The risk of subsequent surgery following bowel resection for Crohn’s disease in a national cohort of 19,207 patients

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TITLE PAGE

Title

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Short Title

Risk of further surgery in Crohn's Disease

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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. The aim of this study was to characterize the risk of and factors associated with further surgery, following a first resection for Crohn's disease.

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 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% relative and 0.3% absolute 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.

What does this paper add to the existing literature?

Further surgery following a first recorded resection in Crohn's disease is high in England. Significant risk factors for further surgery included those coded with extraintestinal manifestations and prior perianal surgery. Over time, index resectional surgery rates have fallen as Crohn's disease prevalence has increased.

Key Words

Inflammatory Bowel Disease, Crohn's Disease, surgery, colectomy, perianal disease, extraintestinal manifestations of inflammatory bowel disease.

Author contributions

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. Manuscript was drafted by DK. The data and manuscript were critically reviewed, revised, and approved by all authors.

Abbreviations

Inflammatory Bowel Disease (IBD), Crohn's Disease (CD), Hospital Episode Statistics (HES), Odds Ratio (OR), interquartile range (IQR).

Data Availability statement:

HES data are available under a data sharing agreement with NHS Digital for the purposes of service evaluation and is not available for open access.

Funding declaration

Nothing to Declare

Conflicts of Interests

NT reports grants from Dr. Falk, MSD, AstraZeneca and Pfizer outside the current work. Other authors have no conflicts of interest to declare.

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 and ileal disease [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 are 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 patients ≥18 years old were included in the study. For study inclusion, patients required a record of a small or large bowel surgical resection between 1st January 2007 and 31st December 2016. Patients 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. Given evidence of different outcomes in patients with Crohn's colitis compared with isolated small bowel disease [23], patients were included in a separate 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. Patients 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. Patients without a recorded age, an age less than 18 and those with a missing or invalid code for sex were excluded, as were patients 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, as the two operations were regarded as one staged episode of resection. The exclusion of operations which were done in order to complete an index surgical procedure (such as re-joining the bowel), rather than further resectional surgery for recurrent disease, was done in order to reduce the risk of overestimating the recurrent surgery rate. 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

Patient 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, 35-44, 45-57 and ≥58 for analysis. Ethnicity was stratified into white, Asian, other minority ethnicities and unknown. The Charlson comorbidity index, a measure of multimorbidity in patients and previously validated in HES [24], 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 [25]. 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 during the follow up period after their first resection until December 31st 2018. 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 [26]. 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 patients 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 (defined as previous perianal surgery), 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 [26,27]. 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 [28]. 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 patients 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 patients were of white ethnicity and 81% of patients 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 patients 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 patients' index surgery were coded as laparoscopic (of 6,148 patients whose procedure started as laparoscopic, 1,050 (17%) were converted to open surgery). 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% (51) of patients 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. Annual infliximab rates and laparoscopic surgery rates are shown in the appendix 11 and 12 respectively.

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 patients 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%) patients 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. 14% (459) of further surgery began as laparoscopic procedures, 2.5% (81) of which were converted to open 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.

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).

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. 13,3368 (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).

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, 21.3% (4,095) of patients underwent a further CD surgical resection during the follow-up period. 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. Infliximab was coded in 16% (81) of patients in the year before or after a further resection. 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 patients in England over this period (p<0.001) (Appendix 10) [26]. 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.

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 [29,30]. Increased recognition and understanding of these conditions with early medical intervention, national IBD audit and standards for IBD care in the UK, changing attitudes to surgery and novel medical therapies are all likely to play important roles in this reduction [29,31–33]. 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 patients in the population) has also increased, leading to a fall in rates of CD index surgery in real terms [34]. 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 [35,36]. Recurrent surgery has also fallen over time, a likely result of an evolving therapeutic armoury in CD and improved surgical care [2,30]. 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 [4,37]. 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 [38]. 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 [30]. Historically, surgical rates have fallen significantly, even before the advent of biologic medications [29,39]. 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 patients 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 [40,41]. 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 [42]. Younger patients 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 [1,43].

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 [36]. Partially obstructing strictures, initially managed conservatively, are at risk by their nature of progressing to complete obstruction requiring emergency intervention [44]. 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 [34,45,46]. This implies that further surgery will not only be for CD recurrence but also relate to previous surgery, e.g. adhesions [36].

