AN INVESTIGATION OF THE INFLAMMATORY BOWEL DISEASES: THEIR EPIDEMIOLOGY, ASSOCIATIONS AND OUTCOMES

By

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Abstract

Background

The inflammatory bowel diseases (IBD), incorporating Crohn's disease (CD) and ulcerative colitis (UC), cause significant morbidity. The aims of this thesis were to explore the UK IBD burden; the outcomes of first acute UC admissions and further surgery risk in CD; and the risk of an IBD diagnosis in those presenting with an extraintestinal manifestation (EIM) of IBD.

Methods

Retrospective cohort studies (cross-sectional for prevalence estimates) in national primary and secondary care databases were used to examine the epidemiology and outcomes of subjects with IBD or those presenting with associated conditions.

Results

These studies demonstrated an increasing prevalence alongside a stable incidence of IBD in UK adults. Increased mortality and colorectal cancer (CRC) risk was observed in those with IBD compared to age/sex-matched controls. Subjects presenting with ophthalmic or dermatological EIMs were at increased risk of subsequently being diagnosed with IBD. Mortality during a first acute UC admission and within 12-months were low and colectomy rates in this group are falling over time. Further surgery in CD remains common although when increasing prevalence is accounted for, index resections appear to be falling.

Conclusions

IBD constitutes a significant disease burden in the UK and increasing prevalence will demand greater resources.

Dedication

I dedicate this thesis to my beloved family; to my wonderful wife, Sarah, who has been a rock in times of self-doubt and worry. To my beautiful children, Annie, Bertie, and Cece who have kept me grounded and continually make me laugh and remind me that there is importance beyond work, even important work. And for Evie, our beautiful little girl, who was taken from us too soon and now sits in heaven.

Acknowledgements

The list of those to thank is significant and demonstrates the kindness of those who have journeyed with me in this effort. I want to recognise that no body of work such as this is ever the work of a single individual but represents the support of some wonderful people.

First, I wish to sincerely thank my supervisors, Dr. Nigel Trudgill, Dr. Nicola Adderley, and Dr. Raoul Reulen. You have been incredibly supportive in this journey. This MD has been challenging for me, as I am sure they always are, but your support, enthusiasm and direction have provided space for me to learn and develop throughout. As a result I am lightyears ahead of where I started, and for this, I am eternally thankful!

I would also like to thank the team at the informatics department at University Hospitals Birmingham and the THINKING group at the Institute of Applied Health Research at the University of Birmingham. They have been not only colleagues, collaborators and teachers but more importantly good friends and I have treasured their support and the relationships I have made here in Joht, Aman, Ben, Tom, Anu, Thaya, Tom, Krishna, Krish, Jemma, James, Phil, and Kitty.

I warmly thank Prof. Denniston, Dr. Braithwaite, Dr. Bhala, Dr. Cole, Dr. Cooney, and Mr. Ward with whom I have received wise words and direction which has led to more rounded perspectives and deeper understanding from great experts in their fields.

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the BCSP team with whom I laughed a lot, but also cried this past year as we remembered a friend and colleague.

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To my in-laws, Kate and Andrew, I am thoroughly indebted, they have been a support to Sarah, the kids, and I throughout a very strange year. Your support has helped me finish this MD despite returning to the wards in the midst of a pandemic!

To my parents, Mum and Dad, and my brothers, Simon and Tim, who, along with Sarah are my wisest counsellors and have a belief in me that exceeds what any decent relative should have, thank you! In all things, first and last, I am thankful for my faith and my relationship with Christ Jesus, without which I would be a ship lost at sea.

Thank you to all mentioned and unmentioned for your support and encouragement, the smallest acts of kindness have been received with awe and I hope that this thesis can be a reflection of your generosity.

Finally and importantly, I wish to thank all those patients without whom this research could not have taken place. Inflammatory bowel disease affects individuals, each with unique experiences and we must never forget that each life is important and has much to teach us. I hope that this research, might move our understanding forwards for them.

Contribution statement

This thesis is the product of my own work, supported in conception, analysis and presentation by my supervisors, Dr Nigel Trudgill, Dr Nicola Adderley and Dr Raoul Reulen.

Given that the work submitted in this thesis is made up of several studies which utilised two databases (IQVIA Medical Research Data UK (IMRD-UK, incorporating– The Health Improvement Network (THIN)) and Hospital Episode Statistics (HES)) and focused on a variety of areas, further support and specialist advice was sought from co-authors.

The IMRD-UK studies were supported by consultant in public health medicine and joint theme lead for health informatics at the Institute of Applied Health Research (IAHR), University of Birmingham, Dr Krishnarajah Nirantharakumar and my fellow doctoral students and research fellows (Dr Joht Singh Chandan, Dr Tom Thomas, Miss Anuradhaa Subramanian, Mr Krishna Gokhale and Dr Rasiah Thayakaran) who are familiar with IMRD-UK, data extraction and methodologies involved in developing studies using this database. They provided educational support to me in terms understanding the methodology and use of IMRD-UK, as well as analysis, code selection, and manuscript proof reading. Medical specialty advice was provided for chapter 3 by consultant gastroenterologist, Dr Neeraj Bhala and chapter 6 by consultant ophthalmologist, Dr Tasanee Braithwaite and Professor of ophthalmology, Alastair Denniston.

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methodology, and manuscript proof reading. Consultant gastroenterologists Dr Rachel Cooney and Dr Andrew Cole provided specialty advice for chapters 4 and 5, respectively, and consultant colorectal surgeon Mr Stephen Ward provided specialty advice for chapter 5

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List of Abbreviations

AHD – Additional health data
AMR – Acceptable mortality recording
ApS – Aphthous stomatitis
AU – Anterior uveitis
BNF – British National Formulary
CARD15 – capsase recruitment domain 15 gene
CARMS – Clinical audit and registries management service
CD – Crohn's disease
CRC – Colorectal cancer
DARs – Data access request service
D-EIM – Dermatological extraintestinal manifestations (of IBD)
DExtER
EIM – Extraintestinal manifestations (of IBD)
EN – Erythema nodosum
GI – Gastrointestinal
HES – Hospital episode statistics
IBD – Inflammatory bowel disease
IBS – Irritable bowel syndrome
IC – Indeterminate colitis
ICD-10 – International Classification of Disease version 10
IMD – Index of multiple deprivation
IMRD-UK
IQR – Interquartile range
LOS – Length of stay
MAR – Missing at random
MNAR – Missing not at random
NHS – National health service
NOD2 – nucleotide-binding oligomerization domain containing 2 gene
O-EIM – Ophthalmic extraintestinal manifestations (of IBD)
ONS – Office for National Statistics
OPCS-4 – Office of Population Censuses and Surveys Classification of Interventions and Procedures version 4
PAS – Patient administrative system
PCCRC – Post colonoscopy colorectal cancer
PG – Pyoderma gangrenosum
PPV – Positive predictive value
PSC – Primary sclerosing cholangitis
Pys – person years

QoF – Quality outcome Framework
SMR – Standardised mortality ratio
SQL – Structured query language
SRC – Scientific review committee
SS – Sweet's syndrome
SUS – Secondary uses service
SWBH – Sandwell & West Birmingham Hospitals
TB – Mycobacterium tuberculosis
THIN – The health improvement network
UC – Ulcerative colitis
UHB – University Hospitals Birmingham
UK – United Kingdom
WHO – World Health Organisation

Thesis Format

This thesis is submitted in accordance with the University of Birmingham guidelines for an alternative thesis submission as detailed in regulation 7.4.1 (g). Therefore published manuscripts or those under submission (chapters 3-6) are inserted directly into this thesis. There is consequently some duplication in terms of methodology among some of the manuscripts and the restrictions of journals in terms of word count and greater detail may have been curtailed. However, chapter 1 (introduction), chapter 2 (materials and methods) and chapter 7 (discussion) provides further background and context to the manuscripts. Publications will not be included in the pagination sequence of the submitted thesis. To ensure clarity of tables and figures, these are self-contained within published manuscripts. This is also the case for references in published manuscripts.

List of achievements during MD

Oral presentations at conferences: BSG and UEGW:

King D, Dosanjh A, Patel P, *et al*. OTU-03 Pancreaticobiliary endoscopic ultrasound in England 2007–2017: changing practice, benefits and harms *Gut* 2019;68:A1-A2.

D. King, B. Coupland, A. Dosanjh, *et al.* OP061 The Risk of Further Resectional Surgery in the Ten Years Following a First Resection for Crohn's Disease in England (2019), UEG Week 2019 Oral Presentations. UEG Journal, 7: 10-188.

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Poster presentations at conferences: BSG, UEGW:

King D., Harvey P., Rees J. P0865 Validation of a scoring system for the quality of view at upper GI endoscopy UEG Journal Volume 7 | October 2019 ISSN 2050-6406

Flais A.1 , Maruf S.1 , Dhanji A.1 , Mahmood M.1 , Dhanji M.1 , King D.2 , Trudgill N. P0866 An audit of Post OGD Upper Gastrointestinal Cancers (POUGIC): 41% are potentially preventable UEG Journal Volume 7 | October 2019 ISSN 2050-6406

D. King[1, 2], J. Chandan[2], T. Thomas[3], *et al.* P0059 Achalasia Is Associated with Atopy in Patients Under 40 Years of Age (2020), Ueg Week 2020 Poster Presentations. UEG Journal, 8: 144-887.

National Audit:

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Publications outside this thesis:

1. King D *et al.* Overview of Gilbert's syndrome Drug and Therapeutics Bulletin (2019).

2. King D *et al.* Achalasia is associated with atopy in patients younger than 40 years of age. Am J Gastroenterol (2021).

3. King D *et al.* Editorial: increasing IBD prevalence and its complications in the context of the COVID-19 pandemic. Authors' reply. Aliment Pharmacol Ther (2020).

CHAPTER 1: INTRODUCTION

As a gastroenterology trainee I have seen the impact of inflammatory bowel disease (IBD) in both an acute and an outpatient setting. Despite its name, the IBDs can affect the whole patient with a spectrum of disease that ranges from a mild condition, easily treated with minimal input from specialists, to a severe, life-threatening and life-changing illness. The work presented in this thesis seeks to explore, through an observational approach, the burden of this disease in England and the UK, and to examine some of the adverse outcomes these diseases can result in. This introductory chapter will therefore provide a broad background for the observational studies, presented as manuscripts, in this thesis. It will seek to broadly describe what is currently known about IBD in terms of aetiology, diagnosis, epidemiology, and management. The rationale for the structure of the thesis will also be explained while more detailed and focused introductions are provided in the manuscripts found in the relevant chapters.

1.1 The inflammatory bowel diseases

IBD is characterised by chronic and relapsing inflammation of the bowel wall. It is a disease of unknown aetiology, thought to be the consequence of multiple susceptibility pathways triggering a dysregulated immune response to the gut flora, otherwise known as the microbiome (1). Unfortunately, however, knowing whether changes in microbial diversity are causative or consequent is a challenging area without firm conclusions at this time. Factors including genetic predisposition, exposure to gut specific communicable diseases, vitamin D, toxins and pollutants (e.g. smoking), improved sanitation, childhood antibiotic use, urbanisation and mode of delivery are just some of the factors known through empirical or observational evidence to contribute to IBD development (2). A complex interplay, therefore,

between a primed, dysregulated immune system and a dysbiosis within the gut microbiome is thought to result in the development of IBD (Figure 1.1).

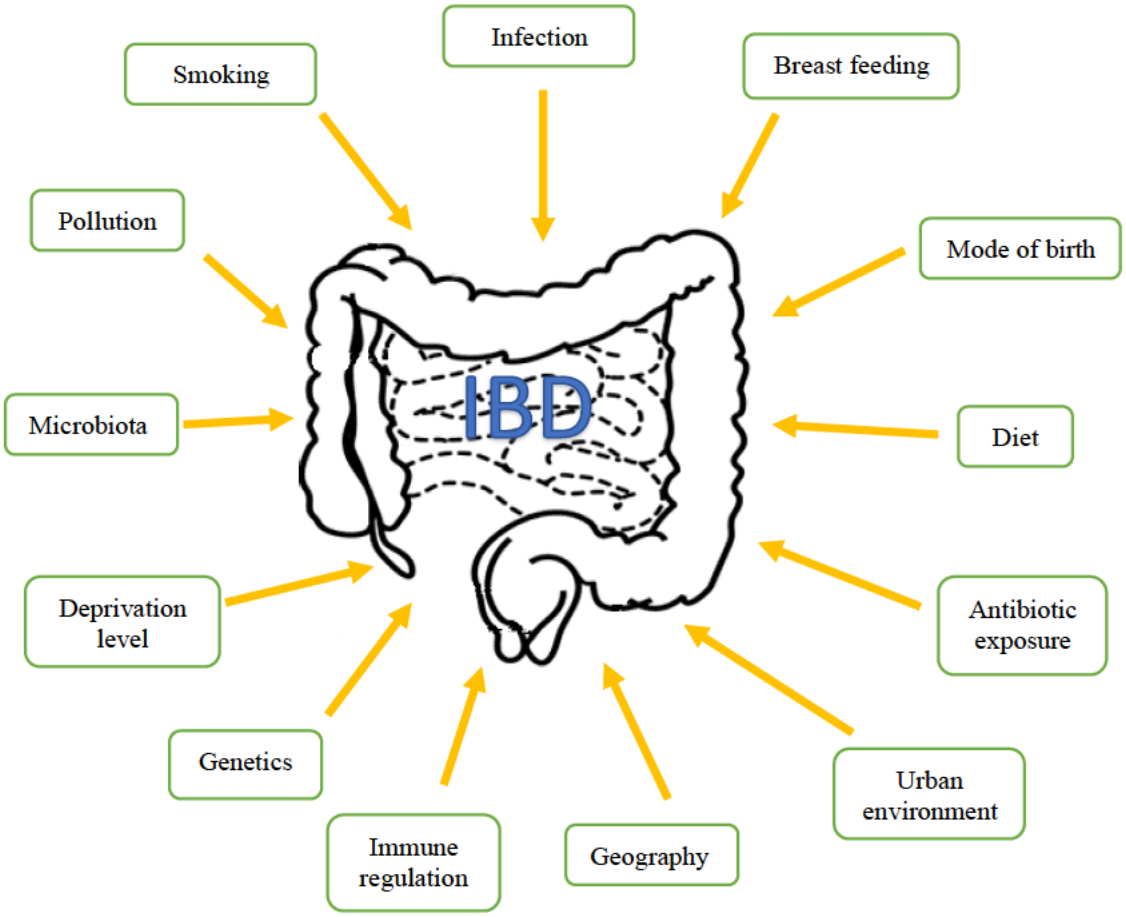


Figure 1.1. Factors contributing to the development of the inflammatory bowel diseases (Adapted from Ananthakrishnan et al. 2018 (2)).

IBD can develop in any age group, with age of onset having consequences for the natural history of the disease (3). There is, however, a particularly significant impact on working age populations, and the spectrum of severity dictates that many will suffer considerable morbidity as a result of these diseases with consequent societal and economic burden (4-6). The consequence of IBD affecting all age groups is that children, teens and young adults develop this condition with a majority diagnosed below the age of 40 (7). This has implications for development, transition between services, mental health and body image, as

well as issues surrounding fertility and the occurrence of voluntary childlessness (8-11). Although these are important areas for research, they lie beyond the scope of this thesis and are mentioned briefly here to demonstrate the multidimensional nature of this disease.

1.1.1 Diagnosis of inflammatory bowel disease

IBD consists of two sub-phenotypes: Crohn's disease (CD) and ulcerative colitis (UC). The diseases known as microscopic colitis also fall under the umbrella term of IBD, however, it is a comparatively benign condition in terms of mortality and cancer risk and for the purposes of this thesis IBD will refer only to UC and CD. There is no gold-standard diagnostic test for UC or CD and the diagnosis is based upon clinical presentation, endoscopic, histological, radiological and laboratory studies (12, 13). Around 10% of IBD cannot be clearly classified as either UC or CD and is considered indeterminate (14). When IBD is suspected, it is important to exclude other conditions from the differential diagnosis including, but not limited to medication related diarrhoea, irritable bowel syndrome (IBS), malignancy and infectious agents such as *Clostridium difficile* and *Mycoplasma tuberculosis* (TB), the latter being of particular concern in CD of the terminal ileum especially in certain areas of the world where TB remains endemic and more common than CD (15).

1.1.2 Crohn's disease

CD is a transmural, inflammatory condition which can affect anywhere along the gastrointestinal (GI) tract but leaves normal healthy areas of bowel between areas of mucosal damage. Endoscopically it is characterised by inflammation that typically spares the rectum, the presence of skipped-lesions, cobble stoning appearance and deep linear ulcers. Histologically, CD demonstrates patchy lymphocyte infiltrate with non-caseating, sarcoid-like granuloma formation, focal cryptitis and sparse crypt abscess formation (12). It is

characterised symptomatically by weight loss, abdominal pain and diarrhoea with or without rectal bleeding (16). Although CD can cause inflammation throughout the GI tract, the location remains relatively stable, with the majority sited in one of three areas – ileal, ileocolonic or colonic – with genetic studies suggesting that ileal CD and CD colitis lie along a spectrum with UC at the other extreme (12, 17, 18). The Montreal classification of IBD is helpful in characterising CD and is presented in Table 1 (19).

Table 1. Montreal classification for Crohn's disease *(Adapted from Satsangi et al. 2006 (19))*

Age (at diagnosis)	**A1 below 16 years old**
	A2 between 17 and 40 years old
	A3 above 40 years old
Location of inflammation in the bowel	L1 ileal
	L2 colonic
	L3 ileocolonic
	L4 isolated upper disease*
Behaviour of disease (phenotype)	B1 non-stricturing, non-penetrating
	B2 stricturing
	B3 penetrating
	p: perianal disease modifier

*L4 is a modifier that can be added to L1–L3 when concomitant upper gastrointestinal disease is present.

Although CD runs a relapsing course, scarring of the bowel may develop. The natural history of CD is that of usually consistent anatomical location but of varying behaviour. The bowel wall becomes inflamed leading to penetration and fistulisation to other organs including the skin, bladder, vagina, and other areas of the bowel. Permanent fibrosis may develop following inflammation and can lead to bowel lumen stricturing (narrowing) and subsequent obstruction. It is important to note that although this is the natural course of the disease, up to

one in five patients will have stricturing or penetrating disease at diagnosis (17). Once established, fibrotic changes will not respond to medical therapy and will require intervention, often surgical, to relieve symptoms. Surgical resection can be a valuable alternative to increased medical therapy in some individuals even before stricturing develops (20), however, recurrent disease following bowel resection for CD is common and in some individuals recurrent resections may be required and at its most severe lead to short bowel syndrome with implications for nutrition (21, 22). Early diagnosis is therefore important to try and achieve early control of the disease and reduce the conversion from potentially medically manageable inflammatory changes to those mandating surgical intervention (23, 24).

1.1.2.1 Aetiological factors in Crohn's disease

Of the many environmental factors implicated in the development of CD, smoking has been most commonly investigated and is known to both increase the risk of developing CD and contribute to a poor prognosis (25). Genetic predisposition is also well described in IBD with parents conferring increased risk of IBD to their offspring, high prevalence seen among Ashkenazi Jews (an ethnically distinct group with genetic homogeneity), while in around one third of monozygotic twins where one is affected, both individuals will go on to develop CD (12, 26). Many genetic foci have now been implicated in the development of IBD, but mutations within the nucleotide-binding oligomerization domain containing 2 (NOD2) gene, otherwise known as capsase recruitment domain 15 (CARD15), is thought to play a key role in the dysfunctional intestinal barrier that leads to CD in some individuals (26). These mutations have been found in certain populations and confer a significantly increased risk of CD, while unaffected first-degree relatives of such individuals have been shown to also have increased bowel wall permeability (27). Many pathways are involved in the development of

CD and many unknowns persist. A dysfunctional relationship between the microbiota and immune system appears to be at the heart of this disease and it is the subsequent recruitment and destructive implications of leucocyte migration to the bowel wall that leads to the clinical entity known as CD (12).

1.1.2.2 Overview of Crohn's disease management

The target of CD therapy has evolved over time from that of clinical remission to sustained endoscopic and histological mucosal healing. This a realisation that although recurrent disease post-surgery, for example, is almost universal, symptoms are not always seen and yet sustained mucosal healing predicts the need for less active intervention (22, 28, 29). The mainstay of CD therapy is that of immunosuppression with guidelines advocating corticosteroids for induction of remission followed by the early introduction of steroid sparing immunomodulators (e.g. thiopurines). Failure of these medications in terms of relapse or incomplete remission or indeed those patients with a high-risk profile (including fistulising disease or perianal disease) may be candidates for a step-down approach where biological therapies (antibodies to inflammatory pathway targets which are either murine or fully humanised) are introduced to achieve sustained remission (30, 31). Although monitoring of therapy is possible through drug levels, clinical scores, and importantly through biomarkers such as the liver derived acute phase reactant c-reactive protein (CRP) or the neutrophil derived faecal calprotectin (32), specific biomarkers that negate the need for invasive endoscopy to ascertain histologic remission remain elusive but are a key research priority highlighted in the recent British Society of Gastroenterology (BSG) guidelines on IBD (30). Bowel obstruction, fistulising disease, abscess formation and bowel perforation may all require surgical intervention, and it is the complementary nature of medicine and the timely

intervention of surgery that can ensure the best outcomes for patients who suffer from this complex disease.

1.1.3 Ulcerative colitis

UC affects the mucosa of the large bowel and is characterised by mucoid diarrhoea and bloody bowel motions. Endoscopically UC demonstrates rectal involvement, a loss of the normal colonic vascular markings, a friable mucosa with spontaneous bleeding as well as erosions and superficial ulceration with late-stage disease leading to a narrowed and shortened colon. Histologically UC is largely a disease of the mucosa and submucosa, in contrast to the full thickness appearance seen in CD. Crypt distortion and shortening is seen while lymphoid infiltrate is more uniform and crypt abscess formation is seen commonly in contrast to their scanty appearance in CD (13). UC may be confined to the rectum (proctitis) but may cause inflammation extending to more proximal areas (left-sided or pan-colonic), however, unlike CD, the inflammation is confluent and does not have skipped-lesions. UC can extend its anatomical location over time. Up to half of patients have distal colitis at diagnosis, but 25-50% will progress more proximally over time and those who present with proctitis and later extend are more likely to require colectomy than those presenting with extensive colitis at baseline (13, 33, 34). The Montreal Classification categorises UC disease phenotype and is shown in Table 2 (19).

Table 2. Montreal classification for ulcerative colitis

(Adapted from Satsangi et al. 2006 (19))

Extent		Anatomical involvement
E1	Ulcerative proctitis	Confined to the rectum.
E2	Left sided UC (distal UC)	Distal to the splenic flexure.
E3	Extensive UC (pancolitis)	Proximal to the splenic flexure

Although, compared to CD, those with UC are often identified at an earlier stage (largely due to symptoms of bloody diarrhoea), the condition can still present acutely and lead to emergency admissions with systemic upset, surgical intervention and increased mortality rates (35).

1.1.3.1 Aetiological factors in ulcerative colitis

As with CD, the aetiology of UC is unknown but is also thought to be a consequence of multiple factors acting in concert. Some factors have been better described than others. To a lesser degree than CD, genetic predisposition is observed in UC with notable risk among monozygotic twins, first-degree relatives and Ashkenazi Jews (13). Smoking, in contrast to CD, is protective with those who smoke appearing to have a milder form of the disease while ex-smokers are more susceptible to UC development than never smokers (36, 37). Nicotine appears to be the key component in smoking for UC, however, its use as a therapeutic agent is limited by its adverse effects (38). Both UC and CD development appear to be more common following a gastrointestinal infection and although dysbiosis of the microbiome is a significant field of interest in IBD, it is in UC that faecal microbiota transplantation (repopulating the colon to restore a healthy gut flora) has been shown to have the most promise (39). Appendicectomy prior to the development of UC appears to be protective against UC and may be related to the microbial triggers associated with the appendix or the immunogenic lymphoid tissue that is removed (40). More recently the role of appendicectomy in those with UC is being explored (41, 42).

1.1.3.2 Overview of ulcerative colitis management

The management of UC is similar to that of CD, with a focus on induction followed by maintenance of remission. Although corticosteroids may be used to induce remission in more severe cases, the mainstay of treatment for most patients is the anti-inflammatory medication mesalazine. Failure to induce remission and those with more severe disease profiles require corticosteroids or rescue therapies to induce remission (infliximab (biologic therapy) or cyclosporine (calcineurin inhibitor)) followed by maintenance immunomodulators (thiopurines), biologic therapies or novel agents such as the small molecule Janus kinase inhibitor (JAK), tofacitinib (13, 30). Failure to control UC medically requires resection of the colon.

1.2 Extraintestinal manifestations of IBD

Although the bowel is the primary target of inflammation, IBD can be considered a systemic disease with anaemia, malnutrition, fatigue and sarcopenia arising directly from the bowel's inflammatory state (43). In contrast, through extraintestinal manifestations (EIM), either as a result of IBD pathophysiology acting outside the bowel (similar pathogenic pathways leading to associated diseases), or as a consequence of pharmacological treatment, IBD may variabl affect multiple organ systems (12, 13, 44, 45) (Figure 1.2).

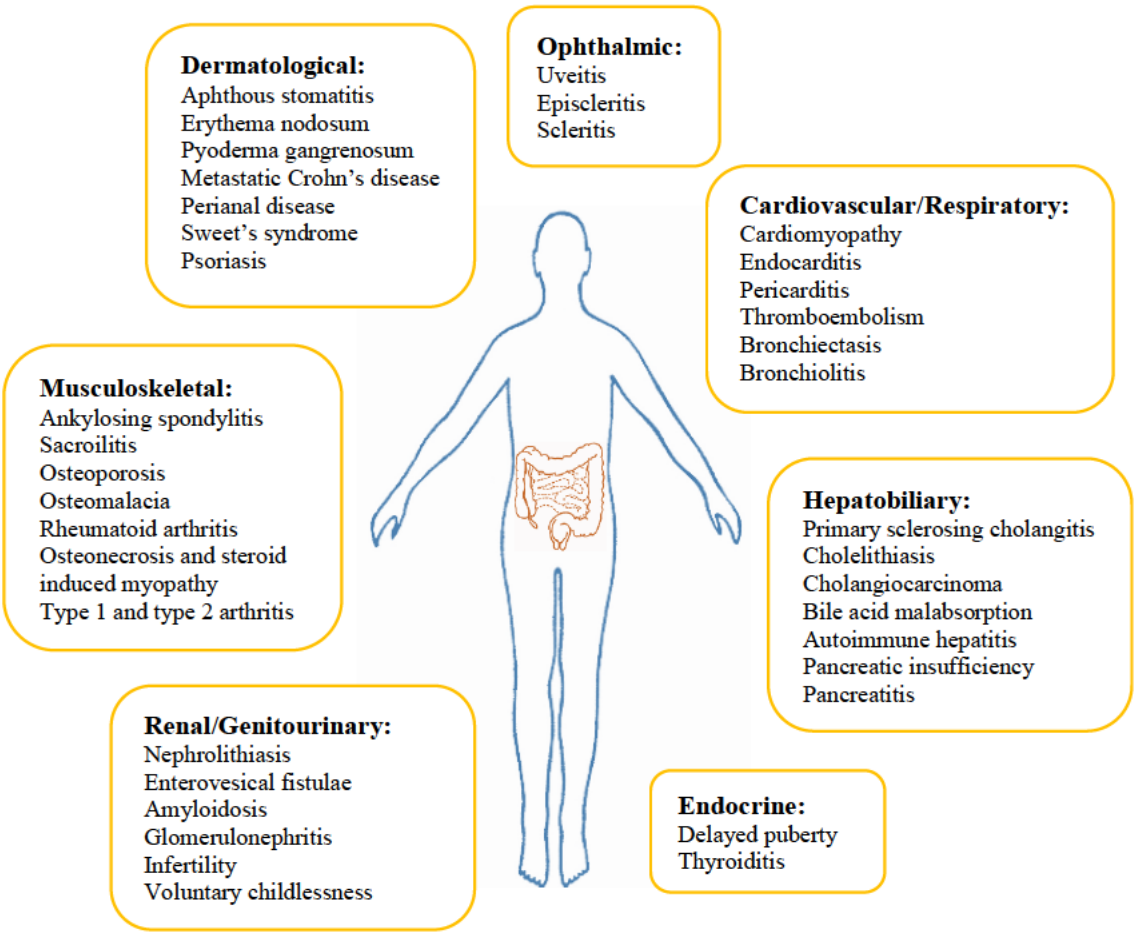


Figure 1.2. Organ systems affected and diseases associated with IBD (Adapted from Ricart & Sandborn, in: Cohen RD (eds) Inflammatory Bowel Disease, 2003 (45))

Although these conditions commonly occur in isolation, when associated they may present at the time of an IBD diagnosis, during the course of or more rarely in advance of a later diagnosis of IBD. Importantly, some EIMs will flare when the bowel is inflamed and run in parallel, settling as the IBD remits while others run an independent course (46, 47). There are, however, accepted *classical* EIMs, some of which have been explored in this thesis.

These classical EIMs can be stratified into four organ systems:

1. Ophthalmic
    i. Uveitis
    ii. Episcelritis
    iii. Scleritis
2. Dermatological
    i. Erythema nodosum
    ii. Pyoderma gangrenosum
    iii. Sweet's syndrome
    iv. Aphthous stomatitis
3. Musculoskeletal
    i. Type 1 and 2 arthritis
    ii. Ankylosing spondylitis
    iii. Sacroiliitis
4. Hepatobiliary
    i. Primary sclerosing cholangitis

A holistic view of the patient suffering from IBD is therefore important. As medicine becomes ever more specialised and subspecialised, patients will present to a variety of healthcare professionals whose focus may not be on these associated pathologies. Many EIMs may not only affect a patient's quality of life but may carry significant morbidity and mortality risks (48-50). Seen from the alternative perspective, those presenting with these

EIMs but who are yet to be diagnosed with IBD, are at potential risk and clinicians should be alert to this possible, often delayed diagnosis.

1.3 The epidemiology of IBD

Both UC and CD can affect any age group with varying incidences reported (51, 52). Differences in IBD risk dependent upon sex have been observed and a hormonal influence is thought to be the reason for an increased CD risk profile for females following puberty (53-55). IBD had been seen as a western disease entity, however, westernisation, changes in diets, improved sanitation, migration away from rural and developing regions and a heightened awareness of these diseases are potential factors that may have contributed to increasing incidence around the world (56). The epidemiology of IBD globally has accordingly changed substantially over time with immigrant risk profiles becoming akin to that of the indigenous population (57, 58). Figure 1.3 highlights countries with the highest recorded prevalence based on recent estimates. A recent systematic review demonstrated an increasing incidence of IBD in developing nations and a stabilisation of the incidence in developed nations (59, 60). While incidence may have stabilised or even declined slightly in some areas of the world, prevalence appears to be increasing (61). Incidence and prevalence data from the UK have been sparse and previously estimates were based on regional populations.

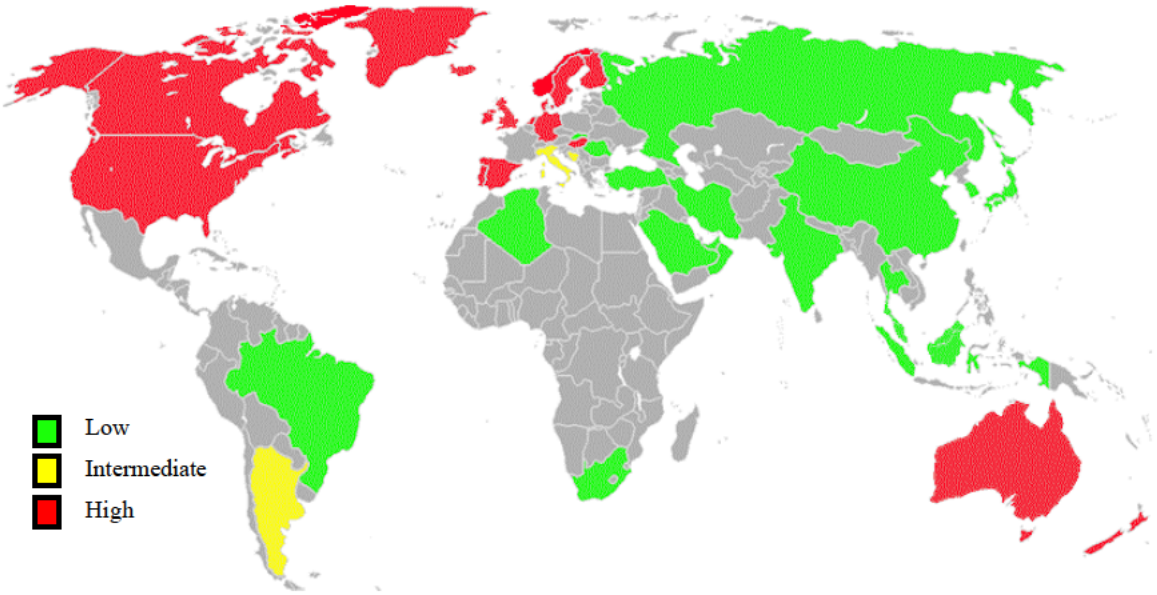


Figure 1.3. Global IBD prevalence ranging from <1 to >300 per 100,000 population (Adapted from Molodecky et al. 2012 and Ng et al. 2018 ((59).(60)))

1.4 Outcomes in IBD – mortality, surgery and colorectal cancer

Although mortality in the IBD population has declined over time (62), and some mortality estimates are comparable to background populations, there does appear to be a slightly increased risk of death compared to background populations dependent on subtype and population studied (63-65). Premature death in the IBD population is not always directly related to the digestive system, (63, 66, 67) however, acute presentations necessitating emergency admissions and surgery still convey a quantifiable mortality risk (35, 68).

1.4.1 Steroids, admissions, and surgery

It was from the 1950s, when Truelove and Witt demonstrated a survival advantage with the use of corticosteroid therapy in acute severe colitis that mortality rates fell dramatically in IBD (69). A further survival effect was seen when early surgery was offered following an

initial therapeutic trial of steroids (70). However, even in this group mortality remains ~5% with age and anaesthetic risk being significant predictors of 30-day mortality (71). IBD is mainly managed in an outpatient setting, with acute admissions declining over time (72). The focus on timely diagnosis, treatment (surgical or medical) provided by the right person in the right place, and multidisciplinary team working is in light of an awareness that acute unplanned admissions and emergency surgery contribute to IBD mortality (73-75). Surgery is an essential tool in the management of IBD and while surgical treatment for UC is curative with later elective surgery often undertaken to reverse stomas and achieve bowel continuity, surgery for CD is not (13). Colectomy in UC is done in a minority of cases now (~10% at 10 years), on the other hand, those with CD will likely require surgery at some point during their illness and the risk of further surgery remains high (76, 77). An appreciation that early recognition of post-surgical recurrence permits goal directed approaches to disease control and has therefore been incorporated into guidelines (16, 78).

1.4.2 Colorectal cancer and IBD

A serious cause of IBD mortality is colorectal cancer (CRC). Thankfully, historical estimates have either fallen significantly or been re-evaluated from population rather than tertiary centre studies (79-82): The 2001 Eaden *et al.* meta-analysis of CRC in UC utilised data from tertiary referral centres and surgical series and presented an overall risk of 3/1000 person years (pys) and a cumulative risk of 2, 7 and 12/1000pys for each decade from diagnosis. More recent evidence, however, incorporating population studies, suggests that the CRC risk is far lower than has previously been reported, with a 2014 review by Castano-Milla *et al.* estimating an overall rate of 1.58/1000pys and a cumulative risk of 0.91, 4.07 and 4.55/1000py for each decade from diagnosis (79, 80). Despite an observed UC-associated CRC rate fall over time,

risks remain high compared to sporadic CRC risk. Importantly, UC disease characteristics (extent, and severity) and duration play a crucial role in CRC and are consistently reported as risks in these reviews (79, 80). CRC in CD has been less extensively examined, although there remains a substantial observed increased CRC risk. In a 2012 meta-analysis by Canavan *et al.* of 14 studies reported cumulative risks of 0.29, 0.56 and 0.83/1000pys for each decade from CD diagnosis and a relative risk of 4.5 (95% CI 1.3-14.9) (83, 84). Screening and then surveillance for those with colonic disease form part of national and international guidance (30). Those with primary sclerosing cholangitis (PSC), most of whom will have colitis, are at particular risk and require annual surveillance (85). As for mortality, rates of this cancer have fallen over time in those with IBD but it often remains a challenging diagnosis to make with a different, potentially more aggressive phenotype and higher mortality rate than in sporadic CRC (80, 86, 87). Although not a focus of this thesis, it is important to mention that other cancers, in particular lymphoma and skin cancer, have been observed in association with IBD, although the absolute risks remain small (88-90).

1.5 Thesis rationale, aims and objectives

The structure of this thesis, in line with the University of Birmingham guidelines for the alternative format, will take the form of published or publish-ready manuscripts. As well as this introduction to the thesis, a methods section is provided to broadly explain the databases used in the studies presented. A final discussion chapter is also presented to summarise the work in this thesis and suggest directions for future research.

1.5.1 Aims

Published IBD epidemiology data and the figures used by health authorities for the United Kingdom (UK) have been out-of-date, extrapolated from other nation's data or based on regional datasets which may not be representative of the UK as a whole (60, 91-93). The IBDs contain a spectrum of severity with IBD-related outcomes including mortality, CRC and acute admissions and surgical interventions. While bowel disease is the primary insult for many, IBD also represents a systemic disease. Many with IBD will have EIMs and in those who present with conditions which are potential EIMs, a minority will later develop IBD.

In light of this knowledge the work of this thesis will aim to estimate (1) the current incidence and prevalence of UC and CD in the UK adult population, as well as the trends in mortality and CRC; (2) the consequence of first recorded acute admissions to hospital for UC subjects; (3) the risks of further surgery for those with an index recorded CD resectional surgery; and (4) the risk of IBD development in those who present with an ophthalmic or dermatological condition which are potential EIMs.

1.5.2 Objectives

1. To describe the epidemiology, mortality and CRC risk of UC and CD in a UK primary care database over time using retrospective cohort and cross-sectional studies.
2. To review the surgical risk in England of those with a first recorded acute UC admission to hospital and the future risk of surgery in those with a first recorded bowel resection in CD using a nationwide hospital database and a retrospective cohort study approach.
3. To describe the risk of IBD in those presenting with potential ophthalmic and dermatological EIMs using a retrospective matched cohort design in a UK primary care database.

CHAPTER 2: METHODS

This chapter will describe the databases used for the purposes of the research presented in this thesis. Data presented in the following chapters are presented in a format suitable for submission for publication in a peer-reviewed journal and as such include detailed methodology and material sections, including study designs and statistical handling of the data presented. However, some of the background and utility of these databases are applicable to several chapters and it is thus fitting that they are described in broad terms here.

2.1 Database research

Routinely gathered patient information, collected, and uploaded to an electronic record and later used in health research has had a fruitful history with studies emerging from as early as the 1980s in the UK (94, 95). However, the aim of such data collection is not primarily for the purpose of observational research, but rather for local service evaluation and remuneration for activity undertaken as well as the planning of healthcare service provision (96). Nonetheless the secondary research use provides a rich data resource for observational studies with large subject numbers and the potential for generalisability given its real-world nature (97). Such databases have both significant strengths and limitations related to the priorities of the primary need for the data.

The challenge in conducting research with routinely collected data is one of compromise between the benefit achieved in terms of sample size and real world setting versus the quality, validity and sort of data that is available (97). Individual patient records may number in the millions, but the accuracy of research findings lies in the quality of the data and the reliability of the coding. With this in mind, the questions that can be answered through these databases are subject to the reality that certain patient-level data that is retrievable in prospective,

dedicated cohort studies or randomised controlled trials are not found in such routinely collected data. Notwithstanding the potential limitations and restrictions that such databases pose for research, the large sample sizes, the longitudinal nature of the data and the relative costs involved in obtaining the data for research purposes provide many benefits where such research would either be impossible or impractical otherwise.

For studies to be conducted using information from these databases, exposures, confounders, and outcomes must be defined and permit reproducibility. Much of the data handling time is therefore spent cleaning and organising the data following its extraction. Defining disease, medication, and procedures for a study via the grouping of code descriptors, allows such research to be conducted and for readers to clearly identify what is being included in a specified definition.

2.1.1 Codes used in healthcare and coding

Clinical codes are usually alphanumeric or numeric strings of digits which allow the hierarchical categorisation of disease and symptoms as well as providing unique identifiers for pharmaceuticals, procedures and additional health data (AHD) such as smoking status or a subject's height and weight. Routinely collected patient information is recorded using these codes either by medical or clerical staff (in the context of primary care) or by dedicated coders (in the context of secondary care). This coding system has become more automated over time as primary care and more latterly, secondary care, has become computerised. In this way clinical staffs' use of the electronic patient record permits auto-coding (98). Clinical coding in secondary care is a professional occupation (99). Clinical coders translate what is written by clinical staff in notes into codes that can be recorded for administrative purposes. It

is a complex task but relatively accurate with improvements seen over time (100, 101). As time moves on and newer, more robust systems of coding are introduced (SNOMED CT) it is envisaged that (and I write from personal experience) more and more secondary care clinicians at the point of care will be involved in coding as computerisation of the patient record becomes widespread (100).

Several code classification systems are employed by the databases used in this thesis:

2.1.1.1 Read codes

Read codes are a system of hierarchical terminology codes used in primary care settings since 1985 (102). The code level structure allows enhanced detail in a thesaurus which aims to be comprehensive. Numbered chapters 0-9 cover codes describing occupation, history, examination and procedures as well as administrative functions, and alphabetical chapters cover codes for diagnoses and conditions. An example of the hierarchical structure of Read codes is shown in Figure 2.1. There have been several iterations of Read codes, however, following a 2018 update, no further updates have been made as a new comprehensive, national coding system was introduced (SNOMED CT) (103).

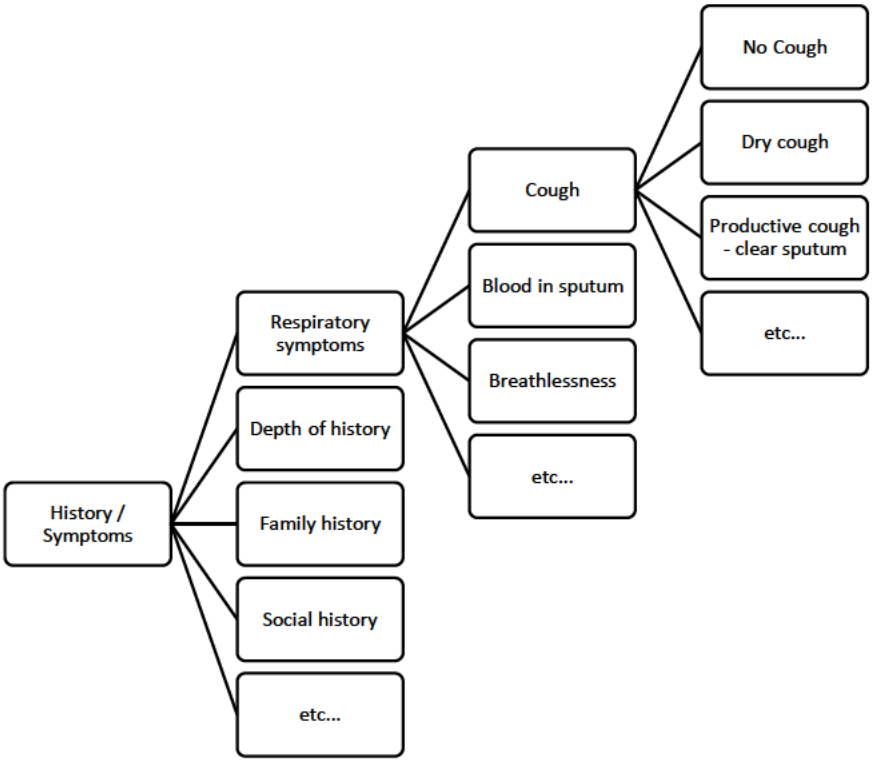


Figure 2.1. Hierarchical structure of Read codes.

2.1.1.2 BNF codes

British National Formulary (BNF) codes identify drugs and follow a numerical format of characters which identify chapter, section, paragraph and sub-paragraph as applicable. An example of this for the aminosalicilate, mesalazine would be: 01.05.01.00 where the chapter is the gastro-intestinal system, the section is the chronic bowel disorders, and the paragraph is the aminosalicylates. The BNF codes do not uniquely identify a drug but rather a class of medicines (e.g. all aminosalicylates – mesalazine, sulfasalazine, balsalazide sodium etc.), however, codes found in the primary care database used in this thesis do uniquely identify drugs, even to the detail of specific doses and preparations. BNF codes are provided alongside such codes in order to aid in identification and usage.

2.1.1.3 ICD-10 codes

The International Classification of Disease version 10 (ICD-10) is the 10th revision of the World Health Organisation's (WHO) compendium of diseases and disorders. It was originally produced in 1893 and its 10th iteration was approved for use in 1990. The ICD-11 was released in 2018 with implementation of use for reporting planned for 2022 (104). Like the Read code classification, the ICD-10 coding system is hierarchical with chapters I – XXII followed by alphanumeric levels. An example of the hierarchical structure of ICD-10 codes is shown in Figure 2.2.

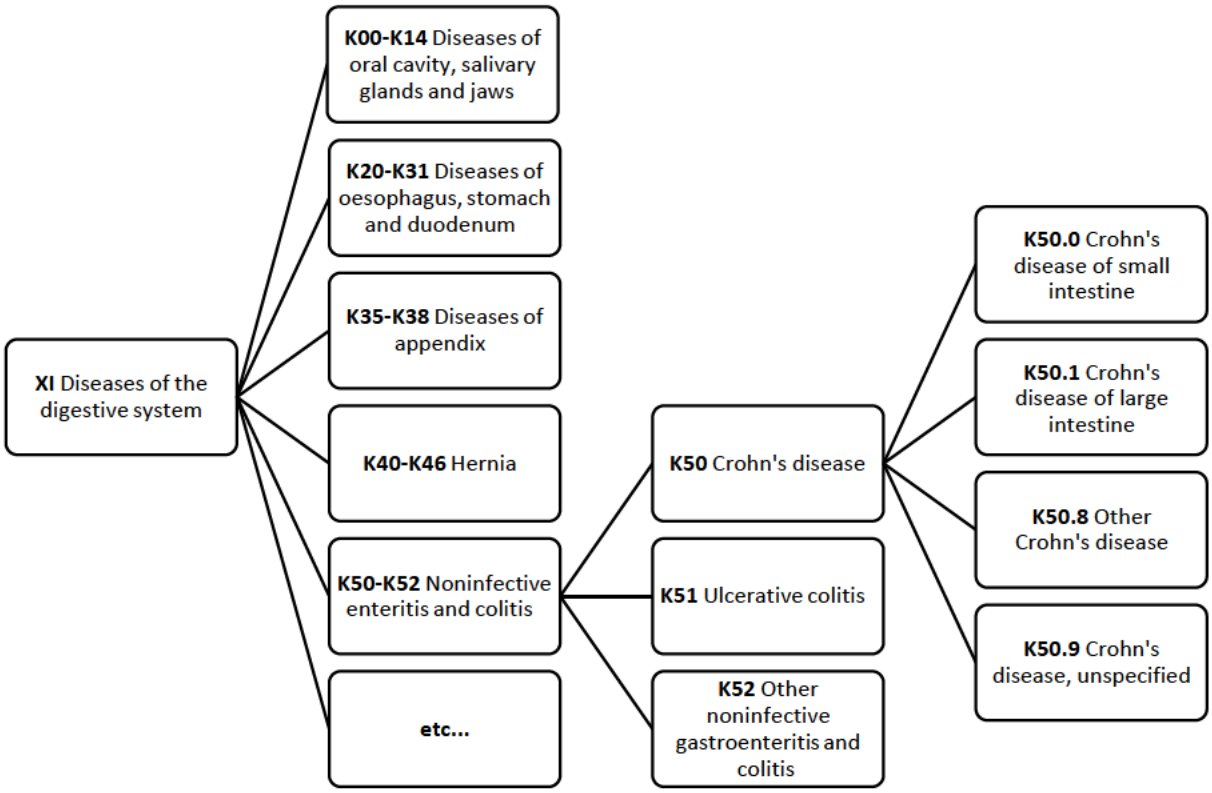


Figure 2.2. Hierarchical structure of ICD-10 codes.

2.1.1.4 OPCS-4 codes

The Office of Population Censuses and Surveys Classification of Interventions and Procedures Version 4 (OPCS-4) codes are used in secondary care in England for the clinical

coding of procedures. From April 2020 version 4.9 has been implemented, while version 4.8 was in use from April 2017. As with the ICD-10 codes, the OPCS-4 codes use four characters to provide detail. The first character is always a letter and signifies the chapter for the code, with subsequent characters being numerical. An example of this coding system for an extended right hemicolectomy with end-to-end anastomosis would be: H06.1 where *H* signifies the chapter for lower digestive system, *06* the extended right hemicolectomy and the final digit: *1* signifying the end to end anastomosis. Several codes may be needed to demonstrate nuances of a certain procedure with chapter codes Y and Z providing methods and sites of operations, respectively (105).

For the purpose of study design the hierarchical code systems for diagnostic and procedure codes require careful inspection and a systematic method for code selection including review of codes used in published studies, existing code lists, and use of a second code reviewer. Thus, a staged approach was used for code selection in databases:

- **Stage 1:** Important words and synonyms for procedures or conditions identified.
- **Stage 2:** Search of look-up tables using key words for codes to develop a list of codes as definite, possible, or not for study inclusion.
- **Stage 3:** Search of published literature or existing published code lists applicable to these databases to identify codes previously used and identify limitations previously encountered in the use of codes.
- **Stage 4:** Discussion within study team as well as external medical and surgical clinicians as appropriate to determine final code lists for use in data extraction.

2.1.2 Validation

Routinely collected data from both primary and secondary care is for administrative purposes including remuneration but also for service planning, commissioning, and benchmarking services. For these reasons the quality of coding is an area of ongoing concern for the NHS and validation processes are embedded in the data acquisition processes of such databases (106, 107). Despite attempts by these databases to ensure that the routinely collected data they store is accurate and reliable, they do rely on the original coding of disease to be correct; as such, a lack of clinical validation is a concern (108). Certain areas of clinical coding are assumed to be accurate, either due to the implications of payment by results (a national tariff system for health care), for example, procedures or high-cost drugs delivered in hospital settings or due to the Quality and Outcomes Framework (QOF) incentivisation in primary care (109). However, these assumptions cannot always be evidenced, and validity of procedures and diagnoses coded is a priority for the generalisability of any research findings. Therefore, where possible, either previous validation studies or validation of codes (incorporated into the research methodology) has been undertaken in the work of this thesis.

The research conducted in this thesis has used two databases which use routinely collected data, one from primary care providers and one from secondary care.

2.2 IQVIA Medical Research Data UK (IMRD-UK) – *previously known as* The Health Improvement Network (THIN)

Almost all UK residents are registered with a general practitioner (GP) and digitisation of the GP surgery is now the norm with some practices having been computerised since the 1980s

(110). IMRD-UK (previously known as THIN) contains 6% of the UK population, derived from over 790 GP practices. It is thought to be representative and generalisable to the UK population with representation from each of the four UK nations (111). The database was created in 2002 as a collaboration between what are now IQVIA (a health research company) and Vision (a GP consultation software developer). An unobtrusive data acquisition process allows data from the patient record to be uploaded to IMRD-UK to produce a pseudoanonymised, longitudinal database with records uploaded from 1994 to the present (112). Data is recorded in IMRD-UK as Read codes (102), additional health data (AHD) codes and drug codes.

2.2.1 Data extraction from IMRD-UK

IMRD-UK data first requires extraction and further formatting before being suitable for use in research. Colleagues, Mr Krishna Gokhale and Dr Krishnarajah Nirantharakumar from the Institute of Applied Health Research (College of Medical and Dental Sciences, University of Birmingham) have developed a user-friendly data extraction tool known as DExtER (Data extraction for epidemiological research) (113). DExtER allows study data extractions to be performed in such a way that the methodology can be reproduced. The tool allows the definition of study parameters including time periods, exit definition and the calculation of patient years at risk by defining the time a subject becomes eligible for follow-up (index date) and the time they leave the study (exit date). DExtER further permits the definition of exposed and unexposed group selection, outcomes of interest and baseline subject characteristics (113). Additionally, extractions of baseline characteristics, outcomes and multiple recordings of events can be later performed and merged to a master extraction file if required. For studies where an unexposed cohort is used for comparison, the index date for an exposed subject was designated to the matched unexposed subject in order to mitigate

immortal time bias; the phenomenon whereby a study's design permits follow-up time to be accrued in the exposed group while an outcome event could not be experienced, thereby biasing in favour of those exposed (114). Figure 2.3 demonstrates the interface for study time determinants in DExtER. Output from the DExtER tool is in .csv format which can then be imported into statistical software package for further data cleaning and analysis (e.g. Stata) (115). Using the DExtER tool I was able to input code lists, design studies, extract data in a state in which I was then able to clean and analyse it.

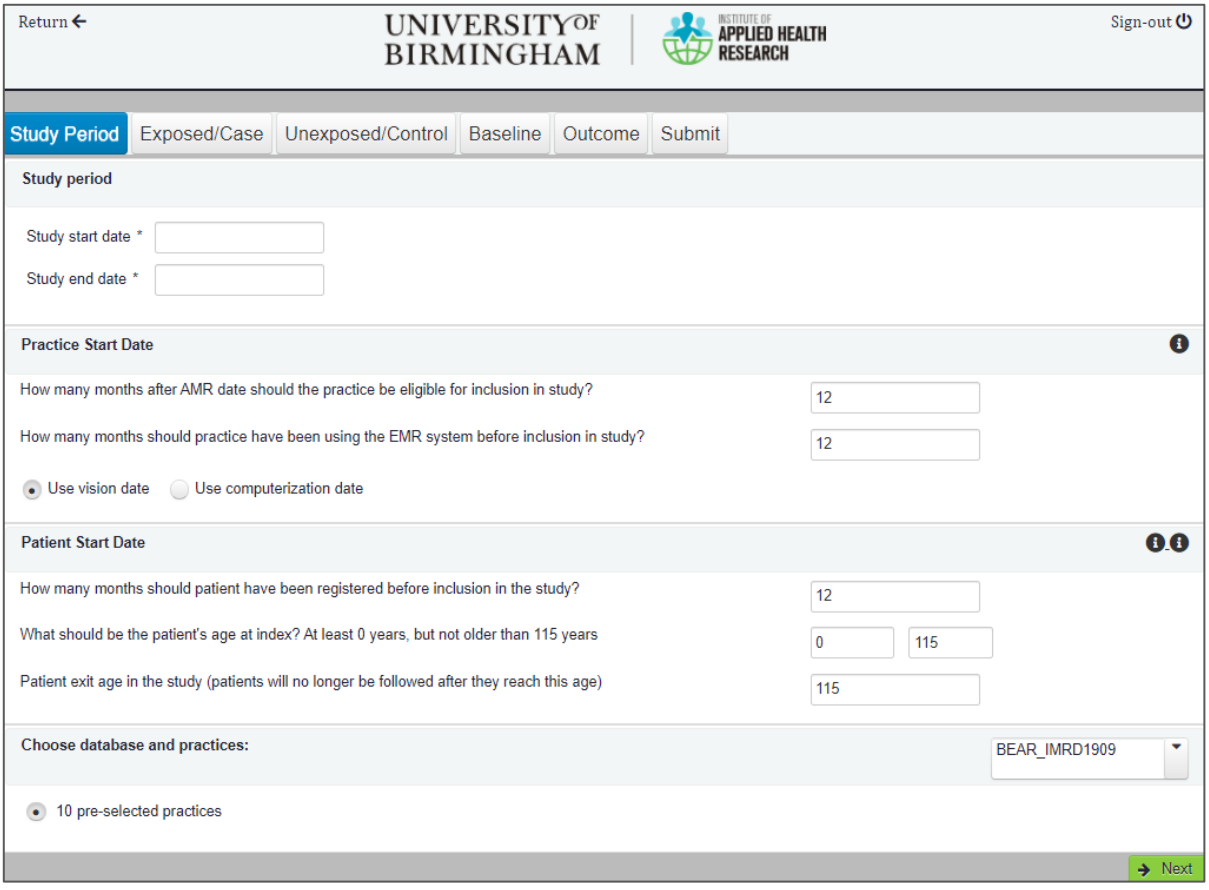


Figure 2.3. DExtER interface example.

2.2.2 General eligibility for study inclusion

The research studies presented in this thesis, using the IMRD-UK database, have required an eligibility assessment before GP practices and or subjects can be included in studies in order to maximise the quality and reliability of the data used. Integral to this is the concept of the acceptable mortality recording (AMR) date. This is a date derived from IMRD-UK practices' recording of death compared with the predicted mortality rate based on national figures given a practice's demographic characteristics. Consequently, when the national and IMRD-UK mortality figures align an AMR date is assigned. For uniformity and validity of study data derived from this database, individual practices become eligible for study inclusion from the later of one year after the installation date of the electronic patient record system; or one year after the AMR date (116, 117). Individual subjects on the other hand, become eligible for inclusion from the later of the date their practice becomes eligible; or one year after registration with their practice in order to ensure a comprehensive recording of baseline characteristics (Figure 2.3).

2.2.3 Data validation in IMRD-UK

Gold-standard data validation in primary care is costly, involving the engagement of several GP practices to confirm a diagnosis uploaded to a database. It may involve several algorithms of code combinations or evidence of a drug having been prescribed to provide a positive predictive value (PPV) of the accuracy of a diagnosis derived from the coding. Validation studies are therefore not straightforward to conduct nor are they always appropriately reported, and generalisability from one disease to another is not assured (118, 119). Such validation studies were not feasible in the presented research although previous studies have suggested that IBD coding is good (118). Due to my concerns about specificity at the expense

of sensitivity, code algorithms used by others were not employed in the studies presented in this thesis (these can variably require multiple codes over time or drug-diagnosis combinations), however, assessment of medication prescribed and surgical procedures compatible with IBD were examined. Where an IBD subtype was coded as both UC and CD the most frequent code was taken as the diagnosis. When IBD was coded as CD and UC in equal frequency, then the earliest date was taken for the diagnosis date and the latest code was taken as the IBD subtype diagnosis. In such a situation the later subtype maybe a revision and perhaps more accurate.

2.3 Hospital Episode Statistics

Hospital Episode Statistics (HES) provide data on secondary care setting activity in England including outpatient appointments, emergency department attendances and inpatient hospital admissions. The primary purpose of the data is in ensuring that hospitals are paid for the services they deliver (96). This is achieved through the accruing of information during a patient's secondary care contact. This data is then supplied to NHS Digital (an NHS body responsible for data and IT systems) in the form of Secondary Uses Service (SUS) data for handling purposes and subsequently outputted as either payment by results or as HES data, following quality assurance procedures. HES data can then be used for a variety of endeavours including healthcare planning and research (120).

Diagnostic data and procedural data are recorded in HES as ICD-10 and OPCS-4 codes, respectively (104, 105). Subjects included in HES are given a unique anonymised HES identification number which allows them to be tracked through secondary care contact without identifying individuals and further permits linkage to other sources of data (e.g. Office for National Statistics (ONS) for cause of death records) (120). In general for HES

data, where less than six subjects are described in isolation; this information is not provided in order to ensure confidentiality, in particular where outcomes may be rare and therefore identifiable. HES data is formed of *episodes* (time a patient has spent under the care of a consultant), while several episodes make up a *spell* (a continuous period of time spent in hospital). For most admissions a patient is cared for by a single consultant and therefore a spell is equal to a single episode (121). HES data is split into years running in concert with the financial year (April 1st to 31st March) and has captured different secondary care settings or 'domains' over time (Figure 2.4) including inpatient admissions but also accident and emergency (A&E) and outpatient attendances.



Figure 2.4. HES setting coverage over time (adapted from Boyd et al. 2017).

Each subject record in HES contains a series of data entries, or fields, obtained from the patient administrative system (PAS). This provides a rich source of information including age, sex, index of multiple deprivation (IMD), ethnic group, admission method and dates of admission and discharge as well as the consultant and specialty a patient is cared for under (122, 123). Information provided by providers can be further interrogated to provide derived fields including e.g. length of stay (LOS). Each episode has procedural (OPCS-4 codes) and diagnostic fields (ICD-10 codes) with a primary diagnosis being the main reason for hospital stay. Subsequent fields for diagnoses include subsidiary and secondary diagnoses (up to 20

for inpatient stays) such that a broad picture of an admission along with complications or other important diseases are contained within the record.

2.3.1 Data extraction from HES

Access to HES data was through collaboration with HES access holders in the informatics department of the University Hospitals Birmingham NHS Foundation Trust. HES data is accessed from an NHS Digital online system and is initially managed through Structured Query Language (SQL), where study parameters are programmed. Extracted study data can then be uploaded to statistical software packages for further management and analysis. Due to the nature of the licensing, study design, coding, and statistical models were planned and supervised by me and implemented by the informatics department with further analysis of outputs conducted by myself.

2.3.2 Data validation in HES

Unlike primary care databases where gold standard validation of diagnostic coding requires costly studies involving practice review of patient records, in HES, validity of codes and procedures can be undertaken at a local hospital level through service evaluation or audit of the patient record. Procedural and diagnostic codes in HES can be extracted for individual hospital trusts and the counts can then be compared to those of the hospital record reviewed through service evaluation and audit. This can then provide an idea of the accuracy of coding as a validation method. Where possible this was done in two hospital trusts of different sizes and catchment; alternatively, a previous validation published from our group was applied (124).

2.3.3 Ethics and Scientific review approval

The IMRD-UK primary care database uses anonymised data provided from IQVIA. The database underwent initial ethical approval for data collection by the South East Multicentre Research Ethics Committee in 2003. Further to this, each study using the data has undergone independent review through a scientific review committee (SRC) before study commencement. SRC reference numbers are provided in relevant chapters.

The HES database requires that a robust data access request service (DARS) process be undertaken by the data holders at University Hospitals Birmingham (UHB) NHS Foundation Trust informatics department. Under license HES data can then be used following approval from the Health Informatics Review Group at UHB with individual studies receiving a clinical audit and registries management service (CARMS) number. A CARMS number is provided in relevant chapters.

CHAPTER 3: CHANGING PATTERNS IN THE EPIDEMIOLOGY AND OUTCOMES OF INFLAMMATORY BOWEL DISEASE IN THE UNITED KINGDOM: 2000-2018

In this chapter I present the findings from retrospective cohort and cross-sectional studies examining the incidence and prevalence of IBD in the UK adult population as well as the risk of death and colorectal cancer in those with IBD compared to age/sex matched controls.

Special acknowledgement is given to Dr Rasiah Thayakaran for his help in the statistical methodology employed in predicting future prevalence of IBD in the UK, using Holt-Winters' double exponential smoothing model.

Supplementary material is found in the appendices for this chapter at the end of the thesis.

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Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018

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Summary

Background: Data regarding incidence, prevalence and long-term outcomes of inflammatory bowel diseases in the UK are limited or outdated.

Aims: To investigate incidence and prevalence of Crohn's disease and ulcerative colitis and risk of colorectal cancer and all-cause mortality in these diseases.

Methods: Inflammatory bowel disease cases between 2000 and 2018 were identified from a national primary care database. Inflammatory bowel disease prevalence was forecast until 2025. The association between inflammatory bowel disease and colorectal cancer and all-cause mortality was investigated using age/sex-matched retrospective cohort studies. Hazard ratios were adjusted for age, sex, deprivation, comorbidity, smoking status and body mass index.

Results: Ulcerative colitis prevalence increased from 390 to 570 per 100 000 population from 2000 to 2017. Prevalence of Crohn's disease increased from 220 to 400 per 100 000. In 2017 male Crohn's disease prevalence was 0.35% (95% confidence interval 0.34-0.36); female prevalence was 0.44% (0.43-0.45). Prevalence of inflammatory bowel disease is predicted to be 1.1% by 2025. Incidence of ulcerative colitis and Crohn's disease was 23.2 (22.8-23.6) and 14.3 (14.0-14.7) per 100 000 person-years respectively. Subjects with ulcerative colitis were more likely to develop colorectal cancer than controls (adjusted Hazard Ratio 1.40 [1.23-1.59]). Colorectal cancer rates remained stable in inflammatory bowel diseases over time. Ulcerative colitis and Crohn's disease were associated with increased risk of all-cause mortality (1.17 [1.14-1.21] and 1.42 [1.36-1.48] respectively).

Conclusions: The UK prevalence of inflammatory bowel disease is greater than previous reports suggest and we predict an 11% increase in prevalence by the year 2025. Mortality risk in inflammatory bowel disease and colorectal cancer risk in ulcerative colitis are increased compared to matched controls.

The Handling Editor for this article was Professor Richard Gearry, and it was accepted for publication after full peer-review.

