID-19 pandemic.

INTRODUCTION

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic inflammatory conditions collectively termed inflammatory bowel disease (IBD).[1] Both conditions can follow a relapsing-remitting course or be continuously active. The disease spectrum ranges from a quiescent state with few or no symptoms to potentially fatal disease. Medical intervention is often required over decades of disease and may include surgery.[2 3] With the global burden of IBD rising, calls for improved treatment options[4] have resulted in the development of several immunomodulatory and biologic therapies.[1]

Current treatment strategies for many people with IBD focus on immunomodulation.[5] Though frequently effective for disease control, such treatments increase infection risk,[6 7] including common and atypical pathogens.[7] Understanding the infection risk in a community-based population with IBD has been brought into sharp focus recently with the onset of the COVID-19 pandemic. The need to protect vulnerable individuals led to recommendations from the British Society of Gastroenterology for people with IBD that was, in part, driven by medication use.[8]

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However, decisions around which individuals required shielding were generally opinion based, largely due to the lack of data around the risks of common infections in people with IBD and their relationship with common comorbidities and medication use. It is notable that coding of comorbidity, the biggest risk factor for COVID-19-related mortality, is more complete in primary than secondary care,[9] and that medications and common infections are not systematically coded in secondary care, thus reinforcing the importance of studying infection risk in the primary care setting. Despite this, existing literature on infection rates in IBD has focused predominantly on secondary care populations.[10–12] Although an increased risk of specific infections including herpes zoster and pneumonia has been observed in primary care,[13 14] the total burden of common infection in individuals with IBD in primary care remains unknown. Similarly, while lymphopenia and neutropenia are known markers of infection risk in the general population,[15] their utility as risk factors for common infections in people with IBD in the primary care setting has not previously been evaluated.

This study aimed to describe the risk of common infections, in a primary care population of individuals with UC and CD, compared with a matched control population. Risk factors for common infections in IBD, with a focus on comorbidity, medication, lymphopenia and neutropenia, were explored.

MATERIALS AND METHODS

Study design

We performed a retrospective, matched cohort study to evaluate infection risk among people with IBD compared with population controls in UK primary care. The study protocol has been previously published.[16]

Data source

The Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network database was used. This UK-based database comprises pseudonymised primary care records of individuals registered with a large network of general practices, providing a representative sample of the primary care population in England.[17] At the time of data extraction, RCGP RSC contained data from 2 million people, providing information on clinical diagnoses, anthropometric measurements, laboratory tests and prescriptions, coded using the Read coding system.[18] UK primary care has been computerised since 1990s, and pay-for-performance data available from 2004 have resulted in high-quality clinical data entry about chronic disease.[19 20] Studies using RCGP RSC have been published across many chronic diseases.[21–24] RCGP RSC is the primary infectious disease sentinel network for the UK, providing weekly infections data since 1967 to monitor trends in infectious disease and investigate real-world vaccine efficacy.[25 26] General practices within the network receive feedback on their coding of infectious diseases, which designates cases as first, new or ongoing, thereby differentiating incidence from prevalence.[27]

Study population

People aged ≥18, registered with a GP practice contributing to the RCGP RSC between 1 January 2014 and 1 January 2019, were eligible for inclusion.

Definition of the exposed cohort with IBD

People with an existing or incident diagnosis of UC or CD, as defined by the presence of at least one disease-specific Read code, were eligible for inclusion in the IBD cohort. Use of diagnosis codes alone has been reported to have a 97% positive predictive value for identifying IBD from electronic health records in the USA[28] and has been validated in UK primary care as a means of identifying IBD.[29 30] Read codes used to identify UC and CD were based on the codes used by Abrahami *et al*,[30] mapped to both Read code versions used within the RCGP RSC (online supplemental appendix 1). Start of follow-up for an individual with IBD was defined as the latest of 1 January 2014 or the date of IBD diagnosis.

Definition of the matched unexposed cohort without IBD

Individuals with a diagnosis of IBD were matched (nearest neighbour matching, with replacement) at their index date (start of follow-up date) with four unexposed individuals at general practice level by current age (per year), sex and time since practice registration. Eligible unexposed individuals at each index date comprised people actively registered at that date with no IBD history and a minimum 1 year registration with their RCGP RSC practice (to minimise the risk they had a non-recorded existing IBD diagnosis). Follow-up for each matched individual was started on the index date of their matched case with IBD. People diagnosed with IBD after the study start date were included in the pool of eligible unexposed individuals, but if matched, they were censored on the date of their IBD diagnosis. This meant individuals were eligible to contribute to unexposed person time prior to an IBD diagnosis. The end of follow-up was defined as the earliest of the study end date (1 January 2019), the date of patient transfer from an included general practice, date of death or the date an individual first developed an infection of interest. Follow-up for the unexposed cohort also ended if they developed IBD, at which point they became eligible for the exposed group. Individuals contributing at least 1 day of follow-up time were included in this study.

Outcomes

Infections

Infection outcomes were defined as the incidence of a new presentation of (1) common infection, (2) viral infection and (3) gastrointestinal (GI) infection during the study period. First or new presentations of an infection are coded accordingly in the database, enabling differentiation of new infections from chronic infections or

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follow-ups for the same episode. Common infection was defined as a composite of upper respiratory tract infections (URTI), pneumonia, acute bronchitis, influenza-like illness (ILI), skin infections, herpes simplex and herpes zoster infections, genital infections, urinary tract infections (UTI) and GI infections. Read codes used to identify common infections were taken from validated indicators used in routine surveillance by the RCGP RSC. Viral infections were defined as a composite of ILI, herpes simplex and herpes zoster infections and any upper or lower respiratory tract infections specifically coded as being viral. GI infection comprised clinical diagnoses of gastroenteritis, enteritis or infective colitis as well as laboratory-confirmed viral, bacterial or protozoan GI tract infections. The incidence of all infection subtypes comprising the primary outcome of common infection was examined in a secondary analysis. To distinguish GI infection from non-infective diarrhoea within the cohorts, a subanalysis of stool culture-confirmed GI infections (a composite of *Clostridium difficile*, *Salmonella*, *Shigella* and *Campylobacter* infections [online supplemental appendix 2]) was performed.

