Associations between prior healthcare use, time to diagnosis, and clinical outcomes in Inflammatory Bowel Disease: a nationally representative population-based cohort study

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Contributorship

The POP-IBD study group is a collaboration between St George's University of London, Imperial College London, and University College London conducting population-based studies in the field of Inflammatory Bowel Disease. NJ and JB prepared the data and carried out statistical analysis overseen by IP and RB, and NJ and RP drafted the paper. All authors contributed to the concept, design, interpreting results, and commented on drafts of the manuscript. RP is guarantor of this article.

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Summary

Time to diagnosis, consultation frequency, intensity and hospitalisation prior to IBD diagnosis is associated with adverse clinical outcomes following diagnosis. Electronic healthcare records contain valuable information regarding pattens of consultation and may be used to expedite timely assessment and identify those at risk of aggressive forms of IBD.

ABSTRACT

BACKGROUND: Timely diagnosis and treatment of inflammatory bowel disease (IBD) may improve clinical outcomes.

OBJECTIVE: Examine associations between time to diagnosis, patterns of prior healthcare use and, clinical outcomes in IBD.

DESIGN: Using the Clinical Practice Research Datalink we identified incident cases of Crohn's disease (CD) and ulcerative colitis (UC), diagnosed between 01/2003 - 05/2016, with a first primary care gastrointestinal consultation during the 3-year period prior to IBD diagnosis. We used multivariable Cox regression to examine the association of primary care consultation frequency (n=1, 2, >2), annual consultation intensity, hospitalisations for gastrointestinal symptoms, and time to diagnosis with a range of key clinical outcomes following diagnosis.

RESULTS: We identified 2,645 incident IBD cases (CD:782; UC:1,863). For CD, >2 consultations were associated with intestinal surgery (adjusted Hazard Ratio (aHR)=2.22, CI:1.45-3.39) and subsequent CD-related hospitalisation (aHR=1.80, CI:1.29-2.50). For UC, >2 consultations was associated with corticosteroid dependency (aHR=1.76, CI:1.28-2.41), immunomodulator use (aHR=1.68, CI:1.24-2.26), UC-related hospitalisation (aHR=1.43, CI:1.05-1.95) and colectomy (aHR=2.01, CI:1.22-3.27). For CD, hospitalisation prior to diagnosis was associated with CD-related hospitalisation (aHR=1.30, CI:1.01-1.68) and intestinal surgery (aHR=1.71, CI:1.13-2.58); for UC, it was associated with immunomodulator use (aHR=1.42, CI:1.11-1.81), UC-related hospitalisation (aHR=1.36, CI:1.06-1.95) and colectomy (aHR=1.54, CI:1.01-2.34). For CD, consultation intensity in the year before diagnosis was associated with CD-related hospitalisation (aHR=1.19, CI:1.12-1.28) and intestinal surgery (aHR=1.13, CI:1.03-1.23); for UC, it was associated with corticosteroid use (aHR=1.08, CI:1.04-1.13), corticosteroid dependency (aHR=1.05, CI:1.00-1.11), and UC-related hospitalisation (aHR=1.12, CI:1.03-1.21). For CD, time to diagnosis was associated with risk of CD-related hospitalisation

(aHR=1.03, CI:1.01-1.68); for UC, it was associated with reduced risk of UC-related hospitalisation (aHR=0.83, CI:0.70-0.98) and colectomy (aHR=0.59, CI:0.43-0.80).

CONCLUSION: Electronic records contain valuable information about patterns of healthcare use that can be used to expedite timely diagnosis and identify aggressive forms of IBD.

Key words

Inflammatory bowel disease, Crohn's disease, Ulcerative colitis, time to diagnosis, consultation frequency, hospitalisation, frequency, intensity, delay, gastrointestinal disorders, duration, diagnostic pathway, general practice, primary care

Key Messages

What is already known?

- Diagnostic delay, from the point of first healthcare consultation, and increased healthcare utilisation may occur prior to inflammatory bowel disease (IBD) diagnosis, but their relationship to subsequent clinical outcomes is not yet established.

What this study adds

- Increased primary care consultation frequency and intensity for gastrointestinal symptoms prior to diagnosis is associated with worse clinical outcomes in IBD, particularly risk of intestinal surgery.
- Hospitalisation for gastrointestinal symptoms before diagnosis is also associated with an increased risk of intestinal surgery following diagnosis.
- Longer time to diagnosis was associated with an increased risk of Crohn's disease-related hospitalisation.
- Paradoxically, a longer time to diagnosis was associated with a milder disease course in ulcerative colitis.

How this study might affect research, practise and policy

- Expedited diagnostic approaches are required for patients who return repeatedly with unresolved gastrointestinal symptoms.
- Electronic records contain valuable information about patterns of healthcare use that can be used to prompt targeted timely referral and identification of aggressive forms of IBD.