Nicola J. Adderley and Nigel Trudgill are joint authors.

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1 | INTRODUCTION

Inflammatory bowel diseases are characterised by chronic and relapsing inflammation of the bowel. They can affect any age group, have a significant impact on working age populations and lead to a considerable societal and economic burden.[1,2] Inflammatory bowel disease largely consists of two sub-phenotypes: Crohn's disease and ulcerative colitis. The global epidemiology of inflammatory bowel disease has changed substantially over time, with a recent review demonstrating an increasing incidence of inflammatory bowel disease in developing nations and a stabilising incidence in developed nations.[3,4] Similarly, all-cause mortality rates within the inflammatory bowel disease cohort have improved significantly, with recent research suggesting rates similar to those of the general population.[5] Historically a key risk factor for mortality in the inflammatory bowel disease cohort was thought to be the association between inflammatory bowel disease and colorectal cancer (CRC)[6]; however, recent evidence suggests that this risk is now much lower than previously thought.[7,8]

Inflammatory bowel disease can lead to hospitalisation and time off work, and its management is costly. Given the individual and societal impact of these diseases, accurate and up-to-date data on prevalence and outcomes are important for service planning. Published United Kingdom (UK) inflammatory bowel disease epidemiology data are out of date or based on small or regional datasets which may not be representative of the United Kingdom as a whole.[4,9-12]

The primary aim of this study was to provide an up-to-date description of the incidence and prevalence of inflammatory bowel diseases in the UK and forecast the expected prevalence of these conditions. The secondary aim was to quantify the risk of all-cause mortality and colorectal cancer (CRC) in the inflammatory bowel disease cohort.

2 | MATERIALS AND METHODS

2.1 | Data source

This study utilised The Health Improvement Network primary care (THIN) database. This is derived from 787 general practices across the UK and incorporates data from approximately 15 million subjects. It is generalisable to the UK population.[13] Longitudinal patient-level data including medication use, primary and secondary care investigations and diagnoses are uploaded electronically using a hierarchy of clinical (Read) codes.[14] Diagnoses of inflammatory bowel disease are derived from general practitioners who receive this data from secondary and tertiary centres where the diagnosis would have been established. Practices were included in the study if they had achieved an acceptable mortality recording threshold and at least one year had elapsed since the installation of the electronic medical record system.[15] Inclusion only after attainment of an acceptable level of data recording (assessed by acceptable mortality recording) reduces the risk of under-recording.

2.2 | Study design

Cross-sectional and retrospective cohort studies were carried out to identify the annual point prevalence and incidence rates, respectively, of ulcerative colitis and Crohn's disease among adults aged 18 years and over between 1 January 2000 and 31 December 2017. Incident cases were defined as new cases during the study period without a previous diagnosis before entry date. Prevalent cases were defined as cases diagnosed/recorded before the annual point prevalence calculation for the year of interest.

The prevalence of ulcerative colitis and Crohn's disease was projected forward to 2025 using Holt-Winters' double exponential smoothing model with 80 and 95% prediction intervals (PI). For the model validation, the dataset was separated into two portions: training (from 2000 to 2012) and test (from 2013 to 2017) data. The model was fitted to the training data and predicted prevalence up to 2017 compared with test data.

The incidence of colorectal cancer was determined in the whole adult, THIN database population and in those with ulcerative colitis and Crohn's disease. Mortality and colorectal cancer incidence rates were quantified using matched cohort studies between 1 January 2000 and the date of the latest data available at the time of study (17 January 2018). Four controls, unexposed to either ulcerative colitis or Crohn's disease, were directly matched for each ulcerative colitis or Crohn's disease subject by age, sex, Townsend deprivation level[16] and index date. Index date was defined as the date of diagnosis of ulcerative colitis or Crohn's disease for incident cases and one year after joining an eligible practice for prevalent cases. If individuals in the colorectal cancer study had a previous record of colorectal cancer prior to the study start date, they were excluded. Subjects with a colectomy code prior to cancer diagnosis were excluded from the colorectal cancer study. Subjects were followed up until the outcome of interest, death or the earlier of a subject leaving the practice or the final collection of data on a subject. If subjects were coded for both ulcerative colitis and Crohn's disease, the later of the two was considered the diagnosis while the earliest diagnosis date was retained.

2.3 | Data validation

Clinical codes used to identify ulcerative colitis, Crohn's disease and colorectal cancer are listed in Appendix S1. Code lists used to identify patients with inflammatory bowel disease have been previously validated.[17,18] For internal validity, 88 practices were examined during the study time period. Subjects coded with ulcerative colitis were assessed to ascertain whether they had ever had medical treatment (thiopurine [azathioprine or mercaptopurine] or mesalazine) or definitive surgical

treatment in the form of colectomy or both. This methodology was replicated in subjects with Crohn's disease; however, all bowel resection surgeries and perianal surgical procedures were also included.

2.4 | Statistical analysis

2.4.1 | Incidence and prevalence

Annual point prevalence of ulcerative colitis and Crohn's disease was calculated on 31 December each year per 100 000 population and was stratified by sex. Point prevalence for ulcerative colitis and Crohn's disease in 2000 and 2017 was standardised to an adult UK age-sex standardised population for these years derived from the Office for National Statistics data (ONS).[19] Incidence rates per 100 000 person-years (py) were calculated from 1 January to 31 December annually. Incidence was stratified by sex and 10-year age bands over the study period and annually. Multivariable Poisson regression models were used to calculate incidence rate ratios (IRR) for ulcerative colitis and Crohn's disease, adjusting for age band, sex and year of study.

2.4.2 | Mortality and colorectal cancer outcomes

Baseline characteristics were compared using Chi-squared tests for categorical variables and Student t-tests for continuous variables. A multivariable Cox proportional hazards model was used to quantify colorectal cancer risk, adjusting for sex, body mass index (BMI) at index date, Townsend deprivation quintile, Charlson comorbidity score and smoking status. A further multivariable Cox proportional hazard model was used to derive adjusted hazard ratios (aHR) to quantify risk of mortality, adjusting for the same variables.[16,20] The proportional hazards assumption was tested using log-log plots. Missing values were included as separate categories. Kaplan-Meier survival analyses for all-cause mortality were performed in ulcerative colitis and Crohn's disease subjects and their controls. Poisson regression models adjusting for year, age at index date and sex were used to assess trends in colorectal cancer in ulcerative colitis and Crohn's disease. Standardised mortality ratios (SMR) annually and overall were produced for both ulcerative colitis and Crohn's disease using UK standardised mortality rates for each year of the study, derived from the Office for National Statistics data.[21] Analyses were performed using Stata version 15.0[22] and $P < 0.05$ were considered statistically significant.

2.5 | Sensitivity analysis

The impact of age on the risk of mortality and colorectal cancer was assessed through sensitivity analysis excluding subjects over 70 years old at index date. This analysis may improve internal validity due to the reduced proportion with inflammatory bowel disease drugs or inflammatory bowel disease surgery observed in older age bands. The colorectal cancer and mortality studies were performed with a combination of incident and prevalent cases. A sensitivity analysis including only incident cases of ulcerative colitis or Crohn's disease and their respective controls was undertaken.

3 | RESULTS

3.1 | Validation

Within the validation cohort there were 2578 subjects with ulcerative colitis (median age 47 [IQR 33-62] years, 49.6% female). Eighty-nine percent of subjects with a diagnostic code for ulcerative colitis had a record of either an inflammatory bowel disease drug or a colectomy. The Crohn's disease validation cohort consisted of 1943 subjects (median age 41 [IQR 27-56] years, 56.3% female). Eighty-seven percent of Crohn's disease subjects had a code with an inflammatory bowel disease drug or an appropriate surgery recorded. When ulcerative colitis or Crohn's disease and an inflammatory bowel disease drug, excluding surgical codes, were examined, co-coding was observed in 87.6% and 81.0% of cases respectively (Appendix S2).

3.2 | Cohort for prevalence and incidence studies

Seven hundred and eighty-seven general practices are included in The Health Improvement Network database. The 787 practices contributed 8 486 415 subjects to the study based on the study period, population age and data quality requirements as previously described. 71.6% of subjects came from English primary care practices, 3.6% from Northern Irish practices, 14% from Scottish practices and 10.8% from Welsh practices.

3.3 | Prevalence of ulcerative colitis and Crohn's disease

The annual point prevalence of ulcerative colitis over the study period increased from 390 per 100 000 population in 2000 to 570 per 100 000 in 2017 (Figure 1), with an average increase of 2.5% per annum. Prevalence of ulcerative colitis was similar among males and females. In 2000, age-sex standardised point prevalence of ulcerative colitis was 365 per 100 000 population for adult males, 372 for adult females and 369 per 100 000 overall. In 2017 the standardised rates were 662 for males, 615 for females and 637 per 100 000 population overall. The prevalence of Crohn's disease increased from 220 to 400 per 100 000 over the 18 years studied, an average rise of 3.5% per annum. When stratified by sex, there were more female subjects with Crohn's disease (Figure 1). The standardised point prevalence of Crohn's disease was 189 for males, 235 for females and 213 per 100 000 population overall. In 2017, Crohn's disease point prevalence for

males was 354 and for females 448 per 100 000, with an overall adult prevalence of 403 per 100 000 population in 2017.

Using Holt-Winters' double exponential smoothing model, ulcerative colitis and Crohn's disease prevalence were forecast forward to the year 2025. Ulcerative colitis prevalence in 2025 was forecast to be 592.6 (95% PI 490.3-694.9) per 100 000 and Crohn's disease prevalence was forecast to be 487.2 (95% PI 470.7-503.8) per 100 000. Time series graphs with actual and forecasted prevalence of ulcerative colitis and Crohn's disease are shown in Appendix S3.

3.4 | Incidence of ulcerative colitis and Crohn's disease

Between 2000 and 2018, in the study of incidence, 12 787 incident cases of ulcerative colitis were identified, with an overall incidence rate of 23.2 (95% CI 22.8-23.6) per 100 000 person-years (py). A bimodal profile of incidence rates by age was identified, with peaks in the 30-40 and 60-80 age groups (Appendix S4). Incidence was higher in males compared to females (24.4 [23.9-25.0] and 22.1 [21.5-22.6] per 100 000 person-years respectively). Adjusting for year and sex, females had a 10% lower risk of developing ulcerative colitis compared to males between 2000 and 2018 (incidence rate ratio 0.90 [0.87-0.93], $P < 0.001$). The overall incidence of ulcerative colitis fell during the study period from 25 per 100 000 person-years in 2000 to 20 per 100 000 person-years in 2017, an average of 1.6% per annum, incidence rate ratio 0.98 (95% CI 0.98-0.99), $P < 0.001$. Incidence remained stable in those aged under 50 years of age (incidence rate ratio 1.02 [95% CI 1.01-1.02], $P < 0.001$) but fell in those aged 50 and over (incidence rate ratio 0.93 [0.93-0.94], $P < 0.001$). Trends in incidence rates overall and among males and females are shown in Figure 2. 7904 incident cases of Crohn's disease were identified in the study of incidence, with an overall incidence rate of 14.3 (14.0-14.7) per 100 000 py. A bimodal incidence rate age profile was again demonstrated, with a higher peak in the 18-30-year age category and a smaller peak in the 60-70 age group (Appendix S4). Crohn's disease incidence rates were stable over the study period with a higher incidence of Crohn's disease in females compared to males (12.8 [12.4-13.2] and 15.8 [15.4-16.3] respectively) (Figure 2). Adjusting for year, females had a 23% higher incidence of Crohn's disease compared to males (incidence rate ratio 1.23 [1.18-1.29], $P < 0.001$). The overall incidence of Crohn's disease, adjusting for year of study, remained stable over the study period (incidence rate ratio 0.99 [0.99-1.00], $P = 0.590$). In those aged under 50 years, the incidence increased slightly over time (incidence rate

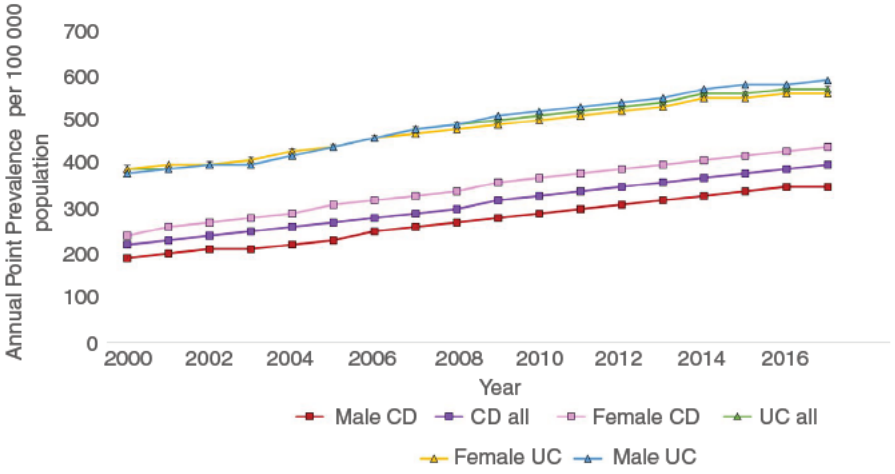


FIGURE 1 Annual point prevalence of ulcerative colitis and Crohn's disease per 100 000 population. CD, Crohn's disease; UC, ulcerative colitis

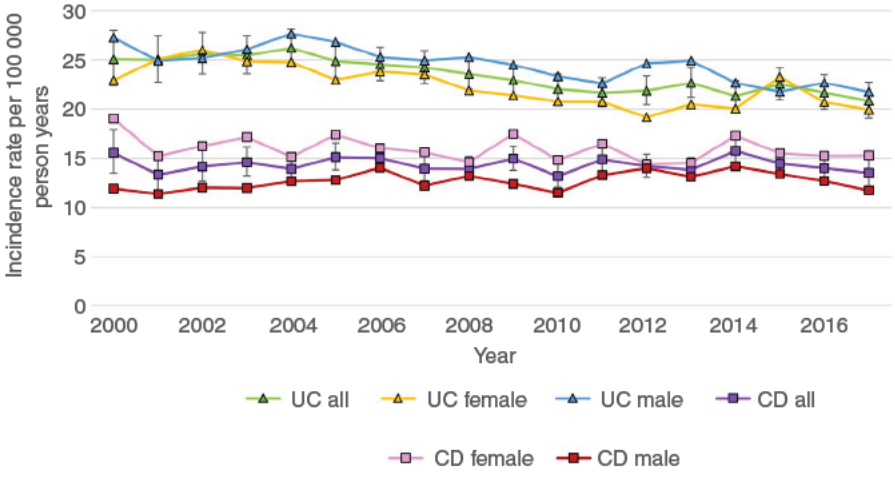


FIGURE 2 Annual incidence rate of ulcerative colitis and Crohn's disease per 100 000 person-years. CD, Crohn's disease; UC, ulcerative colitis

ratio 1.03 [1.03-1.04], $P < 0.001$), but in those aged 50 and over, the incidence fell by 5% (incidence rate ratio 0.95 [0.94-0.96], $P < 0.001$).

3.5 | Colorectal cancer risk in ulcerative colitis and Crohn's disease

The colorectal cancer (CRC) incidence rate for the whole adult THIN population was 64.6 (95% CI 63.9-65.3) per 100 000 py over the study period. The rate in females was 57.3 (56.4-58.2) and in males 72.1 (71.1-73.1) per 100 000 py.

In the matched ulcerative colitis colorectal cancer cohort study, 37 793 subjects with ulcerative colitis (12 319 (33%) incident cases and 25 474 (67%) prevalent cases) were matched to 148 126 control subjects contributing 242 407 and 966 522 person-years at risk respectively. Baseline demographic characteristics are shown in Table 1 and a comparison of incident and prevalent case demographics is shown in Appendix S5. Three hundred and twenty-eight (0.87%) new cases of colorectal cancer were observed in the ulcerative colitis group and 917 (0.62%) new cases in the control group. The incidence rate of colorectal cancer in ulcerative colitis subjects was 135.3 (121.2-150.9) per 100 000 py compared to 94.9 (85.9-97.7) in

TABLE 1 Colorectal cancer study: cohort demographics

	Ulcerative colitis (%)	Ulcerative colitis controls (%)	Crohn's disease (%)	Crohn's disease controls (%)
N	37 793 (20.33)	148 126 (79.67)	26 160 (20.27)	102 881 (79.73)
Male	18 860 (49.90)	73 840 (49.86)	11 534 (44.09)	45 327 (44.06)
Female	18 933 (50.10)	74 286 (50.14)	14 626 (56.91)	57 554 (55.94)
Age, median (IQR)	51 (37-65)	50 (37-64)	43 (31-58)	43 (31-58)
Age, n (%)				
18-30	4723 (12.50)	18 609 (12.56)	5817 (22.24)	22 887 (22.25)
30-40	6519 (17.25)	25 866 (17.46)	5532 (21.15)	22 095 (21.48)
40-50	6793 (17.97)	27 045 (18.26)	4777 (18.26)	18 968 (18.44)
50-60	6896 (18.25)	27 326 (18.45)	3922 (14.99)	15 497 (15.06)
60-70	6088 (16.11)	23 685 (15.99)	3087 (11.80)	12 059 (11.72)
70-80	4328 (11.45)	16 746 (11.31)	1999 (7.64)	7699 (7.48)
>80	2446 (6.47)	8849 (5.97)	1026 (3.92)	3676 (3.57)
Deprivation score				
1 (least deprived)	8672 (22.95)	34 175 (23.07)	5367 (20.52)	21 201 (20.61)
2	7613 (20.14)	29 940 (20.21)	4915 (18.79)	19 400 (18.86)
3	7077 (18.73)	27 841 (18.8)	4915 (18.79)	19 402 (18.86)
4	5592 (14.80)	21 948 (14.82)	4180 (15.98)	16 386 (15.93)
5 (most deprived)	3353 (8.87)	12 894 (8.70)	2970 (11.35)	11 470 (11.15)
Missing	5486 (14.52)	21 328 (14.40)	3813 (14.58)	15 022 (14.60)
Charlson comorbidity score				
0	24 469 (64.74)	103 970 (70.19)	17 344 (66.30)	75 238 (73.13)
1	8134 (21.52)	28 044 (18.93)	6085 (23.26)	19 187 (18.65)
2	2889 (7.64)	8939 (6.03)	1568 (5.99)	4859 (4.72)
3	1282 (3.39)	4185 (2.83)	693 (2.65)	2128 (2.07)
4+	1019 (2.70)	2988 (2.02)	470 (1.80)	1469 (1.43)
Smoking status				
Smoker	4660 (12.33)	29 648 (20.02)	6795 (25.97)	22 259 (21.64)
Nonsmoker	20 492 (54.22)	76 393 (51.57)	12 078 (46.17)	52 991 (51.51)
Ex-smoker	9964 (26.36)	27 056 (18.27)	5417 (20.71)	16 651 (16.18)
Missing	2677 (7.08)	15 029 (10.15)	1870 (7.15)	10 980 (10.67)
Body mass index				
<25 kg/m^2	14 547 (38.49)	50 565 (34.14)	11 422 (43.66)	36 315 (35.3)
25-30 kg/m^2	10 660 (28.21)	39 871 (26.92)	6105 (23.34)	24 640 (23.95)
>30 kg/m^2	5497 (14.55)	23 857 (16.11)	3391 (12.96)	16 095 (15.62)
Missing	7089 (18.76)	33 833 (22.84)	5242 (20.04)	25 831 (25.11)

the control group, giving an unadjusted incidence rate ratio of 1.43 (1.25-1.62), $P < 0.001$. After adjusting for age, year, sex, deprivation quintile, comorbidity, body mass index and smoking status, aHR was 1.40 (1.23-1.59), $P < 0.001$ (Table 2). In a sensitivity analysis, excluding subjects aged > 70, aHR was 1.56 (1.33-1.83), $P < 0.001$. The absolute risk of colorectal cancer in ulcerative colitis subjects was 0.87%. In the incident only analysis, 54 cases of colorectal cancer were observed among 12 319 incident cases contributing 67 334 person-years at risk, compared to the control group where 222 cases were observed in 48 514 control subjects contributing 264 791 person-years at risk. This is lower than was seen in the prevalent and incident data with a crude incidence rate ratio of 0.97 (0.70-1.29), $P = 0.390$ and an adjusted Hazard ratio of 0.91 (0.68-1.23), $P = 0.553$ (incident only data presented in Appendix S8).

In the Crohn's disease colorectal cancer matched cohort study, 26 160 subjects with Crohn's disease (8115 [31%] incident cases and

TABLE 2 Multivariable Cox proportional hazard model of factors associated with colorectal cancer

	Ulcerative colitis					Crohn's disease			
	Hazard ratio	[95% Conf. interval]		*P*		Hazard Ratio	[95% Conf. Interval]		*P*
Ulcerative colitis	**1.40**	**1.23**	**1.59**	**<0.00**	**Crohn's disease**	**1.19**	**0.97**	**1.46**	**0.096**
Age band									
Reference 18-30	1.00					1.00			
30-40	1.45	0.73	2.89	0.290		4.06	1.55	10.61	0.004
40-50	3.64	1.95	6.79	<0.001		9.30	3.72	23.24	<0.001
50-60	7.97	4.34	14.60	<0.001		23.07	9.40	56.61	<0.001
60-70	15.11	8.27	27.60	<0.001		40.53	16.57	99.16	<0.001
70-80	22.57	12.34	41.28	<0.001		65.65	26.75	161.10	<0.001
>80	25.22	13.56	46.90	<0.001		76.55	30.30	193.39	<0.001
Sex									
Reference Male	1.00					1.00			
Female	0.75	0.67	0.84	0.00		0.77	0.65	0.92	0.003
Smoking status									
Reference Nonsmoker	1.00					1.00			
Smoker	0.96	0.81	1.14	0.618		0.83	0.65	1.07	0.159
Ex-smoker	1.03	0.89	1.18	0.727		1.05	0.85	1.31	0.644
Missing	1.03	0.83	1.29	0.782		1.00	0.73	1.37	0.986
Body mass index kg/m^2									
Reference <25	1.00					1.00			
25-30	1.02	0.88	1.17	0.804		1.04	0.83	1.29	0.741
>30	1.08	0.91	1.28	0.362		1.03	0.79	1.34	0.835
Missing	0.95	0.79	1.15	0.608		1.21	0.93	1.59	0.161
Charlson Score									
Reference 0	1.00					1.00			
1	1.10	0.96	1.27	0.176		0.99	0.80	1.23	0.954
2	1.21	1.01	1.46	0.044		1.02	0.76	1.38	0.883
3	1.39	1.08	1.78	0.011		0.65	0.38	1.11	0.114
4+	1.47	1.09	2.00	0.012		1.27	0.78	2.07	0.333
Deprivation score									
Reference 1	1.00					1.00			
2	1.06	0.90	1.24	0.500		1.09	0.84	1.42	0.508
3	1.03	0.87	1.22	0.715		1.15	0.89	1.50	0.285
4	1.03	0.85	1.24	0.774		1.16	0.87	1.53	0.308
5 (most deprived)	1.11	0.89	1.39	0.346		1.14	0.83	1.57	0.422
Missing	0.89	0.73	1.10	0.281		1.01	0.74	1.38	0.954

18 045 [69%] prevalent cases) were matched to 102 881 control subjects contributing a total of 158 906 and 647 624 person-years at risk respectively. Baseline demographic characteristics are shown in Table 1 and a comparison of incident and prevalent case demographics is shown in Appendix S5. One hundred and twenty (0.46%) cases of colorectal cancer were observed in the Crohn's disease group and 423 (0.41%) in the control group. The incidence rate of colorectal cancer in Crohn's disease subjects was 75.5 per 100 000 py (62.6-90.3) compared to 65.3 (59.2-71.8) in the control group, giving an unadjusted incidence rate ratio of 1.16 (0.93-1.42), $P = 0.082$. Following adjustment for covariates, aHR was 1.19 (0.97-1.46), $P = 0.096$. The absolute risk of colorectal cancer in Crohn's disease cases was 0.46%. Increased risk of colorectal cancer in younger subjects with Crohn's disease was seen in a sensitivity analysis, excluding subjects aged over 70 years old: aHR 1.29 (1.01-1.65), $P = 0.043$. Adjusting for age and sex, both the Crohn's disease colorectal cancer rate (incidence rate ratio 0.99 (0.96-1.04), $P = 0.960$) and the ulcerative colitis colorectal cancer rate (1.02 (0.99-1.04), $P = 0.158$), were stable over time. Trends in colorectal cancer rates among the ulcerative colitis and Crohn's disease cohorts are graphically represented in Figure 3. In the incident only analysis, 39 cases of colorectal cancer were observed among 8115 incident Crohn's disease cases accounting for 42 627 person-years at risk. This compared to 117 cases in the unexposed group of 31 946 control subjects which accounted for 169 221 person-years at risk. This gives a crude incidence rate ratio of 1.32 (0.90-1.92), $P = 0.068$. An adjusted hazard ratio for incident Crohn's disease cases was 1.34 (0.93-1.93), $P = 0.118$ (incident only data are presented in Appendix S8).

3.6 | Mortality in ulcerative colitis and Crohn's disease

In the matched ulcerative colitis cohort study addressing mortality risk, 42 179 subjects with ulcerative colitis were matched to 166 083 control subjects contributing 276 312 and 1 099 868 person-years at risk respectively. During the study period 4807 (11.4%) ulcerative colitis subjects and 16 098 (9.7%) matched controls died. The absolute risk difference between ulcerative colitis and control subjects was 1.7%. Cohort characteristics are shown in Appendix S6. Ulcerative colitis subjects were more likely to die than matched controls: aHR 1.17 (95% CI 1.14-1.21), $P < 0.001$ (Table 3 and Appendix S7). In sensitivity analysis, excluding subjects age >70, aHR was 1.13 (1.07-1.20), $P < 0.001$. The factors associated with death in subjects with ulcerative colitis when assessed separately were age above 18-30, $P < 0.001$, current and ex-smoking (1.58 [1.43-1.74], $P < 0.001$ and 1.09 [1.02-1.16], $P = 0.017$ respectively), deprivation levels greater than level 2 and additional comorbidities. The factors associated with a reduced risk of mortality among subjects with ulcerative colitis were female sex (0.77 [0.73-0.82], $P < 0.001$) and body mass index in the range of 25-30 kg/m^2 when compared to those <25 kg/m^2 (0.86 [0.80-0.93], $P < 0.001$). When adjusting for age and sex, ulcerative colitis mortality remained unchanged over the duration of the study period with an incidence rate ratio of 0.99 (0.99-1.00), $P = 0.309$. The standardised mortality ratio for ulcerative colitis subjects was 0.96 (0.93-0.99) and annual standardised mortality ratios for ulcerative colitis are presented in Figure 4. In the incident only analysis, 1134 deaths were observed among 13 122 ulcerative colitis subjects accounting for 73 069 person-years at risk compared to 3533 deaths among 51 927 control subjects contributing 287 404 person-years at risk. This provides a crude incidence rate ratio of 1.26 (1.18-1.35), $P < 0.001$, an adjusted HR of 1.31 (1.23-1.41), $P < 0.001$ and an absolute risk difference of 1.84% (incident only data presented in Appendix S8).

In the Crohn's disease matched cohort study addressing mortality risk, 27 870 subjects with Crohn's disease were matched to 110 005 control subjects contributing 171 906 and 700 975 person-years at risk respectively. During the study period, 2612 (9.4%) Crohn's disease subjects and 7137 (6.5%) matched control subjects died. The absolute risk difference between Crohn's disease and control subjects was 2.88%. Crohn's disease subjects were more likely to die than matched controls: aHR 1.42 (1.36-1.48), $P < 0.001$ (Table 3 and Appendix S7). This risk increased when those > 70 were excluded in the sensitivity analysis to 1.49 (1.40-1.60), $P < 0.001$. The factors associated with mortality in Crohn's disease when assessed separately were age greater than 18-30, current and ex-smoking (1.87

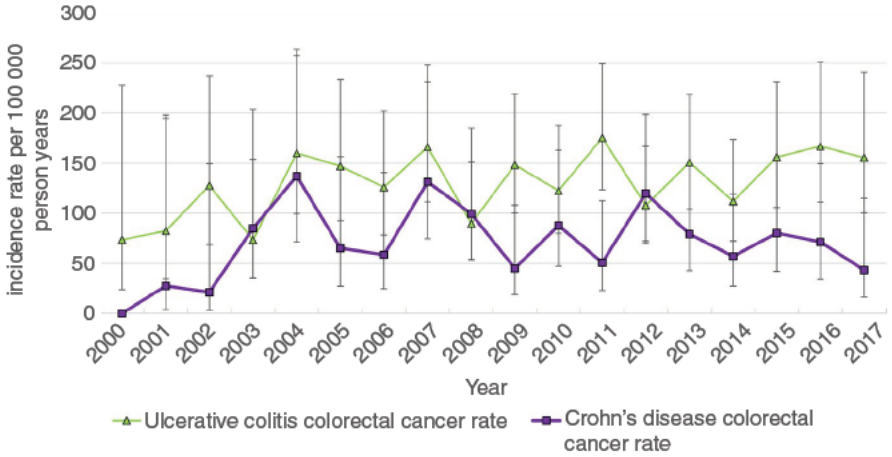


FIGURE 3 Colorectal cancer rates in ulcerative colitis and Crohn's disease subjects over the study period

TABLE 3 Multivariable Cox proportional hazard model of factors associated with all-cause mortality

	Ulcerative colitis					Crohn's disease			
	Hazard ratio	[95% Conf. interval]		*P*		Hazard ratio	[95% Conf. interval]		*P*
Ulcerative colitis	**1.17**	**1.14**	**1.21**	**<0.001**	**Crohn's disease**	**1.42**	**1.36**	**1.48**	**<0.001**
Age band									
Reference 18-30	1.00					1.00			
30-40	2.21	1.69	2.88	<0.001		2.78	2.11	3.65	<0.001
40-50	4.78	3.72	6.14	<0.001		6.20	4.80	8.02	<0.001
50-60	11.76	9.22	15.01	<0.001		16.22	12.65	20.79	<0.001
60-70	29.34	23.04	37.36	<0.001		37.29	29.17	47.68	<0.001
70-80	75.71	59.49	96.36	<0.001		95.99	75.13	122.64	<0.001
>80	196.94	154.68	250.76	<0.001		244.55	191.16	312.86	<0.001
Sex									
Reference Male	1.00					1.00			
Female	0.79	0.77	0.81	<0.001		0.80	0.77	0.83	<0.001
Smoking status									
Reference Nonsmoker	1.00					1.00			
Smoker	1.81	1.74	1.88	<0.001		1.95	1.85	2.06	<0.001
Ex-smoker	1.12	1.08	1.16	<0.001		1.22	1.16	1.28	<0.001
Missing	1.14	1.08	1.20	<0.001		1.28	1.19	1.39	<0.001
Body mass index kg/m^2									
Reference < 25	1.00					1.00			
25-30	0.85	0.82	0.88	<0.001		0.82	0.78	0.87	<0.001
>30	0.95	0.91	0.99	0.011		0.94	0.88	1.00	0.036
Missing	1.25	1.20	1.30	<0.001		1.21	1.14	1.29	<0.001
Charlson Score									
Reference 0	1.00					1.00			
1	1.61	1.56	1.67	<0.001		1.69	1.60	1.78	<0.001
2	2.01	1.93	2.10	<0.001		2.20	2.07	2.33	<0.001
3	2.46	2.34	2.59	<0.001		2.63	2.44	2.83	<0.001
4+	3.68	3.50	3.87	<0.001		3.82	3.54	4.13	<0.001
Deprivation score									
Reference 1	1.00					1.00			
2	1.08	1.03	1.12	0.001		1.11	1.04	1.19	0.002
3	1.23	1.18	1.29	<0.001		1.18	1.11	1.26	<0.001
4	1.35	1.29	1.41	<0.001		1.32	1.24	1.41	<0.001
5 (most deprived)	1.43	1.36	1.51	<0.001		1.42	1.32	1.52	<0.001
Missing	1.17	1.11	1.23	<0.001		1.17	1.09	1.27	<0.001

[1.69-2.07], $P < 0.001$ and 1.17 [1.06-1.29], $P < 0.001$ respectively), deprivation and additional comorbidities. As with ulcerative colitis, the factors associated with a reduced risk of mortality in subjects with Crohn's disease were female sex (0.87 [0.81-0.95], $P < 0.001$) and body mass index in the range of 25-30 kg/m^2 when compared to those <25 kg/m^2 (0.88 [0.78-0.99], $P = 0.045$). Over the study period, adjusting for age and sex, Crohn's disease mortality fell slightly; incidence rate ratio was 0.99 (0.98-0.99), $P = 0.009$. Over the study period the standardised mortality ratio (SMR) for Crohn's disease subjects was 1.26 (1.21-1.30), annual standardised mortality ratios for Crohn's disease are presented in Figure 4. In the incident only analysis, 689 deaths were observed among 8442 Crohn's disease subjects, contributing 44 856 person-years at risk, compared to 1711 deaths observed in 33 371 control subjects contributing 178 235 person-years at risk. This gives a crude incidence rate ratio of 1.60 (1.46-1.75), $P < 0.001$, an absolute risk difference of 3.0% and an adjusted HR of 1.50 (1.37-1.64), $P < 0.001$ (incident only data presented in Appendix S8).

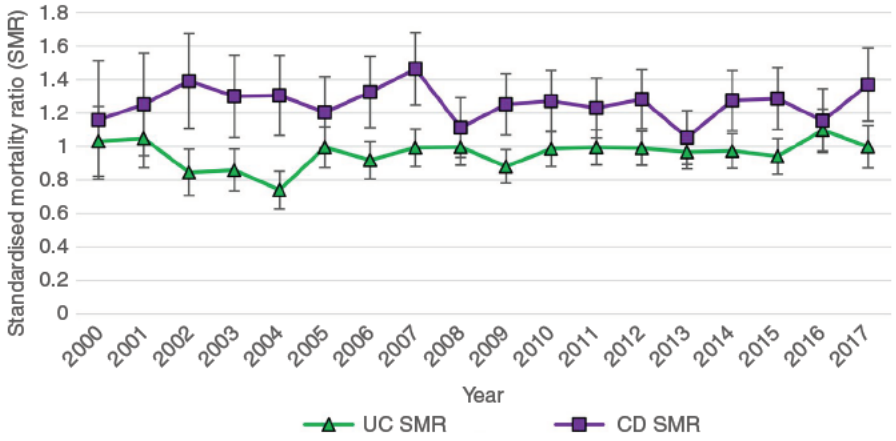


FIGURE 4 Annual standardised mortality ratio for ulcerative colitis and Crohn's disease. CD, Crohn's disease; SMR, standardised mortality ratio; UC, ulcerative colitis

4 | DISCUSSION

This study has examined in detail the UK epidemiology of ulcerative colitis and Crohn's disease using a large, population-based data-set. Previous reports of the epidemiology of ulcerative colitis and Crohn's disease in the UK have used comparatively small datasets or focused on regional areas which may not be generalisable to the UK population as a whole or are now largely historic.[9,11,12] As with other high-prevalence areas,[3,4] this study shows that ulcerative colitis and Crohn's disease prevalence in the UK have been increasing over the past two decades at a rate of 2%-3% per annum. This is in keeping with a recent study from Canada which has forecast a 35% increase in those living with inflammatory bowel disease over the next dec-ade.[23] The UK population in mid-2017 was estimated at 66 million.[24] Applying the findings of this study, an unadjusted estimate of the number of people living with ulcerative colitis in the UK in 2017 would be 376 000 and with Crohn's disease 264 000. This translates to an inflammatory bowel disease prevalence of 640 000 people or 0.97% of the population. The UK population in 2025 is predicted to be 68.9 million.[25] This study has forecast a combined inflammatory bowel disease prevalence of 1080 per 100 000 by 2025, equating to 744 120 living with inflammatory bowel disease in the UK or 1.1% of the population. How novel therapeutics, surgery, an older popu-lation and multidisciplinary management of these conditions might mitigate such an increase in prevalence is uncertain,[26,27] but these findings are fundamental for future planning of services in inflam-matory bowel disease. The increasing prevalence of inflammatory bowel disease likely represents a reduction in mortality over time, given the slight decrease observed in incidence rates for these dis-eases. The cautious forecasting undertaken in this study represents a realisation that prevalence is likely to stabilise as, in due course, life expectancy plateaus.

The incidence of both ulcerative colitis and Crohn's disease is relatively stable, with an observed reduction in ulcerative colitis incidence rates over the study period. This is mainly driven by a more significant reduction in those over 50 years while little change was observed in those under 50 years old. Inflammatory bowel disease diagnosis in the elderly can be challenging due to a range of differential diagnoses and phenotypic differences when compared to younger groups.[28] The internal validation work presented in this study has sought to examine miscoding bias among subjects with inflammatory bowel disease. It was found that the prescription of medication unique to inflammatory bowel disease and surgical procedures commonly utilised in the management of inflammatory bowel disease were highly consistent in THIN but with lower consistency in the oldest age groups. Some studies have previously demonstrated a bimodal, age-stratified distribution of incidence rates, which this study has also documented. However, this is not universal among inflammatory bowel disease epidemiological profiles, and when present, the second peak is often only modest.[3] A higher subsequent peak in ulcerative colitis incidence has been previously demonstrated in a North American cohort [29] and more recently in a Korean study.[30] This has also been replicated in this study and is largely driven by male subjects in the older age group. Stable or slight declines in overall incidence have been demonstrated in a few other studies from the developed world.[4,31,32] The finding of a reduced incidence rate over time in those over 50 is novel, although a study from Québec observed a statistically significant time-trend decline in annual incidence in both ulcerative colitis and Crohn's disease in 40-49-year-olds and among ulcerative colitis subjects aged 20-29 and 50-69 between 2001 and 2008.[33] However, a bimodal peak in age-specific incidence was not reported and it was suggested that a migration effect had changed the nature of the epidemiology of inflammatory bowel disease in Québec.[33] Migration and second generation changes in inflammatory bowel disease risk may also be playing a role in our observations. Previous studies have suggested that second generation migrants to the West have a higher risk of inflammatory bowel disease than first generation migrants (either comparable or greater than the native population risk).[34-36] Disease course in inflammatory bowel disease differs with age, with a more aggressive disease pattern and extensive gastrointestinal involvement in the young.[37]

The differences in the female and male incidence and prevalence of Crohn's disease has been demonstrated previously.[38-40] A hormonal theory based on a reverse in incidence rates between male and female subjects at the time of puberty, as well as an association seen with hormone based medications is hypothesised.[39,41]

The colorectal cancer rate in the THIN population over the study period was comparable to the estimated rate of 64.2 per 100 000 persons for colorectal cancer in 2015 for the UK (age standardised: 69.9 [95% CI 69.2-70.6]).[42] This study found no decline in colorectal cancer rates in ulcerative colitis or Crohn's disease over the study period, despite a significant increase in the available medications used to manage inflammatory bowel disease, however studies going forward may well find improvement. The matched cohort designs allowed for comparison of inflammatory bowel disease subjects with age and sex-matched non-inflammatory bowel disease populations, while further adjusting for residual confounding factors. A significantly increased relative colorectal cancer risk in ulcerative colitis, demonstrates that this condition remains an important risk factor for colorectal cancer. However, in the incident only sensitivity analysis, there was no difference in risk between cases and controls. This most likely reflects a longer follow-up period in prevalent compared to incident cases (Appendix S5). It may also reflect that with newer diagnoses there is better surveillance, and more active and improved treatments, thereby reducing the risk of colorectal cancer in this group.

Ulcerative colitis has consistently been associated with colorectal cancer when compared with the non-inflammatory bowel disease population, this association is not, however, consistently observed in Crohn's disease.[8,43] It should be acknowledged that the potentially differing influence of Crohn's disease colitis and Crohn's disease small bowel disease on colorectal cancer risk were not specifically assessed in this study and the differing frequencies of these phenotypes are relevant in assessing colorectal cancer risk in Crohn's disease. While in this study colectomy was excluded in both ulcerative colitis and Crohn's disease subjects, in Crohn's disease, partial colectomy may precede the development of colorectal cancer and therefore some cases may be missed. More recent population studies and meta-analyses [7,8] have reappraised the very high historic colorectal cancer estimates in these conditions.[6] Although beyond the scope of this study, there remain particular inflammatory bowel disease phenotypes that pose significant risks, as well as inflammatory bowel disease medications that may mitigate colorectal cancer risk in Crohn's disease and ulcerative colitis.[8]

The increased risk of death observed in the current study, in both ulcerative colitis and in particular Crohn's disease subjects, has been previously demonstrated, however previous studies of all-cause mortality in inflammatory bowel disease have been somewhat contradictory; Table 4 summarises the current evidence in this area. Although assessment of cause-specific mortality was beyond the scope of this present study it bears consideration. In a study from Olmsted County, Minnesota, looking at 1970-2016 data, the authors were able to look at disease-specific cause of death and found that gastrointestinal and respiratory causes were increased in Crohn's disease but not in ulcerative colitis. Ulcerative colitis was at a reduced risk of mortality compared to the US population, and when compared to matched, regional controls, the mortality risk was not significantly different; Crohn's disease did not differ from the background population using either methodology. This was a powerful study because all death certificates and ascertainment of cases were based on strict diagnostic criteria. However, comorbidity data were unavailable and it is a uniquely white and wealthy area of the country that may not be generalisable, not least in terms of health access and outcomes.[44]

The use of routinely gathered data from primary care has both limitations and strengths. Many primary care practices contribute to THIN, providing a representative sample of the UK population, and practices were required to achieve a minimum standard of quality with regard to data recording before participating in the study. Furthermore, the internal validation methodology employed has demonstrated that the coding of medications and surgeries commonly utilised in inflammatory bowel disease is frequently co-coded in those with inflammatory bowel disease diagnoses recorded in the THIN database. The inflammatory bowel diseases are generally managed by specialist secondary care physicians. For this reason, several medications will not be prescribed in primary care or coded in THIN (eg anti-TNF therapy). Although this is a potential limitation, it will underestimate the number of subjects with coding of medications rather than implying a true misclassification bias in inflammatory bowel disease diagnosis coding. Nevertheless, miscoding as well as the lack of universal diagnostic definitions for inflammatory bowel disease remain a potential source of bias. This study has demonstrated a high prevalence of inflammatory bowel disease in the UK but did not use codes for indeterminate colitis and may therefore still underestimate the true level of inflammatory bowel disease in the UK. However, a significant rise in

TABLE 4 Studies reporting all-cause mortality risk in inflammatory bowel disease cases compared to matched controls and background populations

Studies reporting increased mortality risk			Studies reporting decrease/equivalent mortality risk		
	Crohn's Disease	Ulcerative Colitis		Crohn's Disease	Ulcerative Colitis
Bewtra 2013[51]	SMR 1.40 (1.34-1.46)	SMR 1.17 (1.14-1.21)	Jess 2007[52]	—	SMR 1.10 (0.90-1.20)
Card 2003[53]	HR 1.73 (1.54-1.96)	HR 1.44 (1.31-1.58)	Manninen 2012[54]	SMR 1.14 (0.84-1.49)	SMR 0.90 (0.77-1.06)
Duricova 2010[55]	SMR 1.39 (1.30-1.49)	—	Aniwan 2018[44]	SMR 1.25 (0.98-1.57)	SMR 0.71 (0.56-0.89)
Jess 2013[56]	HR 1.73 (1.67-1.80)	HR 1.25 (1.22-1.28)	Aniwan 2018[44]	HR 1.26 (0.97-1.63)	HR 0.89 (0.70-1.14)
Olén 2019[57]	HR 1.60 (1.60-1.70)	HR 1.40 (1.40-1.50)			
Canavan 2007[58]	SMR 1.52 (1.32-1.74)	—			

Abbreviations: HR, hazard ratio; SMR, standardised mortality ratio.

prevalence across, in particular, western societies has been previously described.[23,45] This has been attributed to falls in historic levels of mortality in the inflammatory bowel diseases, improved population-wide longevity and high incidence. It is a potential limitation of the use of primary care databases that general practitioners may be improving their coding of prevalent disease over time. However, one would then expect all conditions in these databases to increase in prevalence over time which is not consistently the case.[46-48] Moreover, better coding in and of itself might be expected to lead to a rise in incident cases which was not seen over time.

Eleven percent of ulcerative colitis cases and 13% of Crohn's disease cases did not have a record of an inflammatory bowel disease drug and did not have a record of an inflammatory bowel disease related surgery in the smaller, validation cohort examined. The distribution of ages in this group demonstrated increased nondrug/noncolectomy coding in older age categories. The reasons for this may be multifactorial including medications only prescribed by secondary care: some general practitioners will not prescribe thiopurines due to the risks associated with these medications and biologic agents are not prescribed in general practice. It has been reported that elderly patients are less commonly prescribed medication for their inflammatory bowel disease, and there may be a desire to avoid immunosuppressants by moving early to surgical options, following which recurrence is less common in the elderly.[28,49] It is possible that a milder form of inflammatory bowel disease may also be represented in this group, for instance, a patient who has had a single flare that was managed with induction therapy or steroids prescribed from secondary care could fall into this group. Misclassification of inflammatory bowel disease may be a further risk, with diverticulitis and ischaemic colitis potentially confusing a diagnosis in older age groups.

Although the focus of this study was on the incidence and prevalence of inflammatory bowel disease and the risk of mortality and colorectal cancer in these populations, a significant limitation is in identification of inflammatory bowel disease phenotype. It has previously been shown that disease severity, extent and comorbid primary sclerosing cholangitis are significant factors in the risk of colorectal cancer in inflammatory bowel disease.[6,50] This study has considered all Crohn's disease and all ulcerative colitis as single diseases and the paucity of data in THIN regarding inflammatory bowel disease phenotypic subtypes would not permit a more in-depth analysis of how these factors affect colorectal cancer and mortality risk. The mitigation of potential confounders was considered through matched cohort designs. Unfortunately, ethnicity, exercise and diet were often not coded and so although important factors, could not be included in these analyses.

Prevalence of both ulcerative colitis and Crohn's disease has been increasing in recent decades, while incidence appears to be declining to some extent, particularly in the older population. These conditions remain significant risk factors for early mortality and colorectal cancer, particularly in ulcerative colitis. With an increasing proportion of society affected, research must continue to focus on how best to manage these conditions and prevent adverse outcomes.

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AUTHORSHIP

Guarantor of the article: Nicola Adderley.

Author contributions: Study concept and design was jointly conceived by DK, NT, TT, JSC, NA, KN and RR. Data extraction was performed by DK, AS, JC, TT, RT, KG and analysis was performed by DK, RT, RR, NA and NT. Manuscript was drafted by DK. The data and manuscript were critically reviewed, revised and approved by all authors. NA and NT contributed equally and are joint senior authors.

ETHICS APPROVAL

Anonymised data were provided by the data provider, IQVIA, to the University of Birmingham. Studies using The Health Improvement Network (THIN) database have had initial ethics approval from the NHS South-East Multicentre Research Ethics Committee, subject to prior independent scientific review. The Scientific Review Committee (IQVIA) approved the study protocol (SRC Reference Number: SRC19THIN010).

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SUPPORTING INFORMATION

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

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CHAPTER 4: THE OUTCOMES OF EMERGENCY ADMISSIONS WITH ULCERATIVE COLITIS BETWEEN 2007 AND 2017 IN ENGLAND

In this chapter I present the findings from a retrospective cohort study, examining the risk of colectomy and mortality following a first recorded admission in HES for acute UC.

Supplementary material is found in the appendices for this chapter at the end of the thesis.

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The Outcomes of Emergency Admissions With Ulcerative Colitis Between 2007 and 2017 in England

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Abstract

Background and Aims: Patients with ulcerative colitis [UC] may present as emergencies and require rapid escalation of therapy. This study aimed to assess the mortality, colectomy, and readmission risks, during and following a first emergency admission with UC.

Methods: Using Hospital Episode Statistics, subjects aged between 18 and 60 years, coded with a first emergency admission with UC, were identified between 2007 and 2017. Influences of demographic factors, comorbidity, anti-tumour necrosis factor [TNF] therapy, and provider UC activity on mortality and colectomy were examined.

Results: A total of 10 051 subjects (46% female; median age 33 years [interquartile range [IQR] 25–44]) were identified. Mortality was 0.2% in hospital and 0.5% at 12 months and, following colectomy during acute admission, it was 1.4% in hospital and 2.1% at 12 months. Females had reduced risk of colectomy during admission: odds ratio [OR] 0.73 (95% confidence interval [CI] 0.62–0.85). Comparing the period 2007–2011 with 2012–2017, the rate of colectomy fell during acute admissions: OR 0.85 [0.72–0.99], $p = 0.038$ and at 12 months after admission: OR 0.73 [0.61–0.87]. Anti-TNF therapy increased 4-fold in acute UC admissions from 2007–2017. Those receiving anti-TNF therapy had a 70% increased risk of colectomy during index admission compared with those not receiving anti-TNF: OR 1.72 [1.29–2.31]. Increased time to colectomy during first admission was associated with female sex: hazard ratio [HR] 0.84 [0.72–0.98] and Asian ethnicity: HR 0.61 [0.44–0.85], whereas reduced time was associated with increased comorbidity, lower deprivation, and high provider volume of colectomies for UC: HR 1.59 [1.31–1.93].

Conclusions: Mortality following colectomy was 1.4% in hospital and 2.1% at 12 months, and no significant change over time was observed. Colectomy during emergency admission for UC was less common in females. Rates of anti-TNF therapy during emergency admission for UC have increased and overall colectomy rates have fallen.

Podcast: This article has an associated podcast which can be accessed at https://academic.oup.com/ecco-jcc/pages/podcast
Key Words: Inflammatory bowel disease; ulcerative colitis; colectomy

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1. Introduction

Ulcerative colitis [UC] is a chronic, idiopathic disease of the large bowel affecting the mucosa through inflammation and ulceration.[1] UC has an unpredictable course with flares and periods of remission.[2] The prevalence of UC in the UK is 243 per 100 000, with an incidence of 14 per 100 000 per year,[3] giving the UK one of the highest UC disease burdens in Europe.[4] Most subjects are managed in an outpatient setting, but UC can present as more severe disease, necessitating emergency admission. There remains a small but appreciable mortality risk, particularly in the early years following a UC diagnosis and in older age groups.[5] In the setting of acute severe colitis, 'rescue' medical therapies may be considered[6] in the form of calcineurin inhibitors or, now more commonly, anti-tumour necrosis factor [TNF] therapy with infliximab.[7] Colectomy remains a definitive treatment for UC, though it too has an appreciable mortality risk.[8,9]

The aim of this study, using data on all hospital admissions in England over a 10-year period, was to establish the frequencies of colectomy and mortality following first emergency admission for UC, and associated risk factors for these events.

2. Methods

2.1. Data source

Hospital Episode Statistics [HES] is an administrative database including information on all elective and emergency care episodes in National Health Service [NHS] hospitals in England. A unique identifier allows individual subjects to be followed through their hospital admissions and outpatient attendances. Every recorded episode contains clinical information about diagnoses and procedures, and demographic, administrative, and geographical information. Diagnostic data are coded using the International Classification of Diseases version 10 [ICD-10] and procedures are coded using the Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision [OPCS-4]. HES is linked to the Office of National Statistics [ONS] mortality data, providing information on the date and cause of death.[10]

2.2. Inclusion criteria

The first emergency hospital admissions with UC in England between April 1, 2007 and March 31, 2017, for all subjects aged 18–60 years, were included in the study. Diagnostic data were obtained from ICD-10 coding. Only the primary and secondary diagnostic codes in HES were examined. If the UC code was in the secondary position, the primary code was required to be one from a pre-specified list [Appendix 1, available as Supplementary data at *ECCO-JCC* online]. This was to ensure that UC was the main reason for admission, rather than an admission for an unrelated problem in a subject with UC. Included subjects were permitted to have a single Crohn's disease [CD] code, if more than one other code suggested an actual diagnosis of UC. Subjects were considered incident cases if they had no previous diagnostic code for UC recorded in HES. Subjects were considered to be prevalent cases if they had been previously diagnosed with UC or had activity suggestive of a diagnosis of UC, such as a colonoscopy or flexible sigmoidoscopy or outpatient contact with a gastroenterologist or colorectal surgeon in the 2 years preceding their acute admission.

2.3. Exclusion criteria

Subjects were excluded if they were over the age of 60, due to finding that coding for UC in this subgroup was unreliable in the validation cohort [see Results section]. Subjects were further excluded if they had a diagnosis of cancer before or at the time of admission, if the distinction between a diagnosis of CD or of UC was unclear from subsequent coding, or if CD was more likely from subsequent coding. Further exclusions were made if subject admission duration was less than 2 days [suggesting a much less severe admission] and if subjects had incomplete demographic data [Figure 1].

2.4. Data validation

To assess the validity of the UC cohort, a list of patients meeting the same ICD-10 coding criteria was provided by the local coding departments at Sandwell and West Birmingham Hospitals NHS Trust and the Queen Elizabeth Hospital, Birmingham. The accuracy of coding at each site was then assessed by consulting the electronic patient records, to establish if the admission was with acute ulcerative colitis.

2.5. Demographic data

Demographic data, including age, gender, deprivation,[11] and ethnicity, were extracted from the admission coding. Age was divided into equal age ranges of 18–32, 33–46, and 47–60 years. Ethnicity was classified into White, Asian, and other minority ethnicities [including ethnic groups other than White, Asian, and unknown]. The Charlson comorbidity index was calculated using ICD-10 codes for secondary diagnoses, excluding any form of cancer. The use of the Charlson comorbidity index has previously been validated in HES, when assessing comorbidity in patients with urological cancer.[12] Deprivation was calculated using the Index of Multiple Deprivations 2007, an aggregate score for each English Lower Layer Super Output Area [LSOA], which is based on income, employment, crime, and living environment. Deprivation was analysed in quintiles, with 1 being the most deprived and 5 being the least deprived.

2.6. Outcome measures

Outcome measures included in-hospital, 30-day and 12-month all-cause mortality. Emergency readmission into any hospital within

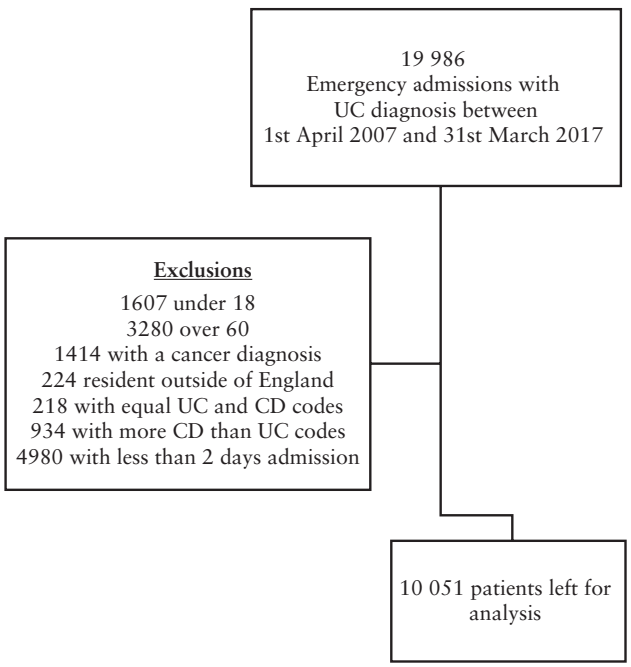


Figure 1. Study flowchart.

30 days of discharge was also identified. The proportion of subjects undergoing emergency colectomy during admission and emergency or elective colectomy within 12 months of admission was identified using OPCS-4 coding [Appendix 1]. Use of infused anti-TNF therapy during a subject's admission was identified using the OPCS-4 code X921.

2.7. Statistical analysis

All statistical analyses were carried out using STATA SE v15.[13] Indirect standardised mortality ratios [SMR] were calculated using age and sex-specific mortality rates in the UC cohort compared with the population of England, taken from the ONS. Univariate analysis for categorical variables was performed using chi square tests. Multivariable logistic regression models were produced to examine associations with mortality, colectomy, and emergency readmission, following adjustment for age, gender, ethnicity, comorbidity, deprivation, use of an infused anti-TNF agent, year of admission, annual provider colectomy volume or provider acute UC admission volume, and whether cases were considered incident or prevalent. A Kaplan-Meier survival curve was produced to show percentage survival over time, in those with and those without colectomy. A Cox proportional hazard model was produced to examine associations with time to colectomy following adjustments for the above variables. Proportional hazards assumptions were tested and satisfied; *p*-values of <0.05 were considered statistically significant.

HES data are available under a data sharing agreement with NHS Digital for the purposes of service evaluation, and as such ethics approval was not required. Numbers less than six are censored from publication to protect subject anonymity. The study was registered at the University Hospital Birmingham.

3. Results

3.1. Validation

Between April 1, 2011 and March 31, 2016, the validation process at Sandwell and West Birmingham Hospitals NHS Trust identified 127 emergency admissions with UC; 119 were coded accurately, eight were miscoded. This gives a 93.7% correlation. However, when split by age, only 5.0% of those patients aged between 18 and 60 were inaccurately coded, compared with 25% of those aged over 60 years. A similar analysis carried out at the University Hospital Birmingham identified 105 emergency admissions with UC, 94.3% of which were coded accurately. In those patients aged between 18 and 60 years, 3.0% were inaccurately coded compared with 13.0% of those aged over 60 years. For this reason, those aged over 60 were excluded from the present study.

3.2. Cohort characteristics

Between April 2007 and April 2017, 10 051 subjects, aged 18–60 years, undergoing their first emergency admission with UC, were identified [Figure 1]. The demographic characteristics of the subjects who were included are summarised in Table 1.

3.3. Selection bias

A univariate analysis comparing the gender, ethnicity, demographic factors, and comorbidity scores of included and excluded subjects was carried out [Appendix 2, available as Supplementary data at *ECCO-JCC* online]. Included subjects had lower levels of depriv-ation, were more likely to be male, less likely to be White, and more likely to be Asian. A higher proportion of excluded subjects had co-morbidities compared with included subjects.

Table 1. The demographics of the study cohort.

		Number of subjects
Age group	18–32	4806 [48%]
	33–46	3350 [33%]
	47–60	1895 [19%]
Sex	Male	5382 [54%]
	Female	4669 [46%]
Charlson comorbidity score	0	9597 [95%]
	1 to 4	333 [3%]
	5+	121 [1%]
Deprivation	1	2017 [20%]
	2	2175 [22%]
	3	2105 [21%]
	4	1923 [19%]
	5	1818 [18%]
	Unknown	13 [0%]
Ethnicity	White	8001 [80%]
	Asian	947 [9%]
	Other minority ethnicities	595 [6%]
	Unknown	508 [5%]
Admission period	2007/08	1181 [12%]
	2008/09	1233 [12%]
	2009/10	1196 [12%]
	2010/11	1016 [10%]
	2011/12	1019 [10%]
	2012/13	954 [9%]
	2013/14	894 [9%]
	2014/15	869 [9%]
	2015/16	861 [9%]
	2016/17	828 [8%]
Anti-TNF during emergency admission	Yes	532 [5%]
	No	9519 [95%]
Prevalent or incident	Prevalent	6851 [68%]
	Incident	3200 [32%]
Days to colectomy [median IQR][a]		8 [4–13]
Provider tertiles: annual volume of acute UC admissions	Low [≤11]	1507 [15%]
	Medium [12 to 18]	3533 [35%]
	High [≥19]	5011 [50%]
Provider tertiles: annual volume of colectomies for UC	Low [≤1]	2769 [28%]
	Medium [2]	3016 [30%]
	High [≥3]	4266 [42%]

TNF, tumour necrosis factor; IQR, interquartile range; UC, ulcerative colitis.

[a]When colectomy occurs during first emergency admission.

3.4. Mortality

Overall, 51 deaths occurred within 12 months of emergency UC admission [0.5% of subjects]. There were 21 deaths [0.2%] while subjects were inpatients and 14 deaths [0.1%] within 30 days of admission. The standardised mortality ratio [SMR] for subjects with a first emergency admission with UC was 0.89 [95% CI 0.74–1.05]. The most common cause of death, as recorded from ONS data, was attributed to UC, accounting for 19 [37%] deaths. There were several other causes of death recorded at a lower frequency than the threshold set, to ensure subject confidentiality within HES [<5]. These causes included recognised complications of acute UC such as perforation, surgical complications, thromboembolism, and oesophageal varices, as well as causes of death unrelated to UC.

A logistic regression analysis examining the impact of demographic factors, time period of admission, provider volume of colectomy for UC, and use of anti-TNF therapy during first admission

on in hospital death, 30-day mortality, and 12-month mortality in the UC cohort is presented in Table 2. Mortality was associated with increasing age and comorbidity. When compared with subjects of White ethnicity, ethnicities other than White or Asian were associated with increased in-hospital and 30-day mortality: odds ratio [OR] 4.98 (95% confidence interval [CI] 1.26–19.71), p = 0.022 and OR 7.34 [1.75–30.77], p = 0.006, respectively. At 12 months, however, no association with ethnicity and mortality was observed. Gender, deprivation, year of admission, use of anti-TNF therapy, and the annual number of colectomies per provider were not associated with mortality. When provider annual volume of acute UC admissions was used as a variable instead of volume of colectomies for UC, similar findings were found with no association with mortality [data not shown].

Following colectomy, 10 subjects [1.41%] died in hospital, six [0.85%] had died at 30 days, and 15 [2.12%] by 12 months. Multivariable regression analysis of the impact of demographic factors, year of admission, use of anti-TNF therapy during first admission, provider volume of colectomies for UC, and time to colectomy on the risk of in-hospital death following colectomy is shown in Table 3. Time to colectomy was not found to be associated with in hospital death following colectomy; however, female sex (OR 6.73 [1.18–38.5], p = 0.032) and increased comorbidity scores increased this risk (Charlson score 1–4: OR 12.33 [2.24–67.92], p = 0.004 and score 5 or more: OR 22.05 [1.94–249.97], p = 0.013).

A Kaplan-Meier survival curve of overall survival alongside survival in those having colectomy and colectomy-free survival is shown in Figure 2.

3.5. Colectomy

Colectomy rates during acute admissions fell between 2007 and 2017 from 103 [8.7%] per year to 51 [6.2%] per year. Colectomy rates within the subsequent 12 months of acute admission also fell over the study, from 71 [6.0%] per year to 38 [4.6%] per year. Seven hundred and nine [7%] subjects underwent colectomy during index admission for acute UC during the study period, and a further 571 [5.7%] within 12 months of admission. Coded infliximab [anti-TNF] use during acute UC admission increased from 28 [2.4%] in 2007/2008 to 107 [12.9%] in 2016/2017. Of subjects undergoing colectomy during index emergency admission, 8% had received anti-TNF compared with 5% of subjects who did not undergo colectomy. A multivariable logistic regression analysis of the impact of demographic factors, year of admission, use of anti-TNF during first admission, and provider volume of colectomies for UC on the risk of colectomy during first admission and within 12 months in the UC cohort is presented in Table 4. A reduced risk of colectomy during the index admission and at 12 months was clearly observed in females (OR 0.73 [0.62–0.85], p <0.001 and OR 0.74 [0.62–0.88], p <0.001, respectively).

Subjects of Asian ethnicity, when compared with White subjects both at index admission and at 12 months, also had a reduced risk of colectomy (OR 0.60 [0.43–0.83], p = 0.002 and OR 0.49 [0.33–0.73], p <0.001, respectively). Charlson comorbidity scores of 1-4 and 5+ were associated with a higher risk of colectomy during the index admission (OR 2.37 [1.72–3.28], p <0.001 and OR 3.05 [1.88–4.95],p <0.001, respectively) but this association was not observed by 12 months. Lower deprivation levels

Table 2. Multivariable logistic regression analysis of factors associated with mortality following first emergency admission with ulcerative colitis.