Baseline measures

Baseline measures comprised sociodemographic characteristics and clinical features and biomarkers associated with IBD or infection risk. Socioeconomic status was defined using the official national measure, the index of multiple deprivation[31] and calculated using patient postcode, with the resultant scores stratified by deprivation quintile. Ethnicity was grouped into white, black, Asian, mixed and others.[32] Body mass index (BMI), smoking status and alcohol use were defined using the most recent recorded data prior to the study start date. For these measures, we used the missing indicator variable method; the robustness of this approach was tested using sensitivity analysis (see below). Diagnostic codes were used to define the following baseline comorbidities (with the absence of a code for a comorbidity assumed to represent the absence of that comorbidity): diabetes mellitus, hypertension, hyperlipidaemia, atrial fibrillation, angina, myocardial infarction, congestive heart failure, peripheral vascular disease, stroke, transient ischaemic attack, chronic kidney disease stages 3–5 (CKD), dementia, rheumatoid arthritis, chronic liver disease, asthma, chronic obstructive pulmonary disease (COPD), joint replacement and fractures. Lymphocyte and neutrophil counts were defined as continuous measures, and with lymphopenia and neutropenia, subgroups were defined, respectively, by cut-offs of absolute lymphocyte count $<1.0\times10^9$ cells/L and absolute neutrophil count $<1.5\times10^9$ cells/L.[33,34] The following medications used in the management of IBD were examined: rectal 5-aminosalicylic acid (5-ASA), rectal glucocorticoids, oral 5-ASA, oral glucocorticoids, nonbiologic immunosuppressants and biologic therapies (online supplemental appendix 3). Baseline medication use was defined as the issue of a prescription 3 months before, to 30 days after, the study start date; information on whether prescriptions were dispensed is not captured in the RCGP database.

Statistical analyses

Risk of infection in IBD

Incident cases comprised individuals with a first-ever diagnostic Read code for infection during the study period. Incidence of common, GI and viral infections were calculated separately for UC and CD, by dividing the number of incident cases by the sum of person-years of follow-up for the total eligible population over the study period and expressed as the number per 100 person-years. Risk of infection in UC and CD was estimated using unadjusted Cox proportional hazards models, stratified by matched set, to provide overall hazard ratios for each infection outcome. Models were subsequently adjusted for baseline measures using multivariable analysis.

Predictors of infection in IBD

Baseline factors associated with an increased risk of infection were evaluated in UC and CD separately using Cox proportional hazards models. Factors evaluated were age, sex, ethnicity, socioeconomic status, BMI, smoking, alcohol use, comorbidities, duration of disease and baseline medication use. To further evaluate the utility of lymphopenia and neutropenia as markers of infection risk, their time-varying association with risk of common infection over study follow-up was explored using unadjusted and adjusted Cox proportional hazards models, with each measure modelled as a continuous time-varying covariate. This time-varying approach maximises power and predictive ability compared with using baseline only measures.[35] Test results recorded in the 2 weeks prior to an infection were excluded to reduce the likelihood the infection itself influenced the test result. As a sensitivity analysis, this exclusion window was extended to the 2 months prior to an infection. Time-updated lymphopenia status and neutrophilia status as binary covariates were examined using the same approach.

Sensitivity analysis

We ran the following post hoc sensitivity analysis to assess the robustness of finding for the primary outcomes: (1) repeating the primary analysis excluding matched controls without a least one recorded consultation in the year before cohort entry (to exclude practice non-attendees), (2) excluding patients with IBD registered within 1 year of the start of study follow-up (the same criteria as applied to controls in the primary analysis, to remove potentially more transient patents from the IBD cohort), (3) without adjustment for baseline medications that may be on the causal pathway between IBD and infection, (4) using a comorbidity count score in multivariable models as opposed to including each comorbidity as an individual term, (5) excluding IBD cases (and their matched controls) with missing data for ethnicity, BMI, smoking, alcohol use and deprivation. Statistical analysis was performed in R V.3.4.1.

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RESULTS

A total of 18 829 people with IBD (UC n=11 360 and CD n=7469) (exposed cohort) were matched to 73 316 people without IBD (unexposed matched cohort). 3118 (16.6%) IBD cases were incident over the study period and 15 711 (83.4%) were diagnosed prior to the study start date. Age, sex, and follow-up time were closely matched (table 1). The cohort with IBD had a greater prevalence of several comorbidities including depression, rheumatoid arthritis, COPD, chronic liver disease and CKD (table 1). People with CD were younger, more likely to be underweight and had fewer comorbidities than those with UC.

Primary analysis: people with IBD have an increased risk of common infection

Of 8581 (46%) people with IBD presented with common infection over the study period, compared with 27 407 (37%) in the control group. Event rates were higher in IBD being 16.4 (95% CI 16.0 to 16.9) per 100 person-years in UC (table 2) and 17.4 (95% CI 16.9 to 18.0) in CD (table 2), compared with 13.0 (95% CI 12.8 to 13.2) per 100 person-years in the UC-matched cohort (table 2) and 12.7 (95% CI 12.4 to 12.9) per 100 person-years in the CD-matched cohort (table 2). Event rates were similarly increased in IBD for viral infections and GI infections (table 2). Figure 1A and table 2 show an association between IBD and the three infection outcomes in unadjusted and multivariable-adjusted analyses. The association of greatest magnitude was for GI infections (adjusted Hazard ratio (aHR) 1.46 (95% CI 1.26 to 1.69) for UC and aHR 1.83 (95% CI 1.56 to 2.15) for CD).

Secondary analysis: risk for infection subtypes

Figure 1B shows the association between UC and CD and time to presentation of each infection subtype. Event rates and aHRs for each infection subtype are reported in online supplemental table 1. URTI, acute bronchitis and skin infections were the most common infections. Associations of the greatest magnitude were stool culture-confirmed *Clostridium difficile*, *Salmonella*, *Shigella* and *Campylobacter* infections and herpes zoster for UC, whereas for CD, pneumonia and herpes zoster were most common.

Secondary analysis: predictors of common infection

Sociodemographic factors and pre-existing comorbidities

In UC and CD, a higher risk of infection was seen in women, people of Asian ethnicity, the overweight or obese and current and ex-smokers (online supplemental table 2). In UC and CD, the presence of depression, dementia, malignancy, COPD and myocardial infarction were associated with an increased risk of common infection. In individuals with UC, type 2 diabetes, CKD, stroke, angina and atrial fibrillation were additional significant risk factors.