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 [47]. 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 [14,48]. 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 [48]. 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 [40]. Others have also shown this risk association and perianal fistulas is an indicator of the need for continued medical therapy following surgical resection [5,49,50].

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.

Study limitations

Database studies of this kind have significant strengths in terms of patient numbers, demographics, and the reliability of procedural coding, which we have been able to validate in a hospital setting. Although the first resectional surgery recording was the method used to include subjects in this study, it is possible that resectional surgery took place historically before HES coding was established. This would mean that some patients in the study would be included who have had previous resectional operations. 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 [40]. Endoscopic balloon dilatation for Crohn's disease strictures is safe and effective and may delay or even prevent further surgery [51]. 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 [52].

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, disease duration, family history and smoking status [53,54]. 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, and oral drugs such as azathioprine are not. This is a significant limitation given the frequent use of adalimumab (either originator or biosimilar) [33]. The IBD audit 2016 demonstrated a fall in surgery prior to medical treatment between 2012 and 2016, demonstrating changing trends potentially linked to therapeutics [33]. 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 [55]. Furthermore, this study was retrospective and includes data that are now several years old, and changes in the use of biologic therapy and surgical technique, including laparoscopic surgery, over this time may limit its applicability to current patients with Crohn's disease.

Conclusions

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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Tables and Figures

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 (1-79)**	2297 (12.0)	340 (14.8)	1731 (12.9)	211 (12.2)
	Med (80-139)	6142 (32.0)	961 (15.6)	4071 (30.5)	524 (12.9)
	High (>139)	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 patients: data not shown to ensure patient anonymity

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

Figure 1 Study flow chart.