		In-hospital mortality		30-day mortality		12-month mortality	
		Odds ratio [95% CI]	*p*-value	Odds ratio [95% CI]	*p*-value	Odds ratio [95% CI]	*p*-value
Age group	18–32	Baseline 1		Baseline 1		Baseline 1	
	33–46	3.52 [0.67–18.45]	0.137	2.45 [0.58–10.41]	0.224	2.07 [0.88–4.86]	0.096
	47–60	12.33 [2.59–58.73]	0.002	4.16 [0.94–18.33]	0.060	6.25 [2.83–13.78]	<0.001
Sex	Male	Baseline 1		Baseline 1		Baseline 1	
	Female	1.50 [0.61–3.69]	0.373	1.74 [0.58–5.16]	0.322	0.99 [0.57–1.76]	0.997
Charlson	0	Baseline 1		Baseline 1		Baseline 1	
comorbidity score	1 to 4	10.35 [3.25–32.93]	<0.001	10.13 [2.53–40.58]	0.001	4.14 [1.77–9.69]	0.001
	5+	26.07 [8.43–80.64]	<0.001	13.87 [2.63–73.22]	0.002	12.93 [5.9–28.31]	<0.001
Deprivation	1	Baseline 1		Baseline 1		Baseline 1	
	2	1.09 [0.36–3.29]	0.873	1.85 [0.43–7.98]	0.409	0.83 [0.4–1.74]	0.620
	3	0.46 [0.11–1.92]	0.286	1.04 [0.2–5.44]	0.960	0.64 [0.28–1.45]	0.283
	4	0.31 [0.06–1.63]	0.167	0.39 [0.04–3.9]	0.421	0.43 [0.16–1.13]	0.086
	5	0.36 [0.07–1.8]	0.212	0.86 [0.14–5.38]	0.876	0.38 [0.13–1.05]	0.063
Ethnicity	White	Baseline 1		Baseline 1		Baseline 1	
	Asian	1.97 [0.51–7.6]	0.323	0.98 [0.12–8.25]	0.985	1.78 [0.79–3.99]	0.163
	Other minority ethnicities	4.98 [1.26–19.71]	0.022	7.34 [1.75–30.77]	0.006	2.16 [0.815.76]	0.122
	Unknown	9.28 [2.56–33.66]	0.001	9.66 [2.24–41.55]	0.002	2.90 [1.08–7.75]	0.034
Admission period	2007/08–2011/12	Baseline 1		Baseline 1		Baseline 1	
	2012/13–2016/17	1.59 [0.65–3.91]	0.312	2.29 [0.77–6.8]	0.134	0.88 [0.49–1.58]	0.665
Anti-TNF during	Yes	1.5 [0.18–12.55]	0.706			1.35 [0.31–5.83]	0.686
emergency admission	No	Baseline 1				Baseline 1	
Prevalent or incident	Prevalent	0.41 [0.16–1.05]	0.064	0.64 [0.21–1.98]	0.440	0.63 [0.35–1.13]	0.118
	Incident	Baseline 1		Baseline 1		Baseline 1	
Provider tertiles:	Low [≤1]	Baseline 1		Baseline 1		Baseline 1	
annual volume of	Medium [2]	1.07 [0.29–3.93]	0.917	0.72 [0.16–3.3]	0.669	0.80 [0.37–1.69]	0.552
colectomies for UC	High [≥3]	1.71 [0.55–5.33]	0.355	1.43 [0.4–5.14]	0.587	0.91 [0.46–1.77]	0.778

TNF, tumour necrosis factor; UC, ulcerative colitis; CI, confidence interval.

Table 3. Multivariable logistic regression analysis of factors associated with in-hospital mortality for subjects having colectomy during their index admission.

		Odds ratio [95% CI]	*p*-value
Age group	18–32	Baseline 1	
	33–46	3.46 [0.31–39.06]	0.316
	47–60	5.48 [0.53–56.6]	0.154
Sex	Male	Baseline 1	
	Female	6.73 [1.18–38.51]	0.032
Charlson comorbidity score	0	Baseline 1	
	1 to 4	12.33 [2.24–67.92]	0.004
	5+	22.05 [1.94–249.97]	0.013
Deprivation	1	Baseline 1	
	2	1.11 [0.17–7.33]	0.914
	3	0.56 [0.06–5.6]	0.619
	4	0.22 [0.02–3.21]	0.269
	5	Omitted	
Ethnicity	White	Baseline 1	
	Asian	4.70 [0.29–45.79]	0.317
	Other minority ethnicities	6.05 [0.16–88.93]	0.414
	Unknown	21.84 [1.77–189.53]	0.015
Admission period	2007/08–2011/12	Baseline 1	
	2012/13–2016/17	1.91 [0.56–11.15]	0.230
Anti-TNF during emergency admission	Yes	0.40 [0.01–6.47]	0.392
	No	Baseline 1	
Prevalent or incident	Prevalent	0.87 [0.21–5.32]	0.946
	Incident	Baseline 1	
Provider tertiles: annual volume of colectomies for UC	Low [≤1]	Baseline 1	
	Medium [2]	2.49 [0.16–23.96]	0.604
	High [≥3]	3.25 [0.33–25.91]	0.337
Time to colectomy [days]		1.09 [1.00–1.19]	0.064

TNF, tumour necrosis factor; UC, ulcerative colitis; CI, confidence interval..

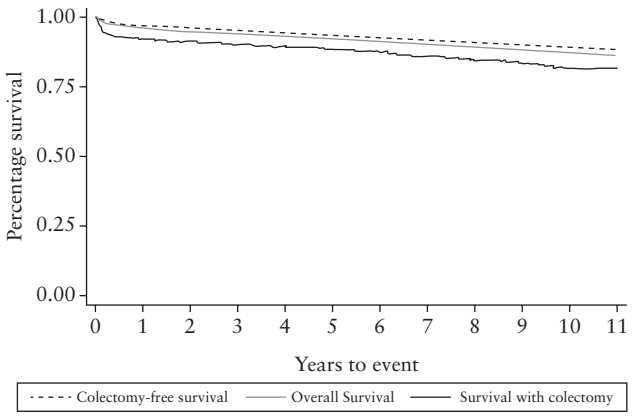


Figure 2. KaplanMeier survival curve of subjects overall, with and without colectomy.

were associated with an increased risk of colectomy during index admission, but this was not observed at 12 months.

During the later years of the study from 2012/13 to 2016/17, there was a reduced risk of colectomy, both during index admission and at 12 months (OR 0.85 [0.72–0.99], p = 0.038 and OR 0.73 [0.61–0.87], p <0.001, respectively). Prevalent cases of UC were 18% less likely to have a colectomy during their index admission when compared with those defined as incident cases (OR 0.82 [0.70–0.97], p = 0.020) but had more than a 2-fold increased risk at 12 months (OR 2.27 [1.82–2.83], p <0.001) [Table 4].

In all, 5% of subjects received anti-TNF therapy during their admission. The use of rescue anti-TNF therapy was associated with an increased risk of colectomy during the index admission (OR 1.72 [1.29–2.31], p <0.001) and within 12 months (OR 2.13 [1.58–2.85], p <0.001). Providers performing three or more colectomies for UC per year were associated with an increased risk of colectomy during index admission (OR 1.53 [1.26–1.87], p <0.001). By 12 months, providers performing three or more colectomies for UC per year were also associated with an increased risk of colectomy (OR 1.43 [1.15–1.77], p = 0.001). When provider annual volume of acute UC admission was examined in place of colectomy volume for UC, no association was observed between annual volume of acute UC admissions and colectomy [data not shown].

A Cox proportional hazards regression analysis was performed to assess the impact of demographic factors, year of admission, use of anti-TNF therapy during index admission, and provider annual volume of acute UC admission on time to colectomy during index admission in those undergoing colectomies [Table 5]. Female sex (hazard ratio [HR] 0.85 [95%CI 0.73–0.99], p = 0.038) and Asian ethnicity (HR 0.60 [0.43–0.83], p = 0.002), were associated with an increased time to colectomy, whereas Charlson scores of 1–4 (HR 1.73 [1.27–2.35], p <0.001), lower levels of deprivation, and high provider volume of colectomies for UC (HR 1.60 [1.31–1.93], p <0.001) were associated with a reduced time to colectomy. When provider annual volume of colectomies for UC was used as a variable in place of annual acute UC admission volume, high annual provider colectomy volume [≥3] was associated with shorter time to colectomy (HR 1.59 [1.31–1.93], p <0.001) [data not shown].

3.6. Emergency readmission

A total of 1240 [12%] subjects had an emergency readmission within 30 days of discharge following acute UC admission. Multivariable logistic regression analysis of the impact of demographic factors, year of admission, use of anti-TNF therapy during index admission, and provider volume of acute UC admissions on the risk of emergency readmission within 30 days revealed that subjects within the older age group of 47–60 were less likely than the younger age category [18–32] to be readmitted within 30 days (OR 0.60 [0.36–0.99], p = 0.048) [Appendix 3, available as Supplementary data at *ECCO-JCC* online]. The later period of this study [2012/13–2016/17] was associated with a 60% increased risk of emergency readmission (OR 1.59 [1.09–2.31], p = 0.016) compared with the period from 2007/08 to 2011/12. Anti-TNF therapy, on the other hand, was associated with a 60% decreased risk of readmission (OR 0.41 [0.18–0.95], p = 0.038). Gender, ethnicity, deprivation levels, Charlson comorbidity score, and provider volume of acute UC admissions were not found to have a significant association with emergency readmission within 30 days.

4. Discussion

The current study examined subjects between 18 and 60 years of age, with a first admission for acute UC between 2007 and 2017. There was no change in mortality rates over the time period studied and the absolute mortality figures were low. Older subjects and those with more comorbidities had an increased risk of death, as did ethnicities other than White and Asian, during index admission and by 30 days. Provider annual volume of colectomies for UC and volume of acute UC admissions were not associated with mortality in our

Table 4. Multivariable logistic regression analysis of factors associated with colectomy following emergency admission with ulcerative colitis.

		Colectomy during admission		Colectomy by 12 months	
		Odds ratio [95% CI]	*p*-value	Odds ratio [95% CI]	*p*-value
Age group	18–32	Baseline 1		Baseline 1	
	33–46	1.24 [1.04–1.47]	0.018	0.81 [0.66–0.98]	0.031
	47–60	1.23 [1.00–1.52]	0.052	0.89 [0.71–1.12]	0.328
Sex	Male	Baseline 1		Baseline 1	
	Female	0.73 [0.62–0.85]	<0.001	0.74 [0.62–0.88]	0.001
Charlson comorbidity score	0	Baseline 1		Baseline 1	
	1 to 4	2.37 [1.72–3.28]	<0.001	0.66 [0.37–1.16]	0.150
	5+	3.05 [1.88–4.95]	<0.001	0.43 [0.14–1.37]	0.154
Deprivation	1	Baseline 1		Baseline 1	
	2	1.46 [1.14–1.89]	0.003	1.04 [0.78–1.37]	0.795
	3	1.35 [1.04–1.75]	0.023	1.06 [0.80–1.40]	0.666
	4	1.60 [1.24–2.07]	<0.001	1.29 [0.98–1.7]	0.072
	5	1.27 [0.97–1.66]	0.083	1.20 [0.91–1.59]	0.201
Ethnicity	White	Baseline 1		Baseline 1	
	Asian	0.60 [0.43–0.83]	0.002	0.49 [0.33–0.73]	<0.00`
	Other minority ethnicities	0.77 [0.53–1.12]	0.164	0.94 [0.64–1.39]	0.768
	Unknown	1.18 [0.85–1.64]	0.310	0.96 [0.64–1.44]	0.860
Admission period	2007/08–2011/12	Baseline 1		Baseline 1	
	2012/13–2016/17	0.85 [0.72–0.99]	0.038	0.73 [0.61–0.87]	<0.001
Anti-TNF during emergency admission	Yes	1.72 [1.29–2.31]	<0.001	2.13 [1.58–2.85]	<0.001
	No	Baseline 1		Baseline 1	
Prevalent or incident	Prevalent	0.82 [0.70–0.97]	0.020	2.27 [1.82–2.83]	<0.001
	Incident	Baseline 1		Baseline 1	
Provider tertiles: annual volume of colectomies for UC	Low [≤1]	Baseline 1		Baseline 1	
	Medium [2]	1.17 [0.94–1.46]	0.165	1.07 [0.84–1.36]	0.599
	High [≥3]	1.53 [1.26–1.87]	0.000	1.43 [1.15–1.77]	0.001

TNF, tumour necrosis factor; UC, ulcerative colitis; CI, confidence interval.

study. Female subjects and increasing comorbidity were associated with post-colectomy inpatient mortality, whereas time to colectomy was not found to be associated.

Colectomy rates for UC have fallen over the past decade. A reduced risk of colectomy was associated with being female or of Asian ethnicity, both during index admission and by 12 months. Higher provider volume of colectomies performed per year, receiving anti-TNF therapy during index admission, and increasing comorbidity score were all associated with an increased risk of colectomy during index admission, with volume of colectomies and anti-TNF therapy on index admission maintaining this association at 12 months. Provider volume of acute UC admissions did not affect colectomy risk. In those subjects who underwent a colectomy during index admission, increased comorbidity, lower levels of deprivation, and providers with the highest annual volume of colectomies for UC, were all associated with a reduced time to colectomy whereas female and Asian subjects were associated with an increased time to colectomy.

Ulcerative colitis management has improved dramatically since early series demonstrated mortality rates ranging from 30% to 60%.[14] Indeed, although improvements were seen with the introduction of steroids, a dramatic fall in mortality came when it was shown that early surgery was indicated if steroid therapy failed to induce remission.[15,16] The Standardised Mortality Rate [SMR] of 0.89 [0.74–1.05] for those with their first emergency admission for acute UC is low, similar to the SMR seen in other UC population analyses,[9,17] and supports the impression that the risk of mortality does not differ from that of the general population.[18–20] It should be noted that the current study examined all-cause mortality [though temporally associated with acute admission and colectomy]. Longer-term studies examining all-cause mortality, however, have not always reported similar mortality rates in UC,[17] and a meta-analysis of SMR in UC found an increase in mortality compared with the background populations reviewed.[18]

There was no significant change in mortality over the duration of this study. We further examined whether provider annual volume of colectomies for UC or annual volume of acute UC admissions was associated with mortality, and found no association during index admission or by 12 months. A Danish study examined 30-day mortality in IBD patients having a colectomy between 1996 and 2010, and reported a much higher 5.2% mortality in those undergoing emergency colectomy for UC.[9] The authors found that comorbidity and age over 40 years were important prognostic factors, similar to the current study. Additionally, they noted that a low volume of colectomies undertaken at an institution was associated with increased mortality, although this was not seen in the present study.[21] This 'volume of procedures' association has been reported elsewhere, with an American study, between 1995 and 2006, demonstrating a high 5.6% mortality rate following emergency colectomy for UC, but a mortality rate ranging from 4% for those dealing with low numbers of patients compared with 0.7% in those dealing with larger volumes.[22] Older age and comorbidity were again associated with mortality. Cause-specific mortality studies have suggested that most mortality due to UC occurs in the early years following diagnosis and is related to surgery, older age, and more extensive colitis.[5,9] This is not surprising, as surgery is a surrogate for a more severe disease phenotype. Analysis of a Scottish UC database reported that age was a particularly important factor, with 44% of UC mortality being in those over 65. The authors suggested that clinical decisions related

Table 5. Cox proportional hazards regression analysis of factors associated with time to colectomy during index admission for acute ulcerative colitis.

		Hazard ratio [95% CI]	*p*-value
Age group	18–32	Baseline 1	
	33–46	1.08 [0.91–1.29]	0.365
	47–60	0.98 [0.80–1.20]	0.858
Sex	Male	Baseline 1	
	Female	0.85 [0.73–0.99]	0.038
Charlson comorbidity score	0	Baseline 1	
	1 to 4	1.73 [1.27–2.35]	<0.001
	5+	1.54 [0.99–2.39]	0.055
Deprivation	1	Baseline 1	
	2	1.43 [1.12–1.84]	0.005
	3	1.41 [1.09–1.82]	0.008
	4	1.67 [1.30–2.15]	<0.001
	5	1.45 [1.11–1.89]	0.006
Ethnicity	White	Baseline 1	
	Asian	0.60 [0.43–0.83]	0.002
	Other minority ethnicities	0.77 [0.53–1.10]	0.149
	Unknown	1.14 [0.84–1.56]	0.400
Admission period	2007/08–2011/12	Baseline 1	
	2012/13–2016/17	0.95 [0.81–1.11]	0.538
Anti-TNF during emergency admission	Yes	0.86 [0.65–1.13]	0.272
	No	Baseline 1	
Prevalent or incident	Prevalent	0.98 [0.83–1.14]	0.756
	Incident	Baseline 1	
Provider volume of acute UC admissions]	Low [≤11]	Baseline 1	
	Medium [12 to 18]	0.89 [0.70–1.13]	0.329
	High [≥19]	1.12 [0.9–1.4]	0.301

TNF, tumour necrosis factor; UC, ulcerative colitis; CI, confidence interval.

to age and comorbidity had an impact on whether to operate, with lower rates of both elective and emergency surgery in the older age group. It was suggested that a more proactive attitude to surgery in this group may lead to improved outcomes.[19] Although age group stratification in the present study highlighted differences, a limitation was that over-60s were unfortunately not included due to validity concerns.

The 32% of subjects categorised as incident cases of UC, who were presenting for the first time with UC, were 18% more likely to undergo colectomy during their index admission. Such differences in outcomes emphasise the importance of early joint gastroenterological and surgical care following admission of patients with a new diagnosis of UC.[23]

White subjects made up 80% of the cohort in this study and had a lower risk of death than subjects of minority ethnicities other than White and Asian, during index admission and at 30 days following admission. Compared with White subjects, Asian subjects had a reduced risk of colectomy both on admission and by 12 months. Other studies have also found a disparity in UC outcomes between ethnic groups. An American study of 23 389 UC hospital discharges did not find differences in hospital mortality between ethnicities, but colectomy rates were lower in Hispanics and African Americans compared with those of White ethnicity. It was suggested that the differences in colectomy rates may reflect not only biological but also socioeconomic disparities between different ethnicities.[24] HES data were used to look at colectomy rates for UC, dependent on ethnic group over a 15-year period from 1997 to 2012, and a younger age at colectomy was reported for ethnicities other than White. It was suggested that this may relate to the differing composition of the microbiota at different ages, as well as differing cultural attitudes towards medication adherence. Indians were more likely to undergo colectomy and Pakistanis were less likely to undergo colectomy than the White cohort.[25]

Several factors were found to impact on the risk of colectomy in our study. Interestingly, female sex was found to have an inverse relationship with colectomy risk and time to colectomy. Others have found an increased hazard ratio for males with UC and emergency colectomy[26,27] and any colectomy,[28] but this has not been consistent.[29] Paediatric cohorts have also shown discrepancy between sexes.[30,31] It is possible that differences between the sexes with regards to smoking and disease severity and extent play an important role in colectomy need, which is information that is unfortunately unavailable from HES. Whether males differ from females in their response to acute illness is unclear, with contradictory studies of the association of sex with intensive care outcomes.[32,33] The decision to undertake a colectomy may be subject to medical and surgical team biases as well as a patient's concerns about life after colectomy, and may not be solely based on apparent medical need. Indeed, others have shown a disparity in the treatment of male and female UC patients, postulating cosmesis and functional outcomes on fertility and continence as key factors determining management strategies.[34,35]

Medical rescue therapies have reduced the short-term need for surgery. Although there is a significant need for colectomy in those having rescue therapy,[36] the majority of surgery occurs in the early phase after initial rescue therapy, suggesting a more severe disease phenotype. The UK IBD audit found that there was a statistically significant increase in use of ciclosporin or anti-TNF therapy over the four rounds of the audit, spanning 2008–2014. There was also a reduction in colectomies from 12% to 11% for non-elective admissions.[7] The present study found no increased mortality in those receiving anti-TNF therapy; however, there was an increased risk of colectomy both during index admission and by 12 months. This is understandable given the 'rescue' nature of anti-TNF therapy in this setting, consistent with a more severe disease phenotype. Maintenance therapy with immunomodulators has reduced the need for colectomy in UC in the long term.[37] Other studies have reported that the rate of emergency colectomy appears to have remained stable, despite reductions in elective colectomy rates.[38] In the pre-sent study, however, the risk of colectomy during emergency index admission and for 12 months [for combined emergency and elective] clearly fell over the study period.

The strength of the HES database is the ability to study admissions from across the whole of England, preventing the tendency seen in literature to focus on expert tertiary centres, which might have limited generalizability. However, this was a retrospective co-hort study and as such is susceptible to a number of biases related to available information and unknown confounding factors. A limi-tation of HES data is the lack of detail related to how individuals are managed and what medications they receive, and biological therapies that can be administered outside hospital are not captured [e.g., adalimumab]. Disease severity, extent[39,40] and smoking history are not captured, and these are known to impact upon UC disease course.[41] Furthermore, although well recorded in HES, the details of surgery including time of day, seniority of the surgeon, and the physiological parameters of a subject are not captured. Prevalent cases were defined based on coding of activity in HES. It is feasible that some subjects were diagnosed a relatively short time before

acute admission. This is a potential confounding factor when comparing incident and prevalent cases, because such cases may not be established on effective therapy before admission.

It was unfortunately not possible to include subjects over 60 years of age in the present study, due to the reduced reliability of a coded acute admission diagnosis of UC in subjects over 60, compared with subjects under 60, found during validation. In older subjects, conditions such as ischaemic colitis, diverticulitis, and segmental colitis are commonly seen and may be confused with UC.

Mortality following a first emergency admission for UC is low and had not changed over the study period. There has been a fall in colectomy rates for acute UC in England over the past 10 years. Female and Asian subjects undergo colectomy for UC less and those with medical comorbidities more often. Given the increased mortality in those with UC and comorbidities, and the lack of an overall improvement in mortality, the close, early, and joint management of acute UC admissions by gastroenterologists and surgeons, including optimisation of comorbidities, should be the standard of care for such patients.

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Conflict of Interest

The work was supported by a grant received from Merck, Sharp and Dohme. Dr. R. Cooney reports personal fees from Janssen, Takeda, Falk and Dr. N. Trudgill personal fees from Janssen and Dr. Falk outside the submitted work. The authors have no other conflicts of interest to disclose.

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Author Contributions

Study concept and design were jointly initiated by DK, JR, NT, and PP. Data extraction was performed by JM and analysis was performed by JM, DK, and NT. Manuscript was drafted by DK. The data and manuscript were critically reviewed, revised and approved by all authors.

Supplementary Data

Supplementary data are available at *ECCO-JCC* online.

Podcast

This article has an associated podcast which can be accessed at https://academic.oup.com/ecco-jcc/pages/podcast

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CHAPTER 5: THE RISK OF FURTHER SURGERY FOLLOWING FIRST RESECTIONAL SURGERY IN CROHN'S DISEASE

This chapter contains two manuscripts exploring the risks of further surgery in those who have had a bowel resection for CD. The first looks at all types of CD index resections and has been submitted to a journal. The second focuses on the risk of further resections at the anastomosis site in subjects with an index right hemicolectomy or ileocaecectomy and is published in the journal Alimentary, Pharmacology & Therapeutics.

Supplementary material for each manuscript is found in the appendices for this chapter at the end of the thesis.

Chapter 5 manuscript 1: The risk of subsequent surgery following bowel resection for Crohn's disease in a national cohort of 19,207 patients

Structured abstract

Background and Aims

Surgery is required for the majority of patients with Crohn's disease (CD) and further surgery may be necessary if medical treatment fails to control disease activity.

Methods

Hospital Episode Statistics from England were examined to identify patients with CD and a first recorded bowel resection between 2007 and 2016. Multivariable logistic regression was used to examine risk factors for further resectional surgery within 5-years. Prevalence-adjusted surgical rates for index CD surgery over the study period were calculated.

Results

19,207 patients (median age 39 (IQR 27-53) years and 55% female) with CD underwent a first recorded resection during the study period. 3,141 (16%) underwent a further operation during the study period. The median time to further surgery was 2.4 (IQR 1.2-4.6) years. 3% of CD patients had a further surgery within one year, 14% by 5 years and 23% by 10 years. Older age (≥58), index laparoscopic surgery and index elective surgery (adjusted odds ratios 0.65 (95% CI 0.54-0.77), 0.77 (0.67-0.88), 0.63 (0.53-0.73), and 0.77 (0.69-0.85), respectively) were associated with a reduced risk of further surgery by 5-years. Prior surgery for perianal disease (1.60 (1.37-1.87)), an extraintestinal manifestation (EIM) of CD (1.51 (1.22-1.86)) and index surgery in a high-volume centre for CD surgery (1.20 (1.02-1.40)) were associated with an increased risk of further surgery by 5-years. A 25% reduction in prevalence-adjusted index surgery rates for CD was observed over the study period.

Conclusions

Further surgery following an index operation is common in CD. This risk was particularly seen in patients with perianal disease, EIMs and those who underwent index surgery in a high-volume centre.

Introduction

Crohn's Disease (CD) is characterised by inflammation of the intestinal wall, which if complicated by fistulisation and fibrotic stricturing usually requires surgical intervention [1]. Although a range of medical therapies have emerged over recent decades, a majority of patients with CD require a surgical bowel resection during their lifetime and the literature suggests a significant minority need further operations due to the high disease recurrence rate in CD [2–4].

Disease recurrence is almost universal and guidelines advocate a surveillance and step up approach following surgical resection for ileocaecal disease and prophylactic medical management, in particular for high risk groups including smokers, those with penetrating disease behaviour and those with a history of surgical resection [5,6]. There is hope that medical therapies will change the natural history of CD and reduce the need for surgery and recurrent surgery in CD. However, with evolving practice in the biologic era, only relatively short follow-up periods in randomised control trials have demonstrated reduced surgical rates which have not translated to population studies [7]. Longer follow up from post-surgical intervention trials is awaited to see if long term benefit of such medical therapies can be realised [7–9].

Although CD is the broad diagnostic label, it actually represents a spectrum of disease with different areas of the bowel predominantly affected in different individuals. Small bowel predominant, upper gastrointestinal, ileocaecal predominant and Crohn's colitis are recognised clinical patterns with ileocaecal being the most common. In addition, patients with CD may suffer with perianal disease, seen most commonly in the young, in those with Crohn's colitis [10–12]. Perianal disease is not easily defined, but includes anal fissuring, abscess formation and perianal fistulas, and some would also include haemorrhoids

and perianal skin tags [13]. Perianal disease complicating CD is challenging to manage and can lead to reduced quality of life and herald a more severe disease course [14]. CD can also be associated with extraintestinal manifestations (EIM). Classical EIMs include hepatobiliary, ophthalmic, dermatological and musculoskeletal conditions [15,16]. Up to half of patients with inflammatory bowel disease (IBD) will experience an EIM during their disease, with most running a parallel course to their intestinal disease [15,17–19]. EIMs are associated with a more extensive, severe phenotype in UC but similar data on CD outcomes is limited [20–22].

The aim of this study was to examine the risk of further surgery in CD following a first episode of resectional surgery and risk factors for such events.

Methods and materials

Data source

Hospital Episode Statistics (HES) contain data on National Health Service (NHS) secondary care episodes of inpatient and outpatient care for England. Diagnostic data is recorded using the International Classification of Diseases version 10 (ICD-10) codes and procedural data is recorded using Office of Population Censuses and Surveys Classification of Interventions and Procedures - 4th revision (OPCS4) codes. Demographic data are also recorded with each episode and patients can be tracked via a unique identification code between different episodes. Patient counts of five and less are suppressed from publication in order to comply with the HES data confidentiality requirements.

Inclusion criteria

Adult subjects ≥18 years old were included in the study. For study inclusion, subjects required a record of a small or large bowel surgical resection between 1st January 2007 and 31st December 2016. Subjects also required a Crohn's disease (ICD-10: K50) diagnosis on their index surgery admission. Two authors identified and came to a consensus for the procedural codes used, a list of which is found in Appendix 1. Patients were included in a CD colitis sub-cohort if they had a CD colitis code (K50.1) and an OPCS-4 code identifying a colectomy procedure.

Exclusion criteria

Patients were excluded if, following a CD diagnosis at index surgery, they had a greater frequency of Ulcerative Colitis (UC) (ICD-10: K51) diagnoses coded subsequently. Subjects were also ineligible for inclusion if they had a cancer diagnosed during the year before index surgery or during follow-up to reduce the risk of resectional surgery being carried out for a cause other than CD. Subjects without a recorded age, an age less than 18 and those with a

missing or invalid code for sex were excluded, as were subjects with residency outside of England. Further resectional surgery that took place either during the same admission episode or within a 30-day period following index surgery was excluded from the primary analysis in order that surgical complications were not counted. Certain index surgical codes (e.g. stoma formation) were deemed to be associated with a high likelihood of subsequent planned elective surgical procedures (Appendix 1). Patients undergoing an operation on an elective admission within a year of such index surgery were also excluded from the primary analysis. These surgical exclusion criteria sought to limit bias associated with planned completion of the initial intent of the index resectional surgery, however, the patients themselves were not excluded from further analysis so further *valid* surgery in these patients would be included.

Data validation

To assess the validity of CD surgical coding, a list of patients meeting the same ICD-10 and OPCS4 coding criteria was provided by the local coding departments at Sandwell & West Birmingham Hospitals NHS Trust. The accuracy of coding at each site was then assessed by consulting the electronic patient records to establish if both the CD diagnosis and the surgical procedural code were accurate.

Demographic data

Subject age, sex, deprivation status and ethnicity were identified from index surgery admission coding. For the overall cohort, age was divided into quintiles 18-26, 27-34, 35-45, 46-57 and ≥58 for analysis. Ethnicity was stratified into white, Asian, other minority ethnicities and unknown. The Charlson comorbidity index, a measure of multimorbidity in subjects and previously validated in HES [23], was calculated using secondary diagnostic coding. Deprivation quintiles were calculated from the Index of Multiple Deprivation, a classification based on income, employment, crime and living environment [24]. Deprivation

quintile 5 is the least deprived quintile and quintile 1 the most deprived. Previous codes for perianal surgery or EIMs prior to the index resectional surgery admission were recorded (Appendix 2 and 3).

Outcome measures

The primary outcome measure was first further resectional surgery. Multiple further surgeries by 1, 5 and 10 years were also examined. Further resectional bowel surgery within 5 years was examined in those with at least 5 years of follow up time for multivariable analysis. Secondary outcomes examined included the trends in CD surgery standardised to the burden of CD for a particular year using the annual point prevalence of CD in England [25]. The use of infliximab in the year prior to and following index surgical resection and the change in infliximab use over time was also investigated (infliximab is coded in HES as a high-cost drug under anti-TNF therapy).

Statistical analysis

Demographic data is presented as number and percentage where applicable. Age and time to surgery are presented as median and interquartile range (IQR). Characteristics of included and excluded subjects were compared using Chi-squared tests for categorical data.

A multivariable logistic regression model was constructed for risk of further surgery within 5 years of index surgery in those with at least 5 years of follow up for both the entire cohort and the Crohn's colitis sub-cohort with estimates presented as adjusted odds ratios (aOR). Variables included in the models were age quintiles, sex, provider volume of index resectional CD surgery, ethnicity, deprivation quintiles, index surgery admission method, Charlson comorbidity score, year of index surgery, prior perianal disease (perianal surgery was used as

a surrogate for severe perianal disease), the presence of an EIM at baseline and whether the index surgery was performed as a laparoscopic procedure.

A Kaplan-Meier plot of time to further surgery was produced for those with index surgery performed as an elective and emergency procedure. A further Kaplan Meier plot of time to further surgery with three curves representing three eras of index surgery was produced with accompanying global and stratified log rank tests.

A sensitivity analysis using multivariable logistic regression, including *all* first further surgery for CD within 5 years of index surgery was constructed. This sensitivity analysis incorporated those operations previously excluded, including surgery within 30 days of index operation and those at risk of staged elective operations within one year of index resection.

Index resectional surgery rates for CD in England were produced by dividing the yearly count of index resectional surgery by CD prevalence in England, derived from a nationally representative primary care database standardised to the English adult population per year, taken from Office for National Statistics data, taking account of the changing population at risk and CD prevalence [25,26]. Linear regression was used to assess the change in rate of index surgery over the time.

All statistical analyses were carried out using Stata SE v16 [27]. P-values of <0.05 were considered statistically significant.

Ethics

HES data is available under data sharing agreements with NHS Digital for the purpose of service evaluation. Ethics approval is not, therefore, required. HES data was granted by the

Health Informatics Request Review Group at University Hospitals NHS Foundation Trust: UHB Registration number CARMS-14875.

Results

Data validation

All admissions at Sandwell & West Birmingham Hospitals NHS trust with an ICD-10 code for CD (K50*) and a surgical code (Appendix 1), excluding individuals with any cancer code, were examined between December 2015 and December 2017. Of the 65 cases identified, all were accurately coded as CD when compared to the electronic patient record. 64 (98%) were correctly coded for the surgical procedure when compared to the operating notes.

Cohort characteristics

From 1st January 2007 until 31st December 2016, 19,270 subjects with CD and a first resectional bowel surgery were identified for study inclusion (Figure 1). The cohort median age was 39 (IQR 27-53) years and 55% were female. 88% of subjects were of white ethnicity and 81% of subjects had a Charlson comorbidity score of 0. 56% (10,768) of index resections took place in providers in the upper tertile of provider volume for these operations (≥139 of these procedures over the 10-year study period). 55% (10,584) of index resections were performed during an elective admission. 8.9% (1,703) of subjects had a perianal disease surgical intervention coded prior to index resection, indicating a severe perianal disease component to their CD. 26.5% (5,098) of subjects' index surgery were coded as laparoscopic. Index surgery recorded as a laparoscopic procedure increased from 11% of cases in 2007 to 37% in 2016. At baseline, 1,035 (5.4%) codes for an EIM of IBD were identified. 0.3% (54) of subjects had multiple EIMs recorded. Infliximab was coded in 12% (2,331) of patients in the year prior to index surgery overall, but over the study period a rise in use from 5.6% in 2007 to 19% in 2016 was observed. 4.9% (932) of patients received infliximab in the year following index surgery (2.9% in 2007 increasing to 7.5% in 2016). 2.3% (438) of patients

received infliximab both before and after index surgery (0.6% in 2007 increasing to 3.9% in 2016). Characteristics of the overall cohort and of those with at least 5 years of follow up are presented in Table 1.

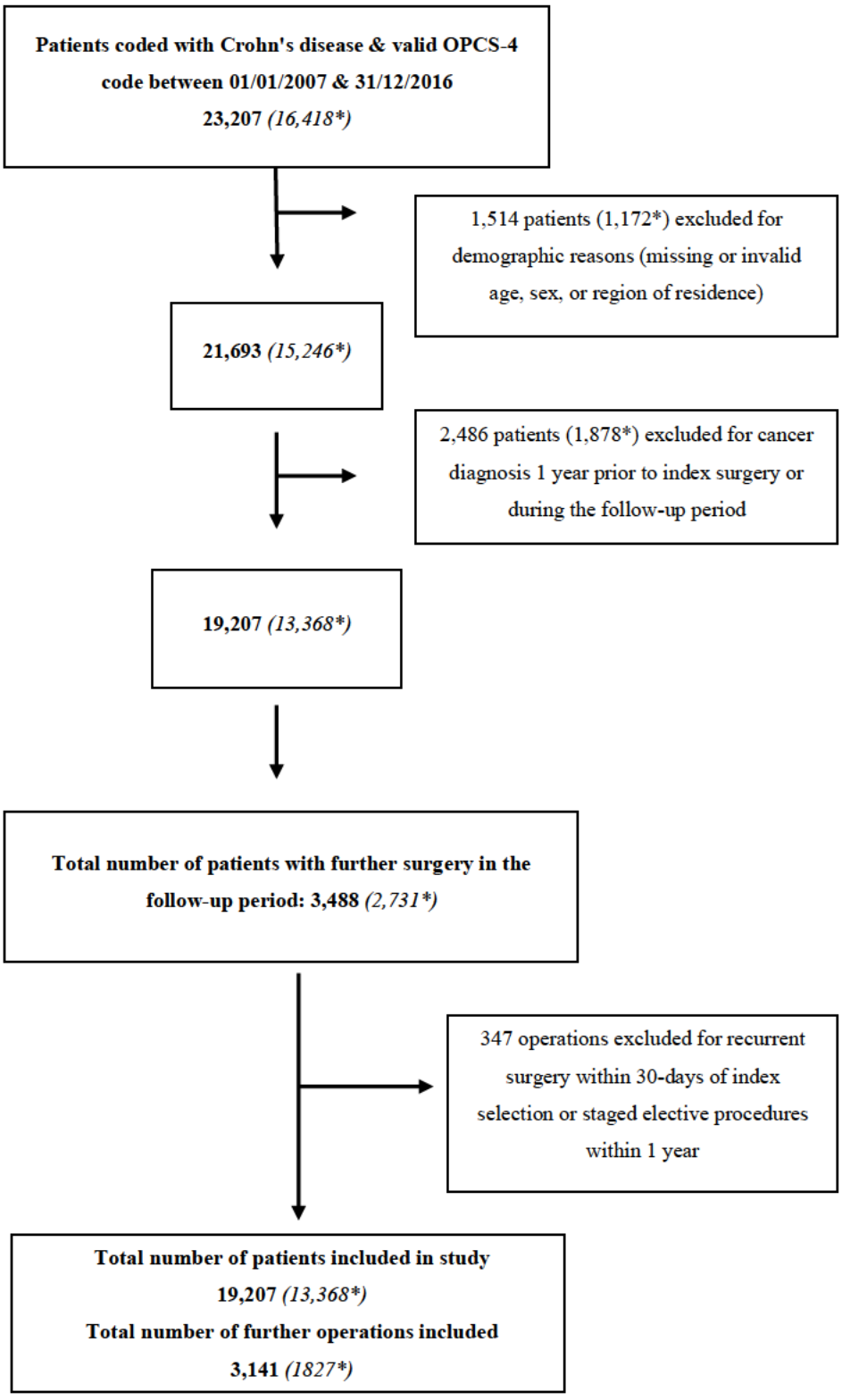


Figure 1. Study Flow Chart
****Patients with at least 5 years of follow up included in primary analysis***

Table 1: Demographic and clinical characteristics of study cohort

Demographics		Patients (%)	Further Surgery (%)	Patients with ≥ 5-year follow-up (%)	Further surgery within 5 years (%)
Sex	**Male**	8677 (45.2)	1474 (17.0)	5971 (44.7)	833 (14.0)
	Female	10530 (54.8)	1667 (15.8)	7397 (55.3)	994 (13.4)
Age quintile	**18-25**	4344 (22.6)	793 (18.3)	2678 (20.0)	400 (14.9)
	26-34	3536 (18.4)	601 (17.0)	2775 (20.8)	394 (14.2)
	35-44	3738 (19.5)	671 (18.0)	2706 (20.2)	387 (14.3)
	45-57	3793 (19.7)	628 (16.6)	2606 (19.5)	374 (14.4)
	58+	3796 (19.8)	448 (11.8)	2603 (19.5)	272 (10.4)
Median (IQR) age		39 (27-53)	37 (27-49)	40 (28-53)	38 (27,50)
Provider volume of index surgery	Low (1-81)	2297 (12.0)	340 (14.8)	1731 (12.9)	211 (12.2)
	Med (82-143)	6142 (32.0)	961 (15.6)	4071 (30.5)	524 (12.9)
	High (144+)	10768 (56.1)	1840 (17.1)	7566 (56.6)	1092 (14.4)
Ethnicity	**White**	16903 (88.0)	2798 (16.6)	11850 (88.6)	1643 (13.9)
	Asian	562 (2.9)	101 (18.0)	350 (2.6)	57 (16.3)
	Other minority ethnicities	609 (3.2)	94 (15.4)	410 (3.1)	48 (11.7)
	Unknown	1133 (5.9)	148 (13.1)	758 (5.7)	79 (10.4)
Deprivation quintile	**1 (Most deprived)**	4127 (21.5)	713 (17.3)	2826 (21.1)	416 (14.7)
	2	4127 (21.5)	690 (16.7)	2879 (21.5)	402 (14.0)
	3	3958 (20.6)	655 (16.5)	2770 (20.7)	378 (13.6)
	4	3650 (19.0)	553 (15.2)	2522 (18.9)	321 (12.7)
	5 (Least deprived)	3345 (17.4)	530 (15.8)	2371 (17.7)	310 (13.1)
Index surgery admission method	**Emergency**	8483 (44.2)	1576 (18.6)	5879 (44.0)	914 (15.5)
	Elective	10584 (55.1)	1546 (14.6)	7385 (55.2)	900 (12.2)
	Unknown	140 (0.7)	19 (13.6)	104 (0.8)	13 (12.5)
Year of index surgery	**2007**	1816 (9.5)	434 (23.9)	1816 (13.6)	260 (14.3)
	2008	1848 (9.6)	429 (23.2)	1848 (13.8)	261 (14.1)
	2009	1886 (9.8)	395 (20.9)	1886 (14.1)	279 (14.8)
	2010	1901 (9.9)	342 (18.0)	1901 (14.2)	252 (13.3)
	2011	1962 (10.2)	304 (15.5)	1962 (14.7)	235 (12.0)
	2012	2004 (10.4)	335 (16.7)	2004 (15.0)	285 (14.2)
	2013	1951 (10.2)	270 (13.8)	1951 (14.6)	255 (13.1)
	2014	1902 (9.9)	269 (14.1)	-	-
	2015	1964 (10.2)	191 (9.7)	-	-
	2016	1973 (10.3)	172 (8.7)	-	-
Charlson comorbidity score	**0**	15620 (81.3)	2594 (16.6)	11009 (82.4)	1497 (13.6)
	1-4	2465 (12.8)	408 (16.6)	1615 (12.1)	241 (14.9)
	5+	1122 (5.8)	139 (12.4)	744 (5.6)	89 (12.0)
Prior perianal surgery		1703 (8.9)	421 (24.7)	1148 (8.6)	231 (20.1)
Extraintestinal manifestation		1035 (5.4)	215 (24.7)	622 (4.7)	119 (19.1)
Laparoscopic Index surgery		5098 (26.5)	662 (13.0)	3051 (22.8)	334 (10.9)
Total		19207	3141 (16.4)	13368	1827 (13.7)

**≤5 subjects: data not shown to ensure subject anonymity*

Of those excluded, deprivation level and ethnicity were comparable to those eligible for study inclusion, p=0.093 and 0.448, respectively. Those excluded from the study had proportionally more males, fewer subjects aged 18-34 and more aged 58 and over. More patients with comorbidities were excluded compared to those included. These inclusion-exclusion differences were similar in those with at least 5 years of follow-up (Appendix 4).

Further surgery during the follow-up period

Overall, 3,141 further resections were recorded during the study period, in 16.4% of patients. 625 (20%) subjects had further surgery performed within the first year that was not considered a staged, elective completion of the index surgical intent. Patients undergoing further surgery had a median (IQR) age of 37 (27-49) and 53% (1,667) were female. Age deciles at which patients underwent index and further surgery are shown in Appendix 5.

65.5% of further resections took place on an elective admission. 21% (662) of further surgeries were coded as laparoscopic procedures. 18.6% of index surgeries performed during emergency admissions had further surgery performed on an emergency admission compared to 14.6% of patients with an elective index surgery. Figure 2 shows a Kaplan-Meier curve for further surgery stratified by the index resection admission method (emergency or elective). 24.7% (421) of further surgery patients had a baseline perianal surgical intervention and 7% (215) had a baseline EIM recorded. The median (IQR) time to further surgery was 2.36 (1.15-4.55) years overall. During follow up 79% (2,488) of patients had only one further resection recorded while 21% (653) of patients had two or more further resections. By two years following the index resection 7% (1,413/19,207) of patients had undergone further surgery, 13.7% (1,827/13,368) at 5 years and 22.6% (830/3,674) at 10 years had further resections. Of

those with 10 years of follow up, 5.9% (215/3,674) of patients had two or more further resections.

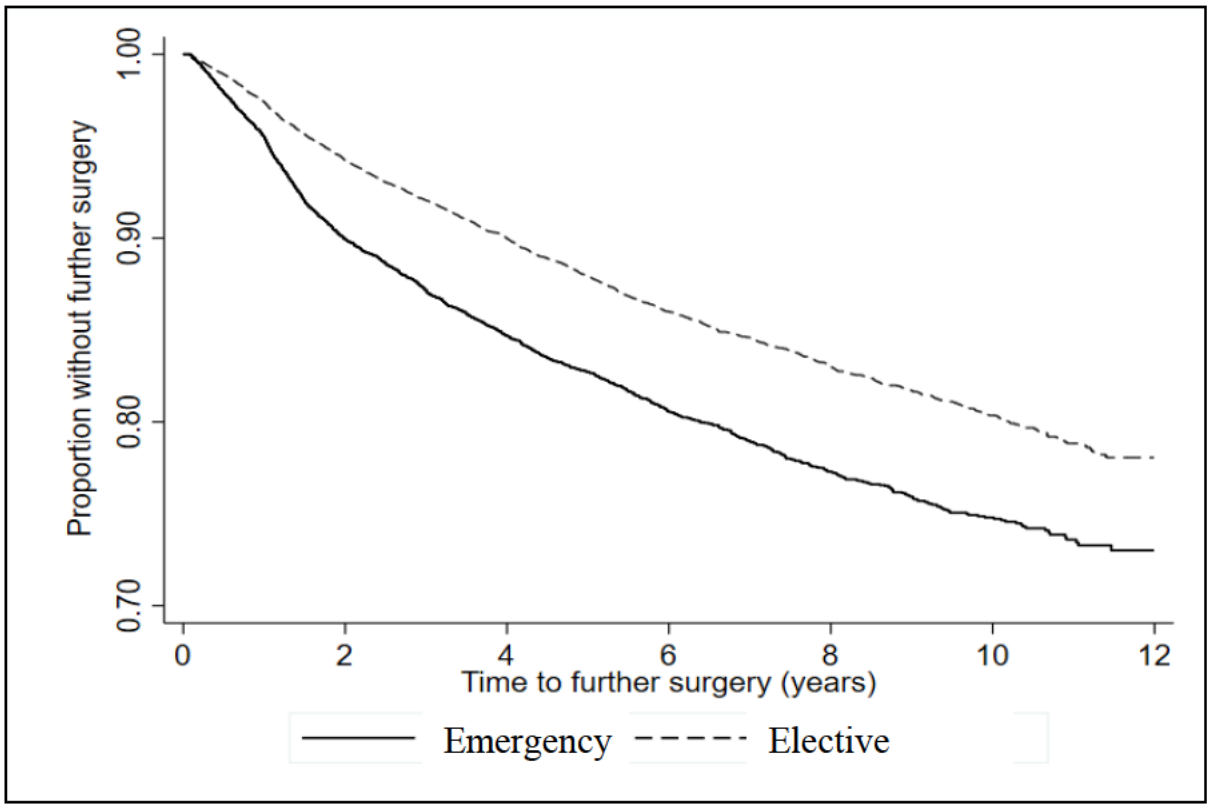


Figure 2. Kaplan-Meier curve showing time to further resection for those who underwent an index resection during an emergency or an elective admission.

When followed from index resection stratified by 3-year eras (2007-9, 2010-12, 2013-15), a separation in the rates of further surgery was observed, Figure 3. Globally a difference between curves was observed, log rank test $p = 0.003$. When stratified, a significant difference between the two earliest and the earliest and latest eras was observed (2007-09 and 2010-12 $p<0.001$, and 2007-09 and 2013-15 $p = 0.048$), though not between the latest two eras (2010-12 and 2013-15 $p = 0.784$).

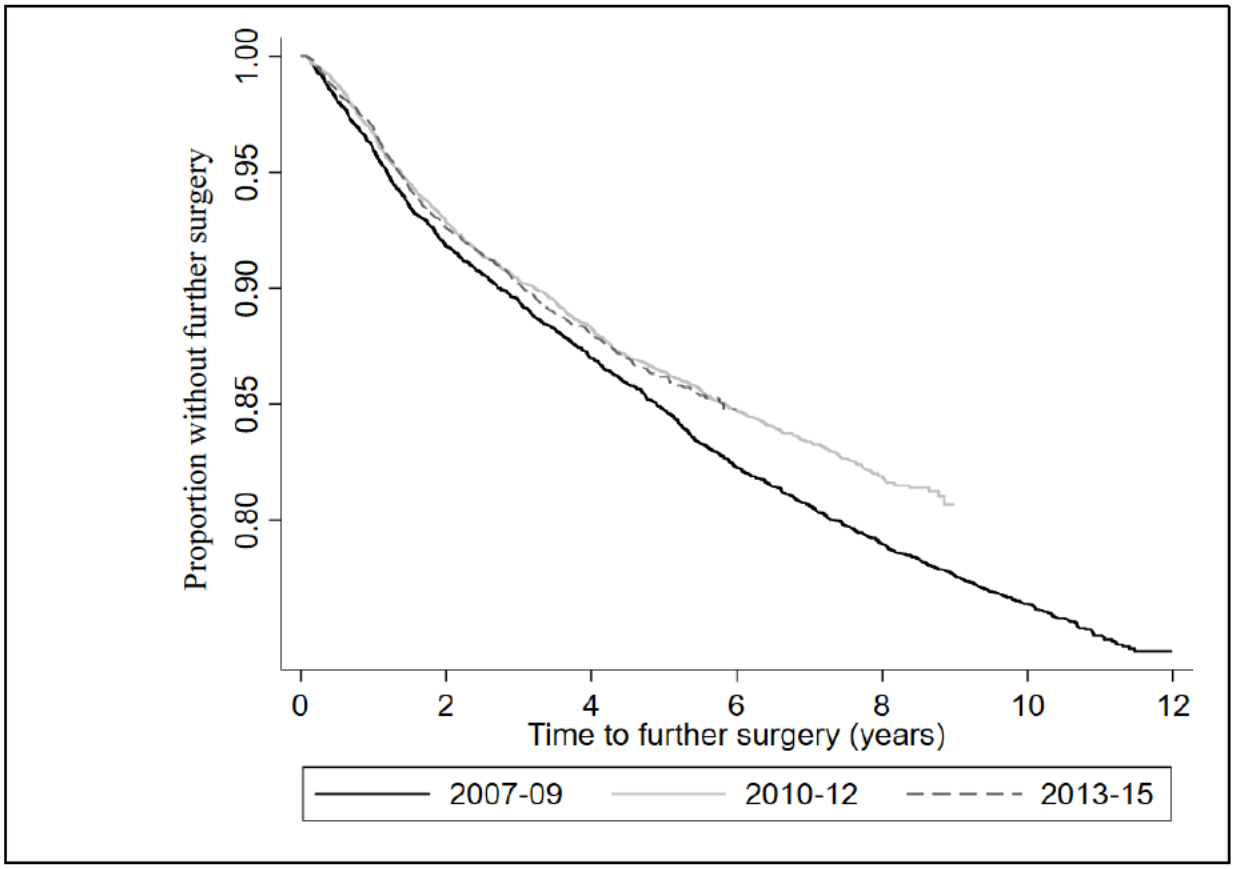


Figure 3. Kaplan-Meier analysis showing the proportion of patients who have further surgery stratified by 3-year time periods of index Crohn's disease resection

Multivariable logistic regression analysis of factors associated with further surgery within 5 years

Table 2 shows the multivariable logistic regression model for factors associated with risk of further surgery within 5 years. Patients with a minimum of 5 years of follow up (those enrolled between 2007 and 2013) were examined using multivariable logistic regression to assess factors associated with further resection within 5 years of index resection. 13,368 (70%) patients were included in the analysis. 13.7% (1,827) of this cohort had a further resection within 5 years of index resection (Table 1). Factors associated with risk of further resection within 5 years were presence of baseline EIM (aOR 1.51 (95% CI 1.22-1.86), p<0.001), baseline previous perianal surgical intervention (1.60 (1.37-1.87), p<0.001), a comorbidity score of 1-4 compared to those with a score of 0 (1.16 (1.01-1.35), p=0.049) and undergoing index resection in the high-volume providers of CD surgery (1.20 (1.02-1.40), p=0.027). Factors associated with a reduced risk of further resection included index surgery performed laparoscopically (0.77 (0.67-0.88), p<0.001), the oldest age quintile (≥58 years old) compared to the youngest quintile (18-25) (0.65 (0.54-0.77), p<0.001) and index resection performed on an elective admission (0.77 (0.69-0.85), p<0.001).

Table 2: Multivariable logistic regression of factors associated with further resection within 5 years of index resection

Factors		Adjusted Odds Ratio	[95% Conf. Interval]		P value
Sex	**Male**	reference			
	Female	1.01	0.91	1.12	0.847
Age quintile	**18-25**	reference			
	26-34	0.95	0.81	1.10	0.470
	35-44	0.95	0.82	1.11	0.512
	45-57	0.97	0.83	1.13	0.663
	58+	0.65	0.54	0.77	<0.001
Provider volume of index surgery	**Low**	reference			
	Medium	1.05	0.89	1.25	0.559
	High	1.20	1.02	1.40	0.027
Ethnicity	**White**	reference			
	Asian	1.10	0.82	1.47	0.532
	Other minority ethnicities	0.79	0.58	1.07	0.126
	Unknown	0.71	0.56	0.90	0.005
Deprivation quintile	**1 (Most deprived)**	reference			
	2	0.95	0.82	1.10	0.503
	3	0.94	0.81	1.09	0.427
	4	0.88	0.75	1.03	0.100
	5 (Least deprived)	0.91	0.77	1.07	0.238
Index surgery admission	**Emergency**	reference			
	Non-emergency	0.77	0.69	0.85	<0.001
Charlson comorbidity Score	**0**	reference			
	1-4	1.16	1.00	1.35	0.050
	5+	0.96	0.75	1.22	0.710
Year of index resection	**2007**	reference			
	2008	0.97	0.80	1.17	0.721
	2009	1.02	0.85	1.22	0.853
	2010	0.89	0.73	1.07	0.214
	2011	0.80	0.66	0.97	0.021
	2012	0.98	0.82	1.18	0.840
	2013	0.90	0.74	1.08	0.263
Prior perianal surgery		1.60	1.37	1.87	<0.001
Presence of extraintestinal manifestations		1.51	1.22	1.86	<0.001
Index surgery performed laparoscopically		0.77	0.67	0.88	<0.001

All further surgery

In the primary analysis, first further surgery was excluded if it took place within 30 days of index resection or was deemed to be a staged procedure, e.g. reversal of a stoma within one year of index resection performed on an elective admission; in this secondary analysis, all further surgery was included. In total, 18.8% (2,514) of patients underwent a further CD surgical resection within 5 years of index surgery. A multivariable logistic regression model of factors associated with all further surgery within 5 years provided similar findings to the primary analysis and can be seen in Appendix 6. The oldest age quintile (≥58 years old) compared to the youngest (18-25), index surgery performed laparoscopically, and elective index resection were all associated with a reduced risk of further resection (0.73 (0.63-0.86), 0.78 (0.67-0.85) and 0.66 (0.61-0.73), respectively). Baseline previous perianal surgery, the presence of an EIM at baseline and index CD resection performed in a high-volume provider of such resections were associated with increased further surgical risk (1.51 (1.31-1.74), 1.53 (1.27-1.85) and 1.19 (1.03-1.36), respectively). In this sensitivity analysis high comorbidity score (5+) was associated with an increased risk of further surgery compared to those with a score of 0 (1.30 (1.07-1.57), p=0.009), however, the association with comorbidity scores 1-4 were not statistically significant. Baseline characteristics and regression model tables are shown in Appendices 6 and 7, respectively.

Crohn's colitis sub-cohort

2,329 patients with a CD colitis code and an index colectomy code were identified for a sub-cohort analysis, of which 507 (21.8%) went on to have a further resection. The median age in this group was 41 (IQR 28-54) years and 57% were female. Charlson comorbidity score and ethnicity were similar to the overall cohort (80% with score 0 and 88% white). 54% (1,257)

of index resectional surgeries took place on an elective admission and 57% (1,321) in providers in the upper tertile of provider volume of these operations (≥18 of these procedures over the 10-year study period). 13% of CD colitis patients had a previous perianal surgical intervention coded prior to index resectional surgery (compared to 9% overall). At baseline, 173 (7%) patients were coded with an EIM. The CD colitis sub-cohort characteristics are shown in Appendix 8.

Further surgery in the Crohn's colitis sub-cohort

In the CD colitis sub cohort, 20% (100) of patients having further surgery had two or more further resections during the follow-up period. By two years following the index resection, 10% (243/2,329) of patients had undergone a further resection, 19% (302/1,623) by 5 years and 28% (123/435) by 10 years. The median (IQR) time to a further resection was 2.14 (1.17-3.97) years in the CD colitis sub-cohort. 18% (136) of further surgery patients had a baseline perianal surgical intervention recorded, and 10% (53) had a baseline EIM recorded. It was again observed in the sub-cohort that those who underwent index resection during an elective admission were associated with a reduced risk of further surgery within 5 years (aOR 0.75 (0.57-0.98), p=0.033). Comorbidity score of 5+ compared to scores of 0 were also associated with a reduced risk of further surgery (0.47 (0.23-0.95), p=0.035) while perianal disease was associated with a 65% increased risk (1.65 (1.16-2.34), p=0.005). Index surgery performed laparoscopically was not significantly associated with 5 year surgery risk (0.99 (0.70-1.39), p=0.950). The multivariable logistic regression model of factors associated with 5-year further resection in the CD colitis sub-cohort is shown in Appendix 9.

Changes in practice over the study period

Levels of infliximab use in the year prior to and following index resection (before further surgery) increased from 5.6% to 19.0% and 2.9% to 7.5%, respectively, between 2007 and

2016. Index resections per year increased from 1,816 in 2007 to 1,973 in 2016. When CD prevalence over time was accounted for, surgical rates actually fell from 12.2 to 9.2 resections per 1000 CD subjects in England over this period ($p<0.001$) (Appendix 10) [25]. A fall in rates was seen for index resections irrespective of whether the admission method was elective or emergency. Figure 4 shows the trends in English CD prevalence and the rates of index resection for CD over the study period, stratified by surgery and admission type.

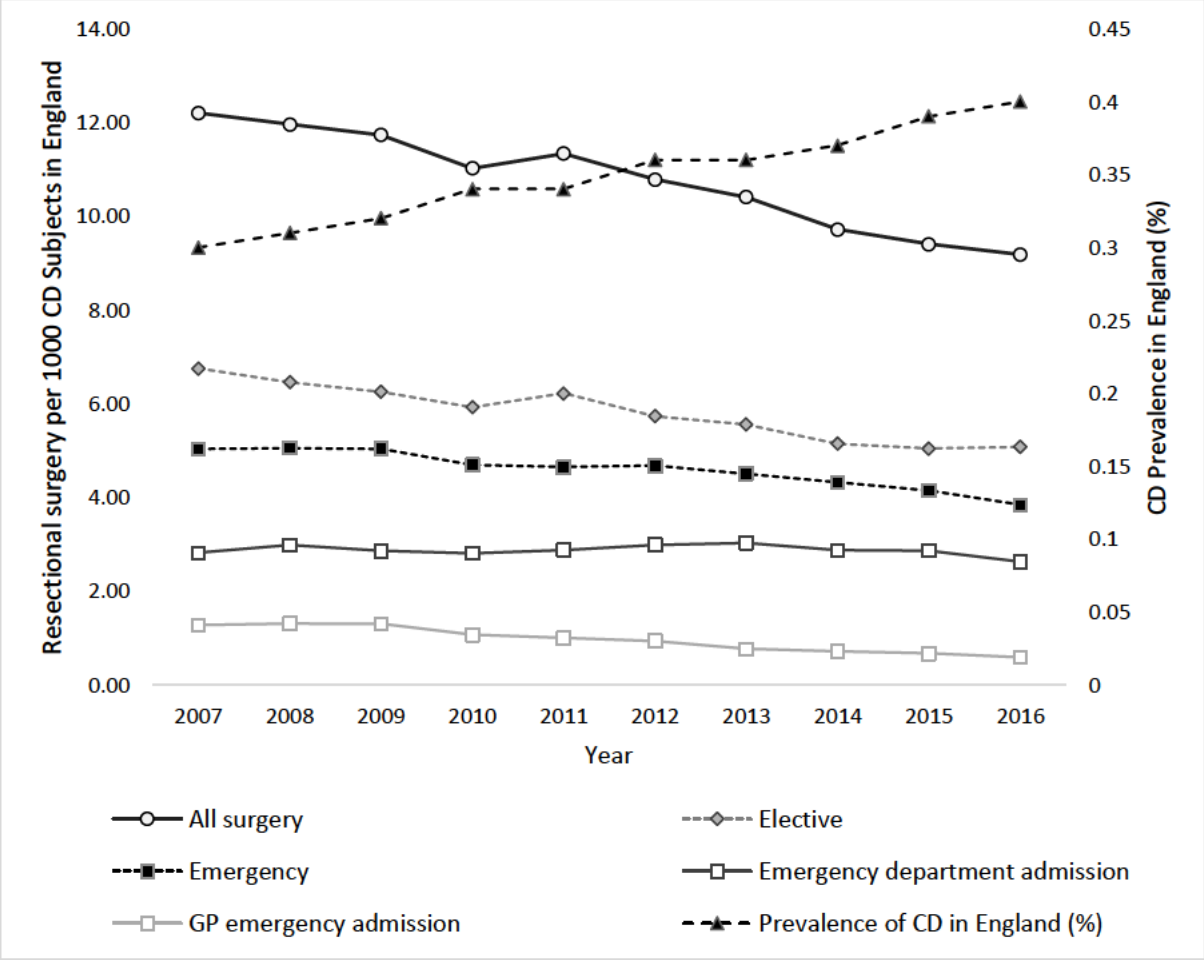


Figure 4. Index resection rates stratified by surgery and admission type, and Crohn's disease (CD) prevalence in England

GP: General practitioner

Discussion

In this study we have shown that 16.4% of patients underwent further surgery after an initial resection of large and/or small bowel for Crohn's disease. The rate of at least one further surgery by 5 years was 14% and by 10 years 23%. 5.9% of those with 10 years of follow up had undergone more than one further operation for CD. Rates were higher still in the CD colitis sub-cohort with 19% undergoing further surgery by 5 years after index surgery and more than 28% by 10 years, of which 8.3% had more than one further surgery. Overall, 21% of patients undergoing further surgery had at least two further surgeries during the study period with 2% having 4 or more operations after an index operation. Older age, index surgery performed laparoscopically and elective admission for index surgery were all associated with a reduced risk of further surgery by 5 years. Prior perianal surgical intervention, an EIM at baseline and high provider volume of index surgery were associated with an increased risk of further surgery by 5 years. In the CD colitis sub-cohort comorbidity scores of 5+ (though not age) were associated with a reduced risk of further surgery while laparoscopic surgery was not found to be associated with further surgery.

Over time index surgery rates for CD have fallen [28,29]. Increased recognition and understanding of these conditions with early medical intervention, changing attitudes to surgery and novel medical therapies are all likely to play important roles in this reduction [28,30,31]. In the current study, we have used previous data showing an increase in CD prevalence over time to demonstrate that although the number of index surgical resections for CD have increased over time, the denominator (CD subjects in the population) has also increased, leading to a fall in rates of CD index surgery in real terms [32]. However, there remains a clear risk of further surgery in patients undergoing resection. Surgery is often the right option in CD, leading to prolonged disease-free periods for many with associated

improvements in quality of life [33,34]. Recurrent surgery has also fallen over time, a likely result of an evolving therapeutic armoury in CD and improved surgical care [2,29]. However, recurrence rates following resectional CD surgery remain high, and while endoscopic recurrence is higher than clinical relapse, the need for further surgery remains substantial [4,35]. The data presented here parallels others' findings. Ahmed *et al,* using HES data, showed that as a proportion of CD hospital admissions, all types of major abdominal surgery for CD have fallen over time [36]. Similarly, a UK primary care study looking at first and further resectional surgery over 10 years from CD diagnosis and index surgery, respectively, found a significant fall in surgical risk [29]. Historically, surgical rates have fallen significantly, even before the advent of biologic medications [28,37]. However, meta-analyses have found that index surgery and further surgery risk, though falling over time, remain high [2,3].

Those in the oldest age quintile were at reduced risk of further surgery compared to the youngest subjects studied. This observation has been demonstrated previously and although date of diagnosis is not available in the HES database, those with new onset CD in older age may be less at risk of surgery than the young [38,39]. Moreover, those who reach older age with CD may experience autoimmune disease "burn-out" where the immune system is less able to mount a severe inflammatory response and so runs a more benign course [40]. Younger subjects known to have a more severe disease course may be less adherent to treatment or less engaged with follow up and thus be at increased risk of emergency presentations as well as higher recurrent risk due to the natural history of CD in the young [1,41].

Index surgery during an emergency admission was associated with an increased risk of further surgery both overall and in the CD colitis sub-cohort. The reason behind such an association is likely to be multifactorial. More aggressive disease may present acutely and be an indication of a more severe disease course; up to 16% of cases of CD may present in such

a way [34]. Partially obstructing strictures, initially managed conservatively, are at risk by their nature of progressing to complete obstruction requiring emergency intervention [42]. Emergency surgery poses a higher risk of complications associated with both the emergency situation (peritoneal contamination, malnourished patient, sepsis, etc.) as well as the increased need for laparotomy rather than laparoscopic surgery in emergency settings [32,43,44]. This implies that further surgery will not only be for CD recurrence but also relate to previous surgery, e.g. adhesions [34].

An increased risk of further surgery was associated with index surgery at higher volume providers. This may represent the fact that more complex disease is seen more commonly in higher volume centres where multidisciplinary teams with surgeons expert in IBD are based [45]. Other factors found to be associated with increased risk of further surgery were prior perianal surgical intervention and the presence of a baseline EIM. Perianal disease has been shown previously to be associated with increased disease relapse [14,46]. Perianal disease and in particular fistulas have an impact not only on the need for index surgery but also on the risk of further surgery. A population based cohort study by Bernell *et al,* found a relative risk of index resectional surgery of 1.2 (95%CI 1.03-1.3) for those with perianal fistulas in CD and a 40% (1.4 (1.2-1.7)) increased relative risk for disease recurrence following index resection [46]. A further study from Bernell *et al,* in 907 patients undergoing ileocaecectomy, found that perianal fistulas conferred a 1.6 (1.2-2.3) relative risk of disease recurrence [38]. Others have also shown this risk association and perianal fistulas is an indicator of the need for continued medical therapy following surgical resection [5,47,48].