Medication exposure

Oral glucocorticoid therapy, immunotherapies and biologic use were all associated with an increased risk of common infection to a similar degree in UC and CD (figure 2). As expected, rectal glucocorticoid use was higher in UC than CD (table 1), but the increase in risk of common infection with these medications was observed only in UC (figure 2).

Lymphocyte and neutrophil count

Of 15 290 (81%) people with IBD had a minimum of one lymphocyte count and neutrophil count during the study period (mean number of counts: 6 per person), compared with 44 324 (59%) people in the control cohorts (mean counts: 4 per person). Figure 3 shows that, in continuous analysis, a lower lymphocyte count was associated with an increased risk of common infection in people without IBD but not in those with IBD. When analysed by lymphocyte count status (where lymphopenia was defined as a lymphocyte count $<1.0\times10^{9}$ cells/L), 18.4% of the IBD cohort had at least one episode of lymphopenia over the study period, compared with 6.5% of controls (online supplemental table 3). Infection risk was increased in individuals with lymphopenia without IBD (HR 1.26 (95% CI 1.17 to 1.36), p<0.001) but not in those with IBD (HR 1.05 (95% CI 0.97 to 1.14), p=0.21) (online supplemental table 3A). Results were consistent when UC and CD were evaluated in separate models (online supplemental table 3B,C). Online supplemental table 4A summarises the absolute numbers of people with and without IBD and recorded infection events according to lymphocyte count categories (severe ($<0.5\times10^{9}$ cells/L), moderate (0.5–0.8), mild (0.8–1.0), normal (1.0–4.0), lymphocytosis (≥4.0)).

Figure 3 also shows that, in continuous analysis, a higher neutrophil count was associated with an increased risk of common infection both in the IBD and the non-IBD cohorts. However, there was no evidence of an increased risk of infection in association with lower neutrophil counts. When categorised by neutrophil count status (neutrophil count $<1.5\times10^{9}$ cells/L vs $\geq1.5\times10^{9}$ cells/L), 1.9% of people with IBD and 1.5% of those without IBD had at least one count in the neutropenic range over follow-up. There was no evidence of an association with infection for either group (HR for IBD 1.12 (95% CI 0.80 to 1.55), p=0.51, HR for controls 1.05 (95% CI 0.87 to 1.27), p=0.60) (online supplemental table 3A). When UC and CD were evaluated in separate models, there was no evidence of an association between neutropenia status and risk of infection (UC HR 1.17 (95% CI 0.78 to 1.77), p=0.45), (CD HR 1.06 (95% CI 0.61 to 1.93), p=0.84) (online supplemental table 3B,C). Online supplemental table 4B summarises the absolute numbers in those with and without IBD and recorded infection events according to the neutrophil count categories (severe ($<0.5\times10^{9}$ cells/L), moderate (0.5–1.0), mild (1.0–1.5), normal (1.5–7.5), neutrophilia (>7.5)). Continuous associations for lymphocyte and neutrophil counts were near

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Table 1 Covariate summary statistics for ulcerative colitis, Crohn's disease and control cohorts

	With CD (n=7469)	Matched cohort without CD (n=29 876)	With UC (n=11 360)	Matched cohort without UC (n=45 440)
Age at study entry (years) Median (IQR)	47 (34, 61)	48 (33, 63)	53 (39, 67)	52 (37, 67)
Male sex	3402 (45.5)	14 085 (47.1)	5737 (50.5)	22 433 (49.4)
Time since GP practice registration (years) median (IQR)	10 (2, 20)	11 (3, 20)	11 (3, 21)	11 (3, 21)
Duration of IBD (years) median (IQR)	9 (2, 17)	NA	9 (2, 18)	NA
Ethnicity				
Asian	247 (4.2)	1402 (6.0)	547 (6.1)	2239 (6.3)
Black	72 (1.2)	599 (2.6)	93 (1.0)	811 (2.3)
Mixed	55 (0.9)	246 (1.1)	63 (0.7)	361 (1.0)
Other	41 (0.7)	235 (1.0)	68 (0.8)	299 (0.8)
White	5399 (92.9)	20 732 (89.3)	8270 (91.5)	32 058 (89.6)
BMI category (kg/m^2)				
Underweight (≤18.5)	369 (4.9)	800 (2.7)	256 (2.3)	1094 (2.4)
Normal weight (18.5–25)	3020 (40.4)	10 170 (34.0)	4230 (37.2)	14 905 (32.8)
Overweight (25-30)	2125 (28.5)	8819 (29.5)	3684 (32.4)	14 399 (31.7)
Obese (≥30)	1304 (17.5)	6307 (21.1)	2223 (19.6)	9744 (21.4)
BMI not recorded	651 (8.7)	3780 (12.7)	967 (8.5)	5298 (11.7)
Smoking status				
Non-smoker	2641 (35.4)	12 511 (41.9)	4255 (37.5)	18 288 (40.2)
Current smoker	1731 (23.2)	6135 (20.5)	1386 (12.2)	8881 (19.5)
Ex-smoker	3028 (40.5)	10 632 (35.6)	5631 (49.6)	17 594 (38.7)
Smoking status not recorded	69 (0.9)	598 (2.0)	88 (0.8)	677 (1.5)
Index of multiple deprivation quintile				
1 (most deprived)	1015 (13.6)	4130 (13.8)	1293 (11.4)	5534 (12.2)
2	1185 (15.9)	4738 (15.9)	1626 (14.3)	6694 (14.7)
3	1484 (19.9)	5867 (19.6)	2143 (18.9)	8779 (19.3)
4	1765 (23.6)	6840 (22.9)	2862 (25.2)	11 024 (24.3)
5 (least deprived)	1860 (24.9)	7704 (25.8)	3230 (28.4)	12 579 (27.7)
IMD not recorded	160 (2.1)	597 (2.0)	206 (1.8)	830 (1.8)
Alcohol intake				
Non-drinker	1158 (15.5)	3945 (13.2)	1495 (13.2)	5799 (12.8)
Within limits	4178 (55.9)	16 449 (55.1)	6724 (59.2)	25 880 (57.0)
Over recommended limits	991 (13.3)	4390 (14.7)	1691 (14.9)	6882 (15.1)
Alcoholism	119 (1.6)	505 (1.7)	172 (1.5)	774 (1.7)
Alcohol intake not recorded	1023 (13.7)	4587 (15.4)	1278 (11.2)	6105 (13.4)
Comorbidities				
Hypertension	1292 (17.3)	5894 (19.7)	2704 (23.8)	10 929 (24.1)
Hyperlipidaemia	1391 (18.6)	7462 (25.0)	3293 (29.0)	13 480 (29.7)
Type two diabetes	436 (5.8)	1992 (6.7)	1052 (9.3)	3674 (8.1)
Peripheral vascular disease	81 (1.1)	276 (0.9)	139 (1.2)	584 (1.3)
Atrial fibrillation	172 (2.3)	797 (2.7)	388 (3.4)	1479 (3.3)
Myocardial infarction	172 (2.3)	694 (2.3)	424 (3.7)	1360 (3.0)
Angina	139 (1.9)	531 (1.8)	337 (3.0)	1101 (2.4)