Introduction

Inflammatory bowel disease (IBD) is a chronic relapsing and remitting gastrointestinal condition, which in its initial stages can be challenging and time consuming to diagnose. [1,2] Timely diagnosis enables early treatment to relieve patients' symptoms and potentially reduces the risk of disease progression, hospitalisation and surgery. [3-5] However, previous studies report that patients can wait for months to several years from symptom onset before receiving a diagnosis of IBD. [1,6]

Reasons for delay in diagnosis are likely complex. Patients may be unaware of the significance of their symptoms or be embarrassed to seek medical advice. One-tenth of patients report excess gastrointestinal symptoms 5 years before their eventual diagnosis with Crohn's Disease (CD) or ulcerative colitis (UC). [1] However, symptoms of IBD may often be mistaken for more prevalent benign gastrointestinal conditions, such as irritable bowel syndrome (IBS) and haemorrhoids, particularly during the early stages of disease. [7,8]

Targeted investigation can expedite diagnosis.[9] Set against this is the rising demand placed on healthcare services, which has been exacerbated in the wake of the COVID-19 pandemic. Individuals may be required to consult repeatedly before receiving a final diagnosis of IBD or, alternatively, need to access emergency hospital services. [10]

Previous studies have reported a higher-than-background prevalence of gastrointestinal symptoms and increased healthcare use and costs encountered in the years prior to IBD diagnosis, of which some encounters may be considered missed opportunities to diagnose, commence timely treatment and prevent disease progression. [1,11] However, the association between patterns of healthcare use in the period prior to IBD diagnosis and subsequent clinical outcomes has not previously been thoroughly evaluated. In other chronic conditions, such as heart failure and malignancy, more frequent consultation, including emergency hospital admission prior to diagnosis, is associated with worse disease-related outcomes. [12,13]

The natural progression of IBD is variable and can range from indolent to an aggressive, rapidly evolving disease behaviour. Whilst some studies have reported an association between diagnostic delay and the risk of disease complications, others have not.[6] Most studies have relied on retrospective estimates of symptom duration before diagnosis, collected using patient questionnaires, from hospital cohorts, and are therefore subject to bias and are not representative. [6]

It is not clear which patients presenting with gastrointestinal symptoms will benefit from expedited investigation. To determine how patterns of consultation are predictive of worse IBD outcomes we designed a nationally representative population-based retrospective cohort study using linked primary care and hospital records. We aimed to examine the association between time to diagnosis, frequency/ intensity of primary care and inpatient hospital episodes for gastrointestinal symptoms in the years before diagnosis, and the risk of subsequent adverse clinical outcomes in patients with IBD.

Methods

Data Source

We analysed routinely collected primary care data from electronic health records from primary care practices that contributed to the Clinical Practice Research Datalink (CPRD), one of the largest validated primary care research databases in the world. [14] It contains longitudinal, patient-level, deidentified electronic health records of 18 million patients from more than 700 general practices and is broadly representative of the UK population. The median follow-up for individuals registered in the CPRD is 9.4 years, allowing the study of long-term outcomes. We used CPRD GOLD version that contains data contributed by practices using Vision® software. Primary care physicians use clinical codes to record symptoms, diagnoses, and prescriptions. Participating practices need to achieve and maintain 'up to standard' status to continue contributing to the dataset. The CPRD GOLD coding system has been extensively validated for use in IBD. [15,16] CPRD primary care records are individually linked to the Hospital Episode Statistics (HES) database, which includes data on admissions and outpatient appointments in National Health Service hospitals in England. We obtained ethical and scientific approval for the use of the CPRD and HES for our study from the CPRD Independent Scientific Advisory Committee [ISAC Protocol number: 20_000248].

Case definition and cohort construction

We identified incident cases of IBD diagnosed between January 2003 and May 2016 who had their first primary care consultation record for gastrointestinal symptoms in the three-year period prior to their IBD diagnosis. We chose this interval since we previously found most individuals with IBD first consulted for gastrointestinal symptoms within this time period prior to diagnosis. [1] All individuals required at least four years of follow-up from registering with their general practice before IBD diagnosis, with the first of these years free of any record of gastrointestinal symptoms (**appendix 1 and 2**). We defined incident IBD cases, using a previously validated and published methodology, as individuals who had a first diagnostic Read code for either CD or UC registered with an 'up to

standard' practice. [17,18] We excluded individuals if they had codes for both CD and UC, or indeterminate codes such as 'non-specific colitis'. All individuals included in the study had linkage between CPRD and HES. We identified individuals who consulted a primary care physician with their first gastrointestinal symptom(s), within the three-year period before their IBD diagnosis, as we have previously shown a higher than background prevalence and incidence of gastrointestinal symptoms occur in this time frame and are therefore likely to be related to IBD. [1] We used previously published and validated lists of Read codes to identify gastrointestinal symptoms of IBD, including abdominal or perianal pain, diarrhoea and rectal bleeding (**appendix 1**). [1] Patients were followed up from the date of IBD diagnosis until the first recorded outcome, de-registration, or death, if these occurred before that time, or the study endpoint defined as 5 years following IBD diagnosis.

Exposures

Time to IBD diagnosis, consultation frequency, consultation intensity and hospitalisation for gastrointestinal symptoms prior to IBD diagnosis were the primary exposure variables. We defined time to diagnosis as the number of months from the first recorded date of consultation for gastrointestinal symptom(s) to the date of IBD diagnosis, defined as the date of the first recorded code for an IBD diagnosis in CPRD. For consultation frequency we allocated patients to groups according to the number of primary care consultations for gastrointestinal symptoms (1, 2, and >2) in the three-year period before receiving a diagnosis of IBD. We examined the impact of consultation intensity, defined as consultation frequency per person in each individual year in the 3-year period prior to IBD diagnosis. Finally, we identified individuals who required hospital admission related to gastrointestinal symptoms prior to IBD diagnosis. This was defined as individuals who had a code (International Statistical Classification of Diseases and Related Health Problems: ICD-10) that included relevant gastrointestinal symptoms: abdominal pain, diarrhoea and per rectal bleeding, listed as their primary reason for admission (**appendix 1**).

Outcomes

Study outcomes were oral corticosteroid use and dependency (surrogate measure of disease activity and severity), treatment escalation requiring immunomodulator use, IBD-related hospitalisation and IBD-related surgery.