EIMs are common in IBD with up to half of patients developing at least one EIM and a higher prevalence in those with CD [15]. EIMs have a spectrum of severity and associated morbidity and those with less clinical consequence may not be reliably recorded in a

secondary care setting (e.g. episcleritis). In light of this limitation, it may be appropriate to consider the EIMs captured in this study as signs of clinical activity, which is consistent with the fact that most EIMs run a parallel course to bowel activity [19]. EIMs were recorded at baseline, rather than at the time of further surgery, suggesting that those with EIMs have a more severe disease course compared to those without.

Database studies of this kind have significant strengths in terms of subject numbers, demographics, and the reliability of procedural coding, which we have been able to validate in a hospital setting. It should be noted that although attempts were made to reduce confounding by excluding suspected staged surgical procedures, there is still a risk of inclusion of such procedures as a new surgical episode if they took place more than one year after the index procedure. A further limitation in terms of procedural coding is the detail which is not available from, for instance, operation notes. Ileocaecal resection, for example, is a common procedure for terminal ileal and caecal disease but is coded under the right hemicolectomy code identifier. Moreover, the length of ileal resections may be a risk factor associated with recurrence but is not available from HES coding [38]. Endoscopic balloon dilatation for Crohn's disease strictures is safe and effective and may delay or even prevent further surgery [49]. However, we found very few episodes of this procedure in HES and it may have been coded under colonoscopy. However, audits of large teaching hospitals in England suggest low annual numbers of endoscopic balloon dilatation [50].

Significant risks shown to be associated with a more severe disease course in CD which are not available in HES include age at diagnosis, disease extent, family history and smoking status [51,52]. Although infused anti-TNF therapy (infliximab or biosimilar) is captured as a high drug cost in HES, it is clear that other biologics, including self-administered subcutaneous medications, are not. This is a significant limitation given the frequent use of adalimumab

(either originator or biosimilar) [53]. The IBD audit 2016 demonstrated a fall in surgery prior to medical treatment between 2012 and 2016, demonstrating changing trends potentially linked to therapeutics [53]. We have shown that there is a separation in risk of further resections between patients who had index resection in 2007-9 and 2010-12 and 2007-9 and 2013-15. It is not possible to ascribe causality to this observation, however it is noteworthy that approval in England for maintenance anti-TNF therapy was introduced in 2010 [54].

This study has shown that further resectional surgery for CD remains common with a quarter of patients in England having one or more further operations over a 10-year follow-up period. Prior perianal disease, the presence of an EIM, index operation in a high-volume provider of such surgery and emergency admission at the time of the first operation for CD are all associated with an increased risk of further surgery by 5 years. We have also demonstrated that rates of first resection, when adjusted for CD prevalence, have fallen over time. Healthcare professionals should be aware of these findings in light of endoscopic surveillance guidelines and the recommendation to proactively manage patients with CD in order to reduce the risk that recurrent disease poses to patients, including recurrent surgery.

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Chapter 5 manuscript 2: The risk of later surgery at the anastomotic site following right hemicolectomy for Crohn's disease in a national cohort of 12 230 patients

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The risk of later surgery at the anastomotic site following right hemicolectomy for Crohn's disease in a national cohort of 12 230 patients

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Summary

Background: Crohn's disease (CD) has a high-risk of bowel resection and later surgery for recurrent disease. Recent guidelines recommend colonoscopy 6-12 months following surgery to reduce further surgical intervention through medical therapy intensification.

Aims: To investigate the risk of further surgery at the anastomosis following right hemicolectomy for CD.

Methods: Hospital Episode Statistics were used to identify patients with CD and a right hemicolectomy between 2007 and 2016. Adherence to post-resection colonoscopy guidance timing and risk of further surgery at the anastomosis were examined. Cox proportional hazards models assessed risk factors for further surgery.

Results: 12 230 patients were identified: 45% male; median age 36 (IQR 26-49) years. Median follow-up was 5.9 (IQR 3.6-8.6) years: totalling 74 960 person-years. Median time to further surgery was 2.9 (IQR 1.2-5.3) years. By 5 years 9% and by 10 years 16.9% of those with sufficient follow-up had at least one further surgery involving the anastomotic site. Older, less deprived patients and those whose index surgery took place on an elective admission had a reduced risk of further surgery. The annual number of right hemicolectomies increased over the study from 1063 to 1317, driven by the increasing prevalence of CD. Overall, 78% of patients did not have a colonoscopy, as recommended, within 6-12 months following index resection.

Conclusions: Further surgery involving the anastomotic site remains common following index right hemicolectomy for CD. Post-surgical colonoscopy was only undertaken in 22% of patients within suggested timeframes. Increased colonoscopy may lead to a reduced need for surgery if early optimisation of medical therapy is undertaken for recurrence.

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1 | INTRODUCTION

Crohn's Disease (CD) is a relapsing and remitting disease of the gastrointestinal tract. Principally localising to the small and/or large bowel, it leads to transmural inflammation, stricturing and fistulisation.[1] The condition can be debilitating, leading to time in hospital, restricting employability and reducing quality of life.[2] Surgical resection is indicated for patients who have struggled with symptoms despite medical management or when fibrosis is established. Although there has been a fall in rates of surgery for CD over time, rates remain high with up to 50% of patients undergoing resection within 10 years of a CD diagnosis and lifetime risks exceeding 70%.[3-5] Recurrent symptomatic disease following surgery is common with the risk of further surgery at 5 and 10 years reported to be 24% and 35% respectively.[6,7] Most commonly seen following ileocaecal resection, recurrent CD at the anastomosis is often severe in terms of mucosal inflammation (Rutgeerts score > i2) but is less often symptomatic.[8-10] However, given that a recommended therapeutic goal in inflammatory bowel disease (IBD) is to achieve mucosal healing to prevent further complications of stricturing and penetrating disease, it is recommended that efforts are made to mitigate the risk of recurrence through proactive investigation and treatment escalation. The recommendation to undertake ileocolonoscopy following resectional surgery such as right hemicolectomy is now established in national and international guidelines.[4,11,12] Improved endoscopic and clinical recurrence rates were reported in CD surgical patients who underwent early colonoscopy and had an escalation in their treatment for recurrent CD.[8,9,13,14]

The aim of this study was to investigate the risk of further surgery following a right hemicolectomy for CD in England and the adherence to post-operative ileocolonoscopy as recommended in guidelines.

2 | METHODS AND MATERIALS

2.1 | Data source

Hospital Episode Statistics (HES) is a database including information on all episodes of National Health Service (NHS) secondary care treatment within England. HES contains diagnostic (International Classification of Diseases version 10 [ICD10]) and procedural (Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision [OPCS-4]) information. Demographic and geographic data for each patient are also recorded. Individuals can be tracked through their hospital admissions via a unique identifier. Mortality data are obtained by linking to the Office for National Statistics (ONS) database. The HES data sharing agreement prohibits the publication of potentially identifiable data and it is for this reason that patient counts of five or less are suppressed from publication.

2.2 | Inclusion criteria

Adult patients over 18 years old were identified for inclusion in the study by extraction of all instances of right hemicolectomy/ileocaecectomy codes (H06 and H07) in HES and then identifying all patients who had their first (index) occurrence of one of these surgical procedures between 1st January 2007 and 31st December 2016. Note that the code encompassing ileocaecectomy is included within the right hemicolectomy code and therefore right hemicolectomy will be used hereafter to include ileocaecectomy. For inclusion, a patient was required to have a Crohn's disease (ICD-10: K50) diagnosis at the time of their index surgery admission.

2.3 | Exclusion criteria

Patients were excluded from the study if they had an ulcerative colitis (UC) (ICD-10: K51) diagnosis coded subsequently, suggesting a misclassification of CD. Patients were further excluded if they had a cancer diagnosis during the year before index surgery or during the follow-up period. Patients without a recorded age, those under the age of 18 at the time of index surgery and those with missing or invalid sex data were also excluded, as were patients not resident in England. Further resectional surgery that took place either during the same spell or within a 30-day period following index surgery were excluded from the analysis. Patients with index surgical codes resulting in a stoma and therefore at risk of requiring a subsequent elective staged procedure not causally related to Crohn's disease were examined (Appendix 1). Further operations undertaken during an elective admission and within one year of such index surgery were excluded from analysis in order to limit bias associated with the planned completion of the initial intent of the index surgery but the patients themselves were not excluded from the analysis of later further resectional surgery at the anastomosis site.

2.4 | Data validation

To assess the validity of CD surgical coding, a list of patients meeting the same ICD-10 and OPCS-4 coding criteria was provided by the local coding departments at Sandwell and West Birmingham Hospitals NHS Trust. The accuracy of coding was then assessed by consulting the electronic patient records to establish if the CD diagnosis and the surgical procedural code were reliable. Colonoscopy undertaken within 6-12 months following right hemicolectomy (as recorded in the patient's notes) was compared to HES data recorded for the hospital.

2.5 | Demographic data

Patient age, sex, region of residence, deprivation status and ethnicity were identified from index surgery admission coding. Age

was divided into quintiles at 18-24, 25-31, 32-41, 42-53 and ≥54. Ethnicity was stratified into White, South Asian, other minority ethnicities and unknown. The Charlson comorbidity index, a measure of multimorbidity in patients and previously validated in HES,[15] was calculated using secondary diagnostic coding. Deprivation quintiles were calculated from the Index of Multiple Deprivations, a classification based on income, employment, crime and living environment.[16] Deprivation quintile 5 is the least deprived quintile, while quintile 1 is the most deprived.

2.6 | Outcome measures

The primary outcome measure in this study was further resectional surgery at the site of index right hemicolectomy surgery. The time interval between index and first further surgery for recurrent CD was examined along with the mechanism of admission (elective or emergency). The end of the follow-up period for further surgery was 31st December 2018, providing a minimum of two and a maximum of 12 years' follow-up. The annual point prevalence of CD in England, derived from a previous primary care study, was used to examine the trends in index right hemicolectomy over the study period.[17]

A secondary outcome measure examined in this study was the number of patients who underwent colonoscopic procedures following index right hemicolectomy. Colonoscopy (ileocaecoscopy) undertaken 6-12 months following index surgery was considered valid. Patients without a colonoscopy within this 6- to 12-month time period were examined for reasonable obstacles, including further surgery within the time period (staged elective or emergency), death, a relevant illness or procedure that might prevent or delay colonoscopy (Appendix 2). Colonoscopy performed at any time from index surgery to 24 months following surgery was also recorded. Imaging modalities with the potential to screen for recurrent disease post-surgery, including MRI, CT, barium or capsule endoscopy were further examined. To demonstrate national trends over the study period, numbers of colonoscopies performed in England and those performed on patients with a CD diagnosis were also examined.

2.7 | Statistical analysis

Demographic tables were produced showing figures for first surgery, further surgery at 1 year and all subsequent surgeries during follow-up. Age and time to follow-up surgery is presented as median and interquartile range (IQR). Index right hemicolectomy counts for CD in England were divided by number of CD patients in England per year of the study and presented as rate per 1000 patients with CD. The number of adults with CD in England per year of the study period was derived from Office for National Statistics (ONS) population data for England and estimates of CD prevalence in England derived from a nationally representative primary care database.[17,18] A linear regression model was fitted to the trend of yearly right hemicolectomy rates over the study period to assess change. Index surgeries were subdivided into those that took place on an elective admission and those that took place on an emergency admission.

A Cox proportional hazards model was produced for time to further surgery with results presented as adjusted hazard ratios (aHR), and a Kaplan-Meier curve of failures defined as further surgery based on index admission method was produced. A further Kaplan-Meier plot with three survival curves representing three periods of index surgery was produced with accompanying global and stratified log rank tests. Proportional hazards assumptions were tested and satisfied. Variables included in the Cox regression model were age, sex, provider volume of right hemicolectomy for CD, ethnicity, deprivation, index surgery admission method, Charlson comorbidity score, year of index right hemicolectomy, prior perianal disease and laparoscopic index surgery. Perianal surgery was used as a surrogate for severe perianal disease. Characteristics of included and excluded patients were compared using Chi-squared tests for categorical data. Demographic data are presented as counts and percentages where applicable.

A sensitivity analysis (Cox proportional hazards model) was undertaken to account for all first further surgery following index right hemicolectomy for CD coded in HES. This included surgery within 30-days of index operation and those at risk of multistage elective procedures within one year of index surgery, which were excluded from the main analysis. A further analysis using multivariable logistic regression was undertaken to assess the risk of undergoing a further surgery at the anastomotic site by 5 years in those with at least 5 years follow-up. The covariates described earlier were included in this model as well as the coding of colonoscopy 6-12 months following index right hemicolectomy.

Statistical analyses were carried out using STATA SE v15.[19] *P*-values of < 0.05 were considered statistically significant.

2.8 | Ethics

HES data are available under data sharing agreements with NHS Digital for the purpose of service evaluation. Ethics approval is not, therefore, required. HES data were granted by the Health Informatics Request Review Group at University Hospitals NHS Foundation Trust: UHB Registration number CARMS-14875.

3 | RESULTS

3.1 | Cohort characteristics

Between 1st Jan 2007 and 31st Dec 2016, 14 517 patients were identified with a CD diagnostic code and a first surgical code for right hemicolectomy. 12 230 patients were eligible for the study following exclusions. Median follow-up was 5.9 (IQR 3.6-8.6) years, contributing 74 960 person-years at risk. 1367 (11.2%) patients had a further surgery before the end of follow-up that was not an elective staged procedure within 1-year of index right hemicolectomy (199) or took place within 30-days of the index procedure (306) and

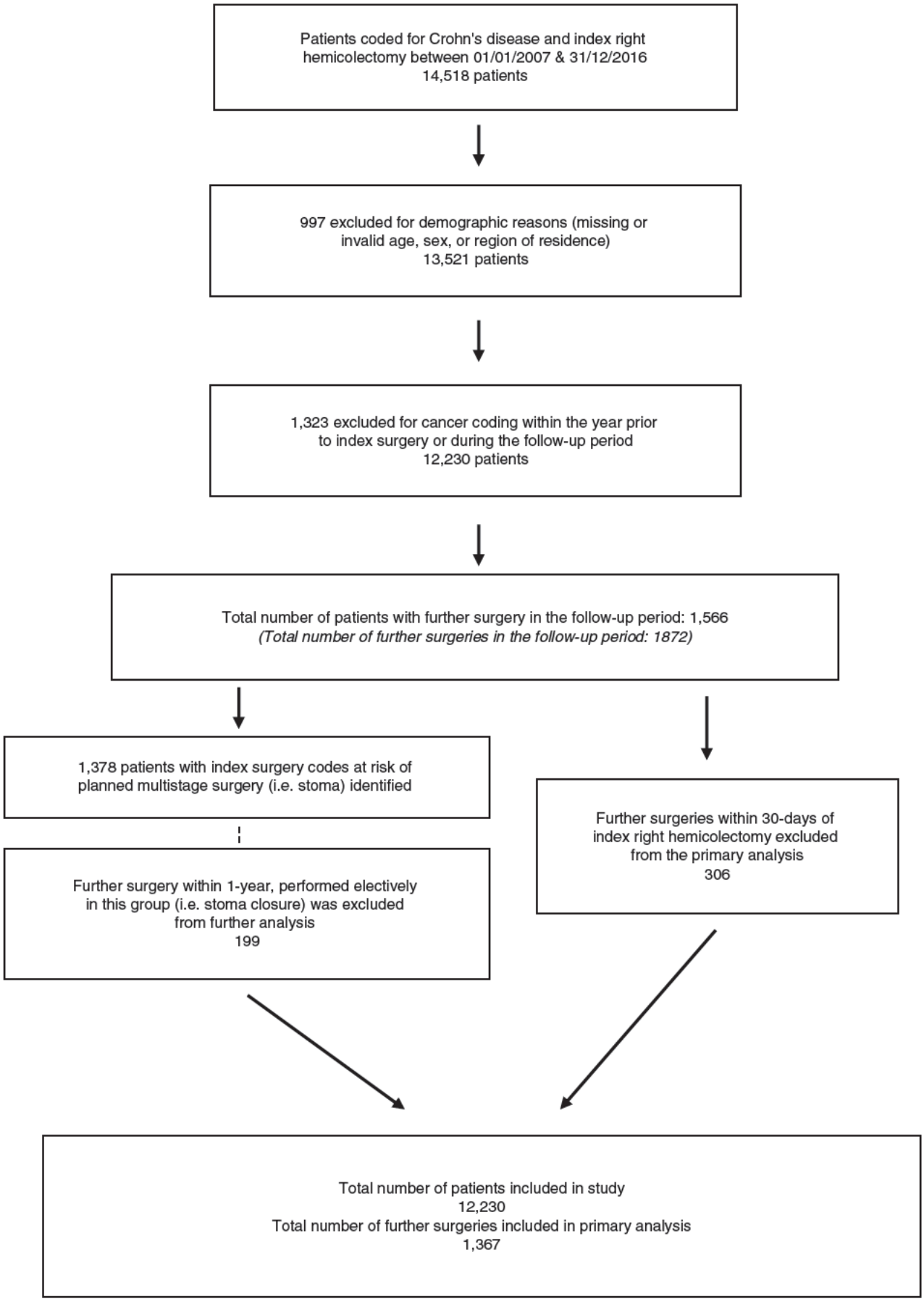


FIGURE 1 Study flow chart

therefore considered valid for inclusion in further analysis (Figure 1). 55.2% (6755) of patients were female and the median age was 36 (IQR 26-49) years. 35% of patients were aged from 18-29 years and 5% of patients were 70 years or older. 88.2% (10 792) had a White ethnicity code, 2.8% (346) were coded as South Asian, 3.3% (409) were coded as other minority ethnicities and 5.7% of patients were not coded for ethnicity. 94.1% (11 510) of patients had no other comor-bidities as defined by a Charlson score of zero. 1.9% of patients had a valid further surgery code within one year of their index operation. By 5 years 9% and by 10 years 16.9% of the right hemicolectomy cohort had undergone at least one further operation at the anastomotic site. Patient demographic characteristics are shown in Table 1.

3.2 | Selection bias

Univariate analyses comparing the sex, age, ethnicity, deprivation quintile and comorbidity categories of included and excluded patients were carried out (Appendix 3). Included patients were more likely to be female and have higher levels of deprivation. Excluded patients had a higher proportion of comorbidities and were older compared to included patients. No difference was observed between ethnicity for included and excluded groups.

3.3 | Index surgical details and risk of further surgery

The number of index right hemicolectomies for Crohn's disease (CD) in England increased from 1063 in 2007 to 1317 in 2016, a 2% average annual rise. In those patients with at least 5 years of follow-up, further surgery fell from 185 procedures in 2007 to 109 procedures in 2013.

Using ONS data, the adult population of England for each index surgery inclusion year was recorded. CD prevalence in England for each year from 2007 to 2016 was used to estimate the yearly CD population in England. CD prevalence increased from 0.3% to 0.4% over this period. Index right hemicolectomy procedures fell from 6.90 to 5.96 per 1000 patients with CD between 2007 and 2016 ($P < 0.001$) (Appendix 4). Changes in index surgical rates per 1000 CD patients during elective or emergency admissions were similar over the period with 4.20 to 3.52 ($P = 0.002$) and 2.69 to 2.44 ($P = 0.003$) respectively. CD prevalence and changes in index sur-gery rates over the study period are shown in Figure 2. The age of patients undergoing right hemicolectomy in England did not change over the study period (data not shown).

Within 1 year of index right hemicolectomy, 232 (1.9%) patients had had a further surgical resection at the site of the index operation, with a median time to further surgery of 229 (IQR 126-286) days. During study follow-up (range 2-12 years), 1367 (11.2%) patients had a further surgical resection at the site of the index operation with a median time to further surgery of 1064 (IQR 456-1922) days or 2.9 years. Most index surgery was performed on an elective admission (59%), as was also the case for further surgery overall (63%). However, 50% of further surgery performed within one year of index surgery was performed on an emergency admission.

A Cox proportional hazards analysis of time to further surgery is shown in Table 2. Those in the older age quintile (54 and over) were at reduced risk of further surgery compared to the youngest age quintile (adjusted hazard ratio [aHR] 0.81 [95% CI 0.67-0.97], $P = 0.022$) and those with an index right hemicolectomy performed as a laparoscopic procedure had an 18% reduced risk of further surgery (0.82 [0.73-0.93], $P = 0.003$). Those in the two least deprived quintiles were at significantly lower risk of further surgery compared to the most deprived quintile (quintile 4: aHR 0.80 [0.68-0.95], $P = 0.009$; quintile 5: aHR 0.79 [0.66-0.94], $P = 0.007$). Those with an elective index surgery admission were at 27% lower risk of further surgery than those with an index right hemicolectomy during an emergency admission (aHR 0.73 [0.65-0.82], $P < 0.001$, Figure 3). Patients with a history of perianal surgery were at increased risk of further surgery (1.49 [1.29-1.72], $P < 0.001$). Patients with a comorbidity score of ≥5 had an increased hazard of further surgery compared to patients with a score of zero (aHR 1.38 [1.03-1.85], $P = 0.032$). Comorbidity scores of ≥5 were mainly seen in the two oldest quintiles (85%) and the median time to further surgery in the highest comorbidity group was 637 (IQR 328-1274) days compared to 1089 (465-1974) days for the low comorbidity group. Other age groups, sex, provider right hemicolectomy volume for CD and ethnicity were not associated with time to further surgery. Not all patients had equal follow-up time, nevertheless, when followed from index right hemicolectomy as 3-year eras (2007-9, 2010-12, 2013-15), a separation in the proportion of further surgery emerged, Figure 4. Globally a difference between curves was observed, log rank test $P = 0.036$. When stratified, a significant difference between the earliest and latest eras was observed (2007-09 & 2012-15; $P = 0.009$), though not between the latest two eras (2010-12 & 2013-15; $P = 0.560$).

3.4 | Sensitivity analysis

1872 (15.3%) patients underwent further surgery that was included in the sensitivity analysis (52.2% female and median age 34 [26-47] years). Factors associated with an increased risk of further surgery included higher comorbidity score and previous perianal surgery in keeping with the primary analysis. Factors associated with a reduced risk of further surgery included those in the least deprived quintile, those who had index laparoscopic surgery or elective index surgery. However, unlike the primary analysis, no significant age relationship was identified. The demographic details and the Cox proportional hazards analysis can be found in Appendix 5.

3.5 | 5 year follow-up cohort

8239 patients (55.8% female and median age 36 [26-49] years) were found to have at least 5 years of follow-up (index surgery

TABLE 1 Demographic characteristics of study patients

Demographic	Patients N (%)	Further surgery (by 1-year) N (%)	Further surgery N (%)
Total	12 230 (100)	232 (1.9)	1367 (11)
Follow-up years—median (IQR)	5.9 (3.6-8.6)		
Sex			
Male	5475 (44.8)	118 (2.2)	646 (11.8)
Female	6755 (55.2)	114 (1.7)	721 (10.7)
Age—median (IQR)	36 (26-49)	34 (25-45.5)	34 (25-46)
Age quintile			
18-24	2478 (20.3)	54 (2.2)	305 (12.3)
25-31	2459 (20.1)	47 (1.9)	291 (11.8)
32-41	2550 (20.9)	53 (2.1)	308 (12.1)
42-53	2428 (19.9)	48 (2.0)	258 (10.6)
54+	2315 (18.9)	30 (1.3)	205 (8.9)
Age deciles			
18-29	4308 (35%)		370 (9%)
30-39	2704 (22%)		369 (14%)
40-49	2232 (18%)		282 (13%)
50-59	1414 (12%)		191 (14%)
60-69	993 (8%)		100 (10%)
70+	579 (5%)		55 (9%)
Ethnicity			
White	10 792 (88.2)	216 (2.0)	1223 (11.3)
Asian	346 (2.8)	[a]	35 (10.1)
Other minority ethnicities	409 (3.3)	[a]	41 (10.0)
Unknown	683 (5.6)	9 (1.3)	68 (10.0)
Charlson comorbidity score			
0	11 510 (94.1)	214 (1.9)	1295 (11.3)
1-4	308 (2.5)	7 (2.3)	29 (9.4)
5+	412 (3.4)	11 (2.7)	43 (10.4)
Deprivation quintile			
1 (most deprived)	2655 (21.7)	47 (1.8)	335 (12.6)
2	2699 (22.1)	55 (2.0)	305 (11.3)
3	2496 (20.4)	41 (1.6)	275 (11.0)
4	2282 (18.7)	42 (1.8)	240 (10.5)
5 (least deprived)	2098 (17.2)	47 (2.2)	212 (10.1)
Index surgery admission method			
Emergency	4924 (40.3)	119 (2.4)	661 (13.4)
Elective	7225 (59.1)	107[a]	696 (9.6)
Further surgery admission method			
Emergency	-	115 (49.6)	504 (36.9)
Elective	-	107[a]	857 (62.7)
Unknown	-	[a]	6 (0.4)
Year of index surgery			
2007	1063 (8.7)	26 (2.4)	185 (17.4)
2008	1100 (9.0)	31 (2.8)	204 (18.5)

(Continues)

TABLE 1 (Continued)

Demographic	Patients N (%)	Further surgery (by 1-year) N (%)	Further surgery N (%)
2009	1149 (9.4)	31 (2.7)	175 (15.2)
2010	1189 (9.7)	23 (1.9)	161 (13.5)
2011	1226 (10.0)	14 (1.1)	127 (10.4)
2012	1274 (10.4)	20 (1.6)	155 (12.2)
2013	1292 (10.6)	28 (2.2)	109 (8.4)
2014	1263 (10.3)	24 (1.9)	114 (9.0)
2015	1357 (11.1)	18 (1.3)	73 (5.4)
2016	1317 (10.8)	17 (1.3)	64 (4.9)
Provider volume of right hemicolectomy			
Low (1-54)	1556 (12.7)	38 (2.4)	173 (11.1)
Medium (55-89)	3801 (31.1)	76 (2.0)	404 (10.6)
High (90+)	6873 (56.2)	118 (1.7)	790 (11.5)
Colonoscopy timing post-index surgery			
0-3 months (very early)	205 (1.7)	8 (3.9)	32 (15.6)
3-6 months (early)	1120 (9.2)	24 (2.1)	123 (11.0)
6-12 months (on time)	2681 (21.9)	60 (2.2)	345 (12.9)
12-18 months (late)	1395 (11.4)	37 (2.7)	190 (13.6)
18-24 months (very late)	817 (6.7)	24 (2.9)	123 (15.1)
Later or never	6012 (49.2)	79 (1.3)	554 (9.2)
Prior perianal surgery	1475 (12.1)	31 (2.1	230 (15.6)
Laparoscopic index surgery	4587 (37.5)	78 (1.7)	385 (8.4)

[a]Patient numbers ≤5 suppressed to maintain anonymity.

from 2007-2013). 747 (9%) patients had undergone further surgery at the anastomotic site by 5 years and the median time to further surgery was 2.88 (1.04-3.58) years. Factors associated with an increased risk of further surgery by 5 years were prior perianal surgery (odds ratio 1.48 [1.20-1.83], $P < 0.001$), colonoscopy between 6 and 12 months post right hemicolectomy (1.45 [1.22-1.74], $P < 0.001$) and a Charlson comorbidity score of 1-4 compared to a score of 0 (1.34 (1.07-1.67), $P = 0.012$). Factors associated with a reduced risk of further surgery included having an elective index procedure (0.78 [0.67-0.92], $P = 0.002$), index laparoscopic surgery (0.79 [0.66-0.94], $P = 0.010$) and being in the oldest compared to the youngest quintile (0.74 [0.57-0.95], $P = 0.017$). The demographic details and the logistic regression analysis of patients with at least 5 years of follow-up can be found in Appendix 6.

3.6 | Post-surgery colonoscopy rates

From 2007 to 2016 colonoscopy rates following a right hemicolectomy in CD patients increased in England from 35.0% to 61.3% of cases during the 24-month period following surgery. The number of colonoscopies per month following index surgery is shown in Figure 5. In the 6- to 12-month period following index right hemicolectomy, colonoscopy rates increased from 13.7% in 2007 to 29.0% in 2016 (Table 3). This accounts for 21.9% of patients undergoing right hemicolectomy for CD over the study period. 78.1% of patients did not have a colonoscopy within the 6- to 12-month period. 40.1% of patients did not have a colonoscopy within this 6- to 12-month window but did have a potential explanation of why this may not have occurred, including a valid further surgical procedure, relevant illness coded, or they had died. This leaves a significant number of patients without a valid explanation for not having a post-resection 6- to 12-month colonoscopy as recommended (41.4% of patients). When provider volume of index right hemicolectomy for CD was compared to 6- to 12-month colonoscopy adherence, a fourfold difference between the 5th and 95th percentile provider was seen. This was consistent for both unadjusted data and when further surgery, patient death, potentially relevant illness or colonoscopy performed between 3 and 18 months were taken into account (Figure 6 and Appendix 7). When those patients who did not have a colonoscopy within 2 years of surgery were reviewed (6012), 30% were coded as having missed a gastroenterology appointment without prior cancellation.

Between 3 and 18 months following index surgery 520 (4%) patients had some form of imaging modality (MRI abdomen/CT abdomen or colon/barium enema/capsule endoscopy), 60% of which also had a colonoscopy within this time period. 202 (40%) patients with imaging between 3- and 18-month- post-index surgery had a

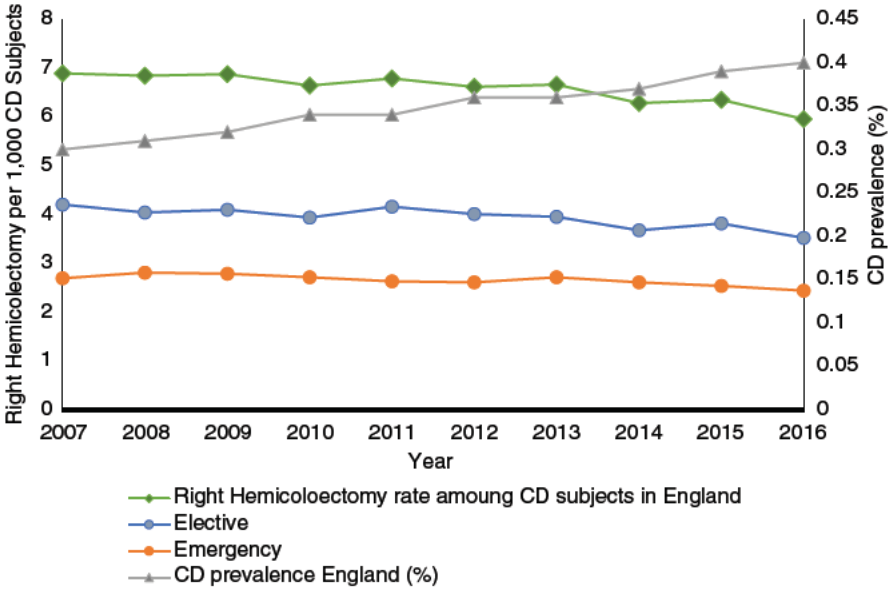


FIGURE 2 Change in rate of right hemicolectomy in comparison with prevalence of Crohn's disease in England

colonoscopy within 6-12 months of index surgery while 60 (12%) had imaging and colonoscopy within 6-12 months.

Between 2007 and 2017 all colonoscopies coded in HES increased from 470 648 to 763 661—a 69% increase over the study period. This equates to a rise of 916 to 1373 per 100 000 population based on Office for National Statistics mid-year population estimates for 2007 and 2017—an increase of 50% when adjusted for population change.[18] In those with a diagnosis of CD, colonoscopies increased from 11 517 to 23 997—an increase of 108% (data shown in Appendix 8).

3.7 | Validation

All admissions at Sandwell & West Birmingham Hospitals NHS trust with an ICD-10 code for CD (K50*) and a surgical code for right hemicolectomy (Appendix 1), excluding any cancer code, were examined between the period of Dec 2015 to Dec 2017. All 65 cases identified were accurately coded as CD when compared to the electronic patient record. 64 (98%) were correctly coded for the surgical procedure when compared to the operating notes. Colonoscopy within 6-12 months of surgery in these patients was coded with greater than 75% agreement between HES data and hospital patient records (figures omitted due to low numbers to preserve patient anonymity). Although these figures are small and the period of time short, previous validation of colonoscopies in HES have been shown over a longer period to be very robust with >95% congruency.[20]

4 | DISCUSSION

Surgery in CD is the rule rather than the exception, with most patients having an intestinal resection during the course of their disease.[3,4] It is a valuable option for patients struggling with symptoms despite optimal medical management.[11,21] Resection of terminal ileal and right sided colonic disease is the most common major surgery performed in those with CD.[22,23] Previous findings suggest that surgery is common in the early period following diagnosis and may be a manifestation of an aggressive disease course as well as diagnostic delay.[24,25] Preventing the need for surgery and subsequent surgery is an important goal of CD therapy. Although when a decision is taken to operate, this is often the best choice for the patient at the time, earlier intervention may change the natural history of the disease and prevent the risks of surgery to a patient.

Index surgery increased over the study period in England. However, when CD burden in England was considered a relative decline was observed, both in elective and emergency settings. Stable and increasing numbers of operations for CD have been noted previously,[26,27] but when the increasing prevalence of this disease is accounted for, others have also found a fall in rates of surgery among CD patients.[28] Indeed, in England, Ahmed et al have previously shown, using HES data, that as a proportion of CD hospital admissions, all types of major abdominal surgery for CD have fallen over time.[29] A UK primary care study, looking at first and further resectional surgery over 10 years from CD diagnosis and index surgery, respectively, found a significant fall in surgical risk.[7] Historically, surgical rates have fallen significantly, even before the advent of biologic medications.[5,30] The reasons for this relative decline in surgery are likely to be multifactorial with both the impact of better medical therapy, falling smoking rates and better systems of management, as well as earlier diagnosis and milder disease being diagnosed playing key roles.[31,32] Evidence of this may be seen in a study from Canada where surgery was adjusted for CD prevalence. In that case, an overall fall in surgery was seen over time due to a decline in emergency surgery, whereas elective surgery was seen to increase over the same period.[28] Furthermore, others have correlated a fall in first resectional surgery with the use of immunomodulators[33] and a preventative strategy of post-operative thiopurine use was clearly shown to be effective, for example in smokers in

TABLE 2 Cox proportional hazards model of factors associated with further resectional surgery during follow-up at the site of previous right hemicolectomy for Crohn's disease

Demographic	Hazard Ratio	95% CI		*P* value
Sex				
Male (baseline)				
Female	0.93	0.84	1.04	0.198
Age quintile				
18-24 (baseline)				
25-31	0.98	0.84	1.16	0.849
32-41	0.99	0.85	1.17	0.945
42-53	0.91	0.77	1.08	0.286
54+	0.81	0.67	0.97	0.022
Ethnicity				
White (baseline)				
Asian	0.80	0.57	1.12	0.197
Other minority ethnicities	0.84	0.61	1.15	0.276
Unknown	0.90	0.70	1.15	0.384
Charlson comorbidity score				
0 (baseline)				
1-4	1.07	0.90	1.26	0.455
5+	1.38	1.03	1.85	0.032
Deprivation quintile				
1 (most deprived) (baseline)				
2	0.87	0.75	1.02	0.082
3	0.86	0.73	1.01	0.072
4	0.80	0.68	0.95	0.009
5 (least deprived)	0.79	0.66	0.94	0.007
Index surgery admission method				
Emergency (baseline)				
Non-emergency	0.73	0.65	0.82	<0.001
Year of index right hemicolectomy				
2007 (baseline)				
2008	1.15	0.94	1.41	0.163
2009	0.99	0.80	1.22	0.890
2010	0.94	0.76	1.17	0.599
2011	0.79	0.62	1.00	0.048
2012	1.08	0.87	1.36	0.476
2013	0.84	0.66	1.08	0.169
2014	1.05	0.82	1.35	0.674
2015	0.78	0.59	1.04	0.089
2016	0.92	0.68	1.24	0.577
Provider volume of Crohn's disease index right hemicolectomies (tertile)				
Low (1-54) (baseline)				
Medium (55-89)	0.96	0.80	1.14	0.628
High (90+)	1.02	0.87	1.21	0.771
Prior perianal surgery	1.49	1.29	1.72	<0.001
Laparoscopic Index Surgery	0.82	0.73	0.93	0.003

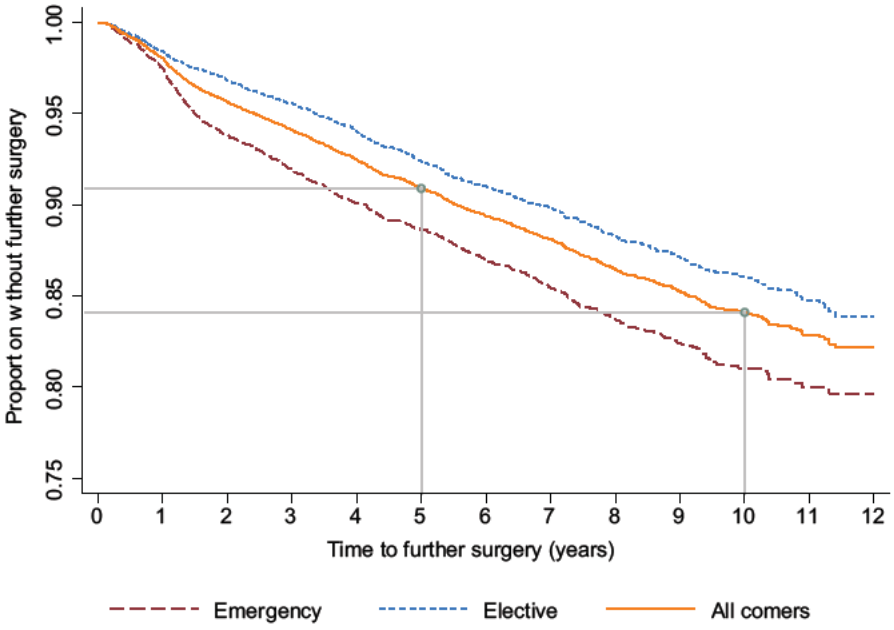


FIGURE 3 Kaplan-Meier analysis of time to further surgery dependent on index surgery admission method

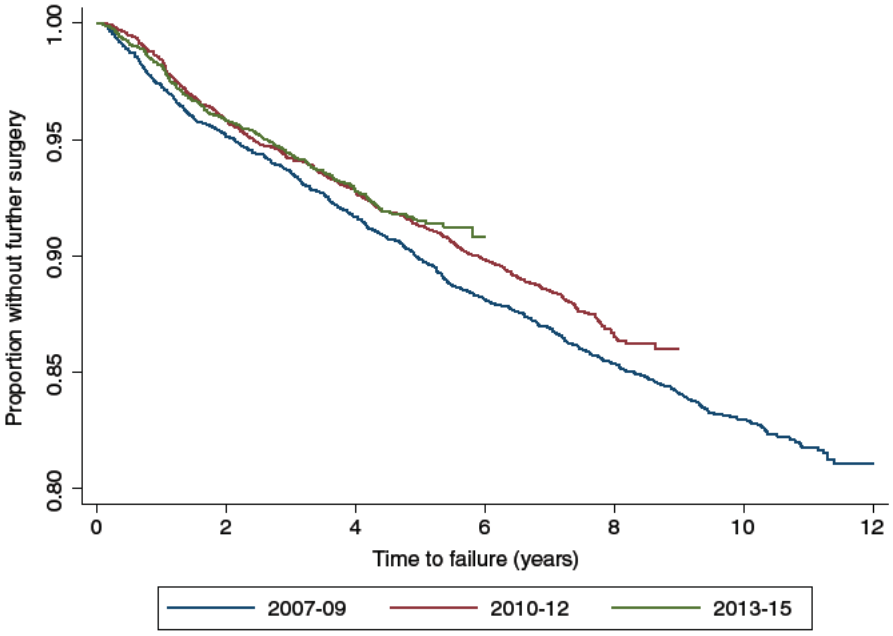


FIGURE 4 Kaplan-Meier analysis showing the proportion of patients from 3-year time periods of index right hemicolectomy who have further surgery

the TOPPIC trial.[24,34] Biologic therapy was not included in this study because self-administered drugs such as adalimumab are not captured in HES, however, biologics have also been linked to a fall in surgery. Certainly, in observational studies, their increasing use has correlated with the observed fall in surgical rates.[5] Their real-world use in terms of timing of initiation, patient selection and confounding in terms of disease severity and loss of response over time has, however, meant that strong evidence of a long-term reduction in surgery rates has been challenging to demonstrate when compared to their impressive performance in short randomised control trial follow-up periods.[35-37] Although causality cannot be ascribed to the differences in further surgery risk observed between eras in this study (Figure 4), it is of interest that significant differences were observed between periods before and after the introduction of maintenance anti-TNF therapy for CD in England.

In this study, further surgery at the site of the anastomosis was 1.9% at 1 year and 11.9% overall on follow-up. Previous studies looking at the risk of surgery in CD patients have highlighted female sex, smoking and ileal disease as significant predictive factors.[38,39] Further surgery has also been associated with continued smoking, previous surgery, the need for steroids or antibiotics and penetrating disease behaviour.[8,11,40] Females made up 55% of the cohort as might be expected given the higher prevalence of CD seen in females.[17] We found no significant reduction in risk of further surgery for females. The phenomenon that males have been shown to be at increased risk of major abdominal surgery in CD has, however, been previously observed,[40] and we have previously shown a protective association of female sex in those with acute ulcerative colitis in relation to surgical intervention.[41] It may be that this study was underpowered to demonstrate a significant difference in the sexes.

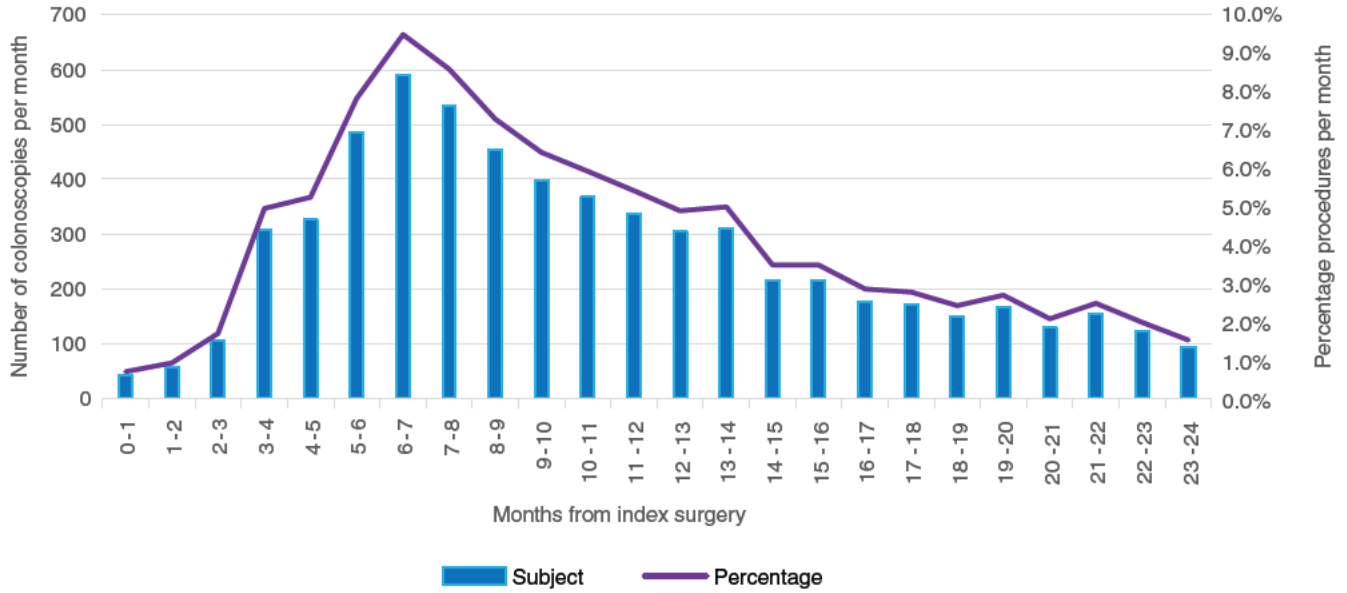


FIGURE 5 Colonoscopy numbers (%) per month following index right hemicolectomies

TABLE 3 Colonoscopy rates between 6 and 12 months of index right hemicolectomy by year of the study period

Index right hemicolectomy year	Colonoscopy 6-12 months (%)
2007	146 (13.7)
2008	168 (15.3)
2009	222 (19.3)
2010	228 (19.2)
2011	251 (20.5)
2012	296 (23.2)
2013	312 (24.1)
2014	330 (26.1)
2015	346 (25.5)
2016	382 (29.0)
Total	2681 (21.9)

We speculate that although studies comparing acute illness outcomes between the sexes have found contradictory results, several factors are likely to be potentially important, including differences in physiological response to illness, disparity in smoking rates and differences in willingness to undergo surgery related to fertility and cosmesis.[42-44]

A reduced risk of further surgery observed in patients from less deprived quintiles may reflect educational levels, as lower education has previously been associated with a more severe disease course. Lower deprivation levels may also be considered a surrogate for smoking. However, in a healthcare system such as the National Health Service, where access to care is not dependent on income, concordance with medical plans and medication regimes may be the cause of such findings.[45] Medication and smoking data are, however, not available in HES which limits this study given that smoking has been shown to adversely affect the natural history of CD.[46,47] The large multicentre TOPPIC trial found that post-operative thiopurine use reduced recurrence of CD in smokers and demonstrated the negative impact of smoking on clinical CD course.[34] Associations found with regards to sex and deprivation may then be confounded by a patient's smoking status. The factor most strongly associated with the risk of further surgery in this study was the admission method for index surgery. Those presenting electively had a reduced risk of further surgery which likely reflects the phenotype of the disease as well as better management processes for some patients and may further relate to educational levels and management adherence.

Although the age groups for analysis were banded into quintiles and so older age encompassed those over 54 years of age, 13% of index surgery patients were 60 or older and 19% of these underwent further surgery. These numbers are relatively small though they are an important minority given the inherent risks associated with major surgery and the physiological changes that come with age. Bernell et al reported that in their cohort of 907 patients with ileocaecal CD, in those who underwent surgical resection, 28% and 36% had recurrent disease at 5 and 10 years respectively. The risk of recurrence was lowest in those of older age.[48] Similarly, in this study, older patients, compared to the youngest, were associated with a lower risk of further surgery. This may reflect a less severe disease course following index surgery. The phenomenon of autoimmune "burn-out" where a vigorous and damaging immune response observed in younger patients is not seen to the same extent due to an aging immune system may be pertinent here.[49] Indeed, the behaviour of CD in the elderly is often different, with reduced penetrating disease and predominance of colonic inflammation.[50] It should be noted that those with elderly onset IBD and aging patients with IBD are not one and the same. Surgery may be a preferred option in the elderly when powerful immunosuppression is

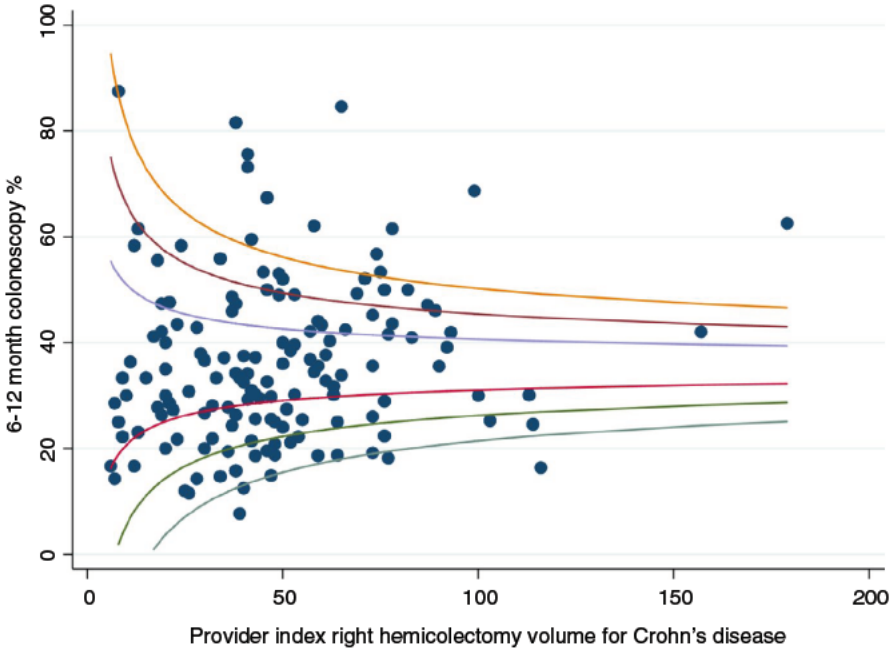


FIGURE 6 Funnel plot of provider volume of index right hemicolectomy for Crohn's disease by 6- to 12-month post-surgery colonoscopy adherence (lines show 1, 2 and 3 standard deviations from the mean) (adjusted for mitigating illness, further surgery, patient death and 3- to 18-month colonoscopy)

the alternative. In the largest cohort study of elderly IBD, CD ran a more benign course and most patients were never exposed to immunosuppressant medications.[51] Uniquely for this population, the study described a strong inverse relationship between the systemic corticosteroids and risk of surgery, in line with the inflammation predominance of the disease in this cohort.

The increase in colonoscopy in the period following resectional surgery over the study period may reflect not only a strong evidence base and more recent guidelines but also accessibility, capacity and lowering of thresholds for colonoscopy in these patients. Despite relatively lenient mitigating reasons in this study for not having a post-operative colonoscopy, large numbers of patients had no obvious reason for not undergoing colonoscopy, with potential alternative imaging modalities coded in a tiny proportion of patients. However, other reasons that are not captured in hospital records are also likely to play a mitigating role and limit this approach. It is important to note that the association between colonoscopy and index surgery is temporal and may be symptom triggered, as opposed to scheduled post-surgery. In the logistic regression analysis examining the risk of further surgery in those with at least 5 years of follow-up, colonoscopy at 6-12 months was associated with a 45% increased risk of further surgery suggesting that symptoms warranting surgical intervention were investigated. It is anticipated that in future, ileocolonoscopy post-surgery will increase in line with guideline recommendations and lead to a further fall in surgical intervention through early medical therapy for recurrent disease. The demographic of patients with CD is often young adulthood, and we have shown high rates of non-attendance at gastroenterology appointments in this cohort which may reflect increased mobility and risky behaviours in this group which would further compound reduced colonoscopy post-surgery. Currently in practice in some settings, though not as well validated or sensitive as colonoscopy,[52] are magnetic resonance enterography (MRE) and ultrasonography which may be preferred by patients over colonoscopy. Although ultrasound for IBD is not specifically coded in HES and was therefore not investigated, we found that 520 patients had imaging investigations (MRI, CT and capsule endoscopy) between 3- and 18-month post-surgery, however, few had these imaging modalities in place of colonoscopy. Biomarkers may play a greater role in detecting recurrence of disease in future and are likely to be more acceptable to patients. Colonoscopy is expensive and faecal calprotectin has been shown to correlate with endoscopic mucosal activity, beyond clinical relapse, which is in keeping with how endoscopic recurrence will often not correlate with the symptomatology of individuals.[8,53]

The HES database has significant strengths in terms of data capture of demographics, diagnoses, admission method and procedures for the whole of England, however, some important data pertinent to CD is not available. Smoking, disease severity and extent, and medications are not captured, and these have been shown to influence the course of CD and the subsequent need for surgery.[54]

Although the validation of surgical coding in our local centre was excellent, there may be differences in quality across hospitals which would also affect colonoscopy coding. It should be noted that coding of procedures allows hospitals to recoup costs and so there is an incentive to ensure coding of procedures is done to a high standard. Unfortunately, endoscopic balloon dilatation or stricture stenting is not well coded in HES and is an important limitation. These techniques have been shown to have low complication rates and may provide long-term relief of symptoms in some patients and delay the need for surgery in others.[55,56] Despite these limitations, this study has highlighted the English experience of recurrent surgery following right hemicolectomy.

We have shown that although right hemicolectomy for CD has increased over a 10-year period, there has been a consistent fall given the overall proportion of CD patients in the population. Older patients are at the lowest risk of further surgery, but those with higher

comorbidity who undergo further surgery, undergo this surgery in a shorter period of time than those without comorbidities. Those with lower deprivation levels had a reduced risk of further surgery, which may reflect medication and management adherence as well as smoking status in high deprivation groups. The factor most strongly associated with risk of further surgery was the admission method of index right hemicolectomy. Those with emergency presentations had the highest risk association which likely reflects severity of disease. Surgery is the right option for many and the focus of clinicians should be on their patients' goals, which will include and may prioritise quality of life.[21,57] As medical options increase, the decision for surgery must be carefully weighed and not delayed in those who would benefit given the higher risk of complications in those with poor physiological reserve and recent immunosuppression exposure.[58] Clinicians managing CD following surgery should be mindful of their patients' understanding of their disease and subsequently adherence to management plans.

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AUTHORSHIP

Guarantor of the article: Dr Nigel Trudgill.

Author contributions: The study concept and design was jointly conceived by DK, BC, AD, PP and NT. Data extraction was performed by BC and AD and analysis was performed by BC and DK. The manuscript was drafted by DK. The data and manuscript were critically reviewed, revised and approved by all authors. All authors approved the final version of the manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from NHS Digital Hospital Episode Statistics. Restrictions apply to the availability of these data, which were used under license for this study.

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SUPPORTING INFORMATION

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

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CHAPTER 6: THE RISK OF LATER DEVELOPING INFLAMMATORY BOWEL DISEASE FOLLOWING A DIAGNOSIS OF AN ASSOCIATED DISEASE

This chapter contains two manuscripts exploring the risk of a new diagnosis of IBD in subjects presenting with EIMs. The first focuses on dermatological EIMs and is published in the journal Inflammatory Bowel Disease and the second, focusing on ophthalmic EIMs has been submitted to the journal BMJ Open.

Supplementary material for each manuscript is found in the appendices for this chapter at the end of the thesis.

Chapter 6 manuscript 1: The risk of later diagnosis of inflammatory bowel disease in patients with dermatological disorders associated with inflammatory bowel disease

King D *et al*, The Risk of Later Diagnosis of Inflammatory Bowel Disease in Patients with Dermatological Disorders Associated with Inflammatory Bowel Disease, *Inflammatory Bowel Diseases* (2021)

The Risk of Later Diagnosis of Inflammatory Bowel Disease in Patients With Dermatological Disorders Associated With Inflammatory Bowel Disease

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Background: Dermatological conditions such as erythema nodosum (EN), pyoderma gangrenosum, Sweet's syndrome, and aphthous stomatitis can occur with inflammatory bowel disease (IBD) and are considered dermatological extraintestinal manifestations (D-EIMs). Rarely, they may precede IBD. Other common conditions such as psoriasis have also been associated with IBD. This study examined the risk of a subsequent IBD diagnosis in patients presenting with a D-EIM.

Methods: A retrospective cohort study compared patients with D-EIMs and age-/sex-matched patients without D-EIMs. Hazard ratios (HRs) were adjusted for age, sex, body mass index, deprivation, comorbidity, smoking, loperamide use, anemia, and lower gastrointestinal symptoms. Logistic regression was used to produce a prediction model for the diagnosis of IBD within 3 years of EN diagnosis.

Results: We matched 7447 patients with D-EIMs (74% female; median age 38 years (interquartile ratio [IQR], 24-65 years) to 29,297 patients without D-EIMs. We observed 131 (1.8%) subsequent IBD diagnoses in patients with D-EIMs compared with 65 (0.2%) in those without D-EIMs. Median time to IBD diagnosis was 205 days (IQR, 44-661 days) in those with D-EIMs and 1594 days (IQR, 693-2841 days) in those without D-EIMs. The adjusted HR for a later diagnosis of IBD was 6.16 (95% confidence interval [CI], 4.53-8.37; $P < 0.001$), for ulcerative colitis the HR was 3.30 (95% CI, 1.98-5.53; $P < 0.001$), and for Crohn's disease the HR was 8.54 (95% CI, 5.74-12.70; $P < 0.001$). Patients with psoriasis had a 34% increased risk of a subsequent IBD diagnosis compared with the matched control patients (HR, 1.34; 95% CI, 1.20-1.51; $P < 0.001$). We included 4043 patients with an incident EN diagnosis in the prediction model cohort, with 87 patients (2.2%) diagnosed with IBD within 3 years. The model had a bias-corrected *c*-statistic of 0.82 (95% CI, 0.78-0.86).

Conclusions: Patients with D-EIMs have a 6-fold increased risk of a later diagnosis of IBD. Younger age, smoking, low body mass index, anemia, and lower gastrointestinal symptoms were associated with an increased risk of diagnosis of IBD within 3 years in patients with EN.

Key Words: extra intestinal manifestations, inflammatory bowel disease, Crohn's disease, ulcerative colitis, erythema nodosum, pyoderma gangrenosum, psoriasis, aphthous stomatitis, Sweet's syndrome, dermatological

The inflammatory bowel diseases (IBD), consisting of Crohn's disease (CD) and ulcerative colitis (UC), can be complicated by the presence of extraintestinal manifestations (EIM). The "classic" EIMs that may complicate IBD include dermatological, ophthalmic, musculoskeletal, and hepatobiliary disorders.[1] EIMs may be diagnosed at the same time, later in the course, or more rarely before diagnosis of IBD.[2-4] Although they are well recognized, EIMs are not seen in all patients with IBD and may be seen in isolation. The reported prevalence of these conditions varies widely, largely because of the varying definitions of an EIM.[5, 6]

Dermatological conditions associated with IBD are among the most common EIMs reported.[7] The classic dermatological EIMs (D-EIMs) include erythema nodosum (EN), pyoderma

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Abbreviations: aHR, adjusted hazard ratio; ApS, aphthous stomatitis; AUC, area under the curve; BMI, body mass index; CD, Crohn disease; EIM, extraintestinal manifestation; EN, erythema nodosum; HR, hazard ratio; IBD, inflammatory bowel disease; IMDR-UK, IQVIA Medical Research Data, United Kingdom; IR, incidence rate; IRR, incidence rate ratio; PG, pyoderma gangrenosum; py, person-year; ROC, receiver operating characteristic; SS, Sweet's syndrome; UC, ulcerative colitis; UK, United Kingdom.

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gangrenosum (PG), Sweet's syndrome (SS), and aphthous stomatitis (ApS). These conditions are associated with IBD or are reactive cutaneous manifestations rather than those directly related to medications used in the treatment of IBD or disease-specific conditions such as perianal or metastatic CD.[8] Although they tend to have a mainly benign course and some are straightforward to manage, such as EN, this is not always the case, and they may be debilitating and have major consequences for quality of life.[9, 10] Although it is not a classic EIM per se, psoriasis is also associated with IBD; in particular, patients with CD seem to be at increased risk of this skin condition. Both conditions (IBD and psoriasis) seem to have overlapping inflammatory regulator pathways, and previous studies have shown an increased risk of IBD in those with an established psoriasis diagnosis.[11, 12]

Although for many EIMs treatment relies on controlling the underlying bowel condition given their parallel nature,[13] effective treatment does rely upon the recognition of the underlying IBD. There is currently little evidence to guide clinicians on the incidence of IBD in those presenting with a D-EIM or on the potential lag time from D-EIM to IBD diagnosis.[4] Health care professionals who diagnose D-EIMs may not consider IBD, the symptoms of which can be nonspecific, leading to extended periods of untreated symptoms.[14]

The principal aims of the study were to investigate the risk of a later diagnosis of IBD in patients presenting with skin conditions compared with those without skin conditions, the risk factors for IBD in these groups, and the time from diagnosis of these skin conditions to a subsequent IBD diagnosis.

MATERIALS AND METHODS

Data Source

This study was conducted using the IQVIA Medical Research Data (IMDR-UK) primary care database. The IMDR-UK is derived from more than 700 general health care practices across the United Kingdom (UK) and contains data on approximately 15 million patients. It is representative of the UK population.[15] Patient-level data are captured longitudinally and include prescriptions, primary and secondary care investigations, diagnoses, and patient demographics. Data are uploaded electronically using a hierarchy of clinical (Read) codes.[16] The IMDR-UK health care practices were required to have achieved an acceptable mortality recording threshold and have had at least 1 year since the installation of an electronic medical record system to be included in this study.[17] These inclusion criteria aimed to ensure improved data reliability and reduce the risk of underrecording.

Study Design

Cohort study

A retrospective matched cohort study was conducted of classic D-EIMs (EN, PG, SS, and ApS), with secondary studies of 2 individual D-EIMs (EN and PG) and of psoriasis. All ages were included in the study. Patients with an incident (first recorded during the study period and then after registration with their health care practice) coded diagnosis of the D-EIM of interest (recorded through Read codes; Supplementary Material 1 and Supplementary Material 2) were compared with patients without D-EIMs and matched by age at cohort entry (±2 years), sex, and health care practice registration on the index date with a ratio of 1:4. The index date was the date of D-EIM diagnosis for the D-EIM group. Only patients without an IBD diagnosis at the index date were included in the study. Patients with an EN code were excluded from the study if they had a record of tuberculosis, sarcoidosis, or sulfasalazine prescription within a 6-month period before EN diagnosis. These factors are strongly associated with the development of EN and may therefore confound interpretation of the results.[18] Individual patients were eligible for inclusion from the later of either the date that their health care practice became eligible or 1 year after they were registered, to ensure that adequate baseline characteristics were captured.

Patients were followed from their index date until the first of the following events (exit date): death, patient left the practice, last data collection from their health care practice, study end date (September 25, 2019), or diagnosis with CD or UC. Patients with a code for both UC and CD were allocated to 1 based on the frequency of coding. For those with equal coding frequency, the earliest diagnosis date and the latest IBD subtype were used.

Prediction model

Patients with an incident diagnosis of EN were investigated to predict the risk of having a diagnosis of IBD within the following 3 years. Case examples were used to show the probability of diagnosis of IBD in patients presenting with EN.

Validation

Clinical codes used to identify UC, CD, D-EIMs, and psoriasis are listed in Supplementary Material 1. Individual D-EIMs and contributions are detailed in Supplementary Material 2. Coding in primary care to identify patients with IBD has been previously validated.[19, 20] The EIM codes were reviewed for validity by 2 gastroenterology clinicians, having been first sourced from other published primary care database studies.[21, 22]

Statistical Analysis

Cohort study

The time from index date to a later diagnosis of IBD in those with and without a baseline D-EIM were presented as median time to IBD (combined), UC, and CD diagnoses with an accompanying interquartile range (IQR). Log-rank tests were used to compare time to IBD diagnosis between

patients with (exposed) and without (unexposed) D-EIMs. Cox proportional hazard models, with time to subsequent diagnosis of IBD as the time metric, were produced to assess the adjusted hazard ratio (aHR) of IBD diagnoses in participants with D-EIM compared with matched unexposed patients. The aHRs were produced for IBD (combined), UC, and CD outcomes. For EN and PG, aHRs were produced only for combined IBD diagnoses because of relatively few IBD diagnoses in these secondary analyses. For psoriasis, aHRs were produced for IBD (combined), UC, and CD outcomes. Hazard ratios (HRs) were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend level of deprivation (quintiles); Charlson-Deyo comorbidity score; and the coding of anemia (<11.9 g/dL for females and <12.9 g/dL for males), abdominal pain, loperamide prescription, diarrhea, or lower gastrointestinal bleeding within 6 months of an EIM diagnosis (if coded prior to IBD diagnosis). Smoking status was dichotomized into current smoker and nonsmoker categories, with missing data for smoking status considered in the nonsmokers category, a method that has been previously validated.[23] Missing data for Townsend deprivation were considered a separate category. The proportional hazards assumption was assessed using log-log plots and the Schoenfeld residuals test. Cumulative incidence plots were produced to show the cumulative risk of IBD diagnosis over time.

Prediction model

Multivariable logistic regression was used to establish a prediction model for IBD diagnosis within 3 years in patients presenting with a new diagnosis of EN. Only those with an IBD diagnosis within 3 years or those who had a minimum of 3 years follow-up were included in the development cohort. Backward stepwise elimination was used to select variables with an elimination alpha-to-remove *P* value of 0.20. Sex, age (categorical), and smoking status were included because of their clinical importance. Candidate predictors recorded within 6 months of EN diagnosis included anemia, abdominal pain, weight loss, lower gastrointestinal bleeding, loperamide prescription, and diarrhea (before an IBD diagnosis). A receiver operating characteristic (ROC) curve with accompanying *c*-statistic was used to assess model discrimination; calibration was assessed using the Hosmer-Lemeshow test for goodness of fit.

A complete case analysis was performed in which patients with missing values were excluded. Of the explored predictors, only BMI had missing values. Patients without BMI values were therefore excluded for the complete case analysis. To further assess missingness, multiple imputation of missing BMI values was performed, producing 10 imputed datasets. The models were well calibrated in both the complete case analysis and when patients with missing BMI values were also included. Multiple imputation had minimal impact upon the discrimination of the model as assessed by the area under the ROC curve c-statistic.