Continued

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Table 1 Continued

	With CD (n=7469)	Matched cohort without CD (n=29 876)	With UC (n=11 360)	Matched cohort without UC (n=45 440)
Stroke	119 (1.6)	430 (1.4)	226 (2.0)	831 (1.8)
Heart failure	87 (1.2)	322 (1.1)	179 (1.6)	675 (1.5)
CKD stages 3–5	406 (5.4)	1344 (4.5)	796 (7.0)	2897 (6.4)
COPD	111 (1.5)	179 (0.6)	235 (2.1)	285 (0.6)
Chronic liver disease	364 (4.9)	922 (3.1)	489 (4.3)	1696 (3.7)
Malignancy	315 (4.2)	1308 (4.4)	689 (6.1)	2479 (5.5)
Dementia	136 (1.8)	611 (2.0)	292 (2.6)	1230 (2.7)
Rheumatoid arthritis	85 (1.1)	194 (0.6)	157 (1.4)	383 (0.8)
History of fracture	612 (8.2)	2371 (7.9)	1017 (9.0)	3721 (8.2)
Depression	1160 (15.5)	3091 (10.3)	1461 (12.9)	4786 (10.5)
Baseline medication use				
Rectal 5-ASA	329 (4.4)	25 (0.1)	2415 (21.3)	35 (0.1)
Rectal glucocorticoids	340 (4.6)	263 (0.9)	1793 (15.8)	395 (0.9)
Oral 5-ASA	2868 (38.4)	97 (0.3)	6986 (61.5)	212 (0.5)
Oral glucocorticoids	2290 (30.7)	1780 (6.0)	2937 (25.9)	3103 (6.8)
Non-biologic immunosuppressants	2274 (30.4)	207 (0.7)	1600 (14.1)	377 (0.8)
Biologic therapies	182 (2.4)	6 (0.0)	59 (0.5)	7 (0.0)

Data are N (%) unless stated.
5-ASA, aminosalicylic acid medications; BMI, body mass index; CD, Crohn's disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; GP, general practitioner; IBD, inflammatory bowel disease; UC, ulcerative colitis.

identical when counts in the 2 months prior to an infection were excluded (online supplemental figure 1).

Sensitivity analysis

Results for the primary outcomes of common infection, viral infection and GI infection were consistent in all sensitivity analyses for both UC and CD (1) excluding controls who were practice nonattendees prior to study start, (2) excluding people with IBD registered within 1 year of study start, (3) without adjustment for medication use in multivariable models, applying a comorbidity count score instead of adjustment for individual comorbidities; including only patients with complete data on sociodemographic and behavioural characteristics (online supplemental table 5).

DISCUSSION

This study showed that people with IBD are more likely to present to primary care with common infections including URTI, acute bronchitis, skin infection, GI infection, herpes zoster, UTI (UC only) and pneumonia (CD only) than matched controls. Treatment with oral glucocorticoid therapy, immunotherapies and biologic therapy, but not with 5-ASA, was associated with additional infection risk. Although mild lymphopenia and neutropenia were more common in individuals with IBD than controls, these were not generally associated with significantly increased infection risk in IBD.

To the best of our knowledge, this is the first study evaluating the risk of a range of infections in people with IBD performed in primary care. Previous studies have largely focused on opportunistic infections or drug-resistant organisms in secondary care settings.[36–38] Similar to this study, Long *et al* found a greater risk for pneumonia in CD (HR 1.71, 95% CI 1.62 to 1.80) than for UC (HR 1.41, 95% CI 1.34 to 1.48).[13] The increased risk for herpes zoster in this study was similar to that found by Gupta *et al* (UC incidence rate ratio: 1.21 (95% CI, 1.05 to 1.40), CD incidence rate ratio: 1.61 (95% CI, 1.35 to 1.92)),[14] suggesting the greatest excess risk is in CD. Ning *et al* demonstrated similar associations in their meta-analysis.[39] In this study, we describe an increase in GI infections in both UC and CD, with the majority being clinically diagnosed. However, a subanalysis of stool culture-confirmed diagnoses of infection with *Salmonella*, *Shigella*, *Campylobacter* or *Clostridium difficile* confirmed that this finding was not confounded by the fact that active IBD could be mistaken for GI infection. Previous studies have similarly shown GI infections are more common in people with IBD.[40–45] Rodemann *et al* observed a threefold increased rate of *Clostridium difficile* infection among people with IBD in secondary care[41] and Singh *et al* reported a 4.8-fold increased risk for *Clostridium difficile* infection in IBD

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Table 2 Associations between ulcerative colitis and Crohn's disease, and each infection outcome.