We defined individuals as 'exposed to oral corticosteroid' if they had at least one prescription for corticosteroid during the study follow-up period. Secondly, we identified individuals with corticosteroid dependency, adapted from European Crohn's and Colitis Organisation guidelines criteria. [19] An individual was defined as 'corticosteroid-dependent' if they had either a prescription for corticosteroid that lasted longer than 3 months or required a repeat corticosteroid prescription within 3 months of stopping the previous corticosteroid course. [19,20]

Immunomodulator use was defined as the first prescription date of azathioprine, mercaptopurine or methotrexate following IBD diagnosis.

We used a previously published list of ICD-10 codes to identify individuals where IBD was the primary reason for admission following diagnosis. [21] We excluded day case activity and 'zero-day admissions', which can represent routine care such as endoscopic surveillance or administration of therapy. [21]

We used previously published OPCS Classification of Interventions and Procedures (OPCS-4) codes to identify surgical procedures in the HES database. [21] CD surgery was subcategorised as either major intra-abdominal (intestinal) surgery or perianal surgery. Colectomy was defined as any colectomy procedure following diagnosis of UC. [17,21]

Factors associated with time to diagnosis and patterns of consultation prior to IBD diagnosis

We identified potential factors associated with time to diagnosis, primary care consultation frequency, intensity, and hospital admission for gastrointestinal symptoms prior to IBD diagnosis, based on clinical knowledge and published literature. Age, low socioeconomic status, and smoking

234 are associated with diagnostic delay in other chronic conditions. [22,23] Younger age at diagnosis is
235 also known to be associated with a more aggressive disease phenotype in IBD. [23] We grouped
236 individuals according to their age at diagnosis of IBD according to the Montreal classification (<17,
237 17-40 and >40 years). We used a postcode-linked marker of social deprivation, the Index of Multiple
238 Deprivation (IMD), to group patients by socio-economic status from IMD 1 (least deprived) to 5
239 (most deprived).

240 IBS and depression have been reported to be associated with a longer time to specialist review in
241 IBD [1] and worse outcomes. [24-26] Poor mental health has been associated with increased
242 healthcare use in other chronic disease. [27] We identified individuals who had codes for IBS,
243 depression, anxiety or symptoms of depression or anxiety before their index presentation with
244 gastrointestinal symptoms.

245 Individuals were classed as 'smokers', 'ex-smokers' or 'non-smokers' based on codes for smoking
246 status in the 10 years before presentation with gastrointestinal symptoms using a previously
247 reported methodology accounting for missing data. [1,20,28] We considered the era of IBD diagnosis
248 to account for secular change over the study period (era 1:2003-2005 era 2:2006-2008; era 3:2009-
249 2011 and era 4:2012-2016).

Statistical analysis

We used simple and multiple Cox regression analysis to calculate hazard ratios (HR) and 95% confidence intervals (CI) for our listed clinical outcome measures in the 5 years following diagnosis, given time to IBD diagnosis, gastrointestinal-related consultation frequency and hospital admission prior to IBD diagnosis. We also analysed the association between intensity of gastrointestinal consultations in primary care for each year in the 3 years prior to diagnosis and subsequent clinical outcomes. Within the multiple regression models, we adjusted for sex, age at diagnosis, social deprivation, smoking status, and era of diagnosis. Analysis was carried out separately for individuals diagnosed with CD and UC.

We used Kaplan-Meier analysis to present time-to-event curves of IBD-related clinical outcomes in the 5 years following diagnosis given consultation frequency in primary care for gastrointestinal symptoms. We used multiple Cox-regression to examine factors that may be associated with time to diagnosis; logistic regression was used to examine factors that may be associated with gastrointestinal-related consultation frequency in primary care and hospital admission prior to diagnosis of IBD. Analyses were performed using STATA 17 (Statacorp LP, College Station, TX, USA).

Results

We identified 2,645 individuals with a new diagnosis of IBD between January 2003 and May 2016 who had their first gastrointestinal-related primary care consultation in the three-year period prior to IBD diagnosis (**Table 1** and **appendix 2**). The median time from the first consultation with gastrointestinal symptoms to diagnosis of CD was 7 months (interquartile range (IQR):2-18 months) compared with 5 months (IQR:2-16 months) for UC; 37% (n=288) and 31% (n=580) of individuals experienced gastrointestinal symptoms for more than a year before being diagnosed with CD and UC, respectively.

The median number of consultations for gastrointestinal symptoms prior to CD diagnosis was 3 (IQR:1-3; total range:1-17) compared with 2 (IQR:1-3; total range:1-15) in UC. We found 41% and 27% of individuals, who went on to be diagnosed with CD and UC respectively, had a primary care consultation for gastrointestinal symptoms more than twice during the 3-year period prior to diagnosis. Amongst the whole cohort, 36% (n=962; CD=339 and UC=623) of individuals required gastrointestinal-related hospital admission prior to IBD diagnosis (**appendix 2**).

Time to IBD diagnosis and clinical outcomes

Amongst individuals diagnosed with CD, we found that a longer time to diagnosis from first consultation for gastrointestinal symptoms was associated with increased risk of hospitalisation (aHR=1.03, CI:1.01-1.68), but not surgery, in the 5 years following diagnosis (**Table 2a**). Amongst individuals diagnosed with UC, a longer time to diagnosis was associated with a lower risk of corticosteroid use (aHR=0.87, CI:0.79-0.97), UC-related hospitalisation (aHR=0.83, CI:0.70-0.98) and colectomy (aHR=0.59, CI:0.43-0.80) in the 5 years following diagnosis (**Table 2b**).