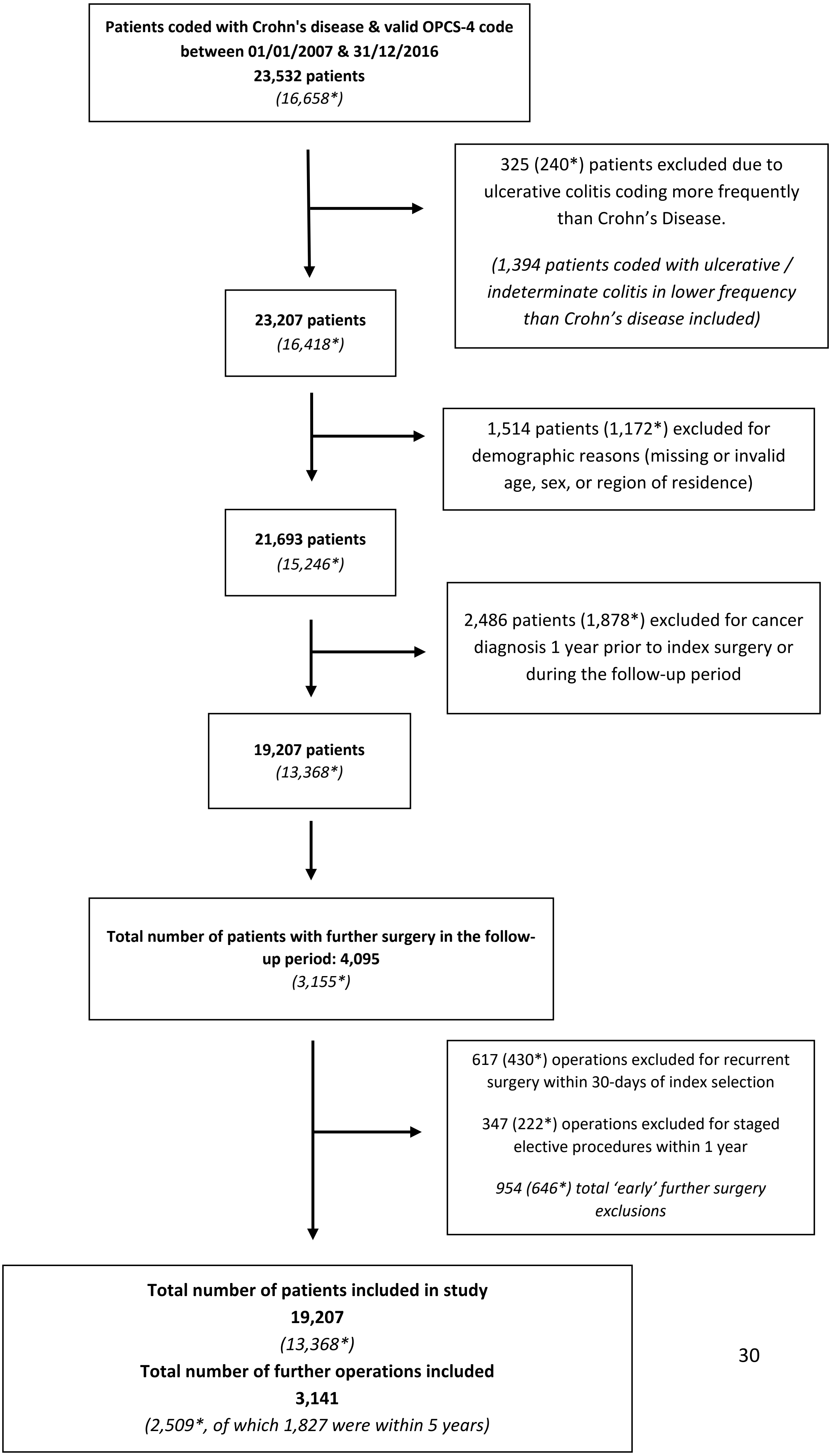

Figure 1. Study Flow Chart *Patients with at least 5 years of follow up included in primary analysis.*