	Number of patients	Patient years at-risk	Events (%)	Event rate (per 100-person years)	Hazard ratio (95% CI) Unadjusted	Adjusted*
A. Associations between ulcerative colitis and each infection outcome						
Any common infection						
Controls	45 440	133 703	17 403 (38%)	13.0 (12.8, 13.2)	1.00 (ref)	1.00 (ref)
Ulcerative colitis	11 360	31 076	5111 (45%)	16.4 (16.0, 16.9)	1.25 (1.21 to 1.29)*	**1.12 (1.07 to 1.18)***
Gastrointestinal infection						
Controls	45 440	134 615	1365 (3%)	1.0 (0.9, 1.1)	1.00 (ref)	1.00 (ref)
Ulcerative colitis	11 360	31 410	510 (4%)	1.6 (1.5, 1.8)	1.61 (1.45 to 1.78)*	**1.46 (1.26 to 1.69)***
Viral infection						
Controls	45 440	136 290	8510 (19%)	6.2 (6.1, 6.4)	1.00 (ref)	1.00 (ref)
Ulcerative colitis	11 360	31 994	2544 (22%)	8.0 (7.6, 8.3)	1.27 (1.21 to 1.33)*	**1.13 (1.05 to 1.20)***
B. Associations between Crohn's disease and each infection outcome						
Any common infection						
Controls	29 876	88 753	11 227 (38%)	12.7 (12.4, 12.9)	1.00 (ref)	1.00 (ref)
Crohn's disease	7469	19 892	3470 (46%)	17.4 (16.9, 18.0)	1.36 (1.31 to 1.41)*	**1.20 (1.14 to 1.26)***
Gastrointestinal infection						
Controls	29 876	89 303	841 (3%)	0.9 (0.8, 1.0)	1.00 (ref)	1.00 (ref)
Crohn's disease	7469	20 170	395 (5%)	2.0 (1.8, 2.2)	2.09 (1.86 to 2.36)*	**1.83 (1.56 to 2.15)***
Viral infection						
Controls	29 876	90 559	5917 (20%)	6.5 (6.4, 6.7)	1.00 (ref)	1.00 (ref)
Crohn's disease	7469	20 531	1797 (24%)	8.8 (8.4, 9.2)	1.33 (1.26 to 1.40)*	**1.15 (1.07 to 1.23)***

*p<0.001.
*Models adjusted for age, sex, IMD quintile, white ethnicity, BMI category, smoking status, alcohol category, hypertension, hyperlipidaemia, type 2 diabetes, peripheral arterial disease, atrial fibrillation, angina, myocardial infarction, stroke, heart failure, chronic kidney disease stage 3–5, chronic obstructive pulmonary disorder, chronic liver disease, malignancy, dementia, rheumatoid arthritis, fracture history, depression and concomitant medication use (from rectal 5-ASA, rectal glucocorticoids, oral 5-ASA, oral glucocorticoids, immunotherapies and biologic therapies).
ASA, aminosalicylic acid; BMI, body mass index; IMD, index of multiple deprivation.

in primary care.[42] The increased risk of GI infection may relate to interconnected local factors such as gut dysbiosis, impaired gut epithelial barrier repair, dysfunctional immune regulation and chronic intestinal inflammation. These factors also play key roles in IBD pathogenesis, particularly in genetically susceptible individuals.[5 46–48]

We also found that a wide range of infections was more common in UC and CD than in controls, even after adjustment for sociodemographic factors, comorbidities and baseline medication use. Medications that suppress the immune system are the most widely recognised risk factor for infection in IBD. In addition, an increased prevalence in IBD of other risk factors for infection including malnutrition, surgery and increased pathogen exposure[36 49] could contribute to the observed increase in infection rates. Pathogenic processes, such as penetrating disease, which occurs in a proportion of individuals with CD, may further contribute to this risk. Finally, low vaccine uptake and, perhaps, an impaired response to vaccines may compound infection risk in IBD.[50]

Oral glucocorticoid therapy, immunotherapies and biologic therapy were associated with additional infection risk in this study. Use of glucocorticoids in people with IBD was common (35.3%), as found previously in primary care studies of other immune-mediated inflammatory diseases such as rheumatoid arthritis.[51 52] While prospective data from the IBD cancer and serious infections in Europe (I-CARE) study are awaited,[53] several studies have examined the impact of medications on infection risk in both UC and CD.[7 11 12 54 55] Toruner *et al* found in a secondary care setting that the risk of opportunistic infection in IBD increased with the use of glucocorticoids (OR 2.2, 95% CI 1.0 to 4.9), azathioprine/6-mercaptopurine (OR 3.4, 95% CI 1.5 to 7.5) and infliximab (OR 11.1, 95% CI 0.8 to 148); the greatest risk was observed when these medications were used in combination.[7] A similar risk for opportunistic infection associated with antitumour necrosis factor-α (TNFα) therapy was shown in a meta-analysis by Ford *et al*.[54] Similarly, Long *et al* showed that corticosteroids (OR 1.73, 95% CI 1.51 to 1.99), anti-TNFα (OR 1.81, 95% CI 1.48 to 2.21) and thiopurines (OR 1.85, 95% CI 1.61 to 2.13) were independent risk factors for herpes zoster in IBD, with the greatest association being for combined thiopurine and anti-TNFα therapy

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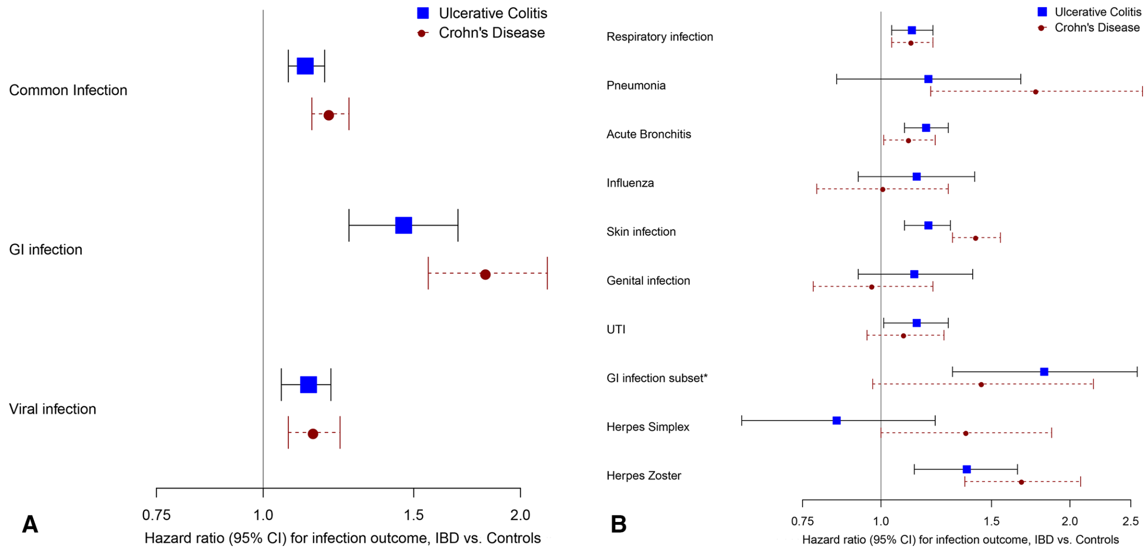