Gastrointestinal consultations before diagnosis and clinical outcomes

Amongst individuals diagnosed with CD, those who presented to primary care with gastrointestinal symptoms more than twice prior to diagnosis had an increased risk of CD-related hospitalisation

(aHR=1.80, CI:1.29-2.50) and intestinal surgery (aHR=2.22, CI:1.45-3.39) in the five years following diagnosis, compared with those who had only one consultation (**Table 2a** and **Figure 1**). Amongst individuals diagnosed with UC, those who presented to primary care with gastrointestinal symptoms more than twice prior to diagnosis had an increased risk of corticosteroid use (aHR=1.60, CI:1.31-1.96), corticosteroid dependency (aHR=1.76, CI:1.28-2.14), immunomodulator use (aHR=1.68, CI:1.24-2.26), UC-related hospitalisation (aHR=1.43, CI:1.05-1.95) and colectomy (aHR=2.01, CI:1.22-3.27) compared with those who had only one consultation (**Table 2b** and **Figure 2**).

Consultation intensity in primary care was highest in the year prior to diagnosis and was associated with worse clinical outcomes in both CD and UC. In the year before diagnosis 26% and 17% of individuals diagnosed with CD and UC, respectively, consulted more than twice, compared with 4% and 2%, and 3% and 1%, in the second and third year before diagnosis, respectively.

In CD, individuals with a higher consultation intensity in the year prior to diagnosis had an increased risk of CD-related hospitalisation (aHR=1.19, CI:1.12-1.28) and intestinal surgery (aHR=1.13, CI:1.03-1.23) in the five years following diagnosis (**Table 3a**)**.** In UC, individuals with a higher consultation intensity in the year prior to diagnosis had an increased risk of corticosteroid use (aHR=1.08, CI:1.04-1.13), corticosteroid dependency (aHR=1.05, CI:1.00-1.11), and UC-related hospitalisation (aHR=1.12, CI:1.03-1.21) (**Table 3b**).

Hospitalisation before diagnosis and subsequent clinical outcomes

Individuals who required hospitalisation for gastrointestinal symptoms prior to CD diagnosis had an increased risk of CD-related hospitalisation (aHR=1.30, CI:1.01-1.68) and intestinal surgery (aHR=1.71, CI:1.13-2.58) in the 5 years following CD diagnosis, compared with individuals who had none (**Table 2a**). Amongst individuals diagnosed with UC, gastrointestinal-related hospital admission prior to diagnosis was associated with an increased risk of immunomodulator use (aHR=1.42, CI:1.11-1.81), UC-related hospitalisation (aHR=1.36, CI:1.06-1.95) and colectomy (aHR=1.54, CI:1.01-2.34) in the 5 years after diagnosis, compared with individuals who had none (**Table 2b**).

Factors associated with time to diagnosis and patterns of consultation before IBD diagnosis

Females and individuals with a diagnosis of IBS or depression and/or anxiety were more likely to have a longer time to diagnosis of IBD compared with those without. Similarly, individuals with a diagnosis of IBS, depression and/or anxiety were more likely to consult more than twice with gastrointestinal symptoms compared with those who presented only once. Individuals under 17 years of age at diagnosis were more likely to consult primary care more than twice and require gastrointestinal-related hospital admission prior to diagnosis, when compared with individuals over 40 years. Smokers were 42% more likely to consult more than twice with gastrointestinal symptoms than never-smokers**.** Individuals aged <17 and between 17 and 39 years were associated with higher consultation intensity in the year prior to diagnosis. Those living in areas of greater socioeconomic deprivation were 29% more likely to require hospitalisation for gastrointestinal symptoms prior to diagnosis when compared with individuals living in more affluent postcodes. Compared with individuals diagnosed during 2003-2005 those diagnosed in the era 2012–2016 were 61% more likely to have hospitalisation for gastrointestinal symptoms prior to IBD diagnosis **(Table 4).**

Discussion

Main findings

In this large population-based study we found more frequent primary care consultation for gastrointestinal symptoms prior to IBD diagnosis was associated with worse clinical IBD outcomes, notably an increased risk of surgery, and, with respect to UC, an increased risk of steroid dependency. Primary care consultation intensity was highest in the 1-year prior to diagnosis and in this year was associated with worse clinical outcomes in both CD and UC. Likewise, hospitalisation for gastrointestinal symptoms before diagnosis was associated with an increased risk of subsequent IBD-related hospital admission and intestinal surgery following diagnosis. A longer time to diagnosis, from the point of first primary care consult with gastrointestinal symptoms, was associated with increased disease related hospitalisation in CD, but not surgery, and a milder disease course in UC.