Figure 2

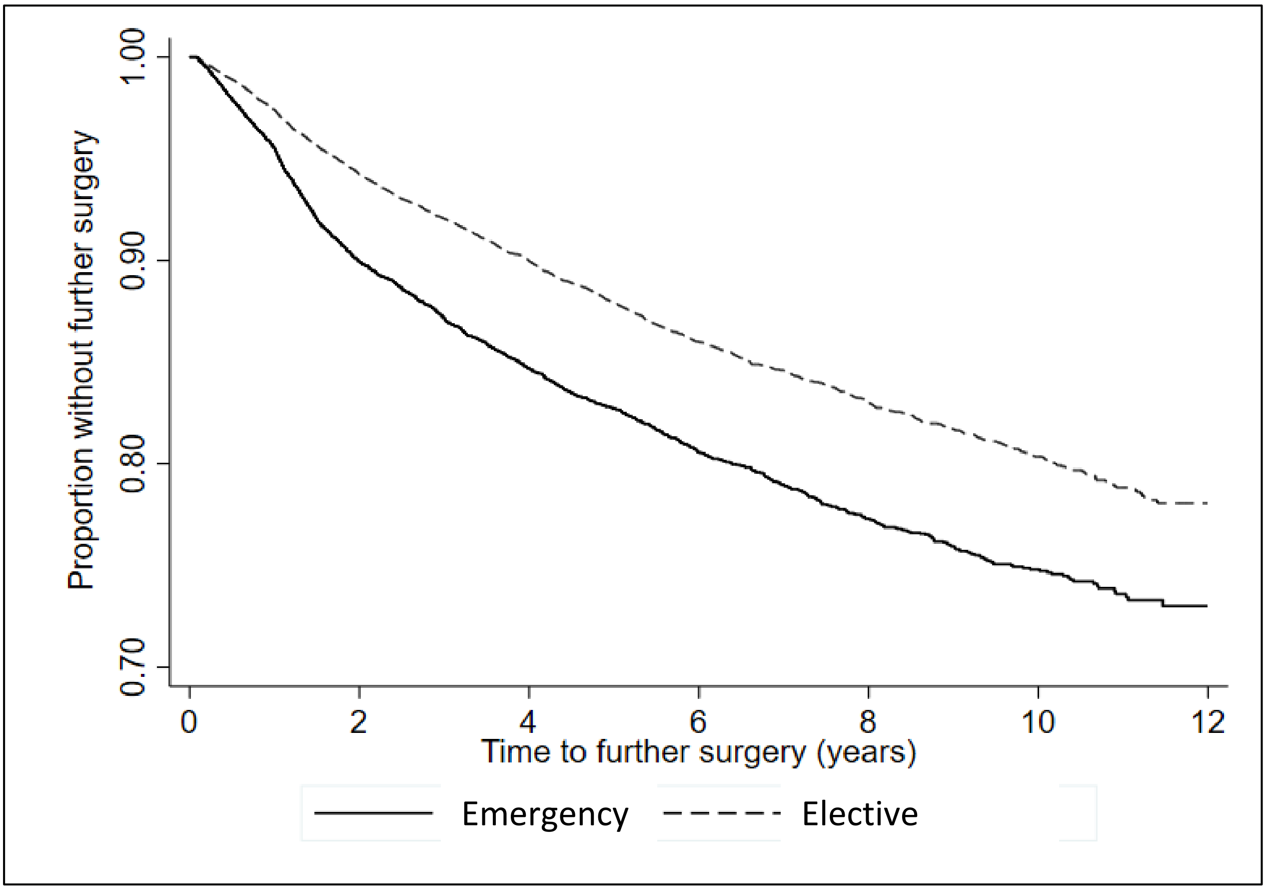

Figure 2. Kaplan-Meier curve showing time to further resection for those who underwent an index resection during an emergency or an elective admission.

Figure 3

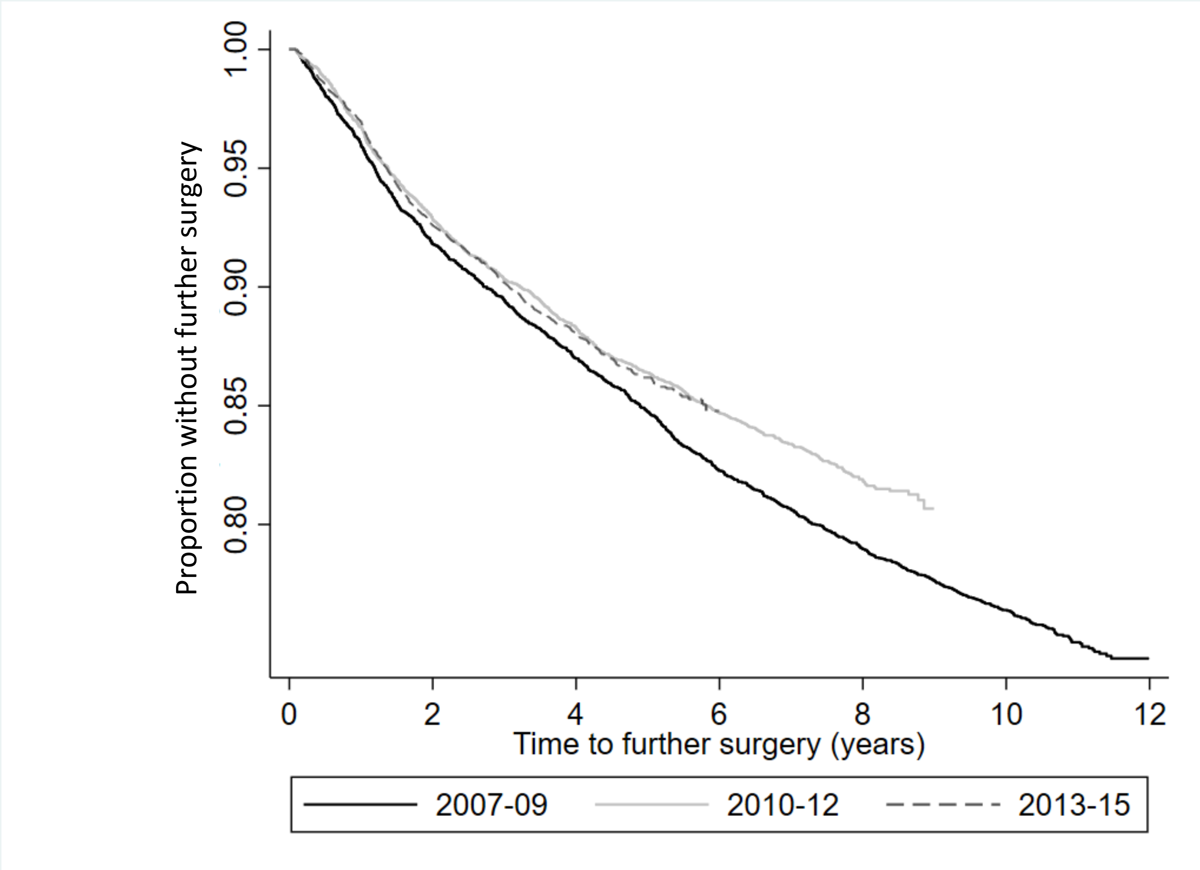

Figure 3. Kaplan-Meier analysis showing the proportion of patients who have further surgery stratified by 3-year time periods of index Crohn's disease resection