Figure 1 Adjusted HRs for associations between ulcerative colitis and Crohn's disease and (A) primary infection outcomes; (B) ssub-infection outcomes. A HR greater than 1 represents an increase in the risk in individuals with IBD compared with matched controls without IBD. Models adjusted for age, sex, IMD quintile, white ethnicity, BMI category, smoking status, alcohol category, hypertension, hyperlipidaemia, type 2 diabetes, peripheral arterial disease, atrial fibrillation, angina, myocardial infarction, stroke, heart failure, chronic kidney disease stage 3–5, chronic obstructive pulmonary disorder, chronic liver disease, malignancy, dementia, rheumatoid arthritis, fracture history, depression and medication use (rectal 5-ASA, rectal glucocorticoids, oral 5-ASA, oral glucocorticoids, immunotherapies and biologic therapies). *Composite of organism specific infection with *Clostridium difficile*, *Salmonella*, *Shigella* or *Campylobacter* infections. ASA, aminosalicylic acid; BMI, body mass index; GI, gastrointestinal;IBD, inflammatory bowel disease; IMD, index of multiple deprivation; UTI, urinarytract infection.

(OR 3.29, 95% CI 2.33 to 4.65).[56] Increased herpes zoster incidence has also been observed in people taking tofacitinib, a Janus kinase inhibitor recently licensed for use in moderate to severe UC.[57 58] Conversely, oral and rectal 5-ASA medications do not appear to increase infection risk in this study. This is also consistent with the findings of Toruner *et al* who found no association between 5-ASA use and opportunistic infections,[7] adding to the data confirming the long-term safety profile of 5-ASA. The association between immunosuppressive drugs and biologics with infection needs to be interpreted in terms of the progressive and destructive nature of uncontrolled inflammation in IBD, which can result in complications such as fibrosis, stenosis and malignancy. Furthermore, active IBD is associated with anxiety and depression and may have socioeconomic repercussions that affect quality of life. Patient concordance with effective therapy is, therefore, paramount, and an association between these drugs and an increased risk of infection should not prevent their use where appropriate.

We did not show an association between mild lymphopenia or neutropenia and increased infection risk in IBD, an interesting finding that warrants further study. The finding that lower lymphocyte counts were associated with a decreased chance of infection in CD might correlate with thiopurine use and consequent lower disease activity. Similarly, a retrospective observational study from Germany found no association between mild lymphopenia and opportunistic infections,[59] while Toruner *et al* found thiopurine-induced lymphopenia or neutropenia in IBD did not increase opportunistic infections.[7] These findings suggest that either IBD itself or the drugs used to treat it result in, or are associated with, immune dysfunction and/or dysregulation that influences infection risk independent of either neutropenia or lymphopenia. Recent studies have indicated that innate lymphoid cells play a key role in mucosal inflammation and immunity against bacterial, viral and parasitic infection, and that an imbalanced accumulation in the population of Th1, Th2, Th17 and natural killer cells not only perpetuates chronic inflammation but also causes a dysfunctional immune response to infection in IBD.[48] It is also likely that additional inhibition of innate and adaptive immunity by drugs used to treat IBD could exacerbate immune and/or cytokine imbalance, contributing to the observed infection risk.

A key strength of this study is the use of the highest quality of real-world data on infectious diseases from the RCGP RSC network, the UK primary care infections surveillance network. The infections explored are part of 34 regularly monitored conditions within the network. Results were consistent in all sensitivity analysis, including exclusion of matched controls who were potential practice nonattendees (a likely over-adjustment). Nonlinear continuous risk models were used in our primary analysis to explore the association between time-updated lymphocyte and neutrophil count and risk of infection, avoiding the need for subgroups defined by the presence or absence of a haematological abnormality. This continuous modelling approach maximises power by avoiding arbitrary dichotomisation and enables our results to be generalisable, given the variability in normal reference range values for

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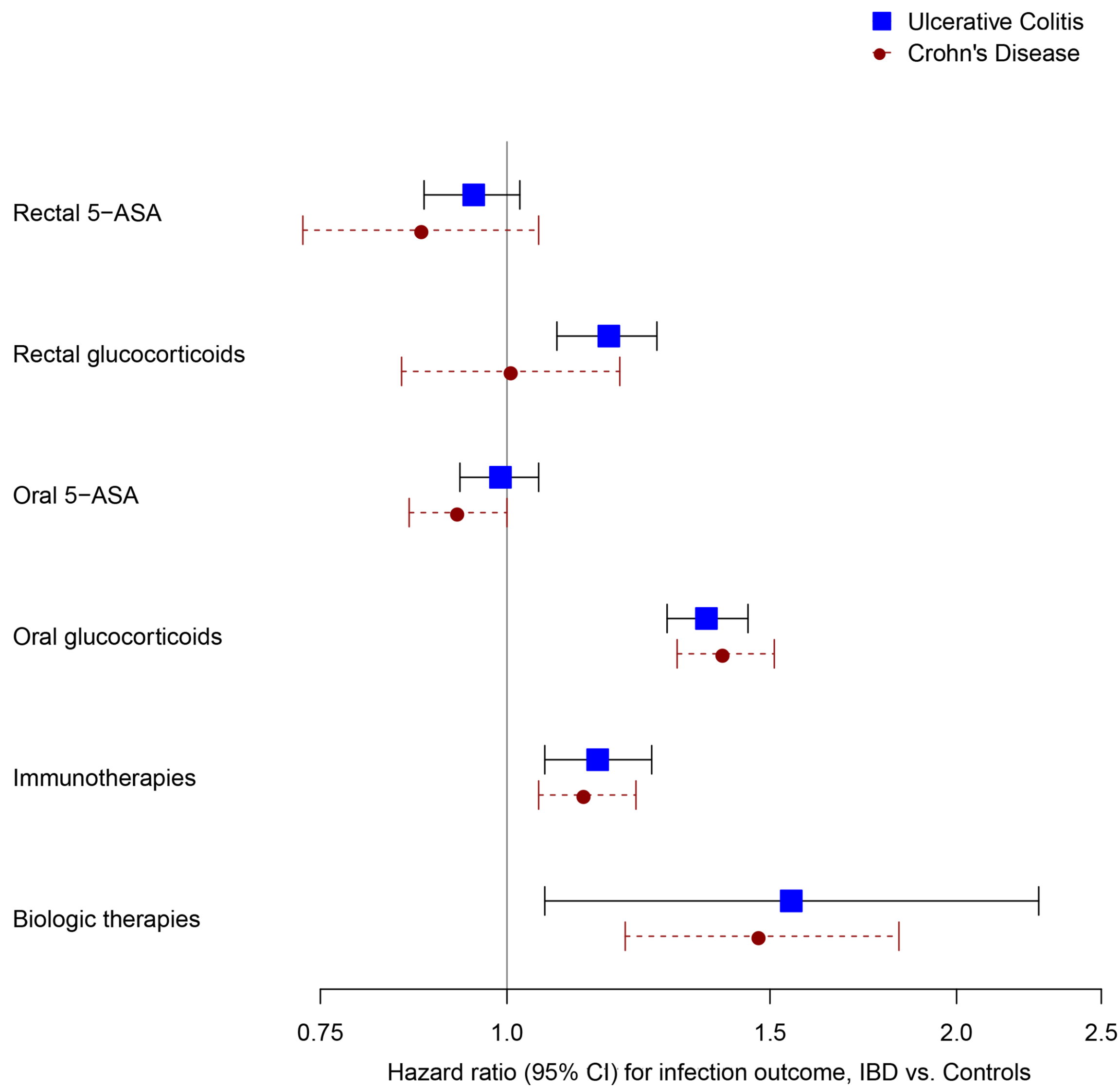