Findings in relation to previous studies

To the best of our knowledge, this is the first nationally representative study to demonstrate an association between consultation frequency and intensity for gastrointestinal symptoms prior to diagnosis with subsequent adverse clinical outcomes following the diagnosis of IBD. Previous studies report a relationship between delayed diagnosis and adverse IBD-related clinical outcomes such as surgery. [2,29] However, the majority of these studies used retrospective questionnaires conducted in secondary healthcare settings, thus likely subject to both recall and referral centre bias.[6]

In our study, a longer time from first primary care consultation to diagnosis was associated with a subsequent increased hospitalisation for CD, but not surgery; in contrast, for UC, it was associated with a milder disease course. Our findings are similar to a previous study, that also utilised UK primary care records, that reported no associated risk between time to diagnosis and worse clinical outcomes. [30]

We also considered the impact of primary care consultation intensity for gastrointestinal symptoms prior to diagnosis, which, was highest in the one-year period immediately before diagnosis, and a greater consultation intensity in this year was associated with worse IBD outcomes. This reflects our previous observation that individuals with CD and UC were four-times more likely to visit their primary care physician for gastrointestinal symptoms when compared with age-sex matched control groups without IBD between 18 and 6 months before diagnosis. [1] Repeat consultations may either be clinician- or patient-initiated, likely driven by both symptom frequency and severity. Our findings suggest that higher primary care consultation frequency and intensity before diagnosis is linked to a more aggressive/severe disease behaviour with worse outcomes, albeit the observed effects are relatively modest. This is in keeping with paediatric studies that show a short fulminant onset of symptoms is associated with worse clinical outcomes following UC diagnosis, including risk of colectomy. [31,32]

Hospitalisation for gastrointestinal symptoms prior to IBD diagnosis was more common in those from deprived postcodes and had an associated higher risk of adverse clinical outcomes following diagnosis. This is consistent with other findings that report emergency hospital presentation prior to diagnosis is associated with worse IBD-related clinical outcomes. [30]

Previous literature reporting the relationship between diagnostic delay and IBD outcomes is inconsistent, with several studies suggesting diagnostic delay based on self-reported symptom onset is associated with worse clinical outcomes following diagnosis, [2,33] while others have not. [30,34] The differences observed between this study and others may relate to how 'diagnostic delay' is defined. Most previous studies have measured total time to diagnosis, including both patient-related and healthcare-related delay, whereas our study measured the interval from first related primary care consult for gastrointestinal symptoms prior to IBD diagnosis. We found that a longer time to UC diagnosis was associated with a lower risk of subsequent hospitalisation and colectomy, suggesting this group may have a milder, more indolent disease course. Our findings are supported by the

observation that asymptomatic or mildly symptomatic individuals, who are diagnosed with IBD at colonoscopy as part of bowel cancer screening initiatives, have a milder pattern of disease behaviour. [35] In contrast, a longer time to CD diagnosis was associated with a small increased risk of hospitalisation but not surgery which contrasts with most reports evaluating delay from the point of symptom onset.

The concept of the 'waiting time paradox', the effect that patients with severe symptoms indicative of a more aggressive and fulminant disease phenotype, present rapidly over a short period of time, are diagnosed, and treated early, thereby leading to an apparent association between longer waits and better outcomes has been reported for cancer diagnoses. It is considered an important source of bias in studies investigating the impact of diagnostic and treatment delays on cancer survival, where the biology of the disease may outweigh the impact of diagnostic delay when determining clinical outcomes. [37,38] Such a phenomenon may also be at play with regard to IBD whereby a fulminant disease course prior to diagnosis, rather than a long symptomatic period prior to diagnosis, may predict a more aggressive/severe disease course. This may be reflected in our findings, particularly regarding UC.

Guidelines recommend that clinicians investigate persistent non-specific gastrointestinal symptoms, which are also prevalent in other common gut disorders such as IBS. [39] Our study found that individuals with a prior diagnosis of IBS were more likely to have experienced a longer time to diagnosis and higher consultation frequency for gastrointestinal symptoms in the period before IBD diagnosis. It is possible individuals with undiagnosed IBD that receive a clinical diagnosis of IBS are less likely to be investigated, resulting in a longer time to diagnosis. [7] Similarly, we found that a prior diagnosis or symptoms of depression-anxiety were associated with both a longer time to diagnosis and increased consultation frequency for gastrointestinal symptoms in the period prior to IBD diagnosis. Gastrointestinal symptoms may be considered more likely to be of functional origin in

these patients. In this respect, we have previously reported increased rates of depression following the onset of undiagnosed gastrointestinal symptoms in the lead up to a diagnosis of IBD. [15]

Strengths and Limitations

We used data drawn from a large, validated, nationally-representative, linked primary care and hospital database. CPRD data is collected at the time of consultation and therefore, unlike most previous studies that have relied on retrospective self-reported data from specialist centres, is free from recall and selection bias. There are limitations to the study design. We estimated time to diagnosis using captured data from primary care consultations and therefore cannot account for the duration of unreported symptoms prior to consultation. When interpreting the findings of our study, it is worth reflecting that they relate to patients with gastrointestinal symptoms presenting to primary care but other extraintestinal symptoms may also herald the onset of IBD.

We were unable to capture data on medications prescribed in the hospital setting, meaning rates of corticosteroid and immunomodulator use reported in this study are likely to be underestimated. However, in the UK, hospital outpatient prescribing is highly regulated, and primary care practices utilising shared care protocols enable General Practitioners to accept the responsibility for the safe prescribing and monitoring of specialist medicines for patients with chronic conditions in the community. Therefore it is likely that we would have captured the large proportion of prescriptions, some of which may be only initiated in secondary care.

We were unable to identify episodes where individuals presented to the emergency department alone without requiring hospital admission, and thus the association between emergency hospital presentation and clinical outcomes may have been underestimated. Data defining endoscopic and radiological disease extent, or biochemical markers, such as C-Reactive Protein and faecal calprotectin that are associated with disease severity were not available for our analysis.