All patients were therefore included in the prediction model development with a missing category for BMI included. Internal validation of the prediction model was performed through bootstrapping by resampling the dataset (with replacement) 200 times and comparing the resulting average of the area under the ROC curve from the bootstrap samples to the original model. Analyses were performed using Stata version 16.0, and *P* values <0.05 were considered statistically significant.[24]

RESULTS

Study Patients

After exclusions (Fig. 1), 7447 patients with D-EIMs were identified: 74% were female, and the median age was 38 years (interquartile ratio [IQR], 24-65 years). Patients with D-EIMs were age-, sex-, and general practice–matched to 29,297 patients without D-EIMs. The median follow-up time for patients was 5.5 years, with a total of 47,377 person-years (py) of follow-up in patients with D-EIMs and 185,889 py in those without D-EIMs. Cohort characteristics are shown in Table 1.

Risk of IBD in Patients With Dermatological Conditions

Among patients with D-EIMs, 131 (1.8%) diagnoses of IBD (33 UC and 98 CD) were observed compared with 65 (0.2%) diagnoses (30 UC and 35 CD) in matched patients without D-EIMs. The median time to subsequent diagnosis of IBD from D-EIM diagnosis (index date) was 205 days (IQR, 44-661 days) compared with 1594 days (IQR, 693-2841 days) for patients without D-EIMs. For UC, the median time to diagnosis was 231 days (IQR, 43-1230 days) and 1544 days (IQR, 551-2359 days), respectively, and for CD it was 159 days (IQR, 47-598 days) and 1690 days (IQR, 915-2962 days), respectively. For IBD, UC, and CD, the log-rank test *P* was <0.001. After adjustment, the HR for an IBD diagnosis in patients with D-EIMs vs that of matched patients without D-EIMs was 6.16 (95% confidence interval [CI], 4.53-8.37; $P < 0.001$). For UC, the aHR was 3.30 (95% CI, 1.98-5.53; $P < 0.001$) and for CD it was 8.54 (95% CI, 5.74-12.70; $P < 0.001$; Table 2; full models are shown in Supplementary Material 3). Fig. 2 shows the cumulative incidence plot for IBD diagnoses in patients with D-EIMs compared with those without D-EIMs.

Risk of IBD in EN and PG

The characteristics of patients with D-EIMs and matched patients without D-EIMs in these subgroup analyses together with full Cox models are shown in Supplementary Material 4 and 5, respectively. We identified 6329 patients with incident EN, with 5917 remaining once tuberculosis, sarcoidosis, and sulfasalazine use had been removed. We then excluded 327 individuals with pre-existing IBD (Fig. 1). After the exclusions, 5590 patients with EN (79% female; median age 38 years [IQR,

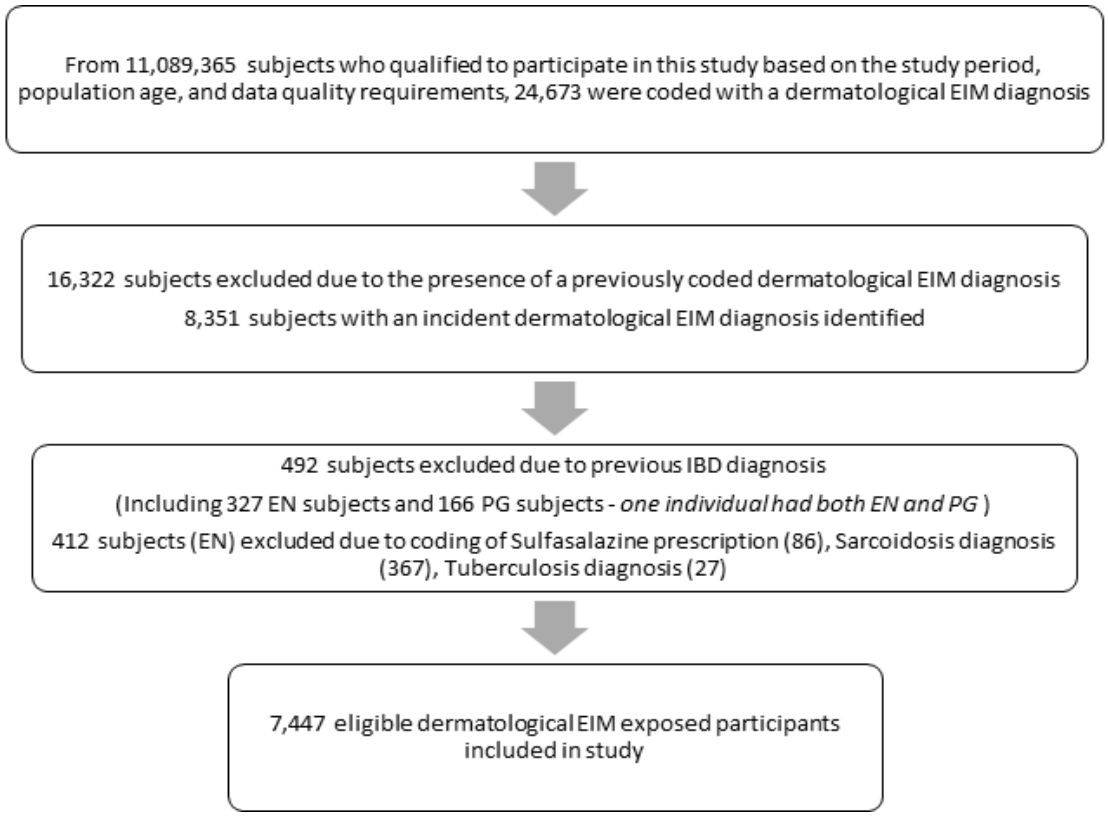


FIGURE 1. CONSORT flowchart.

23-52 years]) were matched to 22,039 patients without EN, contributing 36,324 and 139,304 py of follow-up, respectively. We observed 104 (1.9%) IBD diagnoses (23 UC and 81 CD) in patients with EN and 53 (0.2%) IBD diagnoses (23 UC and 32 CD) in patients without EN. Median time to IBD diagnosis was 151 days (IQR, 42-615 days) for patients with EN compared with 1618 days (IQR, 728-2895 days) for those without EN (log-rank test $P < 0.001$). For UC, the median time to diagnosis was 224 days (IQR, 28-1230 days) for patients with EN and 1620 days (IQR, 1079-2841 days) for those without EN; for CD, the median time to diagnosis was 133 days (IQR, 44-552 days) for patients with EN and 1549 days (IQR, 460-3315 days) for those without EN (log-rank test $P < 0.001$ for both CD and UC). The aHR for an IBD diagnosis in patients with EN vs matched patients without EN was 6.49 (95% CI, 4.62-9.11; $P < 0.001$; Table 2).

In the PG study, 1143 patients with incident PG were identified before exclusions, with 166 having a pre-existing IBD diagnosis (Fig. 1). In the PG subgroup analysis, 977 patients with PG (60% female; median age 57 years [IQR, 39-73 years]) were matched to 3852 patients without PG, contributing 5301 and 23,963 py of follow-up time, respectively. We observed 21 (2.1%) IBD diagnoses (10 UC and 11 CD) in patients with PG compared with 11 (0.3%) diagnoses (6 UC and 5 CD) in those without PG. Median time to IBD diagnosis was 392 days (IQR, 127-1323 days) for patients with PG compared with 1890 days (IQR, 1111-4626 days) for those without PG (log-rank test $P < 0.001$). For UC, the median time to diagnosis was 405 days (IQR, 77-3327 days) for patients with PG and 2816 days (IQR, 1426-4146 days) for those without PG, and for CD, the median time to a diagnosis was 282 days (IQR, 101-946 days) for patients with PG and 2529 days (IQR, 1890-5948 days) for those without PG (log-rank test $P < 0.001$ for both CD and UC). The aHR for an IBD diagnosis in PG was 6.27 (95% CI, 2.84-13.86; $P < 0.001$; Table 2).

Risk of IBD in Psoriasis

In the psoriasis study, 121,195 patients with incident psoriasis and without a pre-existing IBD diagnosis were identified (53% female; median age 45 years [IQR, 29-61 years]). Patients with psoriasis were matched to 476,281 control patients (without psoriasis) by age and sex; patients with psoriasis and matched control patients contributed 759,831 and 2,895,686 py of follow-up time, respectively. Characteristics of patients with and matched patients without psoriasis are shown in Supplementary Material 6. We observed 407 (0.3%) IBD diagnoses (398 UC and 178 CD) in patients with psoriasis compared with 1090 (0.2%) diagnoses (692 UC and 398

TABLE 1. Demographic Characteristics of Exposed Patients and Control Patients

	Exposed Patients With Associated D-EIM	Control Patients
Number	7447	29,297
Median py of follow-up (IQR)	5.5 (2.3-9.6)	5.4 (2.3-9.5)
Median age, y (IQR)	38 (24-56)	38 (23-54)
Age category, y, n (%)		
<18	1149 (15)	5031 (17)
18–30	1356 (18)	5208 (18)
30–40	1360 (18)	5350 (18)
40–50	1113 (15)	4468 (15)
50–60	968 (13)	3746 (13)
60–70	724 (10)	2793 (10)
>70	777 (10)	2701 (9)
Female sex, n (%)	5533 (74)	21,785 (74)
Townsend deprivation quintile, n (%)		
1—least deprived	1532 (21)	6349 (22)
2	1386 (19)	5277 (18)
3	1386 (19)	5402 (18)
4	1239 (17)	4540 (15)
5—most deprived	805 (11)	3282 (11)
Missing	1100 (15)	4447 (15)
Charlson-Deyo comorbidity score, n (%)		
0	4888 (66)	21,804 (74)
1	1706 (23)	5361 (18)
≥2	853 (12)	2132 (7)
Smoking status, n (%)		
Current smoker	1152 (15)	5128 (18)
Nonsmoker	6295 (85)	24,169 (82)
BMI, n (%)		
<25 kg/m^2	2340 (31)	9539 (33)
25–30 kg/m^2	1656 (22)	5991 (20)
>30 kg/m^2	1498 (20)	4251 (15)
Missing	1953 (26)	9516 (32)
Anemia,*,† n (%)	941 (13)	947 (3)
Abdominal pain, * n (%)	190 (3)	600 (2)
Lower gastrointestinal bleeding, * n (%)	83 (1)	164 (1)
Loperamide prescription, * n (%)	139 (2)	212 (1)
Diarrhea[a], * n (%)	240 (3)	503 (2)

*Coded within 6 months of index date.
†<11.9 g/dL (females); <12.9 g/dL (males).

CD) in those without psoriasis. Median time to IBD diagnosis was 1502 days (IQR, 604-2646 days) for patients with psoriasis compared with 1366 days (IQR, 623-4536 days) for those without psoriasis. For UC, the median time to diagnosis was 1378 days (IQR, 558-2410 days) for patients with psoriasis and 1315 days (IQR, 588-2462 days) for those without psoriasis, and for CD, the median time to a diagnosis was 1743 days (IQR, 626-2905 days) for patients with psoriasis and 1481 days (IQR, 721-2583 days) for those without psoriasis (log-rank tests for IBD and CD were $P < 0.001$, and for UC, $P = 0.002$). The aHR for an IBD diagnosis in psoriasis was 1.34 (95% CI, 1.20-1.51; $P < 0.001$). For UC, the aHR was 1.20 (95% CI, 1.03-1.39; $P = 0.020$), and for CD, the aHR was 1.60 (95% CI, 1.34-1.92; $P < 0.001$; Table 2).

TABLE 2. aHRs for Risk of IBD

	aHR	95% CI	*P*
Any associated dermatological condition			
IBD	6.16	4.53-8.37	<0.001
UC	3.30	1.98-5.53	<0.001
CD	8.54	5.74-12.70	<0.001
EN			
IBD	6.49	4.62-9.11	<0.001
PG			
IBD	6.27	2.84-13.86	<0.001
Psoriasis			
IBD	1.34	1.20-1.51	<0.001
UC	1.20	1.03-1.39	0.020
CD	1.60	1.34-1.92	<0.001

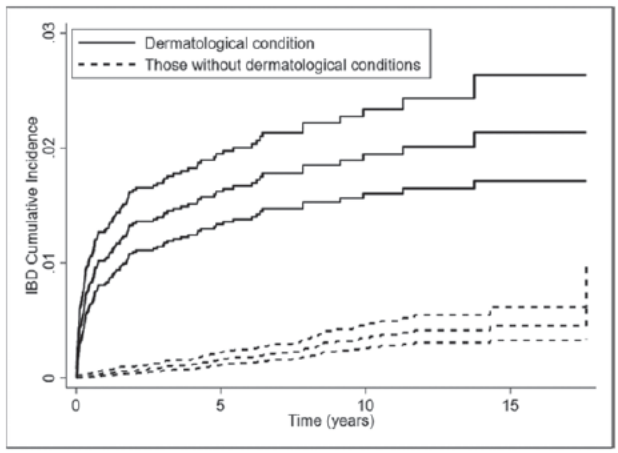


FIGURE 2. Cumulative incidence (with 95% CI) of IBD in patients with dermatological conditions and those without.

TABLE 3. Characteristics of Patients With EN With and Without an IBD Diagnosis by 3 Years

	IBD Diagnosis (87)	No IBD Diagnosis (5486)
Median age, y (IQR)	25 (19-35)	37 (24-52)
Age category, y, n (%)		
<18	14 (16)	604 (15)
18–30	45 (52)	721 (18)
30–40	13 (15)	851 (22)
40–50	5 (6)	662 (17)
50–60	5 (6)	540 (14)
60–70	4 (5)	357 (9)
>70	1 (1)	221 (6)
Female sex, n (%)	72 (79)	3122 (79)
Smoking status, n (%)		
Current smoker	20 (23)	622 (16)
Nonsmoker	67 (77)	3334 (84)
BMI, n (%)		
<25 kg/m^2	42 (48)	1217 (31)
25–30 kg/m^2	14 (16)	908 (23)
>30 kg/m^2	9 (10)	795 (20)
Missing	22 (25)	1036 (26)
Anemia, *,† n (%)	28 (32)	44 (11)
Abdominal pain, * n (%)	9 (10)	104 (3)
Lower gastrointestinal bleeding, * n (%)	3 (3)	42 (1)
Loperamide prescription, * n (%)	7 (8)	55 (1)
Diarrhea, * n (%)	24 (27)	113 (3)

*Coded within 6 months of index date.
†<11.9 g/dL (females); <12.9 g/dL (males).

Prediction Model

We identified 5590 patients with EN, with 4043 eligible for inclusion in the prediction model development cohort based on sufficient follow-up time or an IBD diagnosis within 3 years of EN diagnosis. Eighty-seven patients (2.2%) had the outcome of an IBD diagnosis within 3 years (79% CD). Characteristics of patients with EN with and without an IBD diagnosis by 3 years after EN diagnosis are shown in Table 3. Those with an IBD diagnosis were younger (median age 25 years [IQR, 19-35 years] and 37 years [IQR, 24-52 years], respectively; $P < 0.001$), but no significant difference was seen by sex between the groups, $P = 0.384$. Smoking was more common in patients with IBD although not significant at the 5% level (23% in patients with IBD vs 16% in patients without IBD; $P = 0.067$), and there was a higher proportion within the lowest BMI category (<25 kg/m^2): 48% in patients diagnosed with IBD compared with 31% in those not diagnosed with IBD, $P = 0.003$. When patients diagnosed with IBD within 6 months of an EN diagnosis (64%) were compared with those diagnosed with IBD later than 6 months after an EN diagnosis, there was no statistical difference between the 2 groups for coding of anemia, abdominal pain, and diarrhea.

After backward stepwise regression, sex, lower gastrointestinal bleeding, and loperamide prescription exceeded the alpha-to-remove threshold set at 0.20, but sex was retained in the model. The results of a multivariable logistic regression model to assess the risk of being diagnosed with IBD within a 3-year period after EN diagnosis, including beta coefficients and odds ratios with their 95% confidence intervals, are presented in Table 4. The Hosmer-Lemeshow chi-square test for goodness of fit was applied to the entire data set and was not significant at 0.539, suggesting good model fit. The ROC curve, shown in Fig. 3, produced an area under the curve (AUC) *c*-statistic of 0.83 (95% CI, 0.78-0.87). After internal validation by bootstrapping—resampling the dataset 200 times—the mean difference between the original AUC and the AUC in each bootstrap sample was 0.01. This process produced a bias-corrected *c*-statistic value of 0.82 (95% CI, 0.78-0.86).

A probability calculator was produced to determine the likelihood of an IBD diagnosis within the EN cohort using the following examples:

(1) A female, 34-year-old nonsmoker with a BMI of 21 kg/m^2 and a within-6-months history of anemia and abdominal pain would have a 7% risk of IBD being diagnosed within 3 years of her EN diagnosis.
(2) A male, 17-year-old current smoker with a BMI of 24 kg/m^2 and a history of abdominal pain and diarrhoea would have a 43% 3-year IBD diagnosis risk.
(3) A female, 49-year-old current smoker with a BMI of 30 kg/m^2 and a history of diarrhea and abdominal pain would have an 11% risk of IBD diagnosis within 3 years.

A nomogram for the prediction model is shown in Supplementary Material 7.

DISCUSSION

In this study, we have shown that patients with a D-EIM but without a recorded diagnosis of IBD are at greater risk of being diagnosed later with IBD than matched patients without a D-EIM. A subsequent diagnosis of IBD in those with a new D-EIM diagnosis was recorded at a median of 205 days after D-EIM diagnosis, with 50% of diagnoses recorded between 44 and 661 days. A substantial number of new IBD diagnoses were therefore not made until more than 1 year after an EIM diagnosis. Considering that D-EIMs usually present when bowel disease is active, our findings suggest a missed diagnostic opportunity. Although these skin manifestations may accompany bowel activity, they do not always relate to disease extent or severity,[25-27] and as such it is plausible that symptoms of IBD may not have manifested themselves clinically. That being said, in the prediction model presented, 55% of participants with EN who were later diagnosed with IBD had a record of either anemia, abdominal pain, loperamide prescription, diarrhea, or lower gastrointestinal

TABLE 4. Multivariable Logistic Regression Prediction Model Factors Associated With IBD Diagnosis Within 3 Years of EN Diagnosis

	β Coefficient	Odds Ratio	95% CI	*P*
Sex				
Male (reference)	—	1.00	—	—
Female	0.04	1.04	0.56-1.93	0.90
Age category				
<18 (reference)	—	1.00	—	—
18–30	0.75	2.12	0.97-4.65	0.06
30–40	–0.78	0.46	0.18-1.17	0.10
40–50	–1.22	0.29	0.09-0.94	0.04
50–60	–1.04	0.35	0.11-1.16	0.09
60–70	–0.94	0.39	0.11-1.40	0.15
>70	–2.45	0.09	0.01-0.75	0.03
Smoking status				
Current smoker (reference)	—	1.00	—	—
Nonsmoker	–0.40	0.67	0.38-1.17	0.16
BMI				
<25 kg/m^2 (reference)	—	1.00	—	—
25–30 kg/m^2	–0.59	0.55	0.29-1.06	0.07
>30 kg/m^2	–0.92	0.40	0.19-0.85	0.02
Missing	–0.74	0.48	0.24-0.94	0.03
Anemia*,†				
No (reference)	—	1.00	—	—
Yes	1.41	4.11	2.48-6.79	0.00
Abdominal pain*				
No (reference)	—	1.00	—	—
Yes	0.92	2.51	1.06-5.96	0.04
Diarrhea*				
No (reference)	—	1.00	—	—
Yes	2.60	13.42	7.59-23.74	0.00
Intercept	–3.44	0.03	0.01-0.09	0.00

*Coded within 6 months of index date.
†<11.9 g/dL (females); <12.9 g/dL (males).

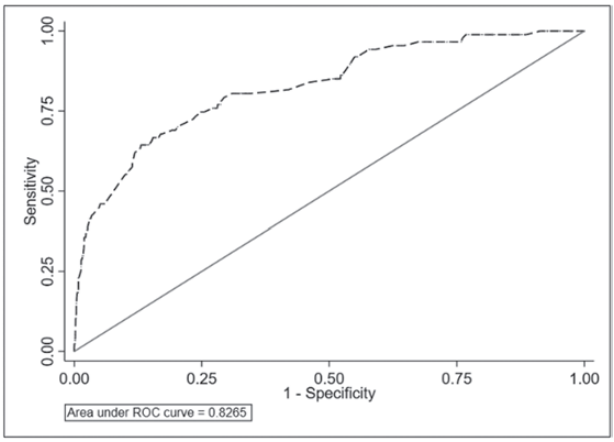


FIGURE 3. ROC curve of diagnostic ability of prediction model to detect an IBD diagnosis within 3 years of an EN diagnosis.

bleeding at the time of D-EIM diagnosis, compared with only 18% of patients without IBD. We found a predominance of CD diagnoses in exposed patients with EIM, which is in keeping with previous observations that EIMs are more common in those with CD. This finding was also observed, although the numbers were small, in the PG cohort, whereas other studies have shown a predominant association of PG with UC.[8, 28, 29]

Research has shown that EIMs of IBD are numerous; however, certain classic EIMs have been accepted. The classic dermatological types include EN, PG, ApS, and SS, conditions examined in this study. Attempts have been made to categorize EIMs based on their presumed biological cause. Other nonclassic EIMs, not included in this study, include mucocutaneous CD, which represents intestinal pathophysiology located outside the gut, and anti-tumor necrosis factor–associated skin conditions, which relate to specific

medications.[30] Classic D-EIMs usually run in parallel with bowel disease activity, with the exception of PG, which may or may not do so.[13] Finally, D-EIMs may occur in isolation or in association with medical conditions other than IBD.

We did not consider psoriasis among the classic D-EIMs in this study; however, it is a common skin condition, and an association with IBD has previously been shown. As such, psoriasis was included as a separate analysis in this study. We show herein that the risk of an IBD diagnosis is greater in psoriasis and that the association seems to be greatest in CD, which is in keeping with existing evidence.[7, 31, 32]

As the most common classic dermatological EIM, EN is thought to be a type IV delayed hypersensitivity reaction leading to panniculitis. Mainly affecting the pretibial area and resulting in raised, tender, red/brown nodules, it is predominantly an idiopathic condition that runs a benign course.[18] It has been reported to affect between 3% and 15% of patients with IBD, with most patients presenting after an established IBD diagnosis.[4, 8, 28] In the current study, 6329 patients with incident EN were identified with 5917 remaining once tuberculosis, sarcoidosis, and sulfasalazine use had been removed. We then excluded 327 individuals with pre-existing IBD, but taken together with the 104 subsequent IBD diagnoses, 7% of exposed patients with incident EN had an IBD diagnosis. In our study, of those patients with EN subsequently diagnosed with IBD, 2% were diagnosed shortly after EN diagnosis and half were diagnosed more than 5 months later.

Research has shown that PG is a neutrophilic dermatosis. It is an immune reactive condition resulting in painful ulceration predominantly on the lower limbs, which can be challenging to treat, exhibits pathergy, and is prone to a relapsing course.[8, 33] Furthermore, PG is rare with a female predominance and a prevalence of 5.8 per 100,000 population.[34] Approximately 34% of patients presenting with PG may have underlying IBD.[35-37] With the excluded 166 pre-existing IBD diagnoses and 21 IBD diagnoses subsequently observed among patients with incident PG, 16% of exposed patients in our study were associated with IBD. As with EN, we found that 2% of patients with IBD were diagnosed after a PG diagnosis. With PG, however, more than 50% of IBD diagnoses were made >12 months after the PG diagnosis.

We did not study ApS and SS individually, but both conditions made up a significant minority (9% and 3%, respectively) of the individuals with D-EIMs. Research has shown that ApS is common, with one-fifth of people suffering from lesions, although diagnostic criteria and populations studied have resulted in a wide variation in prevalence.[38] It is seen in 7% to 10% of patients with IBD in observational studies, with patients with CD predominating.[8, 28] It is likely that ApS, especially milder forms, is underreported. When we reviewed ApS data separately, we found that only 4 (0.6%) participants with ApS were later diagnosed with IBD, three-quarters of which was CD.

Finally, SS (otherwise known as febrile neutrophilic dermatosis) is a rare condition characterized by fever, neutrophilia, and skin lesions. It may be drug-induced, present as a paraneoplastic phenomenon, or be termed as a classic EIM; SS is associated with IBD, streptococcal pharyngitis, and pregnancy or may appear in isolation.[32] Little is known about its prevalence, with the published literature dominated by case reports. However, it predominantly affects females, which was also the case in the present study (62% female).[39] Only 2 (1%) individuals with SS in our study were later diagnosed with IBD. Although their Charlson-Deyo comorbidity scores were both 0, making malignant causes less likely, it remains challenging to comment further on this rare syndrome, other than to say that vigilance for IBD should be exercised if SS is encountered in the absence of an alternative cause.

The use of a large primary care database such as the IMDR-UK has both strengths and limitations. French and Swiss studies of patients with IBD found that a younger age and female sex were significantly associated with D-EIMs and that D-EIMs were associated with familial IBD, and in the French study, PG was associated with Black African ethnicity.[27, 40] A limitation of the IMDR-UK database is the limited ethnicity and family history data that have been recorded. Unfortunately, these limitations mean that assessing the impact of these variables in the diagnosis of IBD in patients with D-EIM was not possible. There is also a lack of nuance in the coding of IBD in primary care with regard to the severity and site of IBD within the bowel. Although this deficit did not affect the study outcome, that of an IBD diagnosis, it is noteworthy that colonic and ileocolonic disease seem to be more strongly associated with EIMs than does isolated small bowel disease; unfortunately, this finding could not be further explored in this study.[4,7] Attempts were made to reduce bias because of other potential confounders that could be causative in terms of EIMs (ie, the exclusion of patients with EN with a recent coding of tuberculosis, sarcoidosis, and sulfasalazine prescription); however, many EIMs have a multitude of associations, making comprehensive exclusions both impractical and, given the unknown etiology and causal pathways for these conditions, inappropriate.

Misclassification bias is a potential concern in all primary care database studies, and the gold standard of external validation is often prohibitive.[41] Conditions diagnosed in secondary care are relayed to general practices, which then upload these diagnoses to their computerized systems. This situation holds for IBD; IBD coding in primary care has previously been validated[19]; furthermore, in our study more than 60% of patients with IBD had at least 2 IBD codes in their patient record. In UK primary care practices, PG has been previously validated, with the code for "pyoderma gangrenosum" generating a positive predictive value of 76% and the code for "pyoderma" producing

a 50% positive predictive value.[22] However, numbers in that study were small and the methodology relied upon general practitioners responding to a questionnaire. Given that PG is a diagnosis of exclusion and that dermatology specialty referral will be involved, it is likely that coded diagnoses record true PG. With our controlled studies, if there were an impact of underclassification, then it would likely be to reduce the hazard associated with patients with IBD compared to control patients, so our findings may in fact be an underestimate of the risk.

A primary care database validation study for EN has not been conducted, and this too warrants further consideration. Research has shown that EN is a relatively benign condition and although causes may be sought, a diagnosis may be made in primary care without further specialty intervention. There is also a risk that EN may be underreported and misclassified, which again may lead to an underestimate of the risk presented.

The presence of multiple EIMs in a single patient may affect the risk of IBD, and having one EIM seems to increase the risk of developing further ones.[8, 26] In the present study, a first recorded D-EIM allowed for study inclusion; however, subsequent EIMs were not examined, meaning that a patient may have several EIMs either previously diagnosed, in the case of non-D-EIMs, or subsequently diagnosed, for all types. This interaction may be important and should be considered in future research. It is clear that delays in the diagnosis of IBD can lead to unfavorable outcomes with increased hospitalization, potential exposure to an avoidable surgical risk, and significant costs.[14, 42, 43]

Few studies have examined the time lag from an EIM diagnosis to a subsequent IBD diagnosis. In the vast majority of patients, an EIM is diagnosed in concert with or after the IBD diagnosis.[4] Furthermore, a longer duration of IBD is associated with a greater risk of EIMs.[44] Consequently, the focus of this study is unique. Given that most D-EIMs present in concert with bowel activity, it is reasonable to presume that patients who went on to be diagnosed with IBD after a diagnosis of a D-EIM may have had active bowel disease that was only mildly symptomatic or uncharacteristic of IBD at the time. The prediction time period in our study was limited to 3 years to capture the maximum subsequent diagnoses in the database and also remain practical for a clinician and patient. However, IBD diagnoses made many years after an EN diagnosis are not accounted for with this model. The prediction model presented here has been internally validated and performs well; however, a limitation was the relatively few IBD outcomes available and external validation is required. Nevertheless, it is noteworthy that the features that increase the likelihood of a subsequent diagnosis of IBD, in particular anemia and lower gastrointestinal symptoms, should be considered by all clinicians who make a diagnosis of an associated dermatological condition.

CONCLUSIONS

We have shown that patients who present with a D-EIM are at increased risk of a subsequent IBD diagnosis. Clinicians who see patients with dermatological conditions should be aware of this risk association, and symptoms of IBD should be sought in such patients. If found, they should be investigated and gastroenterology referral considered to reduce diagnostic delays and avoid harm.

SUPPLEMENTARY DATA

Supplementary data are available at *Inflammatory Bowel Diseases* online.

ACKNOWLEDGMENTS

The use of the IMRD-UK was approved by the UK Research Ethics Committee (reference number: 18/LO/0441). In accordance with this approval, the study protocol was reviewed and approved by an independent scientific review committee in September 2019 (reference number: 19THIN066). The IMRD-UK incorporates data from The Health Improvement Network, a Cegedim database. Reference made to the network is intended to be descriptive of the data asset licensed by IQVIA. This work used de-identified data provided by patients as a part of their routine primary care. The data underlying this article were provided by the IMRD-UK under license and are not available for open access.

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Chapter 6 manuscript 2: The risk of a subsequent diagnosis of inflammatory bowel disease in subjects with ophthalmic disorders associated with inflammatory bowel disease

Structured abstract:

Introduction

Ophthalmic conditions including anterior uveitis (AU), episcleritis and scleritis may occur in association with the inflammatory bowel diseases (IBD) as ophthalmic extraintestinal manifestations (O-EIM). They may predate an IBD diagnosis, but the risk is not well described.

Methods

A retrospective cohort study examined the risk of a subsequent diagnosis of IBD in subjects with O-EIMs compared to age/sex matched subjects without O-EIMs. Hazard ratios (HR) were adjusted for age, sex, body mass index, deprivation, comorbidity, smoking, and baseline axial arthropathy, diarrhoea, loperamide prescription, anaemia, lower gastrointestinal bleeding and abdominal pain.

Logistic regression was used to produce a prediction model for the diagnosis of IBD within 3 years of an AU diagnosis.

Results

38,805 subjects with an O-EIM were identified (median age 51 (38-65), 57% female) and matched to 153,018 subjects without O-EIMs. 213 (0.6%) subsequent IBD diagnoses (102 ulcerative colitis (UC) and 111 Crohn's disease (CD)) were recorded in those with O-EIMs

and 329 (0.2%) (215 UC and 114 CD) in those without. Median time to IBD diagnosis was 882 (IQR 365-2,043) days in those with O-EIMs and 1,403 (623-2,516) in those without. The adjusted HR for a subsequent diagnosis of IBD was 2.25 (95%CI 1.89-2.68), p<0.001; for ulcerative colitis 1.65 (1.30-2.09), p<0.001; and for Crohn's disease 3.37 (2.59-4.40), p<0.001 in subjects with O-EIMs compared to those without.

Within 3 years of an AU diagnosis, 84 (0.5%) subjects had a recorded diagnosis of IBD. The prediction model performed well with a C-statistic of 0.75 (0.69-0.80).

Conclusions

Subjects with O-EIMs have a two-fold increased risk of a subsequent IBD diagnosis. Healthcare professionals should be alert for potential signs and symptoms of IBD in those presenting with ophthalmic conditions associated with IBD.

Introduction

Inflammatory bowel disease (IBD), comprising Crohn's disease (CD) and ulcerative colitis (UC), is a relapsing, inflammatory, autoimmune condition of unknown aetiology. Thought to be the consequence of dysregulation of the immune system at the interface between the microbiome and the bowel wall, IBD shares many of the disturbed pathways observed in other autoimmune conditions[1,2].

A number of conditions are commonly observed in those suffering with IBD and are therefore known as extraintestinal manifestations (EIMs) of IBD. EIMs can be classified as: *IBD-specific* (e.g. metastatic CD); *drug-related* (e.g. anti-TNF associated skin lesions or steroid-induced cataract development); *associated* - signalling a predisposition to autoimmunity (e.g. ankylosing spondylitis); or *reactive* - implying common pathophysiological pathways without histopathological similarity (e.g. pyoderma gangrenosum) [3,4]. Certain conditions belonging to the reactive and associated EIM subtypes have been accepted as *classical* EIMs and include ophthalmic, dermatological, musculoskeletal and hepatobiliary diseases [5,6].

A link between IBD and ophthalmic conditions has long been recognised. The cell surface immune regulation protein Human Leucocyte Antigen B27 (HLA B27) is more common in IBD and uveitis which also links uveitis with the musculoskeletal EIMs, in particular the axial arthropathies (ankylosing spondylitis and sacroiliitis) [7–10]. The *classical* EIMs in the ophthalmic group include anterior uveitis (AU), episcleritis and scleritis. These complications may occur in up to 13% of IBD patients, with the potential for significant morbidity including blindness [11,12].

Ophthalmic EIMs range from mild and benign to severe, requiring urgent intervention to preserve the eye. Uveitis is a sight-threatening condition and is more commonly bilateral and

anterior in the context of IBD; it may run in parallel or independently of IBD activity [12–14]. Treatment for uveitis depends on the severity and the specific location of inflammation, and commonly includes topical, intraocular and systemic corticosteroids, with second-line immunosuppressants and biologics where needed[12]. Episcleritis is a benign condition that is not sight threatening and presents with eye redness and mild to moderate discomfort. It is caused by inflammation of the episcleral tissue which lies above the sclera and below the conjunctiva. It runs a parallel course when associated with IBD and often does not require specific treatment [12,15]. Scleritis on the other hand is a serious, destructive, inflammatory condition and can be sight threatening. It presents with redness of the sclera, deep 'boring' pain and may cause tissue destruction leading to visual impairment. Treatment is essential and may include systemic anti-inflammatory agents, corticosteroids and immunosuppressants [12]. Unlike episcleritis, it may appear independently of IBD activity and is uncommon compared to episcleritis [16].

Classical EIMs may occur prior to a diagnosis of IBD and may occur in isolation in those who never develop IBD [17,18]. The aim of this study was to examine the risk of and time to a subsequent diagnosis of IBD in those with a new diagnosis of a *classical* ophthalmic EIM.

Materials and Methods

Data Source

Data in the IQVIA Medical Research Data (IMRD-UK) database are obtained from over 800 primary care practices across the United Kingdom (UK). IMRD-UK contains data on 15.8 million subjects and is considered representative of the UK population [19]. Data on included subjects is longitudinally captured including: primary and secondary care diagnostics, drug prescriptions, symptoms and diagnoses, and demographic information. Data are uploaded using a hierarchical system of (Read) codes [20]. To be eligible for the study, IMRD-UK primary care practices required at least one year since the installation of the computerised medical record system and achievement of an acceptable mortality recording (AMR) level [21]. These criteria help to ensure data reliability and reduce the risk of under-recording baseline data.

Study Design

Cohort study

A retrospective matched cohort study was undertaken between 1st January 1995 and 25th September 2019 to investigate the association between IBD outcome and all studied O-EIM exposures (anterior uveitis (AU), scleritis and episcleritis), with secondary studies of anterior uveitis alone and combined episcleritis and scleritis. Those subjects with an incident O-EIM diagnosis of interest (recorded through Read codes – Appendix 1)[22] were compared to subjects without the specific O-EIMs of interest for each analysis, matched by age at cohort entry (±2 years) and sex in a ratio of 1:4. Index date was defined as the start of follow up and was the date of O-EIM diagnosis for the O-EIM group. The same date was assigned to matched subjects without an O-EIM in order to mitigate for immortality time bias [23]. Only subjects without a co-existing IBD diagnosis at index date were included in the study.

Individuals were eligible for inclusion from either the date of eligibility of their primary care practice or one year after they were registered, whichever was later.

Subjects were followed from their index date until the first of the following events (exit date): death; subject left the practice; last data collection from their practice; study end date (25th September 2019); diagnosed with IBD (CD or UC) as identified through Read codes. Subjects coded for both UC and CD were assigned to one condition based on frequency of coding. For those with equal coding, the earliest diagnosis date and the latest diagnosis of IBD subtype was used.

Prediction model

Subjects with an incident diagnosis of AU over the same study period were investigated to identify predictors for a diagnosis of IBD within the following 3-years. Case examples were used to determine the probability of diagnosis of IBD in subjects presenting with anterior uveitis.

Validation

Primary care coding to identify patients with IBD has been previously validated [24,25]. O-EIM codes were reviewed by two clinicians, having been first sourced from other published primary care database studies [26–28]. Ophthalmology expert advice was sought for ophthalmic EIM coding decisions. AU codes, excluding uveitis associated with other pathologies (e.g. infective), were selected for inclusion along with episcleritis and scleritis. Clinical codes used to identify UC, CD and ophthalmic EIMs are listed in Appendix 1.

Statistical Analysis

Cohort study

The time from index date to a later diagnosis of IBD in those with and without a baseline O-EIM were presented as median time to IBD and UC or CD diagnoses with accompanying interquartile ranges (IQR). Log-rank tests were used to compare time to IBD diagnosis between those with and without O-EIMs. Cox proportional hazards models, with time to subsequent diagnosis of IBD as the time-metric, were produced to assess the adjusted hazard ratio (aHR) of IBD diagnoses in participants with an O-EIM compared to matched subjects without O-EIMs. For all O-EIMs and when AU was examined alone, aHRs were produced for all IBD, UC and CD outcomes. However, for the combined episcleritis and scleritis study, due to IBD diagnoses being less commonly observed, only an aHR for all IBD was modelled. Hazard ratios were adjusted for age at index; sex; smoking status; body mass index (BMI); Townsend level of deprivation (quintiles); Charlson comorbidity score; baseline axial arthropathy diagnosis; and within 6-months of O-EIM diagnosis (prior to an IBD diagnosis) coding of anaemia (<11.9g/dL for females and <12.9g/dL for males), abdominal pain, loperamide prescription, diarrhoea or lower gastrointestinal bleeding. Smoking status was dichotomised into current smokers and non-smokers with missing data for smoking status considered non-smokers; a method that has been previously validated [29]. Missing data for Townsend deprivation quintile were considered a separate category. Proportional hazards were assessed using log-log plots. Cumulative incidence plots were produced to illustrate the cumulative risk of IBD over time.

Prediction model

Multivariable logistic regression was used to establish a prediction model for IBD diagnosis in subjects presenting with a new diagnosis of anterior uveitis. Only those with an IBD diagnosis within 3-years or those who had a minimum of 3-years follow up were included in the development cohort. Backwards stepwise elimination was used to examine variables with an elimination alpha-to-remove p-value of 0.20. Sex, age (categorical) and smoking status were included due to their clinical importance. Further candidate variables including baseline axial arthropathy, BMI (categorical) and within 6-months coding of anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription and diarrhoea (prior to an IBD diagnosis) were assessed. A receiver operating characteristic (ROC) curve and C-statistic was used to assess model discrimination; calibration was assessed using the Hosmer-Lemeshow test for goodness of fit. Internal validation of the prediction model was performed through bootstrapping by resampling the dataset (with replacement) 200 times and comparing the resulting average of the area under the ROC curve from the bootstrap samples to the original model.

Analyses were performed using Stata version 16.0 and p-values <0.05 were considered statistically significant [30].

Results

Study Subjects

Following exclusions (Figure 1), 38,805 subjects with an O-EIM were identified (median age 51 (38-65) and 57% female). O-EIM cases included those coded as AU: 22,098 (57%); episcleritis: 13,955 (36%); scleritis: 2,482 (0.6%); episcleritis or scleritis (a non-specific code where it was not possible to determine whether subjects were episcleritis or scleritis): 270 (0.01%). O-EIM subjects were age and sex matched to 153,018 subjects without an O-EIM. The median follow-up period was five years with a total of 244,503 person years (py) of follow-up time in O-EIM subjects and 934,847 py in those without O-EIMs.

In those with an O-EIM, 2.9% (1,116) had another, non-ophthalmic EIM at index date compared to 0.9% (1,433) in subjects without O-EIMs. Subject characteristics are shown in Table 1.

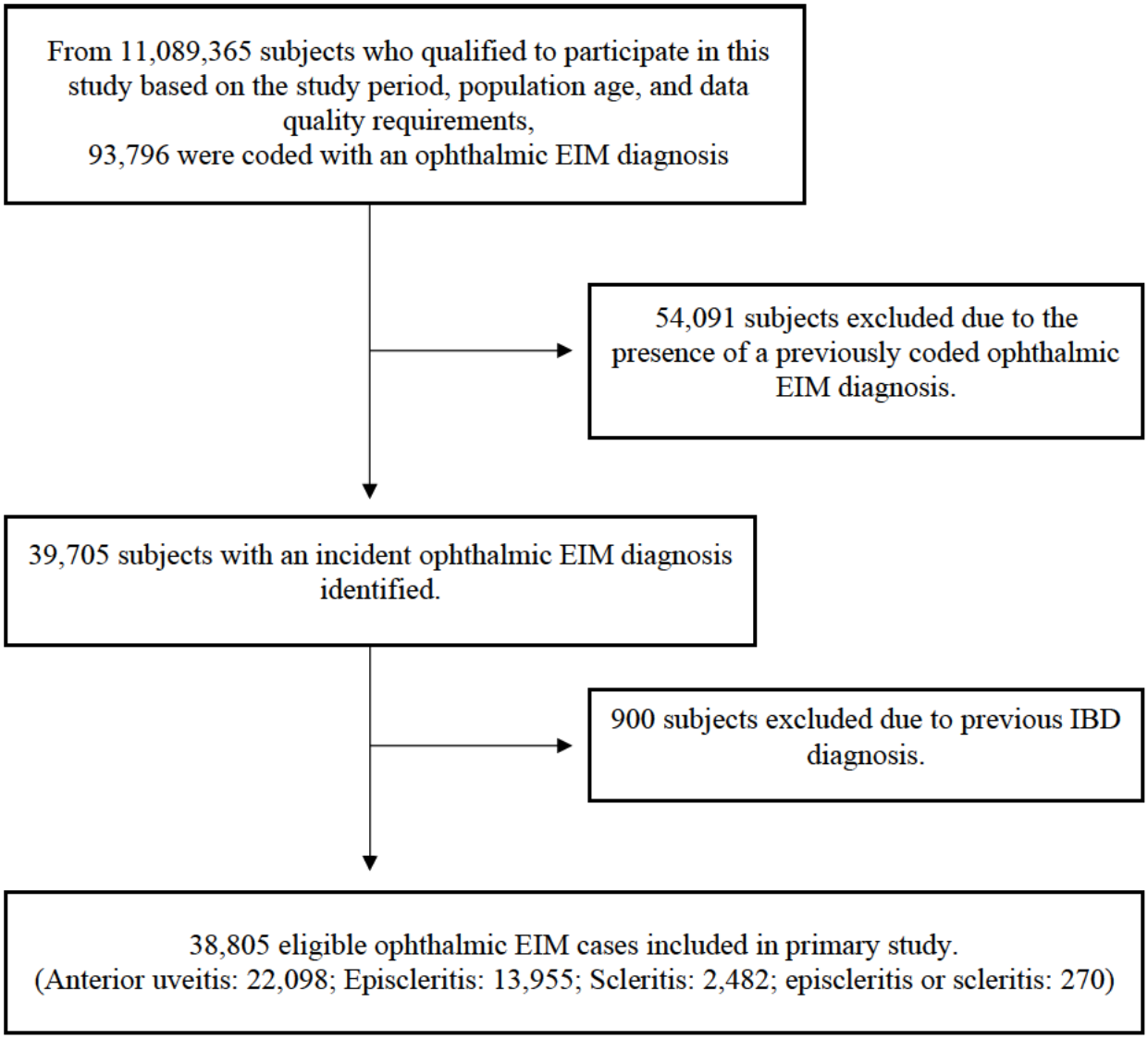


Figure 1. Study flow chart.
Extraintestinal Manifestation (EIM); Inflammatory bowel disease (IBD).

Table 1. Demographics details of study subjects

n (%)	Subjects with ophthalmic EIMs	Matched subjects without ophthalmic EIMs
Number of subjects	38,805	153,018
Median person years of follow-up (IQR)	5.4 (2.3-9.4)	5.2 (2.3-9.2)
Median age (IQR)	51 (38-65)	49 (37-63)
Age category n (%)		
<18 years	2,142 (5.5)	9086 (5.9)
18-30	3,264 (8.4)	13,924 (9.1)
30-40	5620 (14.5)	23,644 (15.5)
40-50	7,589 (19.5)	30,586 (20.0)
50-60	7,221 (18.6)	28,622 (18.7)
60-70	5,989 (15.4)	22,990 (15.0)
>70	6,980 (18.0)	24,166 (15.8)
Female sex n (%)	22,249 (57.3)	87,694 (57.3)
Townsend Quintile n (%)		
1 - least deprived	8,880 (22.9)	34,368 (22.4)
2	7,520 (19.4)	29,210 (19.1)
3	6,989 (18.0)	27,726 (18.1)
4	5,873 (15.1)	23,272 (15.2)
5	3,814 (9.8)	15,312 (10.0)
Missing	5,729 (14.8)	23,130 (15.1)
Charlson comorbidity n (%)		
0	24,457 (63.0)	106,735 (69.8)
1	8,414 (21.7)	28,888 (18.9)
>/=2	5,934 (15.3)	17,395 (11.4)
Smoking status n (%)		
current smoker	6,632 (17.1)	28,586 (18.7)
non-smoker	32,173 (82.9)	124,432 (81.3)
Body mass index n (%)		
<25kg/m^2	12,799 (33.0)	51,136 (33.4)
25-30Kg/m^2	11,200 (28.8)	40,782 (26.6)
>30Kg/m^2	7,683 (19.8)	26,849 (17.6)
Missing	7,123 (18.4)	34,251 (22.4)
Anaemia[†‡]	2,102 (5.4)	5,469 (3.4)
Abdominal pain[†]	837 (2.2)	2,574 (1.7)
Lower gastrointestinal bleeding[†]	363 (0.9)	1,042 (0.7)
Loperamide prescription[†]	558(1.4)	1,506 (1.0)
Diarrhoea[†]	974 (2.5)	2,424 (1.6)
HLA-B27 positive at baseline	35 (0.1)	7 (0.0)
Axial arthropathy at baseline	893 (2.3)	1,013 (0.7)
EIM at baseline (non-ophthalmic)[$]	1,116 (2.9)	1433 (0.9)

† coded within 6 months of Index date

‡ <11.9g/dL (females); <12.9g/dL (males)

$ EIM: Extraintestinal manifestations: axial arthropathies, primary sclerosing cholangitis, erythema nodosum, pyoderma gangrenosum, Sweet's syndrome, aphthous stomatitis

Risk of Inflammatory Bowel Disease Diagnosis in Associated Ophthalmic Conditions

During the study period 213 (0.6%) IBD diagnoses (103 UC and 111 CD) were observed in subjects with O-EIMs compared to 329 (0.2%) (215 UC and 114 CD) in the matched control group. 893 (2.3%) subjects with O-EIMs had an axial arthropathy recorded at baseline and 35 (0.1%) had the HLA-B27 genotype coded, compared to 1,013 (0.7%) controls with an axial arthropathy and 7 (0.005%) with the HLA-B27 genotype. From index date (O-EIM diagnosis date for exposed subjects, with matched controls assigned the same index date as their corresponding exposed subjects), the median time to IBD diagnosis was 882 (IQR 365-2,043) days in subjects with O-EIMs compared to 1,403 (623-2,516) days in those without O-EIMs. For UC, the median time to diagnosis was 922 (410-1,910) days compared to 1,360 (547-2,406) days, while median time to CD diagnosis was 738 (269-2,011) days compared to 1,625 (641-2,779) days, in subjects with and without O-EIMs respectively. For all IBD, UC and CD the log-rank test p-value was <0.001. Following adjustment, the aHR for a diagnosis of IBD in O-EIM subjects compared to those without O-EIMs was 2.25 (95%CI 1.89-2.68), with an aHR of 1.65 (1.30-2.09) for UC and 3.37 (2.59-4.40) for CD, p-values <0.001 (Table 2; full models are shown in Appendix 3). Figure 2 shows the cumulative incidence plot for IBD diagnoses in subjects with O-EIMs compared to those without.

Table 2. Adjusted hazard ratios for risk of inflammatory bowel disease

	aHR	[95% Confidence Interval]		p-value
Any associated ophthalmic condition				
Inflammatory bowel disease	2.25	1.89	2.68	<0.001
Ulcerative colitis	1.65	1.30	2.09	<0.001
Crohn's disease	3.37	2.59	4.40	<0.001
Anterior uveitis				
Inflammatory bowel disease	3.39	2.7	4.25	<0.001
Ulcerative colitis	2.23	1.63	3.04	<0.001
Crohn's disease	5.77	4.04	8.24	<0.001
Episcleritis or scleritis				
Inflammatory bowel disease	1.73	1.31	2.28	<0.001

Adjusted hazard ratio (aHR) – adjustment variables: age at index; sex; Townsend deprivation quintile; Charlson comorbidity score; body mass index; smoking status; anaemia, abdominal pain, lower gastrointestinal bleeding, loperamide prescription, diarrhoea, axial arthropathy.

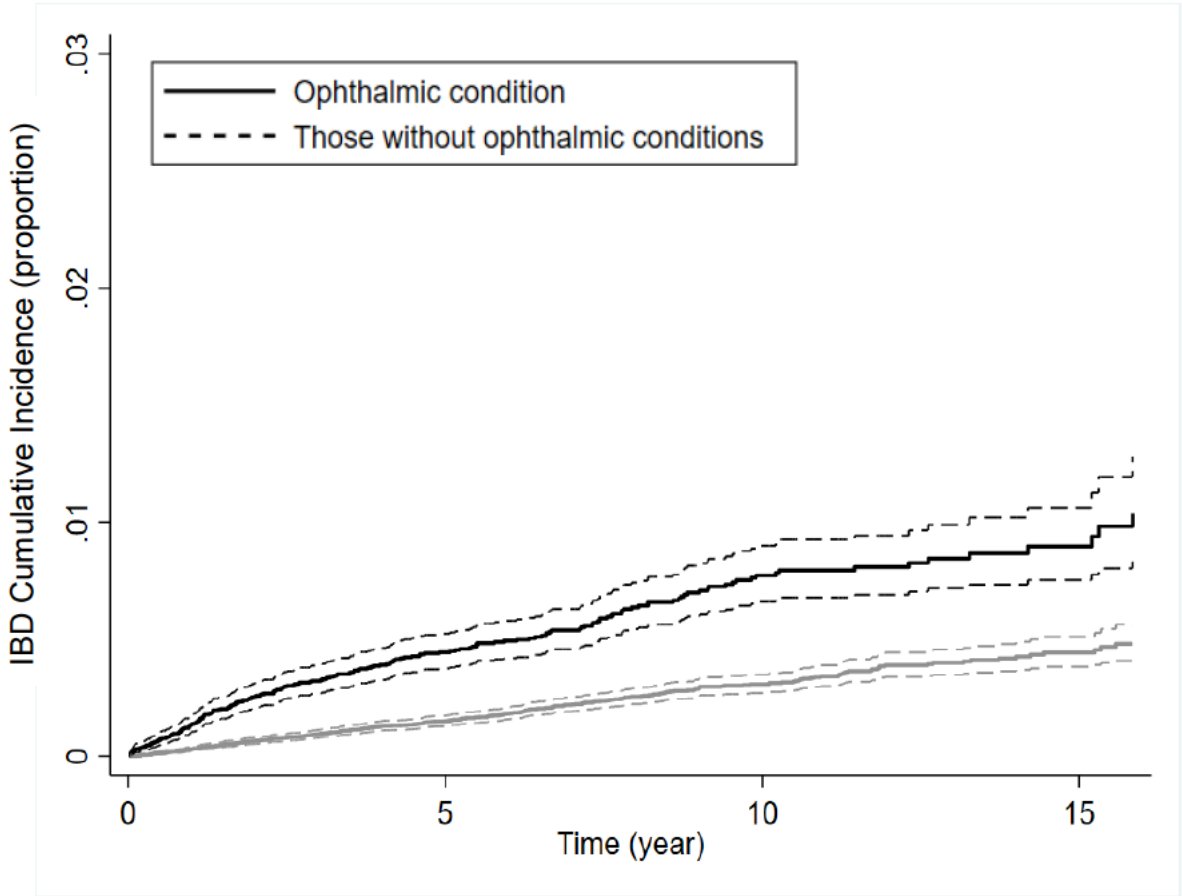


Figure 2. Cumulative incidence of IBD (inflammatory bowel diseases) in subjects with ophthalmic conditions (black line) and those without (grey line) with 95% confidence intervals (dashed lines).

Risk of Inflammatory Bowel Disease Diagnosis in Anterior Uveitis, Episcleritis and Scleritis

Subject characteristics of O-EIM and matched subjects without O-EIMs in these secondary analyses together with the full Cox models are shown in Appendices 2, 4 and 5. Subject numbers for individual O-EIMs differ slightly to those in the combined O-EIM study above because only the first diagnosed incident O-EIM was considered in the combined study, but a subject might be subsequently diagnosed with other O-EIMs and therefore be eligible for inclusion in more than one analysis for the individual O-EIMs presented in this section. In the AU study, 22,547 subjects with a new diagnosis of AU (median age 53 (39-68) years, 54% female) were matched to 89,422 subjects without AU. AU subjects and their matched subjects provided 137,878 and 531,653 py of follow-up, respectively. 152 (0.7%) IBD diagnoses (67 UC and 85 CD) were observed in AU subjects during the study period and 157 (0.2%) IBD diagnoses (107 UC and 50 CD) among subjects without AU. The median time to an IBD diagnosis was 898 (373-2,027) days in the AU subjects compared to 1,457 (539-2,700) in those without AU (log-rank test $p<0.001$). The median time to UC diagnosis was 1,117 (489-2,008) days compared to 1,490 (553-2,553) days and the median time to a CD diagnosis was 687 (286-2,006) days compared to 1,160 (516-2,892) days for AU subjects compared matched subjects without AU, respectively (log-rank tests $p<0.001$ for both CD and UC). The aHR for a subsequent IBD diagnosis in subjects with AU compared to matched subjects without AU was 3.39 (2.70-4.25); for UC aHR was 2.23 (1.63-3.04) and for CD 5.77 (4.04-8.24), all p-values <0.001 (Table 2 (full models are shown in Appendix 4)).

In the analysis of episcleritis and scleritis combined, 17,439 subjects (14,752 (85%) episcleritis and 2,976 scleritis; median age 48 (36-61) and 62% female) were identified and matched to 68,823 controls. Episcleritis and scleritis subjects and matched participants contributed 36,324 and 136,304 py follow-up, respectively. 104 (0.6%) IBD cases (23 UC and

81 CD) were observed among episcleritis and scleritis subjects and 53 (0.1%) (30 UC and 23 CD) among those without these O-EIMs. The median time to an IBD diagnosis in episcleritis and scleritis subjects was 848 (348-2,239) days compared to 1,522 (577-2,838) days in controls, log-rank test $p<0.001$. The aHR for the diagnosis of IBD in those subjects with an incident diagnosis of episcleritis or scleritis compared to matched subjects without these O-EIMs was 1.73 for IBD (1.31-2.28), $p<0.001$ (Table 2 (full models are shown in Appendix 5)).

Prediction Model

22,547 AU subjects were identified with 15,458 eligible for inclusion in the prediction model development cohort based on sufficient follow-up time or an IBD diagnosis within 3 years of the AU diagnosis. 84 (0.53%) subjects had a recorded diagnosis of IBD (63% CD) within 3 years of follow-up. The characteristics of those with and without an IBD diagnosis are shown in Table 3. Those with an IBD diagnosis were younger (median age 44 (IQR 35-56) and 53 (39-68) years respectively, $p<0.001$) but there was no difference in sex, smoking status or body mass index category.

Table 3. Characteristics of anterior uveitis subjects with and without an inflammatory bowel disease diagnosis by 3 years

	IBD diagnosis (n=84)	**No IBD diagnosis (n=15,906)**
Median age (IQR)	44 (35-56)	53 (39-68)
Age category (%)		
<18 years	0 (0)	604 (4)
18-30	17 (20)	1,173 (8)
30-40	18 (21)	2,092 (14)
40-50	18 (21)	2,912 (19)
50-60	14 (17)	2,861 (19)
60-70	12 (14)	2,531 (16)
>70	5 (6)	3,285 (21)
Female sex (%)	45 (54)	8,365 (54)
Smoking status (%)		
current smoker	21 (25)	2,893 (19)
non- smoker	63 (75)	12,565 (81)
Body mass index (%)		
<25kg/m2	37 (44)	4,999 (33)
25-30Kg/m2	23 (27)	4,588 (30)
>30Kg/m2	14 (17)	3,111(20)
missing	10 (12)	2,760 (18)
Anaemia†‡ (%)	12 (14)	828 (5)
Abdominal pain† (%)	4 (5)	351 (2)
Loperamide prescription† (%)	8 (10)	238 (2)
Diarrhoea† (%)	20 (24)	349 (2)
Lower gastrointestinal bleeding† (%)	9 (11)	145 (1)
HLA-B27 positive at baseline (%)	0 (0)	19 (0.1)
Axial arthropathy at baseline (%)	6 (7)	510 (3)

† coded within 6 months of Index date
‡ <11.9g/dL (females); <12.9g/dL (males)
IBD: Inflammatory Bowel Disease

Following backwards stepwise regression, female sex, smoking status, BMI and abdominal pain within 6 months of an AU diagnosis exceeded the alpha-to-remove threshold. However, female sex and smoking status were retained in the model due to their clinical importance. Weight loss within 6 months of an AU diagnosis and HLA-B27 genotype were coded in only 5 and 19 cases respectively and were therefore not included in the analysis. The multivariable logistic regression model to assess the risk of being diagnosed with IBD within a 3-year period following AU diagnosis is presented in Table 4. The Hosmer-Lemeshow chi^2 test for goodness of fit was applied to the prediction model development data set and was not significant at 0.093, suggesting reasonable model fit. The receiver operating characteristic (ROC) curve, shown in Figure 3, produced an area under the curve (AUC) C-statistic of 0.75 (95%CI 0.69-0.80). Following internal validation by bootstrapping, resampling the dataset 200 times, the mean difference between the original AUC and AUC in each bootstrap sample was 0.021. This produced a bias-corrected C-statistic value of 0.71 (0.67-0.77).

A probability calculator was produced to determine the likelihood of an IBD diagnosis within the anterior uveitis cohort using the following examples: 1) a female, 34-year-old, current smoker and a within 6-month history of anaemia would have a 2% risk of IBD being diagnosed within 3 years of an anterior uveitis diagnosis; 2) a male, 18-year-old, non-smoker and a history of axial arthropathy, diarrhoea and loperamide use would have a 25% 3-year IBD diagnosis risk; 3) a female, 49-year-old, current smoker with a history of anaemia, diarrhoea and lower gastrointestinal bleeding would have a 55% risk of an IBD diagnosis within 3 years. A nomogram for the prediction model is shown in Appendix 6.

Table 4. Multivariable logistic regression prediction model of factors associated with developing inflammatory bowel disease within 3 years of an anterior uveitis diagnosis

	β-Coefficient	Odds Ratio	[95% Conf. Interval]		P value
Sex					
Male (reference)		1.00			
Female	0.001	1.00	0.64	1.56	0.995
Age Category					
<18 years (reference)		1.00			
18-30	2.56	12.88	4.57	36.30	<0.001
30-40	2.05	7.75	2.79	21.59	<0.001
40-50	1.69	5.41	1.94	15.05	0.001
50-60	1.40	4.04	1.41	11.52	0.009
60-70	1.30	3.65	1.26	10.54	0.017
>70	0.00	1.00			
Smoking Status					
current smoker (reference)		1.00			
non smoker	-0.17	0.85	0.51	1.42	0.528
Anaemia†					
no (reference)		1.00			
yes	1.13	3.11	1.61	6.00	0.001
Diarrhoea†					
no (reference)		1.00			
yes	2.38	10.76	5.99	19.33	<0.001
Loperamide					
no (reference)		1.00			
yes	0.74	2.10	0.86	5.12	0.102
Lower gastrointestinal bleed					
no (reference)		1.00			
yes	2.27	9.69	4.54	20.70	<0.001
Axial arthropathy*					
no (reference)		1.00			
yes	0.67	1.95	0.83	4.60	0.128
Intercept	-7.08	0.0008	0.0003	0.0024	<0.001

† coded within 6 months of Index date

‡ <11.9g/dL (females); <12.9g/dL (males)

** Coded at baseline*

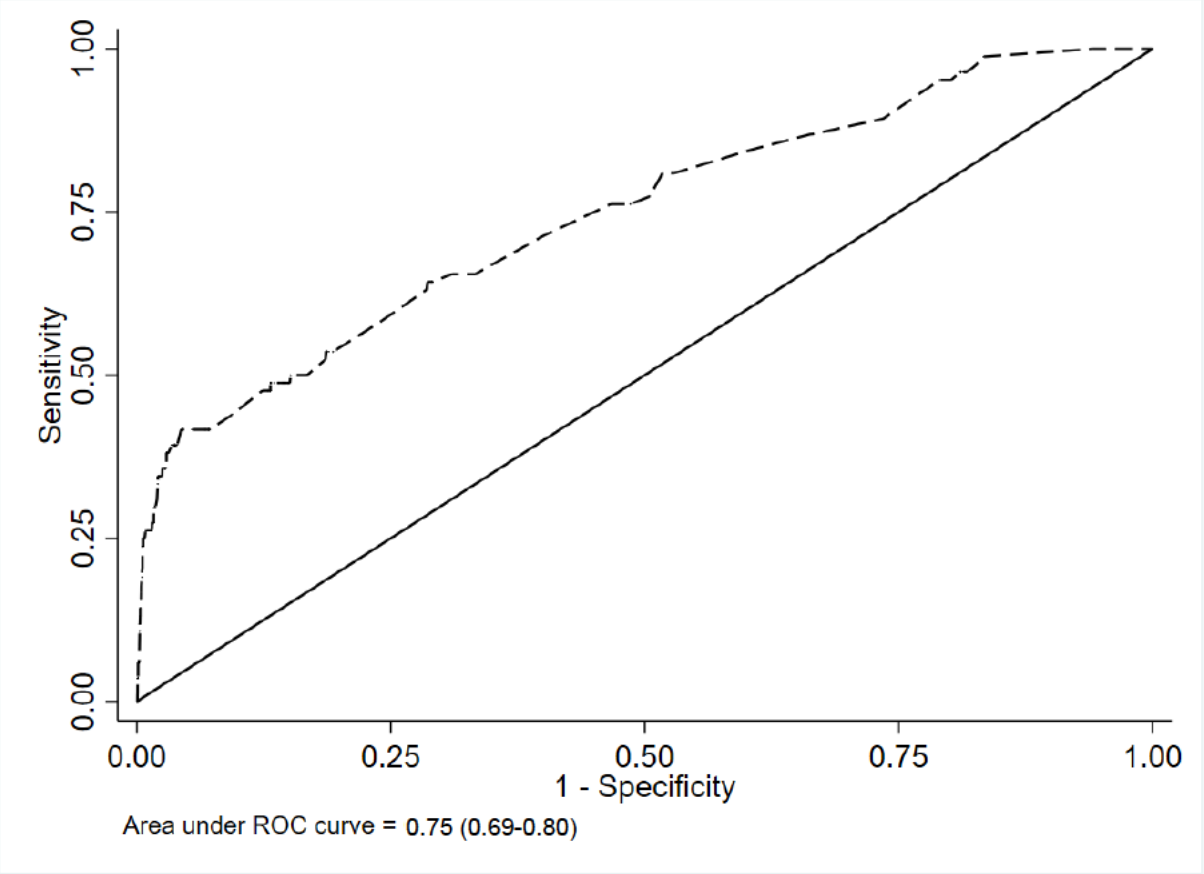


Figure 3. Receiver operating characteristic curve of ability of prediction model to detect an inflammatory bowel disease diagnosis within three years of an anterior uveitis diagnosis.

Discussion

In this study, we have shown that subjects with an O-EIM, but without a recorded diagnosis of IBD, are at a two-fold greater risk (by an average of 5 years follow-up) of subsequently being diagnosed with IBD than matched subjects without an O-EIM. The risk was highest in those who later had a CD diagnosis. A wide time scale was observed between an O-EIM diagnosis and a subsequent IBD diagnosis with a median time to IBD diagnosis of greater than two years. When AU was examined alone, subjects had a 3-fold greater risk of a later IBD diagnosis compared to matched subjects without AU and again the risk was highest for a subsequent CD diagnosis at almost 6-fold.