Figure 2 Adjusted hazard ratios for associations between baseline medication use and subsequent risk of presentation of common infection in individuals with ulcerative colitis and Crohn's disease. A HR greater than 1 represents an increase in the risk of presentation of infection in individuals using the medication of interest compared with individuals not using that medication. Models adjusted for age, sex, IMD quintile, white ethnicity, BMI category, smoking status, alcohol category, hypertension, hyperlipidaemia, type 2 diabetes, peripheral arterial disease, atrial fibrillation, angina, myocardial infarction, stroke, heart failure, chronic kidney disease stage 3–5, chronic obstructive pulmonary disorder, chronic liver disease, malignancy, dementia, rheumatoid arthritis, fracture history, depression and concomitant medication use (from rectal 5-ASA, rectal glucocorticoids, oral 5-ASA, oral glucocorticoids, immunotherapies and biologic therapies). ASA, aminosalicylic acid; BMI, body mass index; GI,gastrointestinal; IBD, inflammatory bowel disease; IMD, index of multiple deprivation.

haematological parameters in different settings.[60] As with all observational studies of this type, a limitation of our analysis is that we were unable to determine any causal associations, and although results were consistent with extensive sensitivity analysis we cannot rule out unobserved confounding as an explanation of our findings, especially given the relatively modest effect sizes observed. Data recording and capture bias might be another study limitation, as symptomatic individuals with IBD may have specific patterns of care meaning they present more frequently to clinicians, who may also investigate infections in people with IBD more proactively. A further potential bias is delayed IBD diagnosis meaning the approach of retaining controls who later becomes a case in the control set meant some person-time in the controls comprised people with IBD, although we expect the effect of this to be a minor attenuation of effect sizes towards the null. Although infections diagnosed in secondary care are often transferred into primary care records, this study is likely to have under-captured such diagnoses that were made or treated solely in secondary care. In addition, biological therapies in the UK are normally prescribed in secondary care and may not be recorded by primary care, which will have resulted in systemic undercapture of biologic use. This issue stems from the lack of linkage between the different data systems used in UK primary and secondary care. UK electronic health record data do not capture the underlying reason for the prescription, meaning we cannot ascertain the

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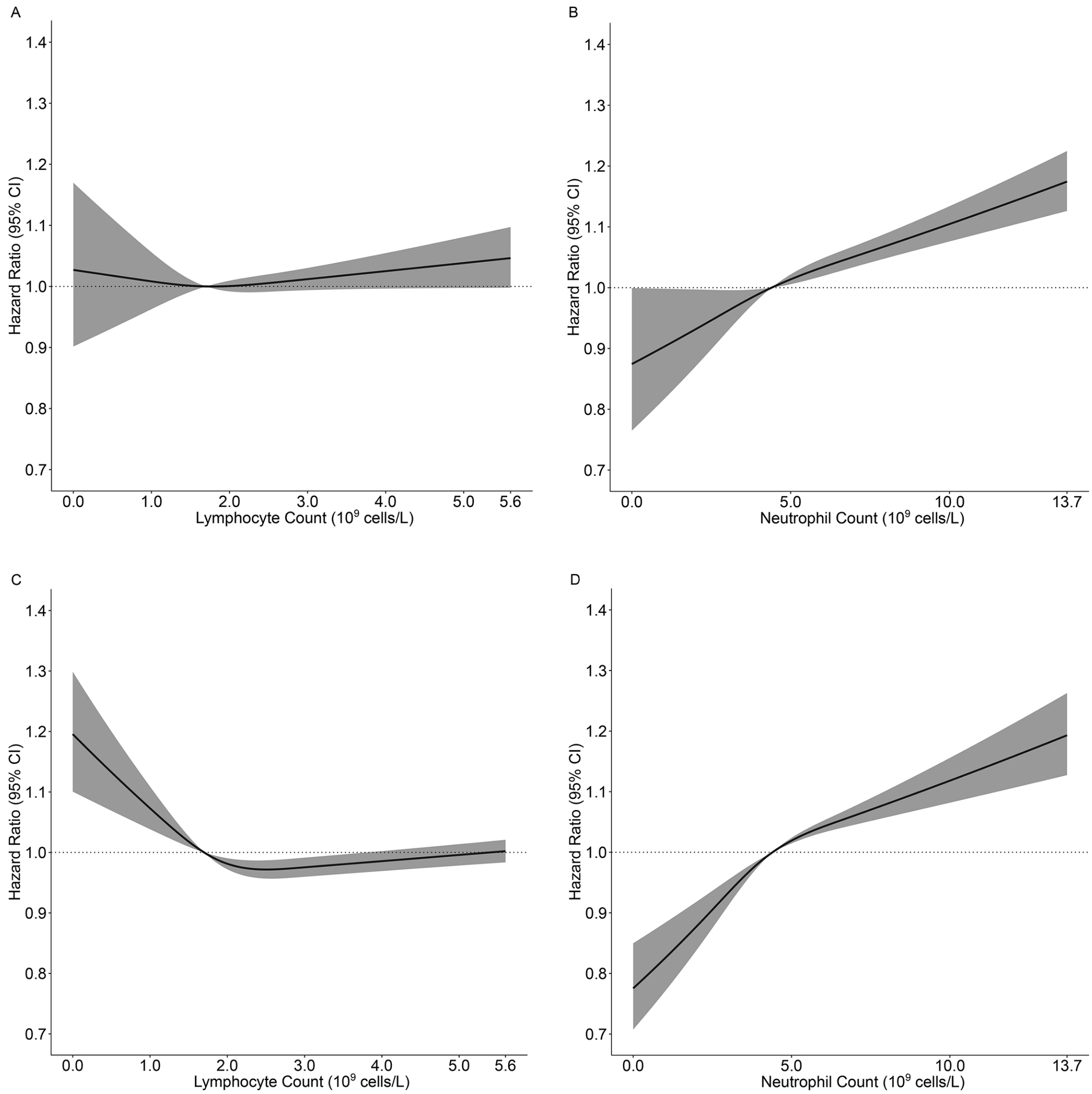