By choosing a methodology that included symptomatic individuals attending primary care in the three years before diagnosis, with no symptom in the preceding year, a small number of individuals may have been omitted but we chose this study design to minimise inclusion of consults for non-IBD-related gastrointestinal symptoms. This time interval was chosen since our previous findings revealed an excess of gastrointestinal symptoms in patients who later develop IBD compared with the background population emerged in this time frame.[1] We found no secular relationship by era of diagnosis regarding IBD outcomes (although hospitalisation prior to diagnosis was more common in the most recent era studied). This suggests diagnostic approaches seemingly have not altered time to diagnosis in the study period. More recently the wider adoption of faecal calprotectin testing in primary care may allow more timely diagnosis. Whilst the association of deprivation was evaluated ethnicity was not reliably coded in the dataset and warrants evaluation in future work. Further work is also needed to determine if our observed findings are replicated in other healthcare systems.

Implications

Our findings highlight the need for expedited diagnostic approaches for patients that consult more frequently or intensely in primary care or require hospital admission for gastrointestinal symptoms. We speculate that some individuals with IBD that have a more aggressive disease behaviour do not necessarily present with a long duration of symptoms but instead with a rapidly progressive fulminant disease course, leading to a higher frequency and intensity of consultation and urgent hospital attendance in the period prior to IBD diagnosis. Clinicians need to be alert to the possibility of IBD when patients return repeatedly with unresolved symptoms. Prior healthcare use can alert clinicians to those at risk of a more aggressive IBD course, prompting targeted timely assessment. Further, prospective studies utilising newly described diagnostic and prognostic biomarker may shed further light on the relationship between symptom onset and healthcare use in the years before diagnosis and subsequent disease prognosis. Our findings, and those of others, indicate a significant burden of disease and healthcare use in the years before IBD diagnosis.[11,35,40] Diagnostic

pathways that take account of patterns of healthcare consultation, alongside appropriate use of surrogate markers of inflammation such as faecal calprotectin, may enable expedited specialist referral and timely treatment. [39,40]

Conclusion

Consultation frequency, intensity and hospitalisation prior to diagnosis is associated with a subsequent risk of adverse IBD outcomes. Electronic healthcare records contain valuable information regarding patterns of consultation and may be used to expedite timely assessment and identify those at risk of aggressive forms of IBD.

DATA AVAILABILITY STATEMENT

Data may be obtained from a third party and are not publicly available.

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FIGURE LEGENDS

FIGURE 1: Probability of **(A)** CD-related intestinal surgery **(B)** CD-related hospitalisation following diagnosis given consultation frequency for gastrointestinal symptoms prior to diagnosis

FIGURE 2: Probability of **(A)** Corticosteroid-use **(B)** Corticosteroid-dependency in UC following diagnosis given consultation frequency for gastrointestinal symptoms prior to diagnosis

RESULTS FIGURES AND TABLES

Table 1 Baseline characteristics of study population

IBD Status	Crohn's Disease n = 782	Ulcerative Colitis n = 1,863
Gender n (%)		
Male	390 (50)	1.021 (55)
Female	392 (50)	842 (45)
Age at diagnosis [Years] n (%)		
<17	86 (11)	63 (3)
17 to 40	380 (49)	612 (33)
>40	316 (40)	1,188 (64)
Social deprivation n (%)		
IMD* 1-3	512 (65)	1,311 (70)
IMD* 4-5	270 (36)	552 (30)
Time to diagnosis from first gastrointestinal consultation		
Median (IQR) months	7 (2 - 18)	5 (2 - 16)
Primary care consultation frequency n (%)		
1	264 (34)	822 (44)
2	200 (26)	533 (29)
>2	318 (41)	508 (27)
Hospitalisation for gastrointestinal symptoms before diagnosis n (%)	339 (43%)	623 (33%)

IMD – Index of Multiple Deprivation; IMD 1 represents the least deprived and IMD 5 the most deprived; IQR – Interquartile range

Table 2 Association of time to diagnosis, consultation frequency and hospitalisation for gastrointestinal symptoms before diagnosis with clinical outcomes following diagnosis of (a) Crohn's disease (b) Ulcerative colitis *