Ophthalmic conditions are among the most common extraintestinal manifestations of IBD and are commonly diagnosed at the time or following a diagnosis of IBD [18]. This study, however, has established that subjects with a diagnosis of an O-EIM associated with IBD, either in combination or as separate entities (anterior uveitis or episcleritis and scleritis), were at increased risk of developing a subsequent diagnosis of IBD over time (combined O-EIM aHR 2.25 (1.89-2.68), $p<0.001$). The time to a diagnosis of IBD was shorter in those with ophthalmic conditions compared to matched controls (median time 2.4 years versus 3.8 years, respectively). However, the time from O-EIM diagnosis to IBD was often greater than two years. This was a significant time lag which may reflect a lack of symptoms to indicate IBD. Relatively few subjects were coded with anaemia, abdominal pain, lower gastrointestinal bleeding, weight loss, diarrhoea or loperamide prescriptions around the time of the diagnosis of the ophthalmic condition. However, given that many EIMs parallel the course of IBD, it is possible that IBD may be present earlier and pauci-symptomatic and as such they may represent a missed opportunity and a delayed diagnosis.

The aetiology of ophthalmic EIMs is not well understood. They are thought to be more common in those with CD rather than UC [12], and our findings support this. A limitation of the IMRD-UK database is that it does not allow for the discrimination of IBD severity, activity or gastrointestinal location. This is pertinent because those with colonic or ileocolonic disease have been shown to have an increased risk of ophthalmic EIMs [16,31,32]. Several studies have suggested that certain peptide targets for the immune system are found in both joints, eyes and the colon [33,34]. It may be that immune dysregulation in relation to the enteric flora and subsequent cross-reactive antigens play a role in some EIM presentations. Moreover, the HLA-B27 antigen appears to play an important role in some mouse models where colitis and arthritis only developed in those where gut flora was present [34]. HLA-B27 positivity was not commonly coded in the IMRD-UK database and is highly likely to be under-recorded given its specialist nature. However, previous reports that this genotype is observed in greater numbers in those with EIMs and its association with arthropathies and ophthalmic conditions makes this an important consideration in such a study [7,16,35]. Arthropathies and the HLA-B27 haplotype were seen in larger numbers at baseline in ophthalmic conditions associated with IBD than in controls in the present study. Previously, it has been found that HLA-B27 is present in 90% of those with ankylosing spondylitis, but just under half of those with CD and sacroiliitis are positive for this allele [8]. IBD is known to have a genetic link with increased risk seen in the offspring of those with IBD, and this is also the case with uveitis in those with IBD. The HLA region of Chromosome 6 contains both major histocompatibility complex genes (HLAs) as well as other important IBD related genes (TNF-α). The vicinity of these genes increases the likelihood of inheriting several important genetic variations (a phenomenon known as linkage disequilibrium) and may help to explain familial traits and the relationship between some EIMs and the IBDs [32]. Other HLA types (HLA-B58) have also

been associated with IBD and uveitis, however it is unclear how the interplay between genetic and environmental factors apply, given that most of those who are HLA-B27 positive will not suffer any ill effect from this genotypic variant and HLA-B27 does not itself appear to increase the risk of IBD [32]. A limitation of this study is the lack of family history data and as a result an assessment of the risk in those with a family history of EIMs or IBD could not be made.

Vavricka *et al*. have reported that multiple EIMs were not uncommon in IBD subjects, with CD and UC subjects studied having more than one EIM in 16% and 8% of cases respectively [36]. Axial arthropathies in the present study were included at baseline given evidence that ophthalmic and joint manifestations may be seen more frequently together in IBD [9]. More than 2% of cases had a pre-existing axial arthropathy compared to less than one percent of matched controls. Other investigators have examined IBD and arthritis in UK primary care databases, however, type 1 and 2 EIM arthropathies are challenging to identify given a lack of specific coding, and, seropositive and negative inflammatory arthritides, although associated, are not classical EIMs and as such were not examined in this study [26]. The presence of an axial arthropathy increased the risk of IBD more than two-fold and was found to be associated with later IBD in anterior uveitis. Although not specifically examined in this study, an increased number of other EIMs in those who develop a new diagnosis of an ophthalmic condition associated with IBD compared to controls has been demonstrated previously. This has been shown to be particularly true among those with arthritic as well as ophthalmic conditions [37].

Prediction Model

The prediction model for IBD diagnosis in subjects with anterior uveitis found associations with several variables. Anaemia, diarrhoea, and lower gastrointestinal bleeding heralded an IBD diagnosis, highlighting the need for careful history taking in ophthalmic care settings and investigation for IBD if such symptoms are revealed. Other inflammatory and autoimmune conditions associated with uveitis can lead to anaemia, including sarcoidosis. Some of these conditions will produce an anaemia of chronic disease, and others a haemolytic anaemia [38,39]. In the context of ophthalmic conditions associated with IBD, iron deficiency anaemia should be investigated to prevent an IBD diagnostic delay. Age was strongly associated with IBD in our model. Those in the age group 18-30 had the highest risk compared to under 18 year-olds, however all ages up to 70 had an increased IBD risk compared to the reference group (under 18 years). Ottaviano et al. reviewed the published literature on ophthalmic EIMs in children and found that there was little data available. They suggested that this may be related to asymptomatic uveitis, as well as a lower prevalence of these EIMs in childhood compared to adults [40]. In the present study, less than 6% of the cohort were aged under 18 and only 0.2% of subjects in this age category developed IBD during the study period, with a slight preponderance towards CD, as has been previously shown in paediatric series [40].

The use of primary care databases has both strengths in terms of subject numbers and subject level data, but also limitations. Perhaps most relevant to the present study are the risk of under-recording and validation. The accuracy of coding in IMRD-UK is related to the primary care practitioner's ability to record diagnoses accurately. Several EIMs (especially episcleritis, which is self-limiting and typically causes only mild discomfort) and IBD symptoms, especially early on in the disease process, may not lead to healthcare-seeking behaviour in primary care and may therefore not be coded in the database in a timely fashion.

Although IBD in primary care has previously been validated [24] and in the present study at least 50% of those with an IBD diagnosis had more than one IBD code recorded, to our knowledge a validation study of the ophthalmic conditions used in the present study has not been previously undertaken. Given the lack of external validation, an often-prohibitive task in terms of cost and time, there is a risk of bias. Episcleritis is the most common ophthalmic condition associated with IBD [18], however, given its benign course it may potentially be under-recorded in the IMRD-UK database. For uveitis and scleritis, however, these diagnoses would be made in a secondary care eye service. For this reason, they may be more reliably recorded when the information reaches primary care. There may also be delays in the recording of data making time-to-event analysis challenging to interpret. IBD is more commonly associated with anterior uveitis and this was therefore the focus of this study, however, IBD can rarely be associated with intermediate, posterior or panuveitis, and so our estimates could be considered to be conservative. Offsetting this were limitations in the way uveitis was coded with a few "unspecified" uveitis Read codes risking the inclusion of some non-anterior phenotypes, although AU is the most common type of uveitis.

Ophthalmic conditions associated with IBD which present prior to an IBD diagnosis are not common. However, an increasing prevalence of IBD both in the UK and around the world has been demonstrated [41–43]. Given the increasing numbers of patients with IBD, the need for clinicians from many disciplines outside gastroenterology to be aware of IBD is important. Those who care for patients presenting with ophthalmic conditions associated with IBD should be attentive to features which may increase the likelihood of an IBD diagnosis, in

order that appropriate investigation and referral can be made in those patients with suggestive clinical features.

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CHAPTER 7: DISCUSSION

A study-specific discussion is contained within each of the chapters presented above. Here I will summarise important findings from the work undertaken, how they fit within the existing literature, how study limitations shape the findings, and future directions and implications for this body of work.

7.1 Summary of findings

7.1.1 Changing patterns in the epidemiology and outcomes of inflammatory bowel disease in the United Kingdom: 2000-2018

In chapter three, I explored the epidemiology of IBD within the UK using primary care data from IQVIA Medical Research Data UK (IMRD-UK - formerly THIN), which may be considered a representative sample of the population. The motivation for this work was the lack of national or up-to-date data available on incidence and prevalence (91, 125). The incidence of IBD (both UC and CD) appears stable or is declining in certain age groups in the UK while prevalence is increasing and appears set to increase further in the future. This data is comparable to findings in other developed nations around the world (59, 61) as well as recently published UK data (92, 126). Despite differing methodological approaches and a robust capture-recapture data linkage study conducted in Lothian, Scotland (92), my study's findings are similar in terms of an increasing prevalence and the largely stable incidence estimates for both UC and CD. The increased data in this area is to be welcomed given the paucity of data previously available on UK IBD epidemiology. A group also using the IMRD-UK database, published shortly after my work, also found similar incidence trends over time with regard to a reduction in incidence in older ages, furthermore they found a largely static

incidence over their study period for younger adults; findings consistent with my own (80, 82, 126).

I further examined the all-cause mortality and colorectal cancer risk in a UC and CD cohort compared to an age- and sex-matched group. Colorectal cancer (CRC) rates in IBD have fallen dramatically over recent decades, and this likely to be due to a combination of better management, novel treatments but also the benefit of data from population-based analyses as opposed to from individual tertiary specialist centres (79, 80, 82). UC subjects had a CRC incidence rate of 135/100,000 pys compared to 94.9 in matched controls and only 64.6/100,000 pys when the entire adult IMRD-UK population rate was examined. In CD the rate was 75.5/100,000 pys compared to 65.3 in matched controls. A CRC aHR of 1.40 (95% CI 1.23-1.59) for UC and 1.19 (0.97-1.46) for CD were produced taking age, sex and smoking status (among other features) into account. When incident only cases of UC and CD were examined the difference in CRC risk was no longer significant for UC (likely related to the shorter follow-up time available in incident cohorts in IMRD-UK). aHR for both UC and CD were both significant and higher when over 70-year-olds were excluded from the analysis. I have shown that the risk has remained stable over the study period, that the absolute risk is low but the aHR for both UC and CD (when under 70s are examined independently) is increased.

CRC associated with IBD is a different entity to that of sporadic CRC, with an *inflammatory-dysplastic-carcinoma* pathway as opposed to the *adenoma-sequence* described in sporadic CRC (127). IBD-CRC develops at a younger age than sporadic CRC and is often associated with a field change of dysplasia in other parts of the bowel; IBD-CRC is associated with increased CRC mortality compared to sporadic type (127-129). Those deemed at high risk of IBD related CRC are surveyed through colonoscopy programmes. Colonoscopy in this group

can be challenging given pseudo-polyps and potential disease activity masking underlying dysplasia and post colonoscopy colorectal cancer (CRC diagnosed within three years of a colonoscopy that did not diagnose CRC) in this group is higher than in the general population (86, 130, 131). Moreover, compliance with surveillance both in terms of guideline adherence from physicians and attendance from patients has an impact with many cancers found outside of surveillance pathways (many earlier in disease duration than would warrant screening) and secondary to symptoms (127). That being said, a systematic review has demonstrated that surveillance finds earlier stage CRC and a lower mortality is observed compared to those not surveyed (132). Despite some contradictory findings with regard to CRC risk in different IBD populations (82), there appears to remain an increased risk in some populations, which my research would support (129, 133).

There remain contradictory findings with regard to mortality in IBD populations (see Table 4 in chapter 3 manuscript). My study found a consistently increased standardised mortality ratio (SMR) in CD, while in UC this was comparable to the background population. In the cohort studies, where IBD subjects were matched by age and sex to upto four controls, aHRs for both CD and UC were significantly increased at 1.42 and 1.31, respectively. Over time CD mortality has fallen slightly while UC mortality has remained stable. I examined all-cause mortality

(cause-specific mortality is not available in IMDR-UK) in all UC and CD adults, while others have sought to identify the cause of death in this group. CRC will account for a proportion of this with some authors suggesting 10-15% of annual mortality is related to CRC (134). Other non-gastrointestinal causes of death (such as respiratory causes) have been highlighted in the literature (63, 67). An important field of research is the association IBD has with many other diseases, which themselves may increase the risk of death and contribute to the all-cause mortality risk in this population.

The incidence and prevalence of IBD in the UK was previously out of date or based on small samples or regional data. This work adds to the literature and will be an important contribution to the organisation of health care provision in IBD in the years ahead.

7.1.2 Outcomes for Hospital Episode Statistics studies

The outcomes of emergency admissions with ulcerative colitis between 2007 and 2017 in England

In chapter four, I explored the outcomes for subjects presenting to English hospitals with a first acute admission for UC. There were few deaths (51 (0.5%)) recorded over the 10-year study period examined (2007-17), which included a total of 10,051 subjects. Mortality rates did not change over the study period and the SMR for all deaths was 0.89 (95% CI 0.74-1.05). This mortality ratio, comparable to the background population, has been shown in population-based studies previously, although not consistently (see chapter 3). However, in another HES based study by Shawihdi *et al.* which involved 44,000 subjects, including all age groups (our validation findings not withstanding) and all emergency admissions for UC (not just first admissions), mortality was investigated for temporal trends and falling rates of death were observed over time (135).

With regard to colectomy risk, I found that both acute admissions for UC and inpatient and 12-month colectomy rates fell over the study period. This is in contrast to the increasing prevalence of UC in the UK population as demonstrated both in the UK data presented in chapter three and demonstrated by others (59, 61, 92). Anti-TNF (infliximab) use on acute first UC admissions increased from 2.4% to 12.9% over the study period which correlates with the fall in colectomy rates seen, although causality in this study cannot be proven.

709 (7%) subjects underwent inpatient colectomy and a further 571 (5.7%) underwent colectomy in the following 12-month period. Anti-TNF use was associated with a 70% and 2-fold increased risk of colectomy during admission and at 12-months, respectively. This illustrates the severity of the disease and need for rescue therapy. However, the fall in

colectomy in concert with increasing use of biologics (as demonstrated by the increased use of infused anti-TNF medication captured in the HES database) suggests an increased familiarity with these medications as well as other changes in practice, which have led to a decline in the severity of acute flares, admissions and need for surgery, including increased access to IBD nurse specialists (136). Indeed, in a further analysis undertaken, looking at emergency readmission risk at 30-days, anti-TNF therapy was associated with reduced risk, signalling at least a delay in colectomy and in some remission and a long term preservation of the colon.

In multivariable analysis, while adjusting for a variety of co-variates, female sex and Asian ethnicity were found to be associated with a reduced risk of colectomy both during an emergency first admission and at 12-months when compared to male and white subjects, respectively. Although others have found that male sex puts a subject at increased risk of colectomy in UC, demonstrated through meta-analysis (137, 138), the reasons for this remain unclear and the association has not been universally shown (139). The finding that ethnicity also appears to play a role in colectomy risk is intriguing. As described in chapter 4's discussion, ethnic differences in IBD risk have been shown previously and, biologically, may be related to differing genetic predisposition or the gut microbiome and the complex interaction between these factors (140). However, ethnic differences in colectomy risk are not consistent in the literature, with some studies suggesting increased risk of surgery in south Asian groups with a more severe IBD phenotype compared to white populations, while others show the inverse and within south Asian group differences. These findings may be the result of patient factors including concordance with treatment, genetic and gut flora differences as previously described but also study design, sample size and coding challenges including preferential coding among white populations, which inevitably limit conclusions (141, 142).

Moreover, numbers in a prospective inception cohort over a one-year period in the UK were relatively small with few colectomies and prospective clarification of my findings is not yet possible (143).

The finding that colectomy risk was associated with increased comorbidity is perhaps surprising given its association with poorer outcomes, however the younger age of the cohort may mean that the normal associations of age, frailty and comorbidity are less clear in this context. Certainly, mortality risk is increased in both those with comorbid disease and increased age, which correlate with one another (68, 144). However, early colectomy, certainly in the emergency setting, may be preferred over delay in those with comorbid disease given evidence of better outcomes and the desire to avoid immunosuppression and polypharmacy in certain groups (3, 71). An example to consider would be a 47-year-old with renal disease, diabetes and an acute UC presentation who may well proceed to surgery more rapidly than a 70-year-old, frail patient with the same comorbidities where the risk of major surgery may be deemed higher than the risk from severe UC.

Provider annual volume of UC colectomies of three or more was associated with an increased risk of colectomy during first admission and at 12 months although this variable was not associated with mortality or with readmission rates. A multivariable logistic regression analysis that modelled risk of colectomy during first admission and at 12-months, however, showed no associated increased risk for provider volume of acute UC care provision (appendix 4 of paper supplementary files). Low provider volume of colectomy for UC has previously been shown to be associated with poorer outcomes, and in specialist IBD restorative surgery this has also been demonstrated, with guidelines advocating a practice of high-volume experience for pouch surgery (146). However, it remains challenging from these

findings in an exceptional cohort (first acute admission) to appreciate what might be the factors involved in a surgical volume effect for particular centres from HES.

A further interesting finding, although one that requires some careful consideration, is the reduced risk of colectomy for prevalent cases compared to incident cases at index acute admission for UC, while at 12 months the risk doubles compared to incident cases. It is probable that incident UC presenting as an emergency is a more severe phenotype leading to an increased risk of colectomy. Prevalent cases, on the other hand, are already established on medical therapy but which has not maintained or achieved remission and may lead to a step up in therapy as an initial management strategy. Cumulative rates of colectomy increase over time with most colectomies taking place within 2 years of a diagnosis. Furthermore, a small but important proportion of distal UC will extend proximally over time and necessitate colectomy (147, 148). However, it is important to note that HES does not provide a diagnosis date and therefore the definitions applied to incident and prevalent cases are not without limitations.

HES studies of Crohn's disease resections

In chapter 5, I examined the risk of further surgery in subjects with CD. Surgery in CD is common with meta-analyses showing not only a high risk of an initial operation, but that subsequent surgery is also expected in a sizeable minority of patients (76, 149). This chapter included two studies:

The risk of subsequent surgery following bowel resection for Crohn's disease in a national cohort of 19,870 patients.

In the first study, 19,870 patients with CD, identified in HES with an index coding of small or large bowel resection, were examined between 2007 and 2016. The risk of further resections was explored in the subsequent 5 years for those with sufficient follow-up time using a multivariable logistic regression analysis. 16% of patients (3,248) had a further surgery recorded of which 20% (655) were recorded in the first year following an index procedure that was not considered a staged, elective procedure or one that took place within 30 days of the index procedure (in order to avoid counting operations performed for surgical complications as opposed to CD recurrence). Overall, 14% (1,895/13,877) of patients at 5 years and 23% (859/3,802) at 10 years had undergone further resections. Of those with 10 years follow-up, 5.7% (215/3,802) had two or more further resections.

A 5-year increased risk of further resections, examined using multivariable logistic regression analysis, was associated with previous perianal surgery (implying severe perianal disease), an EIM at baseline and where the index operation was undertaken at a hospital provider of high-volume CD surgery. In contrast, those factors identified as associated with reduced further 5-year surgery were the oldest age group (when compared to the youngest), index surgery performed laparoscopically and when index surgery was elective. A particularly interesting finding here was that of an EIM-associated risk. As described in the chapter discussion, the limitations of HES means that coding of EIMs may be incomplete and this association may be considered a marker of IBD activity, given that most of these conditions are active when the patient's IBD is also active.

The risk of later surgery at the anastomotic site following right hemicolectomy for Crohn's disease in a national cohort of 12,230 patients.

In the second study, 12,230 patients with CD, coded with right hemicolectomy between 2007 and 2016 were examined. In HES the OPCS-4 code for right hemicolectomy encompasses ileocaecectomy (the most common resection undertaken for patients with CD). Recurrent disease at the site of the anastomosis is reported to be common in such patients (22, 28). The finding, in those with sufficient follow-up time, that 9% had undergone further surgery at the anastomotic site by 5 years and 17% by 10 years was therefore not surprising. Given the acknowledged recurrence of CD post-surgery, the importance of investigation and assessment and step-up therapy if required is now established in national and international guidelines. An interesting finding in this research has been the disparity between providers of CD right-hemicolectomies in terms of 6–12-month surveillance colonoscopy, even when significant efforts to mitigate omissions in this surveillance were undertaken. Overall, 78% had not had a colonoscopy as recommended by guidelines but when mitigation such as further surgery, illness or death were accounted for, there remained 41% without a surveillance colonoscopy within recommended timeframes (and although 4% of the cohort between 3-18-months following index surgery had some form of bowel imaging (capsule endoscopy, MRE, CT or barium), 60% also had colonoscopy and therefore did not account for the majority of those not undergoing surveillance). This is an area of service evaluation that is likely to be a focus of future research and quality improvement given colonoscopy acceptance from patients varies and faecal biomarkers are not as of yet validated for disease monitoring (150).

Incorporating some English data on CD prevalence derived from ONS and chapter three data allowed an estimate of the national rates of index bowel resection surgery using the CD

population in England as the denominator. This was undertaken for both studies and demonstrated a real terms fall in index surgery (both for the ileocaecectomy and right hemicolectomy study as well as all small and large bowel index surgery). This is consistent with a Canadian study by Ma *et al*. who demonstrated a fall in intestinal resections for CD over time, while accounting for CD prevalence. They further identified an increase in elective surgery, however, this was out-weighed by a more significant effect seen in the fall in emergency surgery (74). My findings, however, show a fall in both elective and emergency surgery, akin to HES research conducted by Ahmad *et al.* in showing a fall in all major CD abdominal operations over time. In their study the denominator was CD hospital admissions (72).

7.1.3 Outcomes for IMRD-UK studies

Chapter 6 includes two manuscripts detailing the risk of a subsequent diagnosis of IBD in subjects presenting with either dermatological or ophthalmic conditions associated with IBD. This research used the IMRD-UK primary care database and focused on an area of IBD that is seldom investigated: the risk of IBD in those with other associated conditions. Specifically, I looked at the risk of being diagnosed with IBD, the time lag to such a diagnosis from the point of an EIM diagnosis, and I explored a prediction model for the diagnosis of IBD in the most common conditions among the dermatological and ophthalmic EIMs: erythema nodosum and anterior uveitis, respectively.

The risk of later diagnosis of inflammatory bowel disease in patients with dermatological disorders associated with inflammatory bowel disease.

EIMs are common in IBD, however, most are diagnosed at the time of an IBD diagnosis or subsequently, with an increased risk of developing EIMs during the IBD disease course. Erythema nodosum (EN) is the most common EIM and runs a parallel course to IBD, and therefore developing EN and later being diagnosed with IBD is uncommon. It is seldom that the literature addresses the risk of those developing IBD following a diagnosis of an EIM, however. In the study of dermatological EIMs (D-EIMs), I demonstrated that the risk of an IBD diagnosis is increased compared to a matched population of subjects without such EIMs and that the time to an IBD diagnosis being recorded is also more rapid when compared to controls. EIMs often, though not always, run a parallel course to IBD and as such it is noteworthy that a significant number of subjects later diagnosed with IBD had some symptoms and signs recorded prior to the IBD diagnosis that would be of concern for underlying IBD. In primary care studies delays in uploading a secondary care diagnosis such as IBD would not be surprising, however it was not universal and many of the EIMs would also be subject to such delays. Although many diagnoses of IBD were made relatively shortly after an EIM diagnosis there was a majority not diagnosed until sometime after.

The prediction model produced for EN performed well with an area under the curve (AUC) or c-statistic of 0.82 (95% CI 0.78-0.86). This model has not been externally validated, but the implications, given the factors that increase the IBD risk including smoking, age, BMI, anaemia, abdominal pain and diarrhoea, are that clinicians seeing patients with EN should be mindful of these associations and the more than 6-fold increased risk of IBD diagnosis in this group, so that delayed IBD diagnoses are minimised.

The risk of a subsequent diagnosis of inflammatory bowel disease in subjects with ophthalmic disorders associated with inflammatory bowel disease.

Similarly, the ophthalmic study explored the risk of a later diagnosis of IBD in those presenting with eye conditions associated with IBD. This risk was two-fold greater than in matched controls without ophthalmic EIMs (O-EIMs). As with D-EIMs, many of the O-EIMs run a parallel course and the most common O-EIM is uveitis. In IBD, anterior uveitis is the most common subtype and was the focus of this study's prediction model development. It is important to acknowledge the association that axial arthropathies have with uveitis and for this reason the baseline diagnosis of such musculoskeletal EIMs were included in the prediction model and were found to increase the risk of a subsequent IBD diagnosis in this setting. The diagnostic ability of the anterior uveitis prediction model was not as great as that seen in the D-EIM study at 0.71 (95% CI 0.67-0.77), although it was moderately good, but again, the takeaway message given the associated variables is that clinicians must keep as yet undiagnosed IBD in mind in such patients.

7.2 Limitations

Routinely gathered data used in research is powerful for two reasons, firstly the size of samples may be large enough to be either represent a complete population, as is the case for HES data which includes all NHS secondary care contacts in England, or large enough and with sufficient geographical spread that it may be considered a large representative sample as would be the case for IMRD-UK data. Secondly, the routinely gathered nature of the data means that it is a real-world view of practice and may include a variety of demographics and subsidiary data depending on the data source, e.g. BMI, smoking status and deprivation level. However, caution with such observational data is required to properly appreciate any study

findings while also accepting that the data has limitations. Limitations have already been detailed in the manuscripts found in chapters 3-6, however here I will give a brief overview.

7.2.1 IMRD-UK (THIN) limitations

IMRD-UK data is recorded by GP practices using the electronic medical records software *Vision*. Read codes are used for this purpose and are hierarchical in nature. This allows for the development of code lists which can be combined as a single diagnosis or outcome with the aim to incorporate all relevant codes such that disease or outcome is not missed, biasing any results. Occasionally a rigorous validation process has been undertaken to inform the positive predictive value of such code identifiers, however, this is not commonly done. Validation studies are undertaken through surveys of GP practices in order to pair up a coded diagnosis with a patient's disease (151, 152). This is not only time consuming and costly but is itself at risk of bias. In terms of a primary care database relying, on occasion, on secondary care information, there are distinctive consequences because of the mechanism and timing of a practice receiving information and then uploading it. This process may further confound study design, because, although unlikely to be systematic in nature, the timing of a diagnosis or procedure may not be that of the diagnosis itself but rather the date at which the practice recorded the diagnosis. This becomes a particular issue for studies of prevalence and requires that practices reliably backdate a diagnosis. Previous studies using primary care, however, suggest that this is relatively well performed, but it is important to acknowledge this potential limitation (118, 153).

Misclassification of data, the attribution of a disease to a subject who does not have the disease (or vice versa due to poor recording), is a further bias encountered with routinely collected data. Validation studies, relying on the comparison of codes in the database to contributing GP

practice responses to questionnaires to produce positive predictive values for codes or code algorithms are valuable in quantifying the risk of misclassification. It may be possible to extrapolate from a validation study to other diseases, but many assumptions are made in doing so, and validation studies are not easy to conduct nor are they always appropriately reported (118, 119). An alternative method is to do an internal validation procedure whereby subjects are only considered to be exposed if they have multiple diagnostic codes over time or are taking a drug that is commonly used in such a disease (119, 154). These methods, however, present their own problems with potential for specificity at the expense of sensitivity. In one study of UC clinical course, for example, at 5 years 41% of 420 subjects were not taking medication, a group who may be lost in an algorithmic approach to study inclusion (148). A consequence of this is that milder, indolent disease is missed from studies, which is the strength of real-world data and often a criticism targeted at studies conducted from tertiary referral centres.

No database study can, however, provide data on a diagnosis where the diagnosis was never recorded and this is worth bearing in mind: Disease either diagnosed by a medical professional or the patient themselves but never recorded, for whatever reason, will not appear in IMRD-UK. This is obvious when stated and may be more of a problem for particular diseases or conditions than others, as well as for more mild disease not requiring treatment or impacting on quality of life, but it is an important consideration in observational research using this type of data. Again, this is unlikely to be a systematic error in databases but rather a concern in terms of capturing the full prevalence of a condition in a population.

A limitation with both HES and IMRD-UK data is the lack of data regarding disease severity and disease location, such that even linked primary and secondary care data in this field is limited. Medications may be recorded, however, the challenge here is that not all GPs will be

involved in prescribing for such patients either due to a lack of shared care agreements in terms of thiopurines (azathioprine and mercaptopurine) or in terms of biologic medications most of which are also not captured in HES data as they are self-administered at home by patients.

Another significant limitation with routinely gathered primary care data is the problem of missingness. In the studies detailed in this thesis, missing data has been presented as a category for the relevant variable and in the EIM studies, multiple imputation was applied initially to the missing BMI data for the dermatological EIM prediction model, however, its impact was minimal and therefore imputation was not used. The problem with missingness is whether data is missing at random (MAR) or missing not at random (MNAR), the former limiting the power of data and the latter being a cause for bias (155). A solution to this is to do complete case analysis, however, the same issues develop as detailed above regarding inclusion criteria algorithms, in that those with missing data are different to those with complete data and so the study is no longer representative. Due to varied and often substantial amounts of missingness seen in primary care records (often seen in the same areas e.g. BMI and deprivation status), missing data was presented as separate categories and included in this way in regression analyses. One particular area of importance, ethnicity, was not, however, included in IMRD-UK studies presented in this thesis due to the significant lack of data in this area. Ethnicity data is an area where primary care recording is significantly lacking. In chapter 3, out of 8.5million subjects included for the study of the epidemiology of IBD in the UK, 56% had no recorded ethnicity data. This varied significantly by region, with missing ethnicity data in Wales reaching more than 71% while in Scotland it was 48%. There have been improvements over time and when it is possible to link HES and primary care data,

ethnicity data can be seen in 97% of individuals, while comparing between the databases reaches 85% accuracy for individuals (156).

Despite such limitations, the efforts to ensure that subject data is recorded as robustly as possible in IMRD-UK (e.g. ensuring practices have met criteria for accurate death recording (a hard endpoint) and that subjects are in a practice for sufficient time to ensure that baseline characteristics are recorded) makes this data resource a useful tool for observational research and hypothesis generation.

7.2.2 HES limitations

HES data is recorded by medical coders often with the support of clinicians. Anecdotally some NHS hospitals using digital platforms for both prescribing and case note recording include facilities to record data which is directly used for coding data sent to HES. Certain coding is presumed to be highly accurate (e.g. procedures) and this is in part due to the financial reimbursement to secondary care which HES data is used for. Although HES covers secondary care in England and undergoes quality control processes, it does not capture those who seek treatment not within the services commissioned in England (e.g. private care not funded by the NHS) or those with a coding error that misses important demographic data (123). Where data on age or sex is missing these participants are excluded from the studies in this thesis and this methodology is delineated in HES data-containing chapters. Comparative statistics for those excluded have been presented, however, to demonstrate the potential limitations of not including patients with such omissions. Ethnicity data is coded much more commonly in HES when compared to primary care databases and both have seen ongoing improvements over time. However, outpatient HES recording has been inferior in terms of completeness compared to inpatient recording (156). For all recordings and in particular

diagnosis recording, there has been improvement seen since 2002 when payment by results was introduced (101).

Validation of HES diagnoses and procedures were possible in the studies presented here through service evaluation in local hospital settings or they have been previously undertaken (157). Nevertheless, as with IMRD-UK, HES is at risk of misclassification of procedures and diagnoses and missing data. Diagnostic coding in HES uses ICD-10 and as such does not have the sensitivity seen in the hierarchical Read coding. A significant amount of any diagnostic coding often falls under the NOS (not otherwise specified) indicator, so although, for example, CD may be coded in ICD-10 as colitis or small bowel disease, which would at least partially inform disease location if not extent, CD NOS is often the code recorded. Of course some detail on disease location is possible through surgical coding although even this has limitations, e.g. OPCS-4 code *H07* which codes right hemicolectomy and additional codes include further detail, e.g. *H07.4* details a right hemicolectomy and ileostomy, however ileocaecectomy is included within these codes and is not unique, making specific procedures challenging. Moreover, some procedures known to be undertaken in CD patients, such as strictuloplasty were hardly, if ever, recorded in HES and endoscopic balloon dilatation for CD strictures could not be identified, while recent UK-wide survey data suggests this practice is undertaken, albeit infrequently (158).

As mentioned above, pharmacological data is limited in the IBD cohort in both IMRD-UK and HES databases. Although primary care records prescriptions issued in primary care, only high-cost coded drugs can be identified in HES and therefore only the infused anti-TNF medication, infliximab, could be included. This, however, represents a minority of subjects when compared to self-administered subcutaneous alternatives (e.g. adalimumab). Infliximab

use as a rescue therapy in acute severe UC, however, made this aspect of the research possible given that it is the main medical rescue therapy currently in use. Unfortunately, the alternative, ciclosporin, is not captured in HES coding and represents a missing cohort who may have ciclosporin due to contraindications to infliximab. It has, as of yet, not been possible to say that newer, biological medications have reduced the risk of further surgery outside of short follow-up randomised control trials (RCTs) (159, 160). The TOPPIC trial demonstrated that thiopurines reduce the risk of recurrence in smokers (161) and the POCER trial showed that a step up in treatment for early recognition of recurrence was of benefit (78). These trials have been mentioned to highlight the challenge currently in doing national observational studies in IBD. HES data does not include location or severity of disease, but it also is limited by a lack of smoking data (for CD this perhaps the most important predictor of disease outcomes), biomarker data (e.g. bloods and faecal calprotectin) and pharmacological data.

Despite these significant limitations, interesting observational research on the current status of IBD in England and the UK can be derived and inform future research priorities.

7.3 Key findings, future directions, and conclusions

7.3.1 Key findings

Several key findings from the research presented in this thesis will inform future research priorities: IBD incidence is largely stable in the UK, however, its prevalence is increasing and should be a health service priority, not least due to its impact on working age populations and the increased risk for both CRC and all-cause mortality seen when compared to matched populations.

Operations for both first acute UC admissions and CD are falling over time and coincide with a significant increase in the use of biologic medications. Mortality in first severe UC admissions is low and comparable to the background population (SMR: 0.89 (95% CI 0.74–1.05). The major cause for death over the study period was UC-related (37%). Females and Asian subjects, compared to men and white subjects, respectively, were associated with a reduced risk of colectomy following a first acute admission with UC, both as inpatients and by 12-months.

Despite an increased prevalence of CD in females, no increased risk was seen compared to males for further surgery risk, either at the site of a right hemicolectomy or following any type of bowel resection. This was also the case for ethnicity where no difference was observed between ethnic groups. The variation in colonoscopy post-right hemicolectomy for CD in England, even when multiple mitigations are considered, was striking. Although not a key focus of the CD right hemicolectomy study, an interesting finding was that alternative imaging modalities do not seem to be being used as an alternative to colonoscopy.

The association of perianal disease and EIMs on the increased risk of further surgery was circa 50% in the CD studies. EIMs are common in IBD and often appear in concert with an IBD diagnosis or following. However, this research has shown that even when identified in isolation in patients without diagnosed IBD, the risk of IBD diagnosis remains significant, with the time to such a diagnosis being more rapid than in matched subjects, and for this reason clinicians should be alert to these diagnoses and their symptoms in order to prevent diagnostic delays.

7.3.2 Future directions

Returning to clinical medicine early due to the COVID-19 pandemic whilst continuing the research of this thesis has given me a unique perspective of the feasibility of studies using routinely gathered data and the impact of health inequality and has been instrumental in directing these future research considerations.

The COVID-19 pandemic caused by the novel coronavirus – SARS-CoV-2 - has highlighted health inequalities both globally and at home. One of the many factors that needs addressing is the lack of ethnicity data and the possibility of inaccurate information in routinely gathered healthcare data. This should therefore be a research priority, not least in the field of IBD. Future work, linking routinely gathered data in primary and secondary care would ensure that the most accurate and complete data on ethnicity would be available and lead to greater knowledge of the health impact on different groups of patients. In this way differences in outcomes could be more clearly defined and explored. In the process of addressing the reliability of the coding, the impact of ethnicity on IBD and healthcare access should be examined. Particular areas that warrant exploration are the attitude of different ethnic groups

to treatment both in terms of medication concordance and acceptability of surgery. The differences in accessing healthcare in different groups is also important, for example, whether patients use emergency or elective care differently, and how service engagement differs between groups. It was noteworthy that failed attendances without prior cancellation observed in the study presented in the chapter 5, CD right hemicolectomy study, was high. What, if any, impact ethnicity might play in attendance failures, especially given the shift towards virtual clinics and the ensuing issues that resolve around communication, interpreters, and loss of non-verbal cues, warrants investigation. By understanding these health disparities, policy could be informed to improve outcomes in vulnerable and hard to reach groups.

The predictive capabilities of routinely gathered data have been explored and presented in chapter 6 of this thesis, however, the potential to predict outcomes in IBD using such data is of particular interest to me and I am currently involved in the development of such a project. Primary care data captures a range of information including blood tests and additional health data (e.g. fitness notes, medications, and patient weights). This data may be lacking for an individual, however, using different statistical approaches that account for the sparsity of the data, features may be identified which have predictive power. Groups within IBD cohorts could be identified which are at higher risk of certain outcomes (including e.g. cancers, surgery, mental health diagnoses), based on the trajectory of routinely gathered biomarkers, combinations, or their associated features.

To be able to predict a patient's course based on certain biomarkers prior to clinical features developing would be a powerful tool for both primary and secondary care clinicians both in terms of poor outcomes in those with established IBD but also in terms of developing IBD. Along with the now established use of faecal calprotectin in primary care, a prediction tool

would be helpful for decision making in those with equivocal results or where doubt still remained. Delays in IBD diagnoses, especially CD are costly both financially for health care and in quality-of-life terms as previously discussed (162-164). Analysis of the cost implications for delayed diagnoses in both primary and secondary care when such a diagnosis is delayed or missed would be important to identify where resources could be better utilised. Early diagnosis could lead to improvement in the patient experience with disease modifying medications having greater impact at an early diagnostic stage. Such early, improved care could lead to reduced cost implications for patients and healthcare services.

The exploration of IBD prediction modelling in secondary care that could support decision making in terms of colectomy for UC after acute admission when rapid escalation in therapy is required would be a further important area to research. Such prediction modelling would also be of benefit in CD decision making when a patient's trajectory maybe towards surgery, indeed with an arsenal of novel therapies, a prediction model that could direct towards a preferred therapy to induce and maintain remission would be a vital target for future research.

Finally, a consideration of important severe consequences of IBD in terms of CRC risk and subsequent mortality is necessary. IBD is a well-accepted risk factor for CRC and patients are younger and the disease is missed more commonly than in sporadic CRC. The current surveillance guidance is based on expert opinion rather than high quality evidence and although the need for a surveillance programme is indisputable the time intervals may not be optimal. National Institute for Health and Care Excellence (NICE) research recommendations in this field are for randomised controlled trials for comparing different approaches with 5+ years of follow up (165). Ethical and cost constraints mean this is unlikely, however, NICE used some extrapolation for their Markov modelling based on data from the early 2000s and a

reassessment of this computer-based modelling approach with updated data may be helpful in determining the optimum strategy to prevent harm in those with IBD.

7.3.3 Conclusions

The aims of this thesis were to explore the epidemiology of IBD using routinely gathered primary and secondary care data, with objectives to examine (1) the burden of IBD in the UK, (2) the consequences of a diagnosis of IBD in terms of first acute UC admissions and further surgery in CD, and (3) the risk of an IBD diagnosis in those presenting with an EIM.

The key findings from this work are detailed above, and recommendations based on these are the need to (1) monitor disease prevalence regularly to inform policy around healthcare provision especially in light of an aging population, (2) support coders in their work to ensure robust coding of health care data to enable good quality generalisable research outcomes (this was most noticeable in the lack of accurate data for older adults with acute severe UC admissions leading to their omission), and (3) alert clinicians who see those with EIMs where IBD is not a current diagnosis, of the possibility that they may go on to be diagnosed with IBD to ensure delays in diagnosis are not prolonged.

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APPENDIX

Appendices for chapter 3

Appendix 1

Read Codes:

Ulcerative Colitis:

Code	Description
J410z00	Ulcerative proctocolitis NOS
N031000	Arthropathy in ulcerative colitis
J41z.00	Idiopathic proctocolitis NOS
14C4.11	H/O: ulcerative colitis
J41y.00	Other idiopathic proctocolitis
J412.00	Ulcerative (chronic) ileocolitis
J413.00	Ulcerative pancolitis
Jyu4100	[X]Other ulcerative colitis
N045400	Juvenile arthritis in ulcerative colitis
J410000	Ulcerative ileocolitis
J411.00	Ulcerative (chronic) enterocolitis
J41..00	Idiopathic proctocolitis
J410.00	Ulcerative proctocolitis
J410300	Ulcerative proctitis
J410400	Exacerbation of ulcerative colitis
J41..12	Ulcerative colitis and/or proctitis
J410100	Ulcerative colitis
J410200	Ulcerative rectosigmoiditis
J41yz00	Other idiopathic proctocolitis NOS

Crohn's Disease:

Code	Description
J400.00	Regional enteritis of the small bowel
J400000	Regional enteritis of the duodenum
J400100	Regional enteritis of the jejunum
J40..00	Regional enteritis - Crohn's disease
N031100	Arthropathy in Crohn's disease
ZR3S.11	CDAI - Crohn's disease activity index
J402.00	Regional ileocolitis
J401z11	Crohn's colitis
J400200	Crohn's disease of the terminal ileum
J400300	Crohn's disease of the ileum unspecified
J400400	Crohn's disease of the ileum NOS
J400500	Exacerbation of Crohn's disease of small intestine
J08z900	Orofacial Crohn's disease
J400z00	Crohn's disease of the small bowel NOS
J40z.00	Regional enteritis NOS
J401000	Regional enteritis of the colon
J401100	Regional enteritis of the rectum
J401200	Exacerbation of Crohn's disease of large intestine
J40..12	Granulomatous enteritis
J40..11	Crohn's disease
ZR3S.00	Crohn's disease activity index
J401.00	Regional enteritis of the large bowel
J401z00	Crohn's disease of the large bowel NOS
Jyu4000	[X]Other Crohn's disease
N045300	Juvenile arthritis in Crohn's disease
J40z.11	Crohn's disease NOS

Colorectal Cancer:

Code	Description
B134.00	Malignant neoplasm of caecum
B13y.00	Malignant neoplasm of other specified sites of colon
B13z.11	Colonic cancer
B14..00	Malignant neoplasm of rectum, rectosigmoid junction and anus
B141.11	Carcinoma of rectum
B140.00	Malignant neoplasm of rectosigmoid junction
B141.12	Rectal carcinoma
B14z.00	Malignant neoplasm rectum,rectosigmoid junction and anus NOS
68W2400	Bowel scope (flexible sigmoidoscopy) screen: cancer detected
B137.00	Malignant neoplasm of splenic flexure of colon
B135.00	Malignant neoplasm of appendix
B131.00	Malignant neoplasm of transverse colon
B133.00	Malignant neoplasm of sigmoid colon
B134.11	Carcinoma of caecum
B13z.00	Malignant neoplasm of colon NOS
B141.00	Malignant neoplasm of rectum
B14y.00	Malig neop other site rectum, rectosigmoid junction and anus
B13..00	Malignant neoplasm of colon
B138.00	Malignant neoplasm, overlapping lesion of colon
B136.00	Malignant neoplasm of ascending colon
B132.00	Malignant neoplasm of descending colon
B130.00	Malignant neoplasm of hepatic flexure of colon

Total Colectomy (For ulcerative colitis internal validation)

Code	Description
7710100	Panproctocolectomy anast ileum to anus & pouch creation HFQ
7710111	Parks panproctocolectomy, ileoanal anastom & creation pouch
7711200	Total colectomy and ileostomy NEC
7710200	Panproctocolectomy and anastomosis of ileum to anus NEC
7710.12	Total proctocolectomy
7711000	Total colectomy and anastomosis of ileum to rectum
7717z11	Colectomy NEC
7710000	Panproctocolectomy and ileostomy
7711100	Total colectomy, ileostomy & creation of rectal fistula HFQ
7710300	Proctocolectomy NEC
7717300	Colectomy and ileostomy NEC
7717200	Colectomy and anastomosis NEC
7717400	Colectomy and exteriorisation of bowel NEC
7711.11	Total colectomy
7710.11	Panproctocolectomy
7717.11	Other colectomy

Surgical codes (For Crohn's disease internal validation)

Code	Description
7644300	Resection of ileo-colic anastomosis
7644200	Resection of ileostomy
7713011	Ileocaecal resection
7717600	Ileocolic resection
7721600	Perineal resection of rectum HFQ
7726600	Stapled transanal resection of rectum
14U2.00	H/O: ileostomy
7645	Creation of ileostomy
7645000	Creation of continent ileostomy
7645100	Creation of temporary ileostomy
7645200	Creation of defunctioning ileostomy
7645212	Creation of split ileostomy
7645y00	Other specified creation of ileostomy
7645z00	Creation of ileostomy NOS
7646000	Refashioning of ileostomy
7646100	Repair of prolapse of ileostomy
7646200	Closure of ileostomy
7646211	Reversal of ileostomy
7646300	Dilation of ileostomy
7646500	Resiting of ileostomy
7646y00	Other specified attention to ileostomy
7646z00	Attention to ileostomy NOS
7710000	Panproctocolectomy and ileostomy
7711100	Total colectomy, ileostomy & creation of rectal fistula HFQ
7711200	Total colectomy and ileostomy NEC
7712300	Extended right hemicolectomy and ileostomy HFQ
7713300	Right hemicolectomy and ileostomy however further qualified
7714300	Transverse colectomy and ileostomy HFQ

7715300	Left hemicolectomy and ileostomy however further qualified
7716300	Sigmoid colectomy and ileostomy however further qualified
7717300	Colectomy and ileostomy NEC
8D66.00	Ileostomy bag fitting
8D67.00	Ileostomy bag adjustment
8D68.00	Ileostomy bag changed
J576111	Ileostomy malfunction
J576300	Ileostomy prolapse
Z174G00	Care of ileostomy
ZV44200	[V]Has ileostomy
ZV53500	[V]Fitting or adjustment ileostomy/other intestinal device
ZV55200	[V]Attention to ileostomy
ZV55900	[V]Fitting+adjustment/ileostomy + oth intestinal appliances
7646400	Reduction of prolapse of ileostomy
7646	Attention to ileostomy
14U3.00	H/O: colostomy
7633212	Jejunocolostomy
771B.11	Colostomy
771B000	Loop colostomy
771B100	End colostomy
771B200	Refashioning of colostomy
771B300	Closure of colostomy
771B400	Dilation of colostomy
771Bz11	Colostomy NEC
771W.00	Resiting of colostomy
7720111	Hartmann rectosigmoidectomy and colostomy
7721000	Abdominoperineal excision of rectum and end colostomy
7721015	Abdominoperineal resection of rectum and end colostomy
8D61.00	Colostomy aid training
TB03000	Formation of colostomy with complication, without blame
ZV44300	[V]Has colostomy

ZV55300	[V]Attention to colostomy
771B500	Reduction of prolapse of colostomy
7630200	Total jejunectomy and anastomosis of duodenum to colon
7630.11	Jejunectomy
7630	Excision of jejunum
763..00	Jejunum operations
7632	Jejunostomy
7630z00	Excision of jejunum NOS
7630300	Partial jejunectomy and anastomosis of jejunum to ileum
7630y00	Other specified excision of jejunum
7632000	Creation of jejunostomy
7632100	Refashioning of jejunostomy
7632200	Closure of jejunostomy
7632z00	Jejunostomy NOS
7712100	Extended right hemicolectomy and anastomosis ileum to colon
7633100	Bypass of jejunum by anastomosis of jejunum to ileum
764..00	Ileum operations
7640	Excision of ileum
7640200	Ileectomy and anastomosis of ileum to ileum
7640300	Ileectomy and anastomosis of ileum to colon
7640y00	Other specified excision of ileum
7640z00	Excision of ileum NOS
7642	Bypass of ileum
7642000	Bypass of ileum by anastomosis of jejunum to ileum
7642100	Bypass of ileum by anastomosis of ileum to ileum
7642200	Bypass of ileum by anastomosis of ileum to caecum
7642300	Bypass of ileum by anastomosis of ileum to transverse colon
7642400	Bypass of ileum by anastomosis of ileum to colon NEC
7642y00	Other specified bypass of ileum
7642z00	Bypass of ileum NOS
7643	Other connection of ileum

7643.11	Other anastomosis of ileum
7643000	Anastomosis of ileum to caecum
7643100	Anastomosis of ileum to transverse colon
7643200	Anastomosis of ileum to colon NEC
7643300	Anastomosis of ileum to rectum
7643400	Anastomosis of ileum to anus and creation of pouch HFQ
7643y00	Other specified other connection of ileum
7643z00	Other connection of ileum NOS
7644	Attention to connection of ileum
7644.11	Attention to anastomosis of ileum
7644000	Revision of anastomosis of ileum
7644100	Closure of anastomosis of ileum
7644y00	Other specified attention to connection of ileum
7644z00	Attention to connection of ileum NOS
7647	Intraabdominal manipulation of ileum
7647000	Open reduction of intussusception of ileum
7647z00	Intraabdominal manipulation of ileum NOS
7648	Other open operations on ileum
7648100	Strictureplasty of ileum
7648400	Exclusion of segment of ileum
7648y00	Other specified other open operation on ileum
7648z00	Other open operation on ileum NOS
7649	Therapeutic endoscopic operations on ileum
7649100	Endoscopic dilation of ileum
7649200	Endoscopic insertion of tubal prosthesis into ileum
764B.00	Other operations on ileum
764By00	Other specified other operation on ileum
764Bz00	Other operation on ileum NOS
764y.00	Other specified operations on ileum
764z.00	Ileum operations NOS
7710200	Panproctocolectomy and anastomosis of ileum to anus NEC

7711000	Total colectomy and anastomosis of ileum to rectum
7713000	Right hemicolectomy+end to end anastomosis of ileum to colon
7713100	Right hemicolectomy+side to side anast ileum to transv colon
7714100	Transverse colectomy and anastomosis of ileum to colon
7716000	Sigmoid colectomy+end to end anastomosis of ileum to rectum
7717100	Colectomy and side to side anastomosis of ileum to colon NEC
7719000	Bypass of colon by anastomosis of ileum to colon
7N30500	[SO]Ileum
7647100	Open relief of strangulation of ileum
7647200	Open relief of obstruction of ileum NEC
7712000	Extended right hemicolectomy and end to end anastomosis
7712.11	Extended right hemicolectomy
7712	Extended excision of right hemicolon
7712200	Extended right hemicolectomy and anastomosis NEC
7712400	Extended right hemicolectomy and end to side anastomosis
7712y00	Other specified extended excision of right hemicolon
7712z00	Extended excision of right hemicolon NOS
7713	Other excision of right hemicolon
7713.11	Other right hemicolectomy
7713200	Right hemicolectomy and anastomosis NEC
7713400	Laparoscopically assisted right hemicolectomy
7713500	Right hemicolectomy and end to side anastomosis
7713y00	Other specified other excision of right hemicolon
7713z00	Other excision of right hemicolon NOS
7715	Excision of left hemicolon
7715.11	Left hemicolectomy
7715000	Left hemicolectomy+end to end anastomosis of colon to rectum
7715100	Left hemicolectomy+end to end anastomosis of colon to colon
7715200	Left hemicolectomy and anastomosis NEC
7715400	Left hemicolectomy and exteriorisation of bowel NEC
7715500	Left hemicolectomy and end to side anastomosis

7715y00	Other specified excision of left hemicolon
7715z00	Excision of left hemicolon NOS
7717z12	Hemicolectomy NEC
7714400	Transverse colectomy and exteriorisation of bowel NEC
7710.11	Panproctocolectomy
7710.12	Total proctocolectomy
7710300	Proctocolectomy NEC
7711.11	Total colectomy
7714.11	Transverse colectomy
7714000	Transverse colectomy and end to end anastomosis
7714200	Transverse colectomy and anastomosis NEC
7716.11	Sigmoid colectomy
7716100	Sigmoid colectomy and anastomosis of colon to rectum
7716200	Sigmoid colectomy and anastomosis NEC
7716400	Sigmoid colectomy and exteriorisation of bowel NEC
7716500	Sigmoid colectomy and end to side anastomosis
7717.11	Other colectomy
7717000	Colectomy and end to end anastomosis of colon to colon NEC
7717200	Colectomy and anastomosis NEC
7717400	Colectomy and exteriorisation of bowel NEC
7717411	Mikulicz colectomy and colostomy
7717412	Paul colectomy and colostomy
7717500	Partial colectomy NEC
7717700	Colectomy and end to side anastomosis
7717z11	Colectomy NEC
771..11	Colon and caecum operations
773..12	Perianal region operations
7731.11	Excision of perianal lesion
7738500	Laying open perianal abscess
7738	Other operations on perianal region
773A100	Drainage of perianal abscess

773z.00	Anus and perianal region operations NOS
773..00	Anus, perianal region and other bowel operations
7739300	Excision of anal fissure
7738200	Laying open of anal fistula NEC
7738100	Laying open of high anal fistula
7738000	Laying open of low anal fistula
7738300	Insertion seton in high anal fistula+part lay open track HFQ
7738A00	Removal of anal seton
7738B00	Insertion of anal seton

Appendix 2

Ulcerative colitis and Crohn's disease internal validation: proportion of subjects with inflammatory bowel disease drug prescriptions (mesalazines and thiopruines) or surgery

Drug or surgery co-coded	<18	18-30	30-40	40-50	50-60	60-70	70-80	>80	total
ulcerative colitis, n	108/113	323/355	424/458	431/478	380/421	321/359	218/269	87/115	2,292/2,578
%	95.6	91.0	92.6	90.2	88.2	89.4	81.0	75.7	89.0
Crohn's disease, n	162/180	355/407	308/337	296/345	232/267	191/225	112/133	39/49	1,695/1,943
%	90.0	87.2	91.4	85.8	86.9	84.9	84.2	79.6	87.2

Appendix 3:
Holt-Winters' Exponential Smoothing method

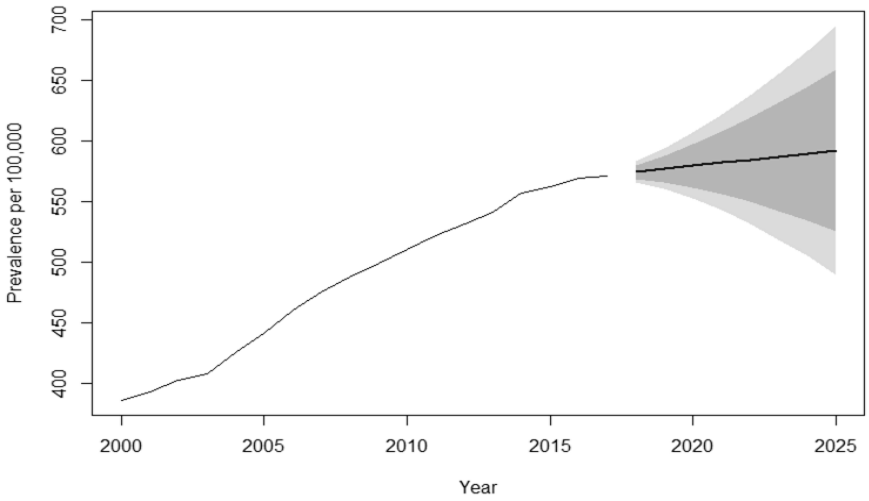


Figure 3.1 Measured and forecast prevalence of ulcerative colitis from 2000 to 2025 with 80 & 95% prediction intervals

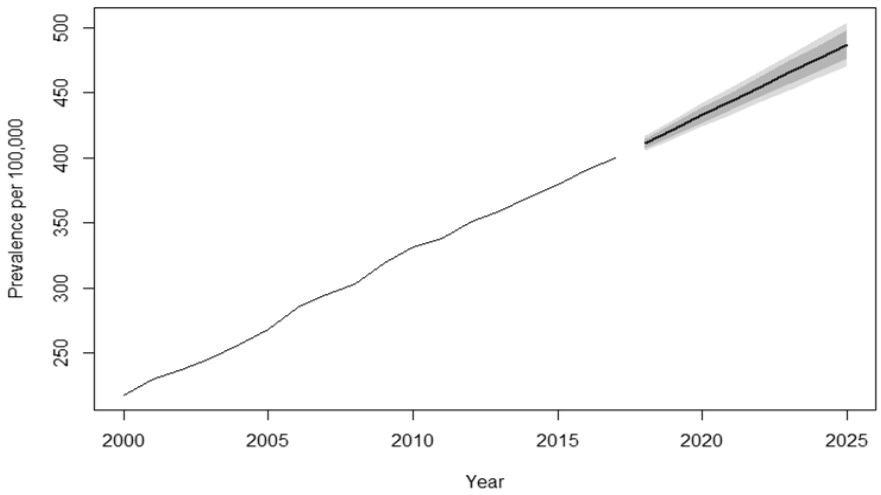


Figure 3.2 Measured and forecast prevalence of Crohn's disease from 2000 to 2025 with 80 & 95% prediction intervals

Appendix 4

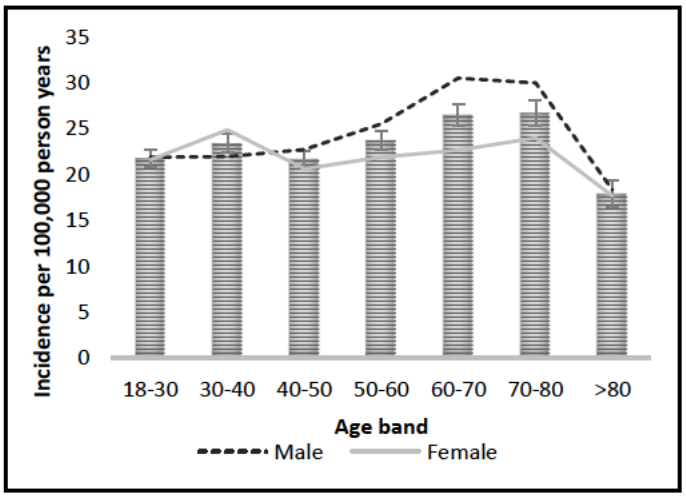


Figure 4.A Incidence of ulcerative colitis by age

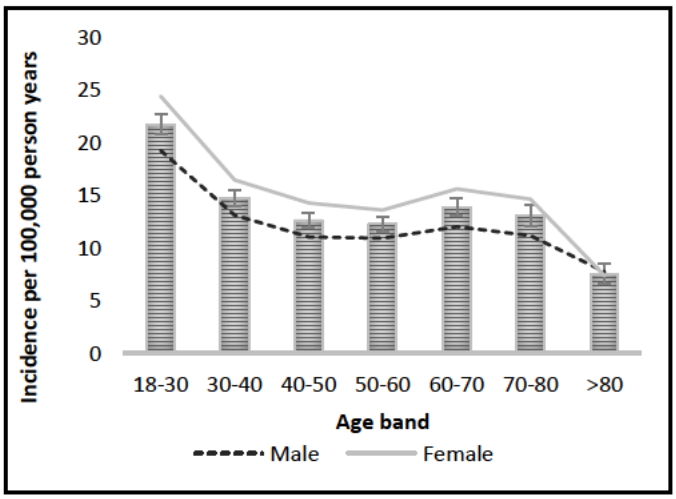


Figure 4.B Incidence of Crohn's disease by age

Appendix 5

Colorectal cancer study: Cohort Demographics for incident and prevalent

cases	Ulcerative colitis prevalent		Ulcerative colitis incident		Crohn's disease prevalent		Crohn's disease incident	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
N	25,474	67.40	12,319	32.60	18,045	68.98	8,115	31.02
Follow-up years, Median (IQR)	5.8 (2.4-10.7)		4.5 (2.0-8.3)		5.4 (2.0-9.8)		4.3 (1.8-7.9)	
Male	6,319	51.29	12,541	49.23	3,592	44.26	7,942	44.01
Female	6,000	48.71	12,933	50.77	4,523	55.74	10,103	55.99
Age, Median (IQR)	51 (38-65)		49 (36-64)		43 (31-57)		44 (30-60)	
Age, n (%)								
18-30	2,905	11.4	1,818	14.76	3,853	21.35	1,964	24.20
30-40	4,359	17.11	2,160	17.53	4,086	22.64	1,446	17.82
40-50	4,553	17.87	2,240	18.18	3,366	18.65	1,411	17.39
50-60	4,762	18.69	2,134	17.32	2,721	15.08	1,201	14.80
60-70	4,131	16.22	1,957	15.89	1,982	10.98	1,105	13.62
70-80	2,936	11.53	1,392	11.3	1,281	7.10	718	8.85
>80	1,828	7.18	618	5.02	756	4.19	270	3.33
Deprivation Score								
1 (least deprived)	5,823	22.86	2,849	23.13	3,694	20.47	1,673	20.62
2	5,145	20.2	2,468	20.03	3,405	18.87	1,510	18.61
3	4,712	18.5	2,365	19.2	3,390	18.79	1,525	18.79
4	3,753	14.73	1,839	14.93	2,868	15.89	1,312	16.17
5 (most deprived)	2,188	8.59	1,165	9.46	1,966	10.89	1,004	12.37
Missing	3,853	15.13	1,633	13.26	2,722	15.08	1,091	13.44
Charlson comorbidity score								
0	16,669	65.44	7,800	63.32	12,273	68.01	5,071	62.49
1	5,298	20.8	2,836	23.02	3,990	22.11	2,095	25.82
2	1,959	7.69	930	7.55	1,065	5.90	503	6.20
3	860	3.38	422	3.43	432	2.39	261	3.22
4+	688	2.7	331	2.69	285	1.58	185	2.28
Smoking status								
Smoker	3,125	12.27	1,535	12.46	4,555	25.24	2,240	27.6
Non-smoker	14,391	56.49	6,101	49.53	8,393	46.51	3,685	45.41
Ex-smoker	5,785	22.71	4,179	33.92	3,512	19.46	1,905	23.48
Missing	2,173	8.53	504	4.09	1,585	8.78	285	3.51
Body mass index								
<25kg/m2	9,828	38.58	4,719	38.31	8,019	44.44	3,403	41.93
25-30Kg/m2	7,055	27.69	3,605	29.26	4,045	22.42	2,060	25.39
>30Kg/m2	3,431	13.47	2,066	16.77	2,104	11.66	1,287	15.86
Missing	5,160	20.26	1,929	15.66	3,877	21.49	1,365	16.82

Appendix 6

Mortality study: Cohort Demographics for Ulcerative colitis, Crohn's disease exposed subjects and controls

	Ulcerative colitis	UC Controls	Crohn's disease	CD Controls
N (%)	**42, 179 (20.25)**	**166,083 (79.75)**	**27,870 (20.21)**	**110,005 (79.79)**
Male	21232 (50.34)	83,526 (50.29)	12250 (43.95)	48308 (43.91)
Female	20947 (49.66)	82,557 (49.71)	15620 (56.05)	72152 (56.09)
Age, Median (IQR)	51 (37-65)	51 (37-65)	43 (31-58)	43 (31-58)
Age category				
18-30	5284 (12.53)	20859 (12.56)	6087 (21.84)	23947 (21.77)
30-40	7206 (17.08)	28563 (17.20)	5910 (21.21)	23617 (21.47)
40-50	7592 (18.00)	30264 (18.22)	5125 (18.39)	20368 (18.52)
50-60	7735 (18.34)	30704 (18.49)	4200 (15.07)	16633 (15.12)
60-70	6813 (16.15)	26723 (16.09)	3307 (11.87)	13073 (11.88)
70-80	4852 (11.50)	19012 (11.45)	2153 (7.73)	8381 (7.62)
>80	2697 (6.39)	9958 (6.00)	1088 (3.90)	3986 (3.62)
Deprivation Score				
1 (least deprived)	9706 (23.01)	38426 (23.14)	5702 (20.46)	22597 (20.54)
2	8525 (20.21)	33712 (20.30)	5235 (18.78)	20762 (18.76)
3	7934 (18.81)	31380 (18.89)	5234 (18.78)	20754 (18.87)
4	6208 (14.72)	24475 (14.74)	4455 (15.98)	17528 (15.93)
5 (most deprived)	3734 (8.85)	14432 (8.69)	3198 (11.4)	12358 (11.23)
Missing	6072 (14.4)	23658 (14.24)	4046 (14.52)	16006 (14.55)
Charlson comorbidity score				
0	27164 (64.40)	116047 (69.87)	18375 (65.93)	80202 (72.91)
1	9012 (21.37)	31346 (18.87)	6430 (23.07)	20429 (18.57)
2	3306 (7.84)	10263 (6.18)	1736 (6.23)	5336 (4.85)
3	1474 (3.49)	4814 (2.90)	779 (2.80)	2364 (2.15)
4+	1223 (2.90)	3613 (2.18)	550 (1.97)	1674 (1.52)
Current smoker	5044 (11.96)	33159 (19.97)	7160 (25.69)	23778 (21.62)
Non-smoker	22980 (54.48)	85316 (51.37)	12886 (46.24)	56545 (51.40)
Ex-smoker	11065 (26.23)	30348 (18.27)	5792 (20.78)	17885 (16.26)
Missing	3090 (7.33)	17260 (10.39)	2032 (7.29)	11797 (10.72)
Body mass index				
<25kg/m^2	16217 (38.45)	56498 (34.02)	12206 (43.8)	38818 (35.29)
25-30Kg/m^2	11862 (28.12)	44675 (26.90)	6468 (23.21)	26419 (24.02)
>30Kg/m^2	6134 (14.54)	26700 (16.08)	3619 (12.99)	17227 (15.66)
Missing	7966 (18.89)	38210 (23.01)	5577 (20.01)	27541 (25.04)