Figure 4

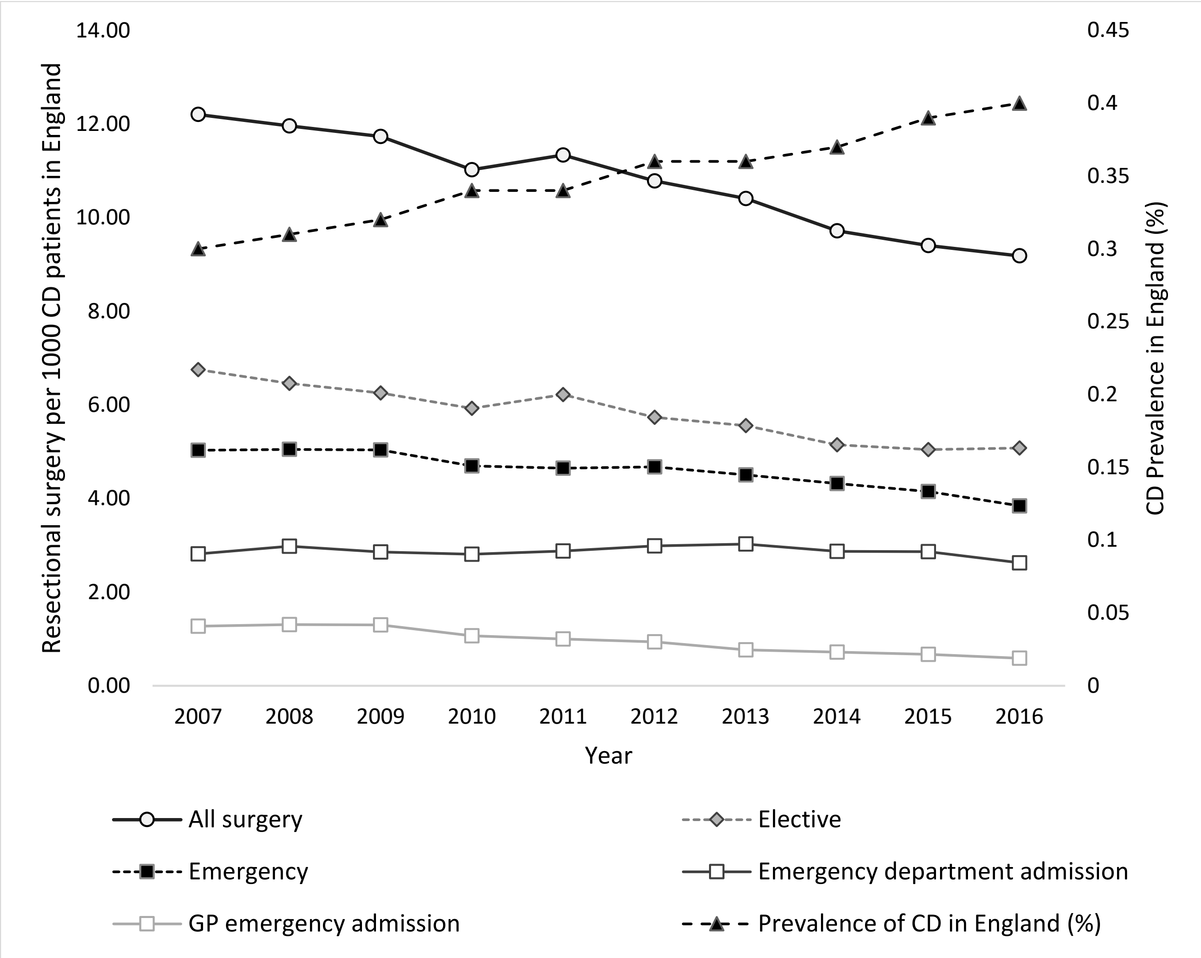

Figure 4. Index resection rates stratified by surgery and admission type, and Crohn's disease (CD) prevalence in England

GP: General practitioner