(a) Crohn's Disease	CS use	CS dependency	IM use	IBD Hospitalisation	Intestinal surgery	Perianal surgery
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Consultation frequency						
1	-	-	-	-	-	-
2	0.90 (0.68 - 1.18)	1.11 (0.74 - 1.65)	1.05 (0.78 - 1.43)	1.35 (0.94 - 1.93)	1.58 (0.99 - 2.51)	1.08 (0.81 - 1.44)
≥ 3	1.21 (0.94 - 1.56)	1.23 (0.84 - 1.80)	1.11 (0.84 - 1.52)	**1.80 (1.29 - 2.50)**	**2.22 (1.45 - 3.39)**	1.00 (0.79 - 1.36)
Time to diagnosis	0.89 (0.78 - 1.01)	0.89 (0.73 - 1.07)	0.92 (0.80 - 1.06)	**1.03 (1.01 - 1.68)**	0.87 (0.71 - 1.06)	1.00 (0.88 - 1.15)
Pre-diagnosis hospital admission	0.96 (0.76 - 1.21)	1.05 (0.78 - 1.42)	0.78 (0.60 - 1.01)	**1.30 (1.01 - 1.68)**	**1.71 (1.13 - 2.58)**	1.19 (0.96 - 1.48)
Sex						
Female	-	-	-	-	-	-
Male	1.13 (0.55 - 0.86)	0.85 (0.62 - 1.15)	1.04 (0.83 - 1.32)	1.12 (0.87 - 1.44)	1.20 (0.86 - 1.66)	1.05(0.84 - 1.30)
Age at IBD diagnosis						
> 40 years						
< 17 years	**1.45** (1.00 - 2.09)	1.20 (0.68 - 2.12)	**3.60 (2.47 - 5.24)**	**2.31 (1.51 - 3.56)**	0.71 (0.37 - 1.36)	**1.72 (1.18 - 2.51)**
17 - 40 years	**1.46 (1.16 - 1.83)**	1.26 (0.90 - 1.76)	**1.89 (1.43 - 2.49)**	**1.52 (1.14 - 2.03)**	1.18 (0.83 - 1.68)	1.27(0.99 - 1.62)
Era of IBD diagnosis						
Era 1	-	-	-	-	-	-
Era 2	1.07 (0.82 - 1.42)	0.88 (0.59 - 1.29)	1.50 (0.66 - 1.41)	1.18 (0.83 - 1.69)	1.34 (0.86 - 2.08)	1.37 (0.98 - 1.92)
Era 3	0.90 (0.91 - 0.68)	0.72 (0.47 - 1.11)	**2.02 (1.41 - 1.26)**	1.15 (0.80 - 1.65)	1.29 (0.81 - 2.06)	**2.21(1.58 - 3.09)**
Era 4	1.32 (0.99 - 1.77)	0.76 (0.49 - 1.18)	**3.32 (2.34 - 4.74)**	**2.00 (1.35 - 2.98)**	1.25 (0.76 - 2.04)	**4.54(3.28 - 6.28)**
Smoking status*						
Never	-	-	-	-	-	-
Ex-smoker	0.85 (0.61 - 1.18)	0.90 (0.55 - 1.48)	0.91(0.65 - 1.26)	0.60 (0.38 - 0.93)	0.96 (0.63 - 1.46)	0.94 (0.67 - 1.31)
Current	0.99 (0.75 - 1.31)	1.22 (0.82 - 1.83)	0.88 (0.65 - 1.19)	1.05 (0.75 - 1.48)	0.76 (0.50 - 1.16)	0.90 (0.67 - 1.20)
Social deprivation						
IMD 1-3	-	-	-	-	-	-
IMD 4-5	1.12 (0.91 - 1.39)	1.14 (0.83 - 1.56)	0.97 (0.76 - 1.24)	1.12 (0.86 - 1.46)	1.11 (0.80 - 1.55)	0.87 (0.69 - 1.08)

(b) Ulcerative Colitis	CS use Adjusted HR (95% CI)	CS dependency Adjusted HR (95% CI)	IM use Adjusted HR (95% CI)	IBD hospitalisation Adjusted HR (95% CI)	Colectomy Adjusted HR (95% CI)
Consultation frequency					
1	-	-	-	-	-
2	**1.26 (1.04 - 1.60)**	1.28 (0.94 - 1.75)	1.12 (0.83 - 1.51)	1.24 (0.93 - 1.66)	0.93 (0.55 - 1.57)
≥ 3	**1.60 (1.31 - 1.96)**	**1.76 (1.28 - 2.41)**	**1.68 (1.24 - 2.26)**	**1.43 (1.05 - 1.95)**	**2.01 (1.22 - 3.27)**
Time to diagnosis	**0.87 (0.79 - 0.97)**	0.95 (0.81 - 1.11)	0.88 (0.76 - 1.03)	**0.83 (0.70 - 0.98)**	**0.59 (0.43 - 0.80)**
Pre-diagnosis hospital admission	1.18 (0.99 - 1.39)	1.04 (0.80 - 1.36)	**1.42 (1.11 - 1.81)**	**1.36 (1.06 - 1.95)**	**1.54 (1.01 - 2.34)**
Sex					
Female	-	-	-	-	-
Male	1.00 (0.85 - 1.17)	**1.37 (1.06 - 1.76)**	1.16 (0.92 - 1.48)	1.01 (0.79 - 1.29)	1.42 (0.93 - 2.16)
Age at IBD diagnosis					
> 40	-	-	-	-	-
< 17	**1.82 (1.24 - 2.69)**	**2.38 (1.37 - 4.12)**	**3.35 (2.07 - 5.43)**	**3.40 (1.47 - 1.89)**	**2.54 (1.09 - 5.95)**
17 – 39	**1.34 (1.14 - 1.60)**	**1.52 (1.17 - 1.98)**	**1.83 (1.42 - 2.34)**	**1.47 (1.14 - 1.89)**	**1.81 (1.17 - 2.79)**
Era of IBD diagnosis					
Era 1	-	-	-	-	-
Era 2	1.14 (0.92 - 1.43)	1.05 (0.76 - 1.44)	1.11 (0.78 - 1.57)	0.82 (0.58 - 1.13)	0.65 (0.38 - 1.09)
Era 3	**1.35 (1.07 - 1.70)**	0.83 (0.58 - 1.20)	**1.53 (1.08 - 2.15)**	0.91(0.66 - 1.29)	0.62 (0.35 - 1.11)
Era 4	**1.44 (1.14 - 1.83)**	0.76 (0.52 - 1.12)	**1.95 (1.36 - 2.80)**	1.15 (0.79 - 1.58)	0.85 (0.46 - 1.54)
Smoking status*					
Never	-	-	-	-	-
Ex-smoker	0.94 (0.99 - 1.54)	0.88 (0.63 - 1.23)	0.89 (0.64 - 1.22)	0.79 (0.51 - 1.03)	1.33 (0.75 - 2.34)
Current	0.97 (1.13 - 1.79)	0.59 (0.32 - 1.05)	0.81 (0.49 - 1.32)	0.78 (0.48 - 1.30)	0.89 (0.36 - 2.20)
Social deprivation					
IMD 1-3	-	-	-	-	-
IMD 4-5	1.06 (0.89 - 1.26)	0.91(0.69 - 1.1)	0.79 (0.61 - 1.02)	1.26 (0.98 - 1.62)	0.65 (0.40 - 1.05)