Appendix 7

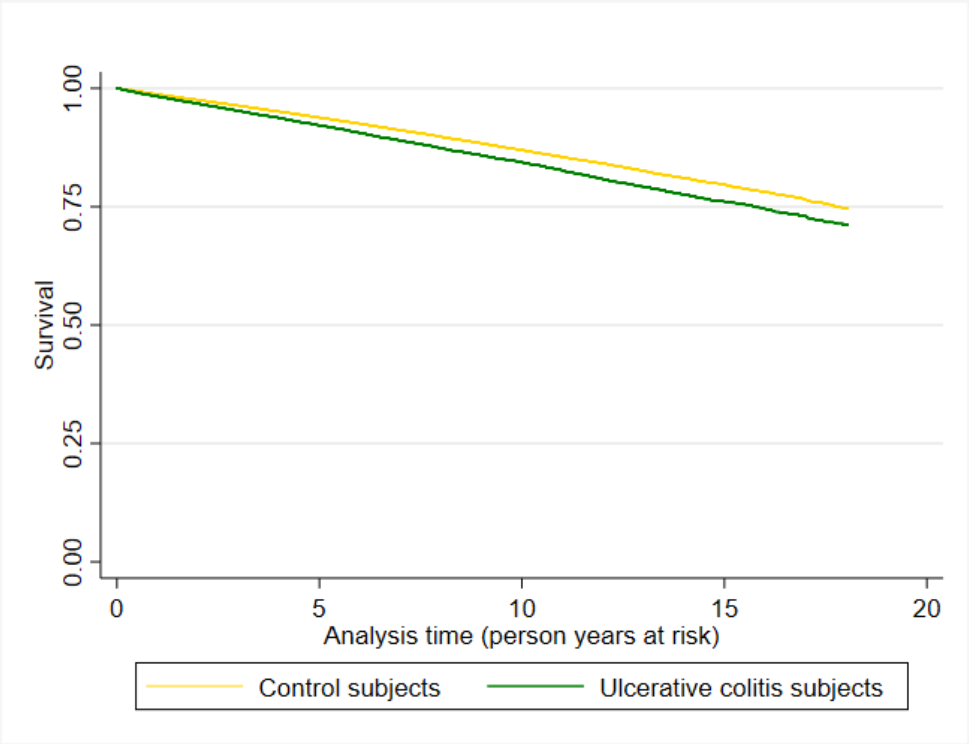


Figure A7.1 Kaplan-Meier survival analysis of all-cause mortality in ulcerative colitis and controls 4,807 deaths/42,179 ulcerative colitis subjects, and 16,098 deaths/166,083 control subjects

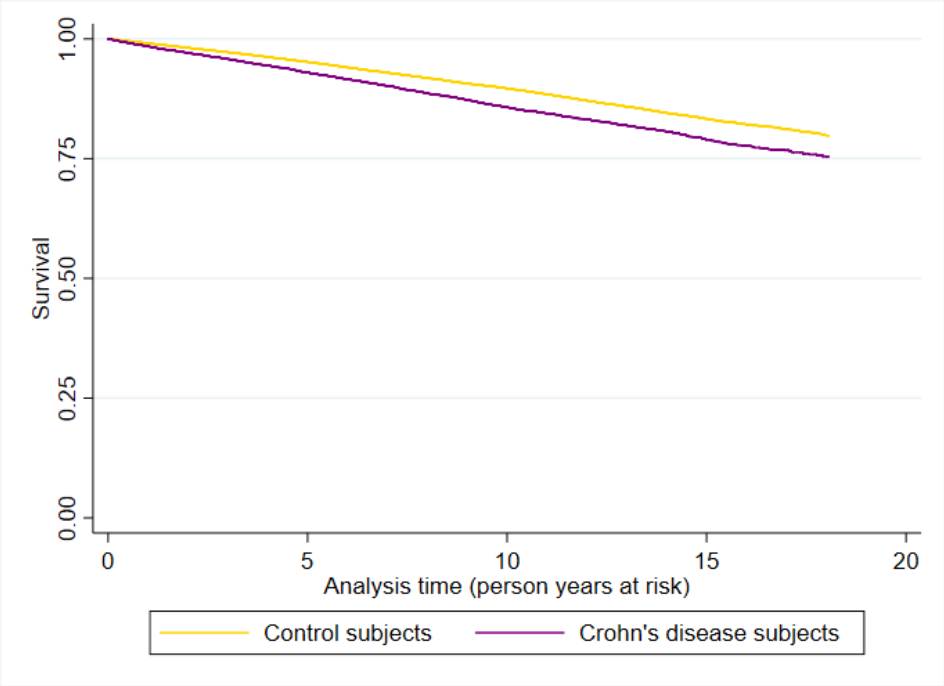


Figure A7.2 Kaplan-Meier survival analysis of all-cause mortality in Crohn's disease and controls 2,612 deaths/27,870 Crohn's disease subjects, and 7,137 deaths/110,005 controls

Appendix 8

8.1 Incident only analysis Colorectal cancer study (incident only cases): Cohort Demographics

	Incident UC		UC Controls		Incident CD		CD Controls	
	N	**%**	**N**	**%**	**N**	**%**	**N**	%
N	12,319	20.25	48,514	79.75	8,115	20.26	31,946	79.74
Male	6,319	51.29	24,865	51.25	3,592	44.26	14,112	44.17
Female	6,000	48.71	23,649	48.75	4,523	55.74	17,834	55.83
Age, Median (IQR)	49 (36-64)		49 (36-63)		44 (30-60)		44 (30-60)	
Age category								
18-30	1,820	14.77	7,183	14.81	1,965	24.21	7,744	24.24
30-40	2,163	17.56	8,601	17.73	1,448	17.84	5,823	18.23
40-50	2,239	18.18	8,920	18.39	1,411	17.39	5,597	17.52
50-60	2,134	17.32	8,526	17.57	1,199	14.78	4,728	14.8
60-70	1,954	1,954	7,629	15.73	1,105	13.62	4,308	13.49
70-80	1,391	11.29	5,366	11.06	718	8.85	2,767	8.66
>80	618	5.02	2,289	4.72	269	3.31	979	3.06
1 (least deprived)	2,849	23.13	11,182	23.05	1,673	20.62	6,532	20.45
2	2,468	20.03	9,662	19.92	1,510	18.61	5,940	18.59
3	2,365	19.2	9,295	19.16	1,526	18.8	5,972	18.69
4	1,839	14.93	7,230	14.9	1,312	16.17	5,131	16.06
5 (most deprived)	1,165	9.46	4,495	9.27	1,004	12.37	3,891	12.18
Missing	1,633	13.26	6,650	13.71	1,090	13.43	4,480	14.02
Charlson comorbidity score								
0	7,802	63.33	33,845	69.76	5,077	62.56	22,765	71.26
1	2,835	23.01	9,400	19.38	2,094	25.80	6,218	19.46
2	930	7.55	2,898	5.97	499	6.15	1,664	5.21
3	422	3.43	1,370	2.82	260	3.20	755	2.36
4+	330	2.68	1,001	2.06	185	2.28	544	1.70
Smoker	1,537	12.48	9,799	20.2	2,242	27.63	7,115	22.27
Non-smoker	6,098	49.50	25,552	52.67	3,684	45.40	16,664	52.16
Ex-smoker	4,172	33.87	9,705	20.00	1,898	23.39	5,682	17.79
Missing	512	4.16	3,458	7.13	291	3.59	2,485	7.78
Body mass index								
<25kg/m^2	4,714	38.27	16,464	33.94	3,404	41.95	11,127	34.83
25-30Kg/m^2	3,600	29.22	13,479	27.78	2,054	25.31	7,949	24.88
>30Kg/m^2	2,066	16.77	8647.00	17.82	1,287	15.86	5,653	17.70
Missing	1,939	15.74	9,924	20.46	1,370	16.88	7,217	22.59

8.2 Multivariable Cox proportional hazards model of factors associated with colorectal cancer

	Ulcerative Colitis					Crohn's Disease			
	Hazard Ratio	[95% Conf. Interval]		p value		Hazard Ratio	[95% Conf. Interval]		p value
Ulcerative colitis	0.91	0.68	1.23	0.553	**Crohn's disease**	1.34	0.93	1.93	0.118
Age category									
Reference 18-30	1.00					1.00			
30-40	0.67	0.09	4.73	0.684		4.95	1.05	23.39	0.043
40-50	5.06	1.17	21.86	0.030		5.50	1.18	25.57	0.03
50-60	15.28	3.72	62.89	<0.001		23.41	5.57	98.36	<0.001
60-70	24.23	5.92	99.18	<0.001		30.78	7.35	128.82	<0.001
70-80	35.89	8.75	147.19	<0.001		74.05	17.80	308.06	<0.001
>80	42.93	10.17	181.17	<0.001		47.67	10.39	218.62	<0.001
Sex									
Reference Male	1.00					1.00			
Female	0.74	0.58	0.95	0.017		0.79	0.57	1.09	0.143
Smoking status									
Reference Non-smoker	1.00					1.00			
Smoker	0.94	0.65	1.35	0.738		0.82	0.52	1.29	0.383
Ex-smoker	1.13	0.86	1.49	0.382		0.88	0.59	1.30	0.521
Missing	0.77	0.40	1.49	0.434		1.77	0.87	3.60	0.112
Body mass index kg/m^2									
Reference <25	1.00					1.00			
25-30	0.72	0.54	0.97	0.031		0.90	0.61	1.32	0.577
>30	0.94	0.68	1.30	0.717		0.75	0.47	1.19	0.216
Missing	0.67	0.43	1.06	0.087		0.68	0.38	1.23	0.202
Charlson Score									
Reference 0	1.00					1.00			
1	1.26	0.94	1.70	0.123		1.21	0.82	1.77	0.344
2	1.77	1.24	2.52	0.002		1.16	0.68	1.98	0.592
3	1.40	0.82	2.38	0.214		0.67	0.27	1.67	0.386
4+	1.46	0.79	2.69	0.224		1.87	0.94	3.72	0.072
Deprivation score									
Reference 1	1.00					1.00			

2	1.06	0.74	1.51	0.751	0.98	0.59	1.61	0.921
3	0.98	0.68	1.43	0.930	1.07	0.65	1.76	0.786
4	1.33	0.91	1.94	0.146	1.16	0.69	1.96	0.574
5 (most deprived)	1.37	0.88	2.11	0.159	1.59	0.94	2.68	0.085
Missing	0.97	0.63	1.50	0.887	0.73	0.39	1.40	0.345

8.3 Mortality study (incident only cases): Cohort Demographics

	ulcerative colitis incident		ulcerative colitis controls		Crohn's disease incident		Crohn's disease Controls	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**
N	13,122	20.17	51,927	79.83	8,442	20.19	33,371	79.81
Male	6,785	51.71	26,837	51.68	3,757	44.5	14,826	44.43
Female	6,337	48.29	25,090	48.32	4,685	55.5	18,545	55.57
Age, Median (IQR)	49 (36-64)		49 (36-63)		44 (30-60)		44 (30-60)	
Age category								
18-30	1,972	15.03	7,795	15.01	2,018	23.9	7,961	23.86
30-40	2,295	17.49	9,108	17.54	1,505	17.83	6,047	18.12
40-50	2,384	18.17	9,522	18.34	1,468	17.39	5,837	17.49
50-60	2,276	17.34	9,106	17.54	1,251	14.82	4,943	14.81
60-70	2,078	15.84	8,192	15.78	1,169	13.85	4,615	13.83
70-80	1,477	11.26	5,776	11.12	752	8.91	2,931	8.78
>80	640	4.88	2,428	4.68	279	3.3	1,037	3.11
Deprivation Score								
1 (least deprived)	3,043	23.19	12,009	23.13	1,735	20.55	6,798	20.37
2	2,636	20.09	10,372	19.97	1,570	18.6	6,205	18.59
3	2,516	19.17	9,938	19.14	1,592	18.86	6,266	18.78
4	1,954	14.89	7,713	14.85	1,368	16.2	5,374	16.1
5 (most deprived)	1,240	9.45	4,814	9.27	1,057	12.52	4,102	12.29
Missing	1,733	13.21	7,081	13.64	1,120	13.27	4,626	13.86
Charlson comorbidity score								
0	8,316	63.37	36,128	69.57	5,255	62.25	23,702	71.03
1	3,004	22.89	9,994	19.25	2,156	25.54	6,450	19.33
2	996	7.59	3,165	6.1	545	6.46	1,790	5.36
3	444	3.38	1,500	2.89	273	3.23	819	2.45
4+	362	2.76	1,140	2.2	213	2.52	610	1.83
Smoking status								
Smoker	1,635	12.46	10,514	20.25	2,299	27.23	7,415	22.22
Non-smoker	6,469	49.3	27,238	52.45	3,840	45.49	17,376	52.07
Ex-smoker	4,460	33.99	10,393	20.01	1,998	23.67	5,983	17.93

Missing	558	4.25	3,782	7.28	305	3.61	2,597	7.78
Body mass index								
<25kg/m^2	4,993	33.86	17,585	34.71	3,538	41.91	11,625	34.84
25-30Kg/m^2	3,841	27.77	14,419	28.07	2,146	25.42	8,347	25.01
>30Kg/m^2	2,202	17.81	9,247	17.6	1,340	15.87	5,891	17.65
Missing	2,086	20.56	10,676	19.62	1,418	16.80	7,508	22.50

8.4 Multivariable Cox proportional hazards model of factors associated with mortality

	Ulcerative Colitis					Crohns Disease			
	Hazard Ratio	**[95% Conf. Interval]**		**p value**		**Hazard Ratio**	**[95% Conf. Interval]**		**p value**
Ulcerative colitis	1.31	1.23	1.41	<0.001	**Crohn's disease**	1.50	1.37	1.64	<0.001
Age band									
Reference 18-30	1.00					1.00			
30-40	1.75	1.07	2.85	0.026		2.62	1.58	4.33	<0.001
40-50	5.24	3.40	8.09	<0.001		6.88	4.37	10.81	<0.001
50-60	11.64	7.65	17.72	<0.001		14.41	9.30	22.34	<0.001
60-70	30.03	19.84	45.46	<0.001		34.45	22.45	52.88	<0.001
70-80	69.94	46.26	105.75	<0.001		80.71	52.64	123.76	<0.001
>80	168.24	111.10	254.77	<0.001		195.35	126.93	300.65	<0.001
Sex									
Reference Male	1.00					1.00			
Female	0.78	0.73	0.83	<0.001		0.80	0.73	0.86	<0.001
Smoking status									
Reference Non-smoker	1.00					1.00			
Smoker	1.97	1.82	2.14	<0.001		2.03	1.82	2.26	<0.001
Ex-smoker	1.17	1.09	1.26	<0.001		1.28	1.16	1.41	<0.001
Missing	1.29	1.14	1.48	<0.001		1.26	1.04	1.54	0.019
Body mass index kg/m^2									
Reference <25	1.00					1.00			
25-30	0.76	0.71	0.82	<0.001		0.81	0.73	0.90	<0.001
>30	0.88	0.81	0.96	0.003		0.83	0.74	0.94	0.002
Missing	1.12	1.01	1.23	0.024		1.19	1.04	1.35	0.012
Charlson Score									
Reference 0	1.00					1.00			
1	1.70	1.57	1.84	0.107		1.88	1.69	2.09	<0.001
2	2.17	1.99	2.37	<0.001		2.43	2.14	2.74	<0.001
3	2.78	2.50	3.09	<0.001		2.93	2.53	3.39	<0.001
4+	4.42	3.99	4.89	<0.001		4.30	3.72	4.97	<0.001
Deprivation score									
Reference 1	1.00								
2	1.08	0.98	1.18	0.117		1.00			

3	1.18	1.08	1.30	<0.001	1.08	0.95	1.24	0.242
4	1.32	1.20	1.45	<0.001	1.19	1.04	1.35	<0.001
5 (most deprived)	1.45	1.31	1.61	<0.001	1.37	1.20	1.57	<0.001
Missing	1.18	1.07	1.31	<0.001	1.35	1.17	1.56	0.004

Appendices for chapter 4

Appendix 1

ICD-10 codes

K51 Ulcerative Colitis

Pre-specified list of additional accepted codes
K52.1 Toxic gastroenteritis and colitis
K52.3 Indeterminate colitis
K52.8 Other specified noninfective gastroenteritis and colitis
K52.9 Non-infective gastroenteritis and colitis, unspecified
K59.3 Megacolon, not elsewhere classified
K63.1 Perforation of intestine (nontraumatic)
K65 Peritonitis
K62.5 Haemorrhage of anus and rectum
R10 Abdominal and pelvic pain

Appendix 2

Univariate analysis comparing included and excluded subjects

		Included Patients n	%	Excluded Patients n	%	p-value
Sex	**Male**	5382	54%	4823	49%	0.000
	Female	4669	46%	5110	51%	
Charlson comorbidity score	**0**	9597	95%	8485	85%	0.000
	1 to 4	333	3%	738	7%	
	5+	121	1%	712	7%	
Deprivation	**1**	2017	20%	1894	19%	0.007
	2	2175	22%	1941	20%	
	3	2105	21%	2035	20%	
	4	1923	19%	1971	20%	
	5	1818	18%	1865	19%	
	Unknown	13	0%	229	2%	
Ethnicity	**White**	8001	80%	8251	83%	0.000
	Asian	947	9%	773	8%	
	Other minority ethnicities	595	6%	504	5%	
	Unknown	508	5%	407	4%	

Appendix 3

Multivariable logistic regression analysis of factors associated with 30 day emergency readmission following index admission for acute UC.

		Odds Ratio (95% CI)	p-value
Age group	**18-32**	baseline 1	
	33-46	0.79 (0.52-1.19)	0.260
	47-60	0.60 (0.36-0.99)	0.048
Sex	**Male**	baseline 1	
	Female	1.05 (0.73-1.53)	0.783
Charlson comorbidity score	**0**	baseline 1	
	1 to 4	1.11 (0.54-2.28)	0.782
	5+	1.54 (0.56-4.21)	0.405
Deprivation	**1**	baseline 1	
	2	1.00 (0.53-1.87)	0.995
	3	1.30 (0.7-2.43)	0.417
	4	1.16 (0.62-2.15)	0.636
	5	1.23 (0.65-2.37)	0.528
Ethnicity	**White**	baseline 1	
	Asian	0.91 (0.42-1.99)	0.820
	Other minority ethnicities	0.51 (0.17-1.51)	0.226
	Unknown	0.45 (0.18-1.23)	0.103
Admission period	**2007/08 - 2011/12**	baseline 1	
	2012/13- 2016/17	1.59 (1.09-2.31)	0.016
Anti-TNF during emergency admission	**Yes**	0.41 (0.18-0.95)	0.038
	No	baseline 1	
Prevalent or Incident	**Prevalent**	1.11 (0.75-1.65)	0.614
	Incident	baseline 1	
Provider volume of acute UC admissions	**Low (≤11)**	baseline 1	
	Medium (12 to 18)	0.98 (0.5-,1.7)	0.931
	High (≥19)	1.32 (0.8-2.12)	0.265

Appendix 4 – not published

Multivariable logistic regression analysis of factors associated with colectomy following emergency admission with ulcerative colitis (volume of acute UC admissions variable)

		Colectomy during admission		Colectomy by 12-months	
		Odds Ratio (95% CI)	**p-value**	**Odds Ratio (95% CI)**	**p-value**
Age group	**18-32**	baseline 1			
	33-46	1.238	0.017	0.808	0.033
	47-60	1.236	0.047	0.895	0.349
Sex	**Male**	baseline 1			
	Female	0.728	<0.001	0.743	<0.001
Charlson comorbidity score	**0**	baseline 1			
	1 to 4	2.412	<0.001	0.678	0.179
	5+	3.010	<0.001	0.423	0.145
Deprivation	**1**	baseline 1			
	2	1.469	0.003	1.027	0.851
	3	1.349	0.023	1.051	0.725
	4	1.600	<0.001	1.275	0.083
	5	1.296	0.059	1.197	0.210
Ethnicity	**White**	baseline 1			
	Asian	0.577	0.001	0.486	0.000
	Other minority ethnicities	0.727	0.096	0.893	0.563
	Unknown	1.192	0.290	0.956	0.826
Admission period	**2007/08 - 2011/12**	baseline 1			
	2012/13- 2016/17	0.842	0.035	0.722	<0.001
Anti-TNF during emergency admission	**Yes**	1.729	<0.001	2.146	<0.001
	No	baseline 1			
Prevalent or Incident	**Prevalent**	0.823	0.019	2.266	<0.001
	Incident	baseline 1			
	Low (≤11)	baseline 1			

Provider volume of acute UC admissions	**Medium (12 to 18)**	0.823	0.111	1.104	0.476
	High (≥19)	1.050	0.665	1.154	0.279

Appendices for chapter 5 Manuscript 1: The risk of subsequent surgery following bowel resection for Crohn's disease in a national cohort of 19,870 patients.

Appendix 1

Surgical Code List

OPCS-4 (Office of Population Censuses and Surveys Classification of Interventions and Procedures 4th revision)

ICD-10 (International Classification of Diseases version 10)

Crohn's Disease	Ulcerative Colitis	Index Surgery	Further Surgery	Index surgery at risk of elective staged procedures
ICD-10	ICD-10	OPCS-4	OPCS-4	OPCS-4
K50	K51	H04 - Total excision of colon and rectum	G74 - Creation of artificial opening into ileum	H151 - Loop colostomy
		H05 - Total excision of colon	G75 - Attention to artificial opening into ileum	H152 - End colostomy
		H06 - Extended excision of right hemicolon	G60 - Artificial opening into jejunum	H158 - Other specified other exteriorisation of colon
		H07 - Other excision of right hemicolon	G63 - Other open operations on jejunum	H159 - Unspecified other exteriorisation of colon
		H08 - Excision of transverse colon	G67 - Other operations on jejunum	H328 - Other specified exteriorisation of colon
		H09 - Excision of left hemicolon	G785 - Exclusion of segment of ileum	H329 - Unspecified exteriorisation of colon
		G613 - Bypass of jejunum, anastomosis of jejunum-colon	G714 - Bypass ileum anastomosis ileum-trans colon	G741 - Creation of continent ileostomy
		H11 - Other excision of colon	H14 - Exteriorisation of caecum	G742 - Creation of temporary ileostomy
		H19 - Other open operations on colon	H15 - Other exteriorisation of colon	G743 - Creation of defunctioning ileostomy
		H29 - Subtotal excision of colon	H32 - Exteriorisation of colon	H064 - Extended right hemicolectomy & ileostomy
		H30 - Other operations on colon	H162 - Caecotomy	H074 - Right hemicolectomy and ileostomy HFQ
		H33 - Excision of rectum	H163 - Colotomy	H084 - Transverse colectomy and ileostomy HFQ
		G715 - Bypass ileum anastomosis ileum-colon	H04 - Total excision of colon and rectum	H094 - Left hemicolectomy and ileostomy HFQ
		G713 - Bypass of jejunum, anastomosis of jejunum-caecum	H05 - Total excision of colon	H104 - Sigmoid colectomy and ileostomy HFQ
		G714 - Bypass ileum, anastomosis ileum-transverse colon	H06 - Extended excision of right hemicolon	H114 - Colectomy and ileostomy NEC
		H10 - Excision of sigmoid colon	H07 - Other excision of right hemicolon	H335 - Rectosigmoidectomy & closure of rectal stump & exteriorisation of bowel
		G724 - Anastomosis of ileum to rectum	H08 - Excision of transverse colon	
		G721 - Anastomosis of ileum to caecum	H09 - Excision of left hemicolon	
		G722 - Anastomosis ileum-transverse colon	H10 - Excision of sigmoid colon	
		G723 - Anastomosis of ileum to colon NEC	H11 - Other excision of colon	
		G694 - Ileectomy & anastomosis ileum-colon	H19 - Other open operations on colon	
		G782 - Strictureplasty of ileum	H29 - Subtotal excision of colon	
		G58 - Excision of jejunum	H30 - Other operations on colon	
		G69 - Excision of ileum	H33 - Excision of rectum	
		G73 - Attention to connection of ileum	G613 - Bypass jejunum anastomosis jejunum-colon	
		G71 - Bypass of ileum	G713 - Bypass ileum anastomosis ileum-caecum	
		G61 - Bypass of jejunum	G721 - Anastomosis of ileum to caecum	
			G722 – Anastomosis ileum-transverse colon	
			G725 - Anastomosis ileum-anus, pouch creation	
			G724 - Anastomosis of ileum to rectum	
			G715 - Bypass ileum anastomosis of ileum to colon NEC	
			G723 - Anastomosis of ileum to colon NEC	
			G734 - Resection of ileocolic anastomosis	
			G694 - Ileectomy & anastomosis ileum to colon	

			G782 - Strictureplasty of ileum	
			G58 - Excision of jejunum	
			G69 - Excision of ileum	
			G73 - Attention to connection of ileum	
			G71 - Bypass of ileum	
			G61 - Bypass of jejunum	
			H661 - Excision of ileoanal pouch	
			H662 - Revision of ileoanal pouch	
			H668 - Other therapeutic operations on ileoanal pouch	
			H669 - Unspecified operations on ileoanal pouch	
			G733 - Resection of ileostomy	

Appendix 2

Perianal surgery codes (including operations undertaken to aid perianal disease healing where no resectional code was recorded)

OPCS-4 Code	Description
H551	Laying open of low anal fistula
H552	Laying open of high anal fistula
H553	Laying open of anal fistula NEC
H554	Insertion of seton into high anal fistula and partial laying open of track HFQ
H555	Fistulography of anal fistula
H557	Repair of anal fistula using plug
H558	Other specified other operations on perianal region
H559	Unspecified other operations on perianal region
H564	Excision of anal fissure
H581	Drainage of ischiorectal abscess
H582	Drainage of perianal abscess
H583	Drainage of perirectal abscess

Appendix 3

Extraintestinal Manifestations of Inflammatory Bowel Disease (EIM) Categories – codes

Ophthalmologic EIMs		Hepatobiliary EIMs		Dermatologic EIMs		Musculoskeletal EIMs	
ICD-10		ICD-10		ICD-10		ICD-10	
Code	Description	Code	Description	Code	Description	Code	Description
H150	Scleritis	K830	Cholangitis	K12	Stomatitis and related lesions	M091	Juvenile arthritis in Crohn's disease
H151	Episcleritis			L40	Psoriasis	M45	Ankylosing spondylitis
H20	Iridocyclitis			L52	Erythema nodosum	M461	Sacroiliitis, not elsewhere classified
				L88	Pyoderma gangrenosum		
				L982	Febrile neutrophilic dermatosis [Sweet]		

Appendix 4

Comparison of inclusion and exclusion characteristics

		All patients			Patients with ≥ 5 years follow-up		
		Included	Excluded	p-value	Included	Excluded	p-value
		N (%)	N (%)		N (%)	N (%)	
Sex	**Male**	8677 (45)	3656 (48)	<0.001	5971 (45)	2753 (48)	<0.001
	Female	10530 (55)	3955 (52)		7397 (55)	2979 (52)	
Total		19207	7611		13368	5732	
Age quintile	**18-25**	4344 (23)	591 (9)	<0.001	2678 (22)	411 (9)	<0.001
	26-34	3536 (18)	778 (12)		2775 (20)	650 (14)	
	35-44	3738 (19)	1254 (20)		2706 (19)	958 (20)	
	45-57	3793 (20)	1462 (23)		2606 (20)	1074 (22)	
	58+	3796 (20)	2322 (36)		2603 (20)	1707 (36)	
Total		19207	6407		13368	4800	
Deprivation quintile	**1 (Most deprived)**	4127 (21)	1490 (20)	0.093	2826 (21)	1147 (21)	0.214
	2	4127 (21)	1520 (21)		2879 (22)	1123 (20)	
	3	3958 (21)	1510 (21)		2770 (21)	1126 (20)	
	4	3650 (19)	1433 (20)		2522 (19)	1096 (20)	
	5 (Least deprived)	3345 (17)	1343 (18)		2371 (18)	1012 (20)	
Total		19207	7296		13368	5504	
Charlson comorbidity category	**0**	15620 (81)	5896 (77)	<0.001	11009 (82)	4538 (79)	<0.001
	1-4	2465 (13)	1071 (14)		1615 (12)	749 (13)	
	5+	1122 (6)	646 (8)		744 (6)	446 (8)	
Total		19207	7613		13368	5733	
Ethnicity	**White**	16903 (88)	6701 (88)	0.448	11850 (89)	5081 (89)	0.603
	Asian	562 (3)	247 (3)		350 (3)	167 (3)	
	Other minority ethnicities	609 (3)	238 (3)		410 (3)	176 (3)	
	Unknown	1133 (6)	427 (6)		758 (6)	309 (5)	
Total		19207	7613		13368	5733	

Appendix 5

Index surgery and further surgery by age decile

Index Surgery Age	(N)	Further Surgery Age	(N)
18-29	5807	**18-29**	759
30-39	3949	**30-39**	753
40-49	3576	**40-49**	674
50-59	2536	**50-59**	476
60-69	1960	**60-69**	297
70+	1379	**70+**	182
Total	19207	**Total**	3141

Appendix 6

All further surgery demographics table including within 30-days and those thought to be an elective staged procedure.

Demographics		Patients with ≥5 years follow-up (%)	All further CD surgery within 5 years (%)
Sex	**Male**	5971 (44.7)	1159 (19.4)
	Female	7397 (55.3)	1355 (18.3)
Age quintile	**18-25**	2678 (20.0)	517 (19.3)
	26-34	2775 (20.8)	550 (19.8)
	35-44	2706 (20.2)	539 (19.9)
	45-57	2606 (19.5)	489 (18.8)
	58+	2603 (19.5)	419 (16.1)
Provider volume of index surgery	**Low**	1731 (12.9)	298 (17.2)
	Medium	4071 (30.5)	723 (17.8)
	High	7566 (56.6)	1493 (19.7)
Ethnicity	**White**	11850 (88.6)	2236 (18.9)
	Asian	350 (2.6)	81 (23.1)
	Other minority ethnicities	410 (3.1)	83 (20.2)
	Unknown	758 (5.7)	114 (15.0)
Deprivation quintile	**1 (Most Deprived)**	2826 (21.1)	560 (19.8)
	2	2879 (21.5)	565 (19.6)
	3	2770 (20.7)	529 (19.1)
	4	2522 (18.9)	447 (17.7)
	5 (Least Deprived)	2371 (17.7)	413 (17.4)
Index surgery admission method	**Emergency**	5879 (44.0)	1333 (22.7)
	Elective	7385 (55.2)	1159 (15.7)
	Unknown	104 (0.8)	22 (21.2)
Year of index surgery	**2007**	1816 (13.6)	341 (18.8)
	2008	1848 (13.8)	364 (19.7)
	2009	1886 (14.1)	369 (19.6)
	2010	1901 (14.2)	359 (18.9)
	2011	1962 (14.7)	341 (17.4)
	2012	2004 (15.0)	395 (19.7)
	2013	1951 (14.6)	345 (17.7)
Charlson comorbidity score	**0**	11009 (82.4)	2034 (18.5)
	1-4	1615 (12.1)	316 (25.8)
	5+	744 (5.6)	164 (26.0)
Prior perianal surgery		1148 (8.6)	296 (25.8)

Presence of extraintestinal manifestations	622 (4.7)	162 (26.0)
Index surgery performed laparoscopically	3051 (22.8)	442 (14.5)
Total	13368 (69.8)	2514 (18.8)

Appendix 7

Sensitivity analysis: Multivariable logistic regression of factors associated with all further surgery within 5 years of index Crohn's disease surgery

Demographic		Odds Ratio	[95% Conf.	Interval]	p-value
Sex	**Male**	reference			
	Female	0.99	0.91	1.09	0.879
Age quintile	**18-25**	reference			
	25-34	1.05	0.91	1.20	0.507
	35-44	1.05	0.92	1.21	0.450
	45-57	0.98	0.85	1.13	0.824
	58+	0.73	0.63	0.86	**<0.001**
Provider volume of index surgery	**Low**	reference			
	Medium	1.04	0.89	1.21	0.634
	High	1.19	1.03	1.36	**0.016**
Ethnicity	**White**				
	Asian	1.18	0.91	1.53	0.201
	Non-White	1.05	0.82	1.35	0.677
	Unknown	0.75	0.61	0.93	**0.008**
Deprivation quintile	**1 (Most Deprived)**	reference			
	2	1.00	0.88	1.15	0.949
	3	1.00	0.88	1.15	0.983
	4	0.92	0.80	1.06	0.255
	5 (Least Deprived)	0.91	0.79	1.05	0.215
Index surgery admission method	**Emergency**	reference			
	Non-Emergency	0.66	0.61	0.73	**<0.001**
Charlson comorbidity score	**0**	reference			
	1-4	1.11	0.97	1.27	0.132
	5+	1.30	1.07	1.57	**0.009**
Year of index surgery	**2007**	reference			
	2008	1.05	0.89	1.23	0.601
	2009	1.04	0.88	1.22	0.684
	2010	0.99	0.83	1.17	0.873
	2011	0.90	0.76	1.06	0.206
	2012	1.05	0.89	1.24	0.527
	2013	0.93	0.79	1.10	0.411
Prior perianal surgery		1.51	1.31	1.74	**<0.001**
Presence of extraintestinal manifestations		1.53	1.27	1.85	**<0.001**
Index surgery performed laparoscopically		0.76	0.67	0.85	**<0.001**

Appendix 8

Crohn's colitis sub-cohort demographic table

Demographic		Patients (%)	Further surgery (%)	Patients with ≥5 year follow-up (%)	Further surgery within 5 years (%)
Sex	**Male**	992 (42.6)	229 (23.0)	691 (42.6)	138 (20.0)
	Female	1337 (57.4)	278 (20.7)	932 (57.4)	164 (17.6)
Age quintile	**18-26**	513 (22.0)	122 (23.8)	360 (22.2)	66 (18.3)
	27-35	428 (18.4)	100 (23.4)	292 (18.0)	56 (19.2)
	36-46	486 (20.9)	116 (23.9)	337 (20.8)	73 (21.7)
	47-59	459 (19.7)	96 (20.9)	325 (20.0)	58 (17.8)
	60+	443 (19.0)	73 (16.5)	309 (19.0)	49 (15.9)
Median (IQR) Age		41 (28-54)	38 (27-51)	41 (28-54)	39 (28-53)
Provider volume of index surgery	**Low (1-10)**	322 (13.8)	58 (18.0)	250 (15.4)	34 (13.6)
	Medium (11-17)	686 (29.5)	155 (22.6)	469 (28.9)	72 (15.4)
	High (18+)	1321 (56.7)	294 (22.3)	904 (55.7)	196 (21.7)
Ethnicity	**White**	2047 (87.9)	449 (21.9)	1437 (88.5)	271 (18.9)
	Asian	79 (3.4)	19 (24.1)	46 (2.8)	11 (23.9)
	Other minority ethnicities	74 (3.2)	16 (21.6)	49 (3.0)	8 (16.3)
	Unknown	129 (5.5)	23 (17.8)	91 (5.6)	12 (13.2)
Deprivation quintile	**1 (Most Deprived)**	499 (21.4)	106 (21.2)	361 (22.2)	71 (19.7)
	2	484 (20.8)	109 (22.5)	333 (20.5)	67 (20.1)
	3	478 (20.5)	106 (22.2)	322 (19.8)	54 (16.8)
	4	448 (19.2)	108 (24.1)	309 (19.0)	62 (20.2)
	5 (Least Deprived)	420 (18.0)	78 (18.6)	298 (18.4)	48 (16.1)
Index surgery admission method	**Emergency**	1058 (45.4)	259 (24.5)	759 (46.8)	155 (20.4)
	Elective	1257 (54.0)	241* (*)	852 (52.5)	140* (*)
	Unknown	14 (0.6)	*	12 (0.7)	*
Year of index surgery	**2007**	204 (8.8)	55 (27.0)	204 (12.6)	37 (18.1)
	2008	231 (9.9)	74 (32.0)	231 (14.2)	51 (22.1)
	2009	225 (9.7)	45 (20.0)	225 (13.9)	35 (15.6)
	2010	228 (9.8)	54 (23.7)	228 (14.0)	40 (17.5)
	2011	236 (10.1)	56 (23.7)	236 (14.5)	45 (19.1)
	2012	240 (10.3)	51 (21.3)	240 (14.8)	47 (19.6)
	2013	259 (11.1)	52 (20.1)	259 (16.0)	47 (18.1)

	2014	222 (9.5)	51 (23.0)	-	-
	2015	244 (10.5)	36 (14.8)	-	-
	2016	240 (10.3)	33 (13.8)	-	-
Charlson comorbidity score	**0**	1862 (79.9)	418 (22.4)	1314 (18.0)	252 (19.2)
	1-4	314 (13.5)	71 (22.6)	208 (12.8)	40 (19.2)
	5+	153 (6.6)	18 (11.8)	101 (6.2)	10 (9.9)
Perianal surgery up to index surgery		309 (13.3)	90 (29.1)	201 (12.4)	54 (26.9)
Median (IQR) time to further surgery (days)			783 (428-1451)		686 (394-1130)
Extraintestinal manifestations		173 (7.4)	53 (30.6)	94 (5.8)	24 (25.5)
Index surgery performed laparoscopically		585 (25.1)	119 (20.3)	336 (20.7)	58 (17.3)
Totals		2329	507 (21.8)	1623	302 (18.6)

**≤5 subjects: data not shown to ensure subject anonymity*

Appendix 9

Multivariable logistic regression of factors associated with further surgery within 5 years in the Crohn's colitis sub-cohort

Factors		Odds ratio	[95% Conf.	Interval]	P-value
Sex	**Male**	reference			
	Female	0.86	0.67	1.12	0.268
Age quintile	**18-26**	reference			
	27-35	1.06	0.71	1.58	0.788
	36-46	1.25	0.86	1.83	0.242
	47-59	1.03	0.69	1.54	0.872
	60+	0.99	0.64	1.53	0.970
Provider volume of index surgery	**Low (1-81)**	reference			
	Medium (82-143)	1.15	0.74	1.81	0.533
	High (144+)	1.70	1.13	2.54	0.010
Ethnicity	**White**	reference			
	Asian	1.30	0.64	2.65	0.467
	Other minority ethnicities	0.85	0.39	1.88	0.695
	Unknown	0.64	0.34	1.20	0.165
Index of multiple deprivation (quintiles)	**1 (Most deprived)**	reference			
	2	1.00	0.68	1.46	0.997
	3	0.86	0.57	1.28	0.445
	4	0.99	0.67	1.46	0.947
	5 (Least deprived)	0.76	0.50	1.14	0.188
Index surgery admission	**Emergency**	reference			
	Non-Emergency	0.75	0.57	0.98	0.033
Charlson comorbidity Score	**0**	reference			
	1-4	0.96	0.65	1.40	0.815
	5+	0.47	0.23	0.95	0.035
Year of index surgery	**2007**	reference			
	2008	1.24	0.77	2.02	0.378
	2009	0.88	0.52	1.48	0.624
	2010	0.93	0.56	1.54	0.780
	2011	1.07	0.65	1.76	0.781
	2012	1.13	0.69	1.84	0.629
	2013	0.98	0.60	1.60	0.933
Prior perianal surgery		1.65	1.16	2.34	0.005
Presence of extraintestinal manifestations		1.53	0.93	2.52	0.095

Index surgery performed laparoscopically	0.99	0.70	1.39	0.950

Appendix 10

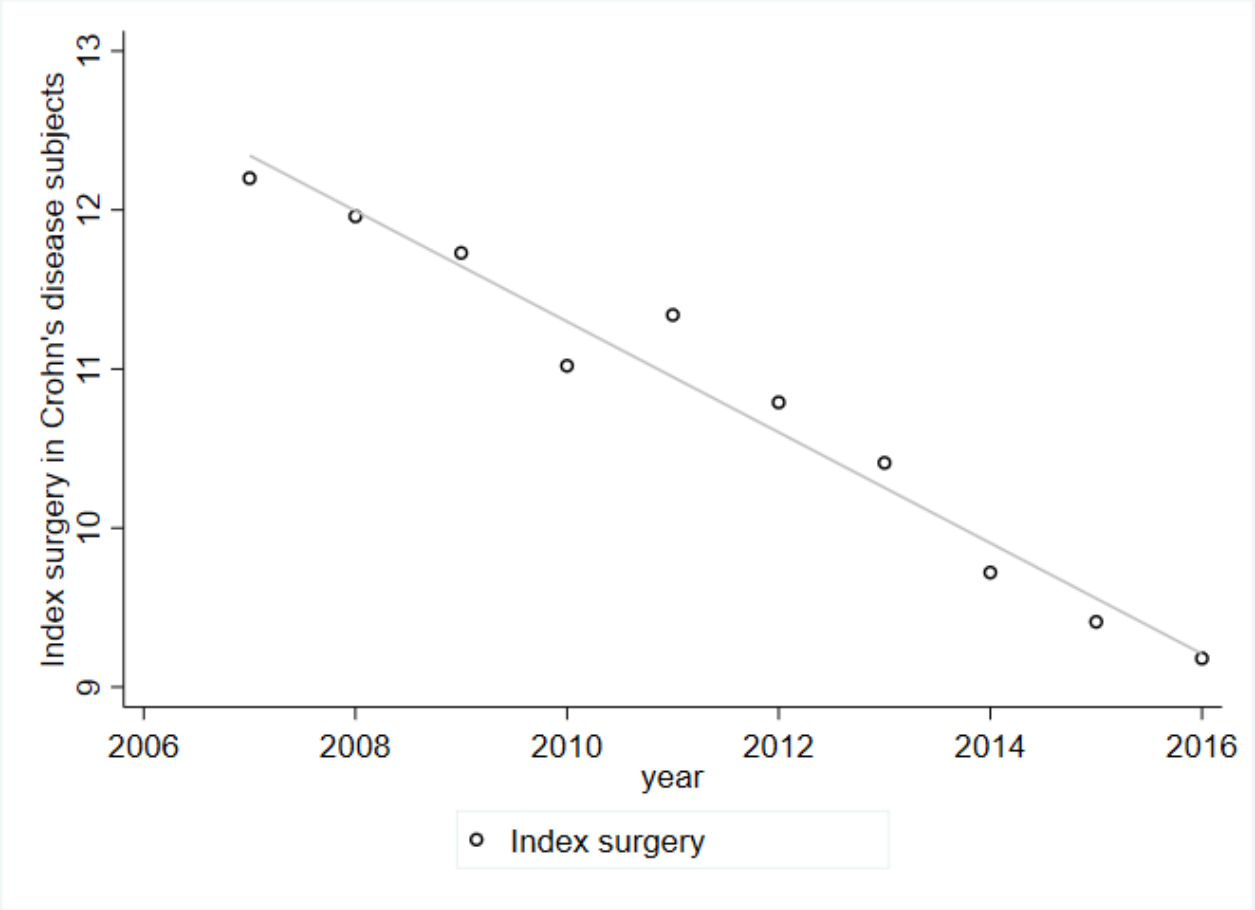


Figure A10: Graph showing fall in index resectional surgery per 1,000 subjects with Crohn's disease (CD) by year of study in England

Appendices for chapter 5 Manuscript 2: The risk of later surgery at the anastomotic site following right hemicolectomy for Crohn's disease in a national cohort of 12,230 patients

Appendix 1

Surgical Code List

Procedure Condition	Index Surgery	Crohn's Disease	Ulcerative Colitis	Further Surgery		Index surgery at risk of elective staged procedures	Imaging modality
Code Type	OPCS-4	ICD-10	ICD-10	OPCS-4		OPCS-4	OPCS-4
Code List	H06 – Right hemicolectomy	K50	K51	G693 – Ileectomy	H084 – Transverse colectomy	H151 – Colostomy	U09.3 – MRI pelvis
	H07 – Extended right hemicolectomy			G694 – Ileectomy	H085 – Transverse colectomy	H152 – Colostomy	U08.5 – MRI abdo
				G698 – Ileectomy	H086 – Transverse colectomy	H158 – Colostomy	U08.1 – CT abdo
				G699 – Ileectomy	H088 – Transverse colectomy	H159 – Colostomy	U09.1 – CT pelvis
				G702 – Ileectomy	H089 – Transverse colectomy	H328 – Exteriorisation of colon	U17.5 – CT Colon
				G714 – Ileal bypass	H112 – Colectomy	H329 – Exteriorisation of colon	U17.4 – Barium enema
				G715 – Ileal bypass	H113 – Colectomy	H335 – Rectal closure/exteriorisation bowel	G80.2 – capsule endoscopy
				G722 – Anastomosis ileum to colon	H114 – Colectomy	G741 – Creation of ileostomy	
				G723 – Anastomosis ileum to colon	H115 – Colectomy	G742 – Creation of ileostomy	
				G731 – Ileal anastomosis manipulation	H116 – Colectomy	G743 – Creation of ileostomy	
				G732 – Ileal anastomosis manipulation	H118 – Colectomy	H064 – Extended right hemicolectomy	
				G734 – Resection ileocolonic anastomosis	H119 – Colectomy	H074 – Right hemicolectomy	
				G741 – Creation of ileostomy	H131 – bypass colon	H084 – Transverse colectomy	
				G742 – Creation of ileostomy	H298 – subtotal excision of colon	H094 – Left hemicolectomy and ileostomy	
				G743 – Creation of ileostomy	H299 – subtotal excision of colon	H104 – Sigmoid colectomy and ileostomy	
				G748 – Creation of ileostomy	H061 – Extended right hemicolectomy	H114 – Colectomy and ileostomy	
				G749 – Creation of ileostomy	H062 – Extended right hemicolectomy		
				G785 – Strictuloplasty	H063 – Extended right hemicolectomy		
				H041 – Pan-proctocolectomy	H064 – Extended right hemicolectomy		
				H048 – Pan-proctocolectomy	H065 – Extended right hemicolectomy		
				H049 – Pan-proctocolectomy	H068 – Extended right hemicolectomy		

				H051 – Total colectomy	H069 – Extended right hemicolectomy		
				H052 – Total colectomy	H071 – Right hemicolectomy		
				H053 – Total colectomy	H072 – Right hemicolectomy		
				H058 – Total colectomy	H073 – Right hemicolectomy		
				H059 – Total colectomy	H075 – Right hemicolectomy		
				H081 – Transverse colectomy	H078 – Right hemicolectomy		
				H082 – Transverse colectomy	H079 – Right hemicolectomy		
				H083 – Transverse colectomy			

Appendix 2

Code list - potential reasons for delayed colonoscopy at 6-12 months

Falls/rehab/accidents	Major disease codes		Other	OPCS-4	
W19 - Unspecified fall	N17 - Acute renal failure	G03 - Meningitis due to other and unspecified causes	K56 - Paralytic ileus and intestinal obstruction without hernia	G75 - Attention to artificial opening into ileum	M06 - Incision of kidney
Z60 - Problems related to social environment	A09 - Other gastroenteritis and colitis of infectious and unspecified origin	G80 - Cerebral palsy	Z45 - Adjustment and management of implanted device	T41 - Other open operations on peritoneum	K52 - Open operations on conducting system of heart
W18 - Other fall on same level	I25 - Chronic ischaemic heart disease	G97 - Postprocedural disorders of nervous system, not elsewhere classified	T85 - Complications of other internal prosthetic devices, implants and grafts	Y16 - Connection of organ NOC	H10 - Excision of sigmoid colon
W10 - Fall on and from stairs and steps	B95 – Streptococcus, staphylococcus as the cause of diseases	B25 - Cytomegaloviral disease	Y84 - Medical procedures as the cause of abnormal reaction of the patient	H15 - Other exteriorisation of colon	H30 - Other operations on colon
Y04 - Assault by bodily force	J44 - Other chronic obstructive pulmonary disease	M02 - Reactive arthropathies	T83 - Complications of genitourinary prosthetic devices, implants and grafts	L91 - Other vein related operations	T87 - Excision or biopsy of lymph node
W01 - Fall on same level from slipping, tripping and stumbling	K65 - Peritonitis	J91 - Pleural effusion in conditions classified elsewhere	Y60 - Unintentional cut, puncture, perforation or haemorrhage	Z29 - Other part of bowel	X50 - External resuscitation
Y86 - Sequelae of other accidents	J90 - Pleural effusion, not elsewhere classified	S36 - Injury of intra-abdominal organs		G72 - Other connection of ileum	X39 - Other route of administration of therapeutic substance
S62 - Fracture at wrist and hand level	R00 - Abnormalities of heart beat	N04 - Nephrotic syndrome		H20 - Endoscopic extirpation of lesion of colon	M15 - Operations on kidney along nephrostomy tube track
W06 - Fall involving bed	I95 - Hypotension	I65 - Occlusion and stenosis of precerebral arteries, not infarct		H55 - Other operations on perianal region	W28 - Other internal fixation of bone
W02 - Fall involving ice-skates, skis, roller-skates or skateboards	Z95 - Presence of cardiac and vascular implants and grafts	E43 - Unspecified severe protein- calorie malnutrition		G73 - Attention to connection of ileum	J12 - Other therapeutic percutaneous operations on liver
W11 - Fall on and from ladder	A41 - Other sepsis	R58 - Hemorrhage,		G69 - Excision of ileum	H13 - Bypass of colon
W50 - Hit, struck, kicked, twisted, bitten or scratched by another person	M06 - Other rheumatoid arthritis	M11 - Other crystal arthropathies		T25 - Primary repair of incisional hernia	L63 - Transluminal operations on femoral artery
Y85 - Sequelae of transport accidents	J98 - Other respiratory disorders	A31 - Infection due to other mycobacteria		Y20 - Biopsy of organ NOC	W37 - Total prosthetic replacement of hip joint using cement

W08 - Fall involving other furniture	I20 - Angina pectoris	J61 - Pneumoconiosis due to asbestos and other mineral fibers		X90 - High cost haematology and nutrition drugs	Q23 - Unilateral excision of adnexa of uterus
W07 - Fall involving chair	R06 - Abnormalities of breathing	I64 - Stroke, not specified as haemorrhage or infarction		G74 - Creation of artificial opening into ileum	V54 - Other operations on spine
V99 - Unspecified transport accident	M13 - Other arthritis	W44 - Foreign body entering into or through eye or natural orifice		R37 - Non-routine obstetric scan for fetal observations	P13 - Other operations on female perineum
W22 - Striking against or struck by other objects	Y95 - Nosocomial condition	A18 - Tuberculosis of other organs		R36 - Routine obstetric scan	T10 - Therapeutic endoscopic operations on pleura
W54 - Bitten or struck by dog	T82 - Complications of cardiac, vascular prosthetic devices, implants, grafts	I07 - Rheumatic tricuspid valve diseases		Y22 - Drainage of organ NOC	W40 - Total prosthetic replacement of knee joint using cement
W00 - Fall on same level involving ice and snow	I50 - Heart failure	R77 - Other abnormalities of plasma proteins		T46 - Other drainage of peritoneal cavity	W47 - Prosthetic replacement of head of femur not using cement
W23 - Caught, crushed, jammed or pinched in or between objects	J22 - Unspecified acute lower respiratory infection	G95 - Other diseases of spinal cord		T31 - Other operations on anterior abdominal wall	T36 - Operations on omentum
W21 - Striking against or struck by sports equipment	R18 - Ascites	A16 - Respiratory tuberculosis, not confirmed bacteriologically or histologically		Y18 - Release of organ NOC	G82 - Other operations on ileum
W03 - Other fall on same level due to collision with, or pushing by another	M45 - Ankylosing spondylitis	Y41 - Other systemic anti-infectives and antiparasitics		J18 - Excision of gall bladder	K59 - Cardioverter defibrillator introduced through the vein
X82 - Intentional self-harm by crashing of motor vehicle	I73 - Other peripheral vascular diseases	K70 - Alcoholic liver disease		H44 - Manipulation of rectum	G67 - Other operations on jejunum
V89 - Motor- or nonmotor-vehicle accident, type of vehicle unspecified	A08 - Viral and other specified intestinal infections	G30 - Alzheimer's disease		T34 - Open drainage of peritoneum	W46 - Prosthetic replacement of head of femur using cement
W55 - Bitten or struck by other mammals	I26 - Pulmonary embolism	J99 - Respiratory disorders in diseases classified elsewhere		T30 - Opening of abdomen	G53 - Other open operations on duodenum
S63 - Dislocation, sprain and strain of joints and ligaments at wrist and hand	J43 - Emphysema	M87 - Osteonecrosis		X89 - High cost immunosuppressant drugs	X70 - Procurement of drugs for chemotherapy for neoplasm Bands 1-5
V59 - Occupant of pick-up truck or van injured transport accidents	I51 - Complications and ill-defined descriptions of heart disease	D47 - lymphoid, haematopoietic and related tissue - neoplasm		G78 - Other open operations on ileum	P05 - Excision of vulva

S13 - Dislocation, sprain and strain of joints and ligaments at neck level	I21 - Acute myocardial infarction	F69 - Unspecified disorder of adult personality and behavior		H58 - Drainage through perineal region	T19 - Simple excision of inguinal hernial sac
S92 - Fracture of foot, except ankle	I08 - Multiple valve diseases	M24 - Other specific joint derangements		Y71 - Late operations NOC	X09 - Amputation of leg
V49 - Car occupant injured in other and unspecified transport accidents	K85 - Acute pancreatitis	N31 - Neuromuscular dysfunction of bladder, not elsewhere classified		E85 - Ventilation support	G58 - Excision of jejunum
W13 - Fall from, out of or through building or structure	R56 - Convulsions, not elsewhere classified	J03 - Acute tonsillitis		R24 - Normal delivery	W25 - Closed reduction of fracture of bone and external fixation
S53 - Dislocation, sprain and strain of joints and ligaments of elbow	I44 - Atrioventricular and left bundle-branch block	T47 - Poisoning by agents primarily affecting the gastrointestinal system		Y05 - Excision of organ NOC	W80 - Debridement and irrigation of joint
S53 - Dislocation, sprain and strain of joints and ligaments of elbow	K81 - Cholecystitis	G57 - Mononeuropathies of lower limb		Y81 - Spinal anaesthetic	B14 - Excision of parathyroid gland
V28 - Motorcycle rider injured in noncollision transport accident	M16 - Coxarthrosis [arthrosis of hip]	I61 - Intracerebral haemorrhage		H07 - Other excision of right hemicolon	B08 - Excision of thyroid gland
V48 - Car occupant injured in noncollision transport accident	I67 - Other cerebrovascular diseases	I31 - Other diseases of pericardium		A84 - Neurophysiological operations	E55 - Open extirpation of lesion of lung
	D70 - Agranulocytosis	J06 - Acute upper respiratory infections of multiple and unspecified sites		Y25 - Suture of organ NOC	X73 - Delivery of oral chemotherapy for neoplasm
	I63 - Cerebral infarction	T93 - Sequelae of injuries of lower limb		H52 - Destruction of haemorrhoid	X71 - Procurement of drugs for chemotherapy for neoplasm in Bands 6-10
	G35 - Multiple sclerosis	S83 - Dislocation, sprain and strain of joints and ligaments of knee		T12 - Puncture of pleura	E59 - Other operations on lung
	T39 - Poisoning by nonopioid analgesics, antipyretics and antirheumatics	M00 - Pyogenic arthritis		T27 - Repair of other hernia of abdominal wall	H17 - Intra-abdominal manipulation of colon
	S72 - Fracture of femur	Y65 - Other misadventures during surgical and medical care		R15 - Other induction of labour	R12 - Operations on gravid uterus
	I42 - Cardiomyopathy	S24 - Injury of nerves and spinal cord at thorax level		R14 - Surgical induction of labour	M53 - Vaginal operations to support outlet of female bladder
	J93 - Pneumothorax	S12 - Fracture of neck		X33 - Other blood transfusion	Q20 - Other operations on uterus

	M17 - Gonarthrosis [arthrosis of knee]	L95 - Vasculitis limited to skin, not elsewhere classified		Y15 - Attention to stent in organ NOC	T26 - Repair of recurrent incisional hernia
	I34 - Nonrheumatic mitral valve disorders	D59 - Acquired haemolytic anaemia		Y26 - Other repair of organ NOC	W19 - Primary open reduction of fracture of bone and fixation
	I46 - Cardiac arrest	T44 - Poisoning by drugs primarily affecting the autonomic nervous system		Y51 - Approach to organ through artificial opening into GI tract	T24 - Primary repair of umbilical hernia
	R02 - Gangrene, not elsewhere classified	T50 - Poisoning by diuretics and other and unspecified drugs,		H56 - Other operations on anus	G63 - Other open operations on jejunum
	S42 - Fracture of shoulder and upper arm	T86 - Failure and rejection of transplanted organs and tissues		H62 - Other operations on bowel	N24 - Operations on male perineum
	S01 - Open wound of head	L88 - Pyoderma gangrenosum		R32 - Repair of obstetric laceration	L76 - Endovascular placement of stent
	R59 - Enlarged lymph nodes	Y91 - Evidence of alcohol involvement determined by level of intoxication		E42 - Exteriorisation of trachea	E54 - Excision of lung
	N19 - Unspecified renal failure	D33 - Benign neoplasm of brain and other parts of central nervous system		Q11 - Other evacuation of contents of uterus	H04 - Total excision of colon and rectum
	I82 - Other venous embolism and thrombosis	G51 - Facial nerve disorders		U28 - Other diagnostic tests on skin	J40 - Endoscopic retrograde placement of prosthesis in bile duct
	J69 - Pneumonitis due to solids and liquids	W78 - Inhalation of gastric contents		J43 - Diagnostic endoscopic retrograde examination of bile duct and pancreatic duct	L67 - Excision of other artery
	I69 - Sequelae of cerebrovascular disease	V18 - Pedal cyclist injured in noncollision transport accident		R17 - Elective caesarean delivery	V29 - Primary excision of cervical intervertebral disc
	R57 - Shock, not elsewhere classified	N15 - Other renal tubulo-interstitial diseases		Y07 - Obliteration of cavity of organ NOC	J72 - Other operations on spleen
	G62 - Other polyneuropathies	I62 - Other nontraumatic intracranial haemorrhage		T28 - Other repair of anterior abdominal wall	U52 - Rehabilitation for psychiatric disorders
	I27 - Other pulmonary heart diseases	Z08 - Follow-up examination after treatment for malignant neoplasms		H48 - Excision of lesion of anus	L90 - Open removal of thrombus from vein
	J81 - Pulmonary oedema	G50 - Disorders of trigeminal nerve		H19 - Other open operations on colon	G21 - Other operations on oesophagus

	N70 - Salpingitis and oophoritis	F02 - Dementia in other diseases classified elsewhere		J38 - Endoscopic incision of sphincter of Oddi	F36 - Other operations on tonsil
	N80 - Endometriosis	I72 - Other aneurysm and dissection		X85 - High cost neurology drugs	J24 - Therapeutic percutaneous operations on gall bladder
	M46 - Other inflammatory spondylopathies	G90 - Disorders of autonomic nervous system		T20 - Primary repair of inguinal hernia	Q43 - Partial excision of ovary
	E05 - Thyrotoxicosis [hyperthyroidism]	H46 - Optic neuritis		H33 - Excision of rectum	L27 - Transluminal insertion of stent graft for aneurysmal segment of aorta
	K75 - Other inflammatory liver diseases	J05 - Acute obstructive laryngitis [croup] and epiglottitis		A55 - Diagnostic spinal puncture	T22 - Primary repair of femoral hernia
	M51 - Other intervertebral disc disorders	K71 - Toxic liver disease		M13 - Percutaneous puncture of kidney	P23 - Other repair of prolapse of vagina
	M80 - Osteoporosis with pathological fracture	S31 - Open wound of abdomen, lower back and pelvis		X86 - High cost anti-infective drugs	J42 - Therapeutic endoscopic retrograde operations on pancreatic duct
	M05 - Seropositive rheumatoid arthritis	A02 - Other salmonella infections		P09 - Other operations on vulva	A14 - Other operations on connection from ventricle of brain
	R91 - Abnormal findings on diagnostic imaging of lung	N11 - Chronic tubulo-interstitial nephritis		G60 - Artificial opening into jejunum	K45 - Connection of thoracic artery to coronary artery
	I35 - Nonrheumatic aortic valve disorders	J13 - Pneumonia due to Streptococcus pneumoniae		H11 - Other excision of colon	H09 - Excision of left hemicolon
	J80 - Acute respiratory distress syndrome	I37 - Pulmonary valve disorders		Y08 - Laser therapy to organ NOC	J04 - Repair of liver
	R17 - Unspecified jaundice	E22 - Hyperfunction of pituitary gland		Y02 - Placement of prosthesis in organ NOC	H42 - Perineal operations for prolapse of rectum
	S02 - Fracture of skull and facial bones	M49 - Spondylopathies in diseases classified elsewhere		E95 - Tuberculosis support	W08 - Other excision of bone
	J84 - Other interstitial pulmonary diseases	Q05 - Spina bifida		Q14 - Introduction of abortifacient into uterine cavity	H21 - Other therapeutic endoscopic operations on colon
	M15 - Polyarthrosis	A40 - Streptococcal sepsis		A73 - Other operations on peripheral nerve	M37 - Other repair of bladder
	G81 - Hemiplegia	G12 - Spinal muscular atrophy and related syndromes		Y50 - Approach through abdominal cavity	K16 - Other therapeutic transluminal operations on septum of heart

	M35 - Other systemic involvement of connective tissue	T91 - Sequelae of injuries of neck and trunk		Y06 - Excision of lesion of organ NOC	K25 - Plastic repair of mitral valve
	D73 - Diseases of spleen	R65 - Systemic Inflammatory Response Syndrome [SIRS]		L79 - Other operations on vena cava	G34 - Artificial opening into stomach
	U88 - Agent resistant to multiple antibiotics	I36 - Nonrheumatic tricuspid valve disorders		L72 - Diagnostic transluminal operations on other artery	N17 - Excision of vas deferens
	R04 - Haemorrhage from respiratory passages	S29 - Other and unspecified injuries of thorax		J13 - Diagnostic percutaneous operations on liver	J11 - Transjugular intrahepatic operations on blood vessel of liver
	I71 - Aortic aneurysm and dissection	J04 - Acute laryngitis and tracheitis		R42 - Obstetric doppler ultrasound	G71 - Bypass of ileum
	Y40 - Systemic antibiotics	S39 - injuries of abdomen, lower backpelvis		R38 - Other non-routine obstetric scan	O20 - Endovascular placement of stent
	N03 - Chronic nephritic syndrome	T87 - Complications peculiar to reattachment and amputation		R40 - Other maternal physiological assessments	W94 - Hybrid prosthetic replacement of hip joint using cemented femoral
	S22 - Fracture of rib(s), sternum and thoracic spine	J94 - Other pleural conditions		Q07 - Abdominal excision of uterus	V62 - ercutaneous intradiscal radiofrequency thermocoagulation
	I74 - Arterial embolism and thrombosis	G61 - Inflammatory polyneuropathy		R27 - Other operations to facilitate delivery	L74 - Arteriovenous shunt
	D37 - Neoplasm of uncertain or unknown behaviour of oral cavity	N10 - Acute tubulo-interstitial nephritis		Y14 - Placement of stent in organ NOC	K49 - Transluminal balloon angioplasty of coronary artery
	T42 - Poisoning by antiepileptic, sedative-hypnotic, antiparkinson drugs	O16 - Unspecified maternal hypertension		B37 - Other operations on breast	H14 - Exteriorisation of caecum
	Z49 - Care involving dialysis	J42 - Unspecified chronic bronchitis		R18 - Other caesarean delivery	L29 - Reconstruction of carotid artery
	J47 - Bronchiectasis	F30 - Manic episode		Y74 - Minimal access to thoracic cavity	Q31 - Incision of fallopian tube
	Z89 - Acquired absence of limb	I33 - Acute and subacute endocarditis		G76 - Intra-abdominal manipulation ileum	J48 - Other therapeutic percutaneous operations on bile duct
	R54 - Age-related physical debility	K73 - Chronic hepatitis, not elsewhere classified		G70 - Open extirpation of lesion of ileum	N06 - Other excision of testis
	G25 - Other extrapyramidal and movement disorders	B44 - Aspergillosis		R22 - Vacuum delivery	X10 - Amputation of foot