Figure 3 Association of continuous time-varying lymphocyte and neutrophil count with risk of presentation of common infection in individuals with and without inflammatory bowel disease. Lymphocyte and neutrophil counts each modelled a restricted cubic spline with three knots in a multivariable model*. Associations are shown relative to the mean count in individuals with IBD (lymphocyte count 1.7×10^9 cells/L; neutrophil count 4.4×10^9 cells/L), up to the 99.5th centile of each count variable. Grey shading represents 95% CIs. *Models adjusted for age, sex, IMD quintile, white ethnicity, BMI category, smoking status, alcohol category, hypertension, hyperlipidaemia, type 2 diabetes, peripheral arterial disease, atrial fibrillation, angina, myocardial infarction, stroke, heart failure, chronic kidney disease stage 3–5, chronic obstructive pulmonary disorder, chronic liver disease, malignancy, dementia, rheumatoid arthritis, fracture history, depression and medication use (rectal 5-ASA, rectal glucocorticoids, oral 5-ASA, oral glucocorticoids, immunotherapies and biologic therapies. With IBD (n=15 290, infection events=6692), (A) lymphocyte count and (B) neutrophil count. Controls (n=44 324, infection events=16 332), (C) lymphocyte count and (D) neutrophil count. ASA, aminosalicylic acid; BMI, body mass index; IBD,inflammatory bowel disease; IMD, index of multiple deprivation.

true indication of the medications evaluated in the study. While we explored associations between baseline medication exposure and risk of infection, these only represent a snapshot of a patient's medication exposure. For this reason, our estimates of medication use are lower than other studies, in particular, a recent analysis by Chhaya *et al* that assesses cumulative medication use in the 5 years after an IBD diagnosis.[61] We did not assess dosage effects, unlike a previous study that showed a higher risk of common infection in people prescribed higher initial doses of glucocorticoid treatment.[62] A time-updated evaluation of the effect of cumulative medication exposure and medication dose on infection risk in IBD, as well as potential drug-by-drug interactions, would be of interest for future work. Finally, this study did not show associations with all the infection subtypes examined. ILI and genital infections were not more common in individuals with IBD. However, the paucity of literature exploring these subtypes in IBD prevents further comparisons.

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CONCLUSIONS

People with IBD are at a higher risk of presenting with a wide range of diagnosed infections compared with matched controls of the same age and gender without IBD. The findings of this study suggest clinicians must be vigilant for infections in IBD, particularly in the context of use of systemic corticosteroids, immunotherapies and biologic agents. As highlighted by the recent COVID-19 pandemic, this is of importance in people who have comorbidities. Infection risk mitigation should be a multifactorial, pre-emptive approach involving early preventative screening (including appropriate vaccination),[36 43] and optimisation of nutritional status[63] and comorbidities. Further research is necessary to elucidate the mechanisms underlying specific infection susceptibility in the IBD population, the role of infection in the IBD pathological process, and the effect(s) of long-term use of immunomodulatory therapeutics on the course of IBD and on outcomes.

Acknowledgements Patients and practices who are members of the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC) network, who allow their data to be shared for surveillance, research, quality improvement and education. The collaboration of primary care computerised medical record system providers EMIS, TPP, InPractice Systems and Well-being in facilitating the RCGP RSC data. Medical writing and statistical support, funded by Pfizer, were provided by John Dennis, Andrew McGovern, and Annick Moon (Momentum Data), with project management support from Filipa Ferreira (University of Oxford).

Contributors KB, SdeL, DT, MN and PMI designed the study, supervised the data analysis, provided the interpretation of results and contributed to the drafting and critical review of the manuscript. All authors approved the final draft. As corresponding author, PMI attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. PMI is the guarantor and accepts full responsibility for the conduct of the study, had access to the data and controlled the decision to publish.

Funding This study, and medical writing support, was funded by Pfizer. As study authors, representatives of Pfizer contributed to the design and conduct of the study, interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Competing interests KB has received honoraria from Tillots, Thermo Fisher Scientific, Boehringer Ingelheim, Pfizer, and Yakult. SdeL is director of the RCGP RSC, he has received funding through his universities from Eli Lilly, GSK, Astra Zeneca, MSD, Sanofi, Seqirus, and Takeda. DT and MN are employees of Pfizer. PMI has received lecture fees from AbbVie, Celgene, Falk Pharma, Ferring, MSD, Janssen, Pfizer, Takeda, Tillotts, Sapphire Medical, Sandoz, Shire, and Warner Chilcott; financial support for research from MSD, Pfizer, and Takeda; advisory fees from AbbVie, Arena, Genentech, Gilead, Hospira, Janssen, Lilly, MSD, Pfizer, Pharmacosmos, Prometheus, Roche, Sandoz, Samsung Bioepis, Takeda, Topivert, VH2, Vifor Pharma, and Warner Chilcott.

Patient consent for publication Not required.

Ethics approval Study approval was granted by the Research Committee of the RCGP RSC. The study did not require a formal ethics board review, as defined using the NHS Health Research Authority research decision tool (http://www.hra-decisiontools.org.uk/research/).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The RCGP RSC dataset is held securely at Oxford University and the University of Surrey and can be accessed by bonefide researchers. Approval is on a project-by-project basis (www.rcgp.org.uk/rsc). Ethical approval by an NHS Research Ethics Committee may be needed before any data release/other appropriate approval. Researchers wishing to directly analyse the patient-level pseudonymised data will be required to complete information governance training and work on the data from university secure servers. Patient-level data cannot be taken out of the secure network.

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