	E23 - Hypofunction and other disorders of pituitary gland	V17 - Pedal cyclist injured in collision with fixed or stationary object		Y32 - Re-exploration of organ NOC	A76 - Chemical destruction of sympathetic nerve
	S82 - Fracture of lower leg, including ankle	N25 - Disorders resulting from impaired renal tubular function		H06 - Extended excision of right hemicolon	W81 - Other open operations on joint
	S32 - Fracture of lumbar spine and pelvis	A19 - Miliary tuberculosis		H46 - Other operations on rectum	M83 - Other operations on urinary tract
	F01 - Vascular dementia	M14 - Arthropathies in other diseases classified elsewhere		K75 - Percutaneous transluminal balloon angioplasty, insertion of stent coronary	X17 - Separation of conjoined twins
	E80 - Disorders of porphyrin and bilirubin metabolism	D80 - Immunodeficiency with predominantly antibody defects		H41 - Other operations on rectum through anus	Y47 - Burrhole approach to contents of cranium
	N12 - Tubulo-interstitial nephritis, not specified as acute or chronic	D65 - Disseminated intravascular coagulation [defibrination syndrome]		U31 - Pacemaker testing	R34 - Other obstetric operations
	R34 - Anuria and oliguria	F00 - Dementia in Alzheimer's disease		W38 - Total prosthetic replacement of hip joint not using cement	E52 - Other operations on bronchus
	D72 - Other disorders of white blood cells	I22 - Subsequent myocardial infarction		Q47 - Other open operations on ovary	H29 - Subtotal excision of colon
	B02 - Zoster [herpes zoster]	M32 - Systemic lupus erythematosus		L71 - Therapeutic transluminal operations on other artery	Q51 - Other operations on ovary
	M23 - Internal derangement of knee	E84 - Cystic fibrosis		M49 - Other operations on bladder	P25 - Other repair of vagina
	Z94 - Transplanted organ and tissue status	X41 - Accidental poisoning antiepileptic, sedative, antiparkinsonic drugs		R21 - Forceps cephalic delivery	A83 - Electroconvulsive therapy
	R72 - Abnormality of white blood cells, not elsewhere classified	M72 - Fibroblastic disorders		K60 - Cardiac pacemaker system introduced through vein	V25 - Primary decompression operations on lumbar spine
	S06 - Intracranial injury	G24 - Dystonia		Q22 - Bilateral excision of adnexa uterus	X11 - Amputation of toe
	M08 - Juvenile arthritis	G82 - Paraplegia and tetraplegia		P29 - Other operations on vagina	K57 - Other therapeutic transluminal operations on heart
	K72 - Hepatic failure, not elsewhere classified	T37 - Poisoning by other systemic anti-infectives and antiparasitics		W20 - Primary open reduction of fracture of bone	H18 - Open endoscopic operations on colon

	T84 - Complications of internal orthopaedic prosthetic devices, implants and grafts	M09 - Juvenile arthritis in diseases classified elsewhere		K50 - Other therapeutic transluminal operations on coronary artery	P17 - Excision of vagina
	S09 - Other and unspecified injuries of head	J86 - Pyothorax		W24 - Closed reduction of fracture of bone and internal fixation	A75 - Excision of sympathetic nerve
	K74 - Fibrosis and cirrhosis of liver	I24 - Other acute ischaemic heart diseases		H12 - Extirpation of lesion of colon	H40 - Operations on rectum through anal sphincter
	E21 - Hyperparathyroidism and other disorders of parathyroid gland	G45 - Transient cerebral ischaemic attacks and related syndromes		H08 - Excision of transverse colon	G51 - Bypass of duodenum
	G20 - Parkinsons disease	G09 - Sequelae of inflammatory diseases of central nervous system		J37 - Other open operations on bile duct	W41 - Total prosthetic replacement of knee joint not using cement
	G55 - Nerve root and plexus compressions in diseases	G63 - Polyneuropathy in diseases classified elsewhere		Q41 - Other operations on fallopian tube	N20 - Other operations on spermatic cord
	D46 - Myelodysplastic syndromes	Q24 - Other congenital malformations of heart		A57 - Operations on spinal nerve root	L13 - Transluminal operations on pulmonary artery
	G31 - Other degenerative diseases of nervous system, not elsewhere classified	Q76 - Congenital malformations of spine and bony thorax		M33 - Percutaneous ureteric stent procedures	T23 - Repair of recurrent femoral hernia
	B18 - Chronic viral hepatitis	J40 - Bronchitis, not specified as acute or chronic		A81 - Other operations on sympathetic nerve	A20 - Other operations on ventricle of brain
	G83 - Other paralytic syndromes	I81 - Portal vein thrombosis		M66 - Other therapeutic endoscopic operations on outlet of male bladder	W82 - Therapeutic endoscopic operations on semilunar cartilage
	S27 - Injury of other and unspecified intrathoracic organs	M31 - Other necrotizing vasculopathies		J21 - Incision of gall bladder	L59 - Other bypass of femoral artery
				L89 - Other endovascular placed stent	W33 - Other open operations on bone
				T07 - Open excision of pleura	G33 - Other connection of stomach to jejunum
				A12 - Creation of connection from ventricle of brain	V40 - Stabilisation of spine
				J51 - Laparoscopic ultrasound examination of bile duct	H54 - Dilation of anal sphincter
				K40 - Saphenous vein graft replacement of coronary artery	H70 - Diagnostic endoscopic examination of enteric pouch

				V38 - Primary fusion of other joint of spine	W58 - Other reconstruction of joint
				Q08 - Vaginal excision of uterus	T29 - Operations on umbilicus
				A48 - Other operations on spinal cord	X63 - Radiotherapy Volume Definition
				R10 - Other operations on amniotic cavity	W26 - Other closed reduction of fracture of bone
				L97 - Other operations on blood vessel	W15 - Division of bone of foot
				W23 - Secondary open reduction of fracture of bone	H27 - Other therapeutic endoscopic operations on sigmoid colon
				K23 - Other operations of wall of heart	T21 - Repair of recurrent inguinal hernia
				W30 - Other external fixation of bone	J32 - Repair of bile duct
				A13 - Attention to component of connection from ventricle of brain	H16 - Incision of colon
				M02 - Total excision of kidney	X72 - Delivery of chemotherapy for neoplasm
				Q54 - Operations on ligament of uterus	
				Q24 - Other excision of adnexa of uterus	
				M10 - Other therapeutic endoscopic operations on kidney	

Appendix 3

Comparison of included and excluded patients

		Included (N)	Percentage (%)	Excluded (N)	Percentage (%)	P Value
Sex	Male	5,475	45%	1,174	51%	
	Female	6,755	55%	1,113	49%	
Total		12,230		2,287		<0.001
Age Quintile	18-24	2,478	20%	61	4%	
	25-31	2,459	20%	77	5%	
	32-41	2,550	21%	144	10%	
	42-53	2,428	20%	282	19%	
	54+	2,315	19%	912	62%	
Total		12,230		1,476		<0.001
Ethnicity	White	10,792	88%	1,960	86%	
	Asian	346	3%	77	3%	
	Other minority ethnicities	409	3%	89	4%	
	Unknown	683	6%	162	0%	
	Total	12,230		2,288		0.006
Deprivation Quintile	1 (Most Deprived)	2655	22%	414	19%	
	2	2699	22%	405	19%	
	3	2496	20%	460	21%	
	4	2282	19%	447	21%	
	5 (Least Deprived)	2098	17%	416	19%	
Total		12,230		2,142		<0.001
Charlson Co-morbidity score	0	10,250	84%	1,766	77%	
	1-4	1511	12%	340	15%	
	5+	4469	4%	182	8%	
Total		12,230		2,288		<0.001

**'Excluded' group consists of patients with valid a Crohn's disease diagnosis and index surgery between 2007-2016, but who were excluded either due to a cancer diagnosis, a date discrepancy, surgery prior to the start of the study or some missing or invalid demographic data.*

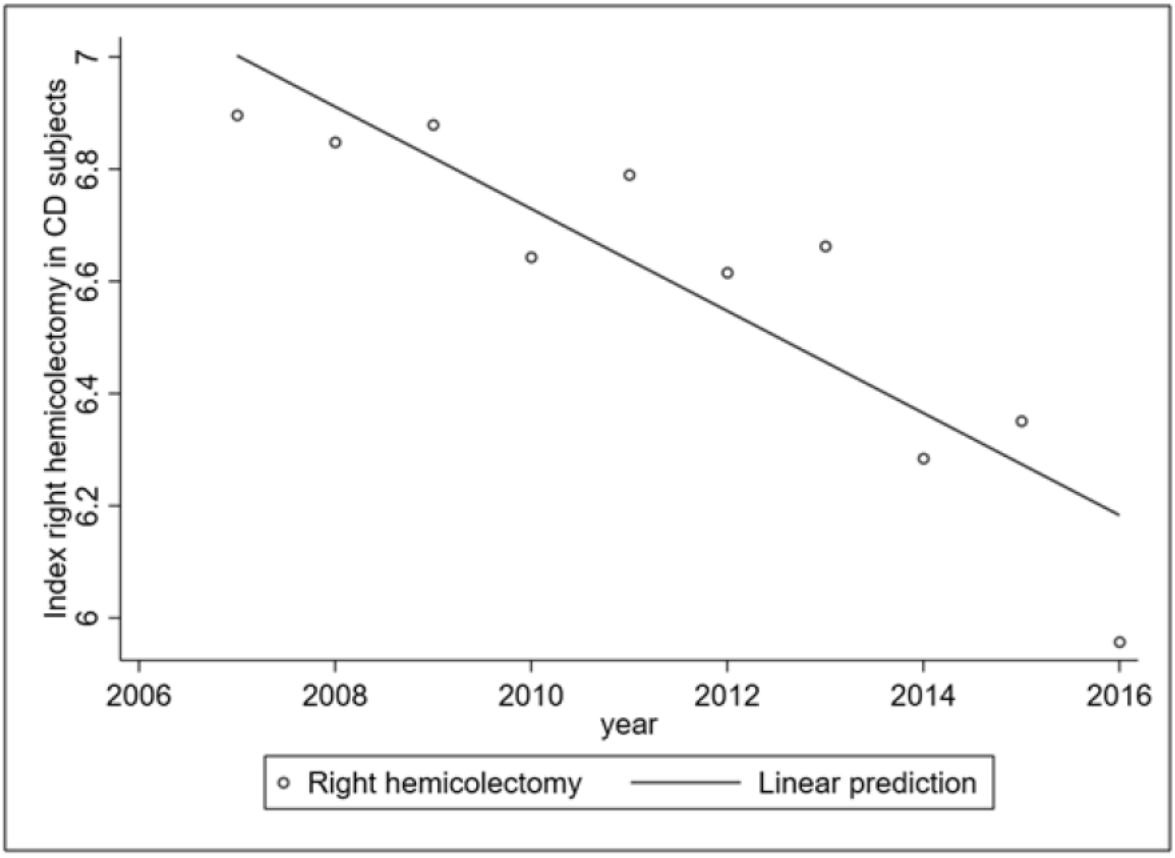


Figure A4: Graph showing fall in index right hemicolectomy procedures per 1,000 subjects with Crohn's disease (CD) by year of study in England.

Appendix 5

5.1 Demographic characteristics of patients including subjects with further surgery within 30-days of index procedure and surgery at risk of being a staged completion of the index procedure

Demographic		**Patients N (%)**		**Further surgery (inclusive) N %**	
Total		**12,230**	**100**	**1,872**	**15.3%**
Follow-up years Median (IQR)				5.7 (3.3-8.5)	
Sex	**Male**	5475	44.8%	895	16.3%
	Female	6755	55.2%	977	14.5%
Age Median (IQR)		36 (26,49)		34 (26,47)	
Age Quintile	**18-24**	2478	20.3%	402	16.2%
	25-31	2459	20.1%	395	16.1%
	32-41	2550	20.9%	424	16.6%
	42-53	2428	19.9%	344	14.2%
	54+	2315	18.9%	307	13.3%
Ethnicity	**White**	10792	88.2%	1653	15.3%
	Asian	346	2.8%	57	16.5%
	Other minority ethnicities	409	3.3%	67	16.4%
	Unknown	683	5.6%	95	13.9%
Charlson Comorbidity Score	**0**	10250	83.8%	1572	15.3%
	1-4	1511	12.4%	219	14.5%
	5+	469	3.8%	81	17.3%
Deprivation Quintile	**1 (Most Deprived)**	2655	21.7%	402	15.1%
	2	2699	22.1%	395	14.6%
	3	2496	20.4%	424	17.0%
	4	2282	18.7%	344	15.1%
	5 (Least Deprived)	2098	17.2%	307	14.6%
Index Surgery Admission Method	**Emergency**	4924	40.3%	934	19.0%
	Elective	7225	59.1%	923	12.8%
	Unknown	81	0.7%	15	18.5%
Further Surgery Admission Method	**Emergency**	-	-	711	38.0%
	Elective	-	-	1148	61.3%
	Unknown	-	-	13	0.7%
Year of Index Surgery	**2007**	1063	8.7%	222	20.9%
	2008	1100	9.0%	242	22.0%
	2009	1149	9.4%	220	19.1%
	2010	1189	9.7%	217	18.3%
	2011	1226	10.0%	184	15.0%

	2012	1274	10.4%	218	17.1%
	2013	1292	10.6%	155	12.0%
	2014	1263	10.3%	173	13.7%
	2015	1357	11.1%	137	10.1%
	2016	1317	10.8%	104	7.9%
Provider Volume of right hemicolectomy	**Low (1-54)**	1556	12.7%	244	15.7%
	Medium (55-89)	3801	31.1%	553	14.5%
	High (90+)	6873	56.2%	1075	15.6%
Colonoscopy Timing post Index Surgery	**0-3 Months (Very Early)**	205	1.7%	41	20.0%
	3-6 Months (Early)	1120	9.2%	166	14.8%
	6-12 Months (On Time)	2681	21.9%	434	16.2%
	12-18 Months (Late)	1395	11.4%	256	18.4%
	18-24 Months (Very Late)	817	6.7%	152	18.6%
	Later or Never	6012	49.2%	823	13.7%
Prior perianal surgery		1475	12.1%	297	20.1%
Laparoscopic index surgery		4587	37.5%	523	11.4%

*Patient numbers ≤5 supressed to maintain anonymity.

5.2 Cox proportional hazards model of factors associated with further resectional surgery at the site of previous right hemicolectomy for Crohn's disease including subjects with surgery within 30-days of index operation and surgery at risk of being a staged completion of the index procedure

Demographic		Haz. Ratio	[95% CI]		P Value
Sex	**Male (Baseline)**				
	Female	0.92	0.84	1.01	0.084
Age quintile	**18-24 (Baseline)**				
	25-31	1.03	0.89	1.18	0.705
	32-41	1.06	0.93	1.22	0.373
	42-53	0.93	0.80	1.07	0.316
	54+	0.88	0.76	1.03	0.114
Ethnicity	**White (Baseline)**				
	Asian	0.99	0.76	1.29	0.939
	Other minority ethnicities	1.05	0.82	1.35	0.687
	Unknown	0.93	0.75	1.14	0.475
Charlson (comorbidity) score	**0 (Baseline)**				
	1-4	1.05	0.91	1.21	0.515
	5+	1.47	1.16	1.85	**0.001**
Deprivation quintile	**1 (Most Deprived) (Baseline)**				
	2	0.94	0.82	1.07	0.337
	3	0.92	0.80	1.05	0.224
	4	0.90	0.78	1.03	0.130
	5 (Least Deprived)	0.85	0.73	0.98	**0.028**
Index surgery admission method	**Emergency (Baseline)**				
	Non-Emergency	0.69	0.63	0.76	**<0.001**
Year of index right hemicolectomy	**2007 (Baseline)**				
	2008	1.13	0.94	1.36	0.187
	2009	1.03	0.85	1.25	0.754
	2010	1.05	0.87	1.27	0.611
	2011	0.92	0.75	1.12	0.409
	2012	1.19	0.98	1.44	0.084
	2013	0.88	0.71	1.09	0.249
	2014	1.11	0.90	1.37	0.316
	2015	0.94	0.75	1.18	0.605
	2016	0.83	0.65	1.06	0.133
Provider volume of Crohn's disease	**Low (1-54) (Baseline)**				
	Medium (55-89)	0.92	0.79	1.07	0.297

index right hemicolectomies (tertile)	**High (90+)**	0.99	0.86	1.14	0.915
Prior Perianal Surgery		1.36	1.20	1.55	**<0.001**
Laparoscopic Index Surgery		0.79	0.70	0.88	**<0.001**

Appendix 6

6.1 Demographic table of patients with at least 5-years of follow-up following right hemicolectomy

Demographic		Patients N %		Further surgery by 5-years N %	
Total		**8293**	**100%**	**747**	**9.0%**
Sex	**Male**	3668	44.2%	340	9.3%
	Female	4625	55.8%	407	8.8%
Age Median (IQR)		1709	20.6%	172	10.1%
Age Quintile	**18-24**	1642	19.8%	144	8.8%
	25-31	1760	21.2%	172	9.8%
	32-41	1548	18.7%	126	8.1%
	42-53	1634	19.7%	133	8.1%
	54+	1709	20.6%	172	10.1%
Ethnicity	**White**	7393	89.1%	673	9.1%
	Asian	216	2.6%	18	8.3%
	Other minority ethnicities	262	3.2%	17	6.5%
	Unknown	422	5.1%	39	9.2%
Charlson Comorbidity Score	**0**	7046	85.0%	614	8.7%
	1-4	961	11.6%	101	10.5%
	5+	286	3.4%	32	11.2%
Deprivation Quintile	**1 (Most Deprived)**	1753	21.1%	178	10.2%
	2	1831	22.1%	169	9.2%
	3	1704	20.5%	156	9.2%
	4	1553	18.7%	125	8.0%
	5 (Least Deprived)	1452	17.5%	119	8.2%
Index Surgery Admission Method	**Emergency**	3319	40.0%	351+*	*
	Elective	4917	59.3%	388	7.9%
	Unknown	57	0.07%	*	*
Further Surgery Admission Method	**Emergency**	-	-	269+*	*
	Elective	-	-	469	62.8%
	Unknown	-	-	*	*
Year of Index Surgery	**2007**	1063	12.8%	103	9.7%
	2008	1100	13.3%	108	9.8%
	2009	1149	13.9%	117	10.2%
	2010	1189	14.3%	105	8.8%
	2011	1226	14.8%	86	7.0%
	2012	1274	15.4%	123	9.7%

	2013	1292	15.6%	105	8.1%
	2014	1063	12.8%	103	9.7%
	2015	1100	13.3%	108	9.8%
	2016	1149	13.9%	117	10.2%
Colonoscopy Timing post Index Surgery	**0-3 Months (Very Early)**	140	1.7%	16	11.4%
	3-6 Months (Early)	709	8.5%	66	9.3%
	6-12 Months (On Time)	1623	19.6%	206	12.7%
	12-18 Months (Late)	911	11.0%	106	11.6%
	18-24 Months (Very Late)	536	6.5%	59	11.0%
	Later or Never	4374	52.7%	294	6.7%
Prior perianal surgery		940	11.3%	118	12.6%
Laparoscopic index surgery		2721	32.8%	197	7.2%
Median (IQR) time to further surgery (years)		-	-	2.88 (1.04-3.58)	

*Patient numbers ≤5 supressed to maintain anonymity

6.2 Multivariable logistic regression analysis of factors associated with further surgery at the anastomotic site within 5 years in patients undergoing right hemicolectomy between 2007 and 2013

Demographic		Odds Ratio	[95% CI]		p-value
Sex	**Male (Baseline)**				
	Female	0.99	0.85	1.15	0.873
Age quintile	**18-24 (Baseline)**				
	25-31	0.83	0.66	1.06	0.131
	32-41	0.95	0.76	1.19	0.643
	42-52	0.79	0.62	1.01	0.055
	53+	0.74	0.57	0.95	**0.017**
Charlson (comorbidity) score	**0 (Baseline)**				
	1-4	1.34	1.07	1.67	**0.012**
	5+	1.40	0.94	2.08	0.098
Ethnicity	**White (Baseline)**				
	Asian	0.79	0.48	1.29	0.345
	Other minority ethnicities	0.63	0.38	1.05	0.078
	Unknown	1.03	0.73	1.45	0.857
Deprivation Quintile	**1 (Most Deprived) (Baseline)**				
	2	0.87	0.70	1.09	0.235
	3	0.89	0.71	1.12	0.327
	4	0.76	0.60	0.97	**0.028**
	5 (Least Deprived)	0.79	0.62	1.01	0.065
Index Surgery Admission Method	**Emergency (Baseline)**				
	Elective	0.78	0.67	0.92	**0.002**
Year of Index Surgery	**2007 (Baseline)**				
	2008	1.01	0.76	1.35	0.924
	2009	1.04	0.79	1.38	0.773
	2010	0.89	0.66	1.18	0.409
	2011	0.70	0.52	0.95	**0.021**
	2012	0.98	0.74	1.30	0.912
	2013	0.82	0.61	1.10	0.179
Provider volume of Crohn's disease index right hemicolectomies (tertile)	**Low (1-54) (Baseline)**				
	Medium (55-89)	0.92	0.71	1.18	0.492
	High (90+)	0.93	0.74	1.17	0.551
Prior Perianal Surgery		1.48	1.20	1.83	**<0.001**
Laparoscopic Index Surgery		0.79	0.66	0.94	**0.010**
Colonoscopy 6-12 months post right hemicolectomy		1.45	1.22	1.74	**<0.001**

Appendix 7

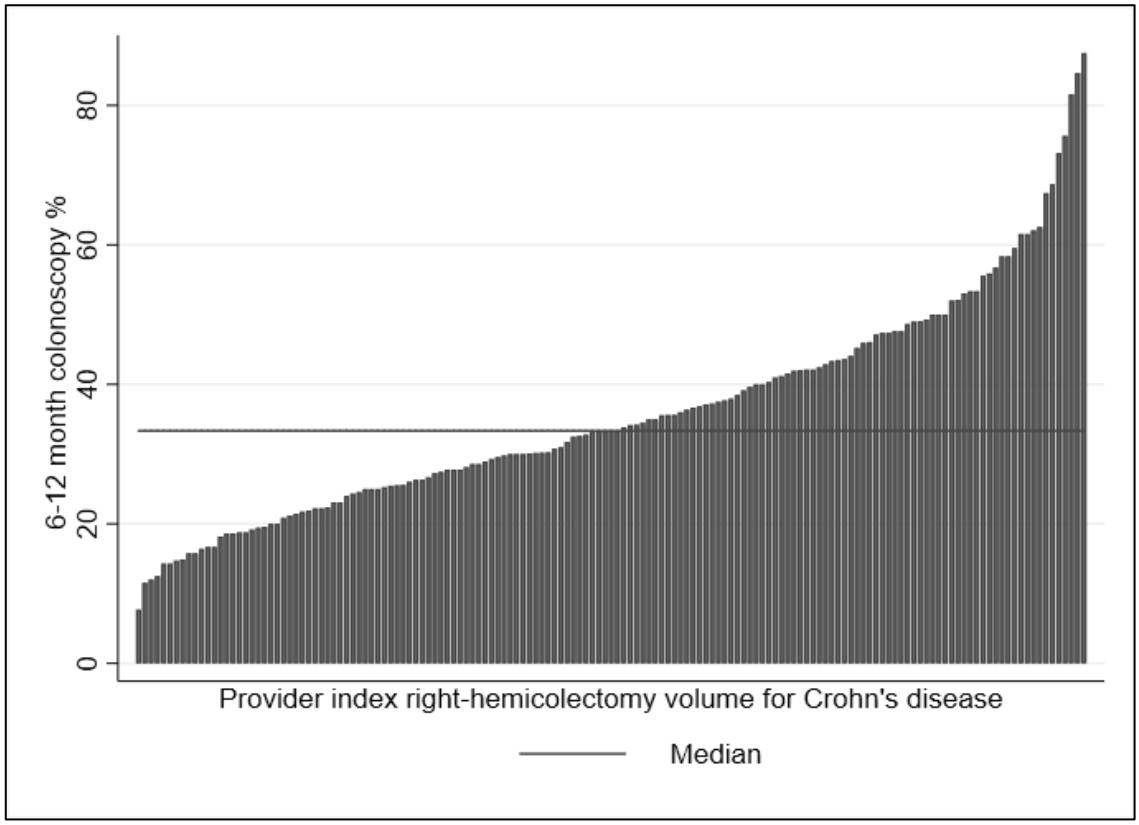


Figure A7: Graph showing differences in 6-12 month colonoscopy provision by right-hemicolectomy provider

Appendix 8

Table of colonoscopy numbers performed in England over the study period and the number and percentage of these performed on subjects with a Crohn's disease diagnosis

Colonoscopy Numbers for England coded in Hospital Episode Statistics			
Year	**All colonoscopies**	**With Crohn's Diagnosis**	**Percentage**
2007	470648	11517	2.4%
2008	509653	13141	2.6%
2009	544313	14562	2.7%
2010	565781	15694	2.8%
2011	593476	17225	2.9%
2012	662922	18876	2.8%
2013	635306	19517	3.1%
2014	671819	21292	3.2%
2015	707833	21821	3.1%
2016	738837	23541	3.2%
2017	763661	23997	3.1%

Appendices for chapter 6 Manuscript 1: The risk of later diagnosis of inflammatory bowel disease in patients with dermatological disorders associated with inflammatory bowel disease

Appendix 1

Read Codes:

Ulcerative Colitis:

Code	Description
J410z00	Ulcerative proctocolitis NOS
N031000	Arthropathy in ulcerative colitis
J41z.00	Idiopathic proctocolitis NOS
14C4.11	H/O: ulcerative colitis
J41y.00	Other idiopathic proctocolitis
J412.00	Ulcerative (chronic) ileocolitis
J413.00	Ulcerative pancolitis
Jyu4100	[X]Other ulcerative colitis
N045400	Juvenile arthritis in ulcerative colitis
J410000	Ulcerative ileocolitis
J411.00	Ulcerative (chronic) enterocolitis
J41..00	Idiopathic proctocolitis
J410.00	Ulcerative proctocolitis
J410300	Ulcerative proctitis
J410400	Exacerbation of ulcerative colitis
J41..12	Ulcerative colitis and/or proctitis
J410100	Ulcerative colitis
J410200	Ulcerative rectosigmoiditis
J41yz00	Other idiopathic proctocolitis NOS

Crohn's Disease:

Code	Description
J400.00	Regional enteritis of the small bowel
J400000	Regional enteritis of the duodenum
J400100	Regional enteritis of the jejunum
J40..00	Regional enteritis - Crohn's disease
N031100	Arthropathy in Crohn's disease
ZR3S.11	CDAI - Crohn's disease activity index
J402.00	Regional ileocolitis
J401z11	Crohn's colitis
J400200	Crohn's disease of the terminal ileum
J400300	Crohn's disease of the ileum unspecified
J400400	Crohn's disease of the ileum NOS
J400500	Exacerbation of Crohn's disease of small intestine
J08z900	Orofacial Crohn's disease
J400z00	Crohn's disease of the small bowel NOS
J40z.00	Regional enteritis NOS
J401000	Regional enteritis of the colon
J401100	Regional enteritis of the rectum
J401200	Exacerbation of Crohn's disease of large intestine
J40..12	Granulomatous enteritis
J40..11	Crohn's disease
ZR3S.00	Crohn's disease activity index
J401.00	Regional enteritis of the large bowel
J401z00	Crohn's disease of the large bowel NOS
Jyu4000	[X]Other Crohn's disease
N045300	Juvenile arthritis in Crohn's disease
J40z.11	Crohn's disease NOS

Dermatological Extraintestinal Manifestations:

Code	Description
M070200	Pyoderma gangrenosum
M070.00	Pyoderma
M070z00	Pyoderma NOS
M152.00	Erythema nodosum
M228.00	Sweet's syndrome
J082400	Aphthous stomatitis
M161H00	Erythrodermic psoriasis
M16y000	Scalp psoriasis
Myu3000	[X]Other psoriasis
M166.00	Palmoplantar pustular psoriasis
M161J00	Flexural psoriasis
M161D00	Pustular psoriasis
M161C00	Psoriasis punctata
M161F00	Psoriasis vulgaris
M16y.00	Other psoriasis and similar disorders
M161E00	Psoriasis universalis
M161B00	Psoriasis plantaris
M161A00	Psoriasis palmaris
M16..00	Psoriasis and similar disorders
M161.00	Other psoriasis
M16z.00	Psoriasis and similar disorders NOS
M161F11	Chronic large plaque psoriasis
38Gg.00	Psoriasis area and severity index
M161800	Psoriasis inveterata
M161z00	Psoriasis NOS
M161700	Psoriasis gyrata
M161900	Psoriasis ostracea
M161400	Psoriasis discoidea
M161300	Psoriasis diffusa
M161600	Guttate psoriasis

M161200	Psoriasis circinata
M161100	Psoriasis annularis
M161500	Psoriasis geographica
M161000	Psoriasis unspecified

Appendix 2.

Individual dermatological extraintestinal manifestation contribution

Dermatological condition	Subject numbers	Percent (%)
Aphthous stomatitis	702	9.43
Pyoderma Gangrenosum	967	12.99
**Pyoderma code*	*457*	*6.14*
**Pyoderma gangrenosum*	*508*	*6.82*
**Pyoderma-NOS*	*2*	*0.03*
Erythema nodosum	5,581	74.94
Sweet's syndrome	197	2.65

**Codes combined to generate a combined pyoderma gangrenosum (PG) cohort*

NOS: Not otherwise specified

Appendix 3.

Multivariable Cox proportional hazards models for all dermatological conditions associated with inflammatory bowel disease diagnosis.

	Inflammatory Bowel Disease (all)				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Conf. Interval]		p-value	aHR	[95% Conf. Interval]		p-value	aHR	[95% Conf. Interval]		p-value
Combined dermatological conditions	**6.16**	**4.53**	**8.37**	**<0.001**	**3.30**	**1.98**	**5.53**	**<0.001**	**8.54**	**5.74**	**12.70**	**<0.001**
Sex (reference) Male	1.00				1.00				1.00			
Female	1.02	0.73	1.44	0.89	0.80	0.46	1.40	0.442	1.15	0.74	1.79	0.523
Age Category (reference) <18 years	1.00				1.00				1.00			
18-30 years	2.25	1.33	3.81	0.003	7.39	2.07	26.40	0.002	1.49	0.81	2.74	0.197
30-40 years	1.06	0.58	1.95	0.849	5.75	1.50	22.11	0.011	0.57	0.28	1.16	0.122
40-50 years	0.86	0.45	1.67	0.664	5.11	1.28	20.46	0.021	0.43	0.19	0.97	0.042
50-60 years	0.94	0.47	1.85	0.849	5.23	1.28	21.43	0.021	0.46	0.20	1.08	0.075
60-70 years	0.83	0.39	1.75	0.622	5.46	1.28	23.35	0.022	0.37	0.14	0.97	0.043
>70 years	0.66	0.3	1.43	0.291	3.03	0.64	14.38	0.162	0.39	0.15	1.00	0.051
Smoking Status (reference) current smoker	1.00				1.00				1.00			
non smoker	0.72	0.51	1.03	0.069	1.26	0.63	2.52	0.513	0.59	0.40	0.89	0.013
Charlson comorbidity score (reference) 0	1.00				1.00				1.00			
1	1.25	0.89	1.75	0.200	2.00	1.14	3.52	0.016	0.98	0.64	1.51	0.924
>/=2	1.11	0.63	1.96	0.729	1.64	0.67	4.01	0.280	0.93	0.44	1.97	0.848
Body mass index (reference) <25 kg/m^2	1.00				1.00				1.00			
25-30 kg/m^2	0.94	0.64	1.37	0.742	0.81	0.41	1.62	0.552	1.02	0.64	1.61	0.941
>30 kg/m^2	0.64	0.4	1.02	0.061	0.68	0.31	1.51	0.348	0.62	0.35	1.12	0.117
Missing	0.89	0.58	1.35	0.574	1.54	0.79	3.03	0.207	0.66	0.39	1.14	0.134
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.73	1.06	2.81	0.027	1.28	0.56	2.90	0.561	2.01	1.09	3.70	0.025
3	1.64	1.01	2.66	0.047	1.60	0.74	3.47	0.232	1.65	0.88	3.09	0.116
4	1.17	0.69	2	0.556	1.02	0.42	2.48	0.971	1.31	0.67	2.56	0.426
5	1.78	1.05	3.03	0.032	1.10	0.42	2.90	0.841	2.28	1.19	4.36	0.013
Missing	1.45	0.85	2.5	0.175	0.99	0.38	2.57	0.990	1.77	0.91	3.45	0.095
Anaemia[†‡] (reference) no	1.00				1.00				1.00			
yes	2.96	2.08	4.21	<0.001	1.78	0.86	3.68	0.123	3.51	2.34	5.26	<0.001
Abdominal pain[†] (reference) no	1.00				1.00				1.00			
yes	2.73	1.65	4.5	<0.001	2.33	0.84	6.49	0.106	2.89	1.62	5.15	<0.001
Lower GI[†] (reference) no	1.00				1.00				1.00			
yes	6.58	3.74	11.55	<0.001	11.72	5.12	26.80	<0.001	4.28	1.96	9.38	<0.001
Loperamide prescription[†] (reference) no	1.00				1.00				1.00			
yes	2.16	1.21	3.86	0.009	3.59	1.40	9.16	0.008	1.58	0.75	3.36	0.231

Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	6.03	3.91	9.3	<0.001	5.36	2.42	11.89	<0.001	6.17	3.68	10.34	<0.001

† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males)

Appendix 4.

Cohort demographics for erythema nodosum (EN) and pyoderma gangrenosum (PG)

	EN subjects	EN controls	PG subjects	PG controls
Number of subjects	5,590	22,039	977	3,852
Median py of follow-up (IQR)	5.7 (2.5-9.8)	5.4 (2.3-9.6)	4.5 (1.8-8.1)	5.3 (2.3-9.2)
Median age (IQR)	38 (23-52)	37 (22-50)	57 (39-73)	56 (39-72)
Age category, n (%)				
<18 years	837 (15)	3764 (17)	84 (9)	338 (9)
18-30 years	1166 (21)	4474 (20)	74 (8)	317 (8)
30-40 years	1161 (21)	4569 (21)	87 (9)	332 (9)
40-50 years	870 (16)	3428 (16)	132 (14)	575 (15)
50-60 years	717 (13)	2787 (13)	140 (14)	561 (15)
60-70 years	481 (9)	1811 (8)	147 (15)	608 (16)
>70 years	358 (6)	1206 (5)	313 (32)	1121 (29)
Female sex, n (%)	4406 (79)	17380 (79)	587 (60)	2323 (60)
Townsend deprivation quintile, n (%)				
1 - least deprived	1177 (21)	4799 (22)	171 (18)	808 (21)
2	1030 (18)	4076 (18)	194 (20)	726 (19)
3	1030 (18)	3937 (18)	203 (21)	737 (19)
4	930 (17)	3486 (16)	170 (17)	648 (17)
5	574 (10)	2332 (11)	116 (12)	445 (12)
Missing	849 (15)	3409 (15)	123 (13)	488 (13)
Charlson comorbidity score, n (%)				
0	3858 (69)	16912 (77)	452 (46)	2527 (66)
1	1275 (23)	3866 (18)	249 (25)	722 (19)
>/=2	457 (8)	1261 (6)	276 (28)	603 (16)
Smoking status, n (%)				
current smoker	880 (16)	4095 (19)	180 (18)	669 (17)
non- smoker	4710 (84)	17944 (81)	797 (82)	3183 (83)
Body mass index, n (%)				
<25 kg/m^2	1748 (31)	7306 (33)	291 (30)	1225 (32)
25-30 kg/m^2	1245 (22)	4445 (20)	243 (25)	1042 (27)
>30 kg/m^2	1136 (20)	3154 (14)	253 (26)	674 (18)
Missing	1461 (26)	7134 (32)	190 (19)	911 (24)
Anaemia[†‡], n(%)	683 (12)	703 (3)	194 (20)	190 (5)
Abdominal pain[†], n (%)	157 (3)	503 (2)	17 (2)	63 (2)

Lower gastrointestinal bleeding†, n (%)	61 (1)	120 (1)	13 (1)	30 (1)
Loperamide prescription†, n (%)	81 (1)	145 (1)	50 (5)	45 (1)
Diarrhoea†, n (%)	181 (3)	374 (2)	34 (3)	66 (2)

† coded within 6 months of Index date

‡ <11.9g/dL (females); <12.9g/dL (males)

EN: erythema nodosum; PG: pyoderma gangrenosum; IQR: interquartile range

Appendix 5

Multivariable Cox proportional hazards models for Erythema Nodosum (EN) and Pyoderma Gangrenosum (PG) and association with inflammatory bowel disease diagnosis.

	Inflammatory Bowel Disease (all)					Inflammatory Bowel Disease (all)			
	aHR	[95% Conf. Interval]		p-value		aHR	[95% Conf. Interval]		p-value
EN	**6.49**	**4.62**	**9.11**	**<0.001**	**PG**	**6.27**	**2.84**	**13.86**	**<0.001**
Sex (reference) Male	1.00					1.00			
Female	0.88	0.59	1.31	0.524		0.80	0.37	1.73	0.576
Age Category (reference) <18 years	1.00					*No <18 cases*			
18-30 years	1.65	0.96	2.85	0.071	*ref*	1.00			
30-40 years	0.89	0.48	1.64	0.705		0.24	0.04	1.33	0.102
40-50 years	0.35	0.15	0.78	0.010		0.39	0.10	1.49	0.167
50-60 years	0.43	0.19	0.97	0.042		0.56	0.17	1.91	0.356
60-70 years	0.58	0.25	1.31	0.189		0.27	0.06	1.22	0.088
>70 years	0.23	0.07	0.72	0.012		0.64	0.19	2.21	0.482
Smoking Status (reference) current smoker	1.00					1.00			
non smoker	0.64	0.44	0.93	0.018		0.66	0.27	1.60	0.358
Charlson comorbidity score (reference) 0	1.00					1.00			
1	1.40	0.96	2.03	0.077		0.94	0.41	2.20	0.892
>/=2	2.01	1.05	3.86	0.035		0.17	0.04	0.73	0.017
Body mass index (reference) <25 kg/m^2	1.00					1.00			
25-30 kg/m^2	0.83	0.54	1.27	0.384		1.20	0.52	2.79	0.670
>30 kg/m^2	0.46	0.26	0.81	0.007		0.56	0.19	1.69	0.306
Missing	0.72	0.45	1.14	0.162		0.43	0.11	1.66	0.220
Townsend (least deprived) (reference) 1	1.00					1.00			
2	0.90	0.54	1.50	0.693		2.90	0.71	11.81	0.137
3	0.79	0.47	1.33	0.376		3.90	0.97	15.71	0.056

4	0.78	0.45	1.33	0.355	0.91	0.14	5.93	0.925
5	1.26	0.74	2.15	0.399	3.24	0.73	14.40	0.123
Missing	1.00	0.58	1.72	1.000	3.78	0.86	16.62	0.079
Anaemia†‡ (reference) no	1.00				1.00			
yes	2.47	1.64	3.71	0.000	4.76	1.84	12.27	0.001
Abdominal pain† (reference) no	1.00				1.00			
yes	3.05	1.81	5.15	0.000	1.04	0.13	8.41	0.968
Lower GI† (reference) no	1.00				1.00			
yes	3.19	1.46	7.00	0.004	38.30	14.31	102.48	0.000
Loperamide prescription† (reference) no	1.00				1.00			
yes	1.61	0.76	3.40	0.214	10.01	3.40	29.50	0.000
Diarrhoea† (reference) no	1.00				1.00			
yes	6.24	3.86	10.09	0.000	4.27	1.26	14.48	0.020

† coded within 6 months of Index date

‡ <11.9g/dL (females); <12.9g/dL (males)

Appendix 6

Cohort demographics for psoriasis

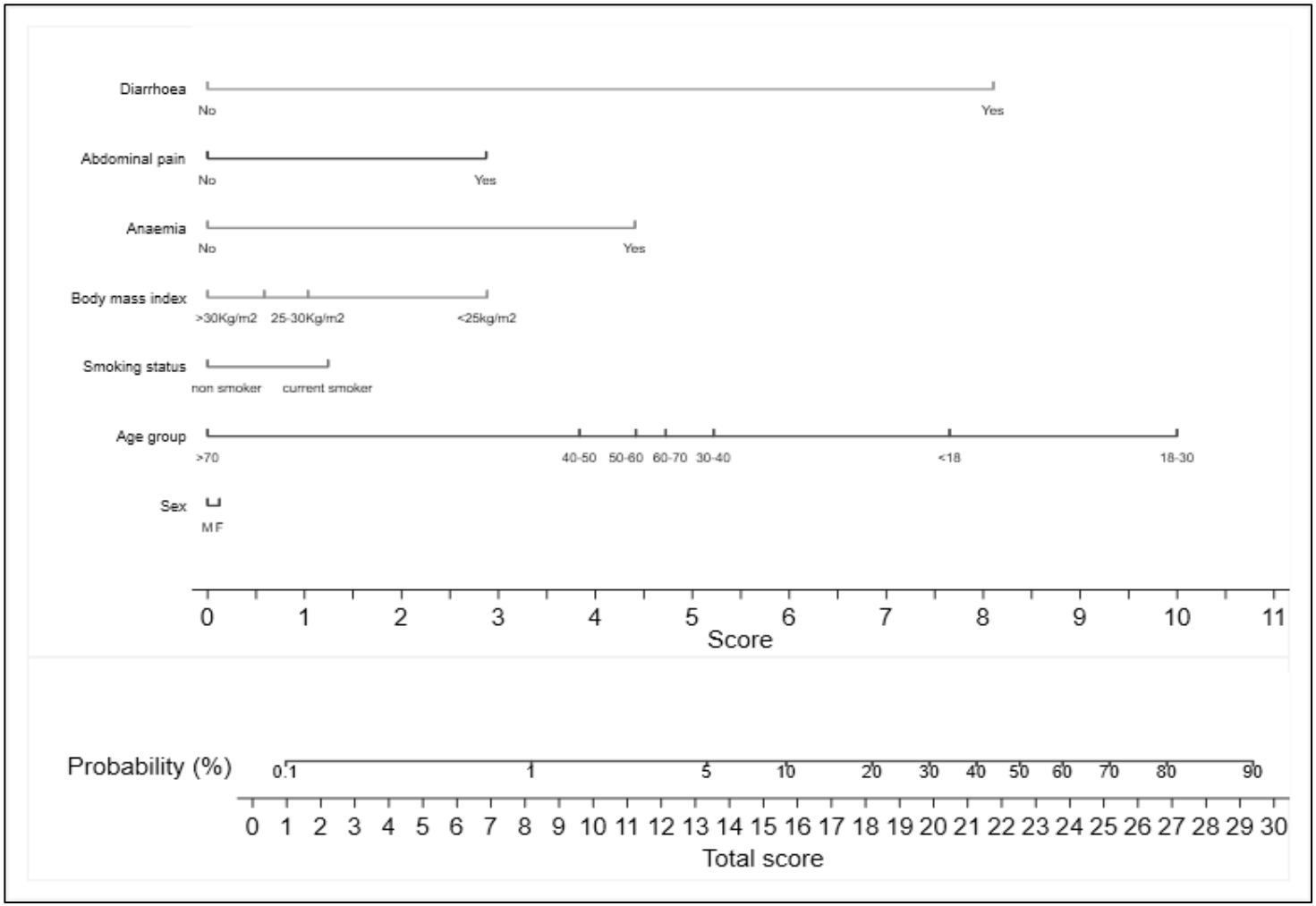
	Psoriasis cases	**Psoriasis controls**
Number of subjects	121,195	476,281
Median py follow-up(IQR)	5.34 (2.39-9.37)	5.10 (2.20-9.16)
Median age (IQR)	45 (29-61)	44 (28-59)
Age category (%)		
<18 years	11896 (10)	53895 (11)
18-30	18476 (15)	72865 (15)
30-40	18930 (16)	76680 (16)
40-50	18982 (16)	76244 (16)
50-60	19762 (17)	79185 (17)
60-70	17591 (15)	64975 (14)
>70	15558 (13)	52437 (11)
Female sex (%)	63,806 (53)	250,766 (53)
Townsend Index (%)		
1 - least deprived	23991 (20)	98545 (21)
2	21585 (18)	86132 (18)
3	22117 (18)	86143 (18)
4	19578 (16)	73681 (15)
5	14685 (12)	54880 (12)
missing	19239 (16)	76900 (16)
Charlson comorbidity (%)		
0	82409 (68)	345452 (73)
1	25565 (21)	88436 (19)
>/=2	13221 (11)	42393 (9)
Smoking status (%)		
current smoker	30003 (25)	90144 (19)
non- smoker	91192 (75)	386137 (81)
Body mass index (%)		
<25kg/m^2	34565 (29)	146719 (31)
25-30Kg/m^2	30965 (26)	113544 (24)
>30Kg/m^2	24962 (21)	74123 (16)
missing	30703 (25)	141895 (30)
Anaemia[†‡] (%)	4220 (3)	14388 (3)
Abdominal pain[†] (%)	4717 (4)	15605 (3)

Lower gastrointestinal bleeding† (%)	1143 (1)	2901 (1)
Loperamide prescription† (%)	1417 (1)	4077 (1)
Diarrhoea† (%)	2269 (2)	6823 (1)

† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males)

Appendix 7

Nomogram: prediction of inflammatory bowel disease diagnosis within 3-years of a diagnosis of erythema nodosum



Appendices for chapter 6 Manuscript 2: The risk of a subsequent diagnosis of inflammatory bowel disease in subjects with ophthalmic disorders associated with inflammatory bowel disease

Appendix 1
READ Codes:
Ulcerative Colitis:

Code	Description
J410z00	Ulcerative proctocolitis NOS
N031000	Arthropathy in ulcerative colitis
J41z.00	Idiopathic proctocolitis NOS
J41y.00	Other idiopathic proctocolitis
J412.00	Ulcerative (chronic) ileocolitis
J413.00	Ulcerative pancolitis
Jyu4100	[X]Other ulcerative colitis
N045400	Juvenile arthritis in ulcerative colitis
J410000	Ulcerative ileocolitis
J411.00	Ulcerative (chronic) enterocolitis
J41..00	Idiopathic proctocolitis
J410.00	Ulcerative proctocolitis
J410300	Ulcerative proctitis
J410400	Exacerbation of ulcerative colitis
J41..12	Ulcerative colitis and/or proctitis
J410100	Ulcerative colitis
J410200	Ulcerative rectosigmoiditis
J41yz00	Other idiopathic proctocolitis NOS

Crohn's Disease:

Code	Description
J400.00	Regional enteritis of the small bowel
J400000	Regional enteritis of the duodenum
J400100	Regional enteritis of the jejunum
J40..00	Regional enteritis - Crohn's disease
N031100	Arthropathy in Crohn's disease
ZR3S.11	CDAI - Crohn's disease activity index
J402.00	Regional ileocolitis
J401z11	Crohn's colitis
J400200	Crohn's disease of the terminal ileum
J400300	Crohn's disease of the ileum unspecified
J400400	Crohn's disease of the ileum NOS
J400500	Exacerbation - Crohn's disease - small intestine
J08z900	Orofacial Crohn's disease
J400z00	Crohn's disease of the small bowel NOS
J40z.00	Regional enteritis NOS
J401000	Regional enteritis of the colon
J401100	Regional enteritis of the rectum
J401200	Exacerbation - Crohn's disease - large intestine
J40..12	Granulomatous enteritis
J40..11	Crohn's disease
ZR3S.00	Crohn's disease activity index
J401.00	Regional enteritis of the large bowel
J401z00	Crohn's disease of the large bowel NOS
Jyu4000	[X]Other Crohn's disease
N045300	Juvenile arthritis in Crohn's disease
J40z.11	Crohn's disease NOS

Ophthalmic Extraintestinal Manifestations:

Code	Description
F443.11	Uveitis NOS
F443000	Anterior uveitis
F441200	Chronic anterior uveitis
F443.00	Unspecified iridocyclitis
F443100	Iritis
F440z00	Acute or subacute iritis NOS
F442.00	Certain types of iridocyclitis
F442z00	Certain types of cyclitis NOS
F441z00	Chronic iridocyclitis NOS
F44..12	Iridocyclitis
F441.00	Chronic iridocyclitis
F441.11	Chronic iritis
F441000	Unspecified chronic iridocyclitis
F441100	Chronic iridocyclitis due to disease
F440300	Recurrent iridocyclitis
F440500	Secondary noninfected iridocyclitis
F440000	Unspecified acute iridocyclitis
F440100	Unspecified subacute iridocyclitis
F440200	Primary iridocyclitis
F440.11	Iritis - acute
F440.00	Acute and subacute iridocyclitis
F4K0z00	Scleritis or episcleritis NOS
F4K0.12	Scleritis
F4K0.11	Episcleritis
F4K0.00	Scleritis and episcleritis
FyuD800	Scleritis+episcleritis in diseases
F4K0700	Posterior scleritis
F4K0000	Unspecified scleritis
F4K0200	Nodular episcleritis
F4K0300	Anterior scleritis
F4K0600	Brawny scleritis
F4K0100	Episcleritis periodica fugax

Appendix 2.

Demographic details of the anterior uveitis and episcleritis & scleritis cohorts and their controls

	Anterior uveitis subjects	Matched subjects without anterior uveitis	Episcleritis & Scleritis subjects	Matched subjects without episcleritis & scleritis
Number of subjects	22,547	89,422	17,439	68,823
Median py of follow-up (IQR)	5.1 (2.3-9.1)	4.9 (2.2-8.9)	5.9 (2.7-9.8)	5.5 (2.4-9.5)
Median age (IQR)	53 (39-68)	52 (38-67)	48 (36-61)	47 (35-59)
Age category (%)				
<18 years	887 (3.9)	3,952 (4.3)	1266 (7.3)	5223 (7.6)
18-30	1,934 (8.5)	8,239 (9.1)	1403 (8.1)	5994 (8.7)
30-40	3171 (13.6)	12,690 (14.0)	2702 (15.5)	11494 (16.7)
40-50	3,071 (17.7)	16,373 (18.2)	3859 (22.1)	15480 (22.5)
50-60	4,020 (17.7)	15,933 (17.8)	3521 (20.2)	13915 (20.2)
60-70	3,587 (15.8)	14,051 (15.7)	2667 (15.3)	10026 (14.6)
>70	5,190 (22.8)	18,341 (21.0)	2021 (11.6)	6691 (9.7)
Female sex (%)	12,145 (53.5)	47,868 (53.4)	10860 (62.3)	42939 (62.4)
Townsend Index (%)				
1 - least deprived	4,822 (21.3)	19,181 (21.4)	4381 (25.1)	16706 (24.3)
2	4,316 (19.0)	17,162 (19.1)	3479 (20.0)	13279 (19.3)
3	4,058 (17.9)	15,946 (17.8)	3181 (18.2)	12636 (18.4)
4	3,577 (15.8)	13,811 (15.4)	2480 (14.2)	10281 (14.9)
5	2,498 (11.0)	9,652 (10.8)	1444 (8.3)	6051 (8.8)
missing	3,428 (15.1)	13,827 (15.4)	2474 (14.2)	9870 (14.3)
Charlson comorbidity score (%)				
0	13,574 (59.8)	60,673 (67.7)	11671 (66.9)	49861 (72.5)
1	5,033 (22.2)	17,263 (19.3)	3697 (21.2)	12641 (18.4)
>/=2	4,092 (18.0)	11,643 (13.0)	2071 (11.9)	6321 (9.2)
Smoking status (%)				
current smoker	4,126 (18.2)	16,754 (18.7)	2738 (15.7)	13079 (19.0)
non- smoker	18,573 (81.8)	72,825 (81.3)	14701 (84.3)	55744 (81.0)
Body mass index (%)				
<25kg/m2	7,344 (32.4)	29,447 (32.9)	5908 (33.9)	23455 (34.1)
25-30Kg/m2	6,709 (29.5)	24,625 (27.4)	4940 (28.3)	17708 (25.7)
>30Kg/m2	4,661 (20.6)	16,187 (18.1)	3322 (19.1)	11885 (17.3)
missing	3,985 (17.6)	19,320 (21.6)	3269 (18.8)	15775 (22.9)
Anaemia†‡ (%)	1,490 (6.5)	3,503 (3.9)	691 (4.0)	2126 (3.1)

Abdominal pain† (%)	469 (2.1)	1,421 (1.6)	402 (2.3)	1212 (1.8)
Lower GI† (%)	204 (0.9)	642 (0.7)	172 (1.0)	446 (0.7)
Loperamide prescription† (%)	367 (1.6)	988 (1.1)	213 (1.2)	555 (0.8)
Diarrohea† (%)	552 (2.4)	1,441 (1.6)	459 (2.6)	1073 (1.6)
B27 positive at Index	34 (0.2)	2 (0.0)	3 (0.02)	5 (0.01)
Axial arthropathy at baseline	734 (3.2)	588 (0.7)	221 (1.3)	494 (0.7)

† coded within 6 months of Index date

‡ <11.9g/dL (females); <12.9g/dL (males)

Appendix 3

Multivariable Cox proportional hazards models for ophthalmic extraintestinal manifestations associated with inflammatory bowel disease

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	**[95% Confidence Interval]**		**p-value**	**aHR**	**[95% Confidence Interval]**		**p-value**	**aHR**	**[95% Confidence Interval]**		**p-value**
All ophthalmic EIMs	2.25	1.89	2.68	**<0.001**	1.65	1.30	2.09	**<0.001**	3.37	2.59	4.40	**<0.001**
Sex (reference) Male	1.00				1.00				1.00			
Female	0.92	0.77	1.09	0.342	0.78	0.62	0.98	0.030	1.17	0.89	1.54	0.264
Age Category (reference) <18 years	1.00				1.00				1.00			
18-30	1.75	1.05	2.92	0.033	1.76	0.83	3.76	0.143	1.62	0.80	3.27	0.181
30-40	1.42	0.86	2.35	0.167	1.93	0.94	3.96	0.072	0.99	0.49	2.01	0.971
40-50	1.02	0.62	1.69	0.933	1.54	0.75	3.15	0.238	0.60	0.29	1.24	0.171
50-60	1.22	0.74	2.01	0.439	1.75	0.86	3.59	0.125	0.78	0.38	1.60	0.504
60-70	1.01	0.60	1.70	0.975	1.46	0.70	3.06	0.312	0.64	0.30	1.36	0.246
>70	0.76	0.44	1.31	0.320	1.02	0.47	2.19	0.968	0.55	0.25	1.19	0.129
Smoking Status (reference) current smoker	1.00				1.00				1.00			
non smoker	0.77	0.63	0.95	0.015	1.16	0.86	1.56	0.334	0.48	0.36	0.64	<0.001
Charlson comorbidity score (reference) 0	1.00				1.00				1.00			
1	1.11	0.90	1.37	0.313	1.14	0.86	1.50	0.363	1.09	0.79	1.50	0.616
>/=2	1.06	0.78	1.43	0.709	1.18	0.81	1.73	0.386	0.89	0.54	1.44	0.626
Body mass index (reference) <25kg/m^2	1.00				1.00				1.00			
25-30Kg/m^2	0.95	0.77	1.18	0.658	0.88	0.67	1.17	0.380	1.06	0.75	1.49	0.752
>30Kg/m^2	0.89	0.69	1.14	0.354	0.73	0.52	1.03	0.074	1.14	0.78	1.66	0.508
Missing	0.87	0.67	1.14	0.311	0.78	0.55	1.10	0.162	1.02	0.68	1.54	0.908
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.08	0.84	1.39	0.545	1.15	0.83	1.60	0.39	0.98	0.65	1.47	0.919
3	1.11	0.86	1.44	0.424	1.20	0.86	1.67	0.276	0.98	0.65	1.48	0.932
4	0.92	0.69	1.22	0.571	0.84	0.57	1.24	0.378	1.02	0.67	1.55	0.929
5	0.94	0.68	1.30	0.689	0.87	0.55	1.36	0.537	1.02	0.63	1.63	0.948
Missing	0.80	0.59	1.09	0.164	0.89	0.60	1.31	0.545	0.69	0.42	1.14	0.146
Anaemia[†‡] (reference) no	1.00				1.00				1.00			
yes	1.68	1.17	2.42	0.005	1.20	0.69	2.08	0.519	2.34	1.44	3.81	<0.001
Abdominal pain[†] (reference) no	1.00				1.00				1.00			
yes	1.56	0.99	2.44	0.054	1.27	0.65	2.47	0.488	1.94	1.05	3.58	0.033
Lower gastrointestinal bleeding[†] (reference) no	1.00				1.00				1.00			
yes	6.45	4.48	9.29	<0.001	8.13	5.23	12.64	<0.001	4.25	2.23	8.11	<0.001

Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.09	1.34	3.27	0.001	2.44	1.34	4.44	0.004	1.82	0.94	3.52	0.077
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.46	3.25	6.13	<0.001	3.37	2.12	5.34	<0.001	5.99	3.87	9.27	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.77	1.77	4.36	<0.001	2.49	1.32	4.71	0.005	3.15	1.66	5.99	<0.001

† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males); *recorded at baseline
EIM: extraintestinal manifestations

Appendix 4

Multivariable Cox proportional hazards models for anterior uveitis associated with inflammatory bowel disease

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value
Anterior uveitis	3.39	2.70	4.25	<0.001	2.23	1.63	3.04	<0.001	5.77	4.04	8.24	<0.001
Sex (reference) Male	1.00				1.00				1.00			
Female	0.81	0.65	1.02	0.077	0.75	0.56	1.02	0.067	0.89	0.63	1.26	0.500
Age Category (reference) <18 years	1.00				No <18 cases	-	-	-	1.00			
18-30	2.60	1.07	6.35	0.035	1.00 (reference)					1.46	0.56	3.810
30-40	2.25	0.93	5.40	0.07	1.45	0.73	2.92	0.291	0.89	0.34	2.34	0.815
40-50	1.56	0.65	3.77	0.321	1.22	0.61	2.42	0.572	0.48	0.18	1.30	0.148
50-60	1.91	0.79	4.60	0.149	1.38	0.69	2.73	0.361	0.66	0.25	1.76	0.407
60-70	1.36	0.55	3.35	0.501	1.21	0.60	2.46	0.599	0.33	0.11	0.96	0.041
>70	1.05	0.42	2.62	0.909	0.96	0.46	1.99	0.913	0.24	0.08	0.71	0.01
Smoking Status (reference) current smoker	1.00				1.00				1.00			
non smoker	0.86	0.65	1.13	0.282	1.32	0.88	1.99	0.185	0.55	0.38	0.80	0.002
Charlson comorbidity score (reference) 0	1.00				1.00				1.00			
1	0.93	0.70	1.24	0.621	1.02	0.70	1.50	0.914	0.84	0.54	1.30	0.434
>/=2	0.99	0.68	1.45	0.955	1.06	0.66	1.73	0.799	0.90	0.49	1.67	0.748
Body mass index (reference) <25kg/m^2	1.00				1.00				1.00			
25-30Kg/m^2	1.11	0.84	1.46	0.48	0.91	0.63	1.31	0.598	1.44	0.94	2.21	0.09
>30Kg/m^2	0.82	0.58	1.16	0.271	0.73	0.47	1.15	0.175	0.95	0.55	1.63	0.853
Missing	0.83	0.58	1.17	0.289	0.81	0.51	1.27	0.357	0.88	0.52	1.52	0.653
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.05	0.75	1.47	0.786	1.14	0.72	1.82	0.567	0.94	0.57	1.56	0.811
3	1.04	0.73	1.48	0.813	1.17	0.72	1.88	0.525	0.91	0.54	1.54	0.734
4	1.14	0.80	1.62	0.475	1.33	0.82	2.16	0.241	0.95	0.56	1.61	0.86
5	0.78	0.50	1.22	0.273	0.86	0.46	1.62	0.647	0.69	0.37	1.31	0.262
Missing	0.76	0.50	1.15	0.196	1.08	0.65	1.82	0.759	0.44	0.22	0.90	0.024
Anaemia[†‡] (reference) no	1.00				1.00				1.00			
yes	1.70	1.07	2.69	0.024	1.36	0.70	2.63	0.364	2.19	1.15	4.17	0.017
Abdominal pain[†] (reference) no	1.00				1.00				1.00			
yes	1.62	0.92	2.86	0.096	1.17	0.47	2.89	0.737	2.16	1.04	4.49	0.039

Lower gastrointestinal bleeding†												
(reference) no	1.00				1.00				1.00			
yes	5.97	3.71	9.62	0<0.001	6.73	3.60	12.57	<0.001	5.29	2.54	11.03	<0.001
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.13	1.22	3.72	0.007	3.19	1.53	6.64	0.002	1.46	0.63	3.35	0.376
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	4.87	3.23	7.36	<0.001	2.72	1.42	5.21	0.003	8.01	4.74	13.55	<0.001
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.08	0.58	2.64	0.008	1.45	0.59	3.56	0.421	2.75	1.38	5.50	0.004

† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males); *recorded at baseline

Appendix 5

Multivariable Cox proportional hazards models for episcleritis & scleritis associated with inflammatory bowel disease

	Inflammatory Bowel Disease				Ulcerative colitis				Crohn's Disease			
	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value	aHR	[95% Confidence Interval]		p-value
Combined episcleritis & scleritis	**1.73**	**1.31**	**2.28**	**<0.001**	**1.43**	**0.97**	**2.11**	**0.067**	**2.13**	**1.42**	**3.19**	**<0.001**
Sex (reference) Male	1.00				1.00				1.00			
Female	1.05	0.79	1.38	0.749	1.03	0.71	1.49	0.887	1.07	0.71	1.62	0.743
Age Category (reference) <18 years	1.00				0.70	0.23	2.10	0.521	1.00			
18-30	1.11	0.52	2.36	0.786	1.00				0.80	0.28	2.30	0.683
30-40	1.02	0.51	2.03	0.956	1.12	0.49	2.55	0.796	0.60	0.22	1.62	0.317
40-50	1.11	0.57	2.17	0.749	1.43	0.66	3.09	0.369	0.51	0.19	1.36	0.179
50-60	1.12	0.57	2.19	0.749	0.81	0.35	1.87	0.620	0.97	0.38	2.51	0.955
60-70	1.45	0.73	2.87	0.292	1.68	0.75	3.76	0.207	0.79	0.29	2.14	0.637
>70	0.65	0.28	1.49	0.306	0.89	0.33	2.38	0.817	0.26	0.07	0.99	0.049
Smoking Status (reference) current smoker	1.00				1.00				1.00			
non smoker	0.83	0.60	1.16	0.277	0.98	0.62	1.56	0.941	0.70	0.44	1.11	0.129
Charlson comorbidity score (reference) 0	1.00				1.00				1.00			
1	1.15	0.83	1.58	0.402	1.15	0.75	1.78	0.524	1.14	0.71	1.84	0.587
>/=2	0.82	0.49	1.38	0.465	0.83	0.42	1.66	0.603	0.82	0.38	1.79	0.626
Body mass index (reference) <25kg/m^2	1.00				1.00				1.00			
25-30Kg/m^2	0.96	0.69	1.33	0.800	0.76	0.48	1.21	0.249	1.21	0.76	1.94	0.418
>30Kg/m^2	0.71	0.47	1.07	0.103	0.86	0.51	1.44	0.561	0.53	0.27	1.05	0.071
Missing	0.98	0.65	1.46	0.912	1.12	0.67	1.86	0.675	0.80	0.42	1.53	0.495
Townsend (least deprived – reference) 1	1.00				1.00				1.00			
2	1.15	0.78	1.71	0.479	1.10	0.67	1.79	0.713	1.26	0.64	2.47	0.497
3	1.78	1.24	2.58	0.002	1.27	0.78	2.07	0.334	2.80	1.56	5.03	0.001
4	1.05	0.67	1.65	0.836	0.58	0.29	1.15	0.117	1.98	1.02	3.84	0.044
5	0.76	0.41	1.41	0.389	0.44	0.17	1.14	0.092	1.38	0.59	3.25	0.459
Missing	0.89	0.55	1.44	0.629	0.89	0.49	1.62	0.710	0.88	0.38	2.04	0.765
Anaemia[†‡] (reference) no	1.00				1.00				1.00			
yes	2.02	1.14	3.58	0.016	1.02	0.37	2.81	0.965	3.36	1.66	6.80	0.001
Abdominal pain[†] (reference) no	1.00				1.00				1.00			
yes	1.08	0.48	2.45	0.846	1.01	0.32	3.21	0.981	1.17	0.37	3.70	0.794

Lower gastrointestinal bleeding† (reference) no	1.00				1.00				1.00			
yes	5.18	2.71	9.93	<0.001	6.71	3.06	14.71	<0.001	3.26	1.01	10.50	0.048
Loperamide prescription† (reference) no	1.00				1.00				1.00			
yes	2.97	1.47	6.02	0.002	2.89	1.11	7.53	0.030	3.19	1.14	8.95	0.027
Diarrhoea† (reference) no	1.00				1.00				1.00			
yes	3.01	1.72	5.26	<0.001	3.19	1.50	6.77	0.003	2.76	1.21	6.32	0.016
Axial arthropathy* (reference) no	1.00				1.00				1.00			
yes	2.96	1.31	6.68	0.009	4.50	1.83	11.08	0.001	1.07	0.15	7.67	0.949

† coded within 6 months of Index date; ‡ <11.9g/dL (females); <12.9g/dL (males); *recorded at baseline

Appendix 6

Nomogram: prediction of inflammatory bowel disease diagnosis within 3-years of a diagnosis of anterior uveitis