*** See supplementary appendix 3 for unadjusted analyses**

Bold indicates statistical significance in adjusted model. CS, Corticosteroids; IM, Immunomodulator; HR, Hazard Ratio; CI, confidence interval; IMD, index of multiple deprivations

IMD categories 4 and 5 [most deprived] vs IMD categories 1, 2 and 3 [least deprived]

Era 1: 2003 – 2005, Era 2 2006 – 2008, Era 3 2009 – 2011 and Era 4 2012 – 2016

First CS use: Time to first CS prescription following diagnosis

CS dependency: Corticosteroid dependency defined as a repeat steroid prescription within 3 months of the end of a previous steroid prescription or patients with steroid prescriptions for greater than 3 consecutive months

Hospitalisation: IBD-related hospital admission following diagnosis

Time to diagnosis: Time from first primary care consultation for gastrointestinal symptom(s)

Abbreviation gastrointestinal (GI)

Table 3: Association of consultation intensity with gastrointestinal symptoms in the years before diagnosis with clinical outcomes following (a) Crohn's disease diagnosis (b) Ulcerative colitis *

(a) Crohn's disease

Year before diagnosis	CS use	CS dependency	IM use	IBD Hospitalisation	Intestinal surgery	Perianal surgery
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Year 1	1.03 (0.98 - 1.08)	1.01 (0.96 - 1.07)	1.00 (0.95 - 1.06)	**1.19 (1.12 - 1.28)**	**1.13 (1.03 - 1.23)**	1.05 (0.98 - 1.13)
Year 2	1.00 (0.92 - 1.09)	0.99 (0.90 - 1.09)	1.03 (0.94 - 1.12)	**1.13 (1.01 - 1.25)**	0.86 (0.71 - 1.03)	1.00 (0.90 - 1.12)
Year 3	0.96 (0.95 - 1.08)	0.99 (0.88 - 1.11)	0.90 (0.80 - 1.02)	1.10 (0.91 - 1.33)	1.25 (0.99 - 1.48)	0.98 (0.87 - 1.11)

(b) Ulcerative colitis

Year before diagnosis	CS use	CS dependency	IM use	IBD Hospitalisation	Colectomy
	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
Year 1	**1.08 (1.04 - 1.13)**	1.05 (1.00 - 1.11)	1.03 (0.98 - 1.08)	**1.12 (1.03 - 1.21)**	1.12 (0.99 - 1.26)
Year 2	1.03 (0.96 - 1.11)	1.07 (0.98 - 1.15)	1.03 (0.95 - 1.13)	1.05 (0.92 - 1.20)	0.91 (0.68 - 1.20)
Year 3	1.02 (0.93 - 1.12)	1.05 (0.96 - 1.16)	1.03 (0.93 - 1.13)	1.00 (0.81 - 1.23)	1.00 (0.73 - 1.28)

*** See supplementary appendix 4 for unadjusted analyses**

Bold indicates statistical significance in adjusted model. CS, Corticosteroids; IM, Immunomodulator; HR, Hazard Ratio; CI, confidence interval; IMD, index of multiple deprivations

IMD categories 4 and 5 [most deprived] vs IMD categories 1, 2 and 3 [least deprived]

Era 1: 2003 – 2005, Era 2 2006 – 2008, Era 3 2009 – 2011 and Era 4 2012 – 2016

First CS use: Time to first CS prescription following diagnosis

CS dependency: Corticosteroid dependency defined as a repeat steroid prescription within 3 months of the end of a previous steroid prescription or patients with steroid prescriptions for greater than 3 consecutive months

Hospitalisation: IBD-related hospital admission following diagnosis

Consultation intensity consultation frequency per person, as a continuous variable, in each individual year over the 3-year period before diagnosis

Abbreviation gastrointestinal (GI)

Table 4 Factors associated with time to diagnosis, consultation frequency, consultation intensity and hospitalisation before diagnosis of IBD *

	Time to diagnosis	Consultation frequency	Consultation Intensity	Prior GI hospitalisation
	Adjusted HR (95% CI)	Adjusted OR (95% CI)	Adjusted Coefficient (95% CI)	Adjusted OR (95% CI)
Age				
> 40	-	-	-	-
< 17	0.99 (0.82 - 1.17)	**2.32 (1.40 - 2.01)**	**0.44 (0.20 - 0.67)**	**1.74 (1.21 - 2.48)**
17-39	0.99 (0.91 - 1.07)	**1.68 (1.60 - 3.38)**	**0.37 (0.25 - 0.48)**	0.95 (0.80 - 1.14)
Sex				
Male	-	-	-	-
Female	**0.89 (0.82 - 0.96)**	1.12 (0.94 - 1.33)	0.00 (-0.11 - 1.11)	0.96 (0.81 - 1.13)
Social Deprivation				
IMD 1-3	-	-	-	-
IMD 4-5	1.01 (0.93 - 1.10)	1.09 (0.91 - 1.30)	0.10 (-0.02 - 0.22)	**1.29 (1.09 - 1.54)**
Smoking status*				
Never	-	-	-	-
Ex-smoker	0.91 (0.82 - 1.01)	1.06 (0.84 - 1.34)	0.03 (-0.10 - 0.25)	1.16 (0.93 - 1.46)
Current	0.93 (0.88 - 1.08)	**1.42 (1.07 - 1.88)**	**0.34 (0.16 - 0.51)**	1.23 (0.94 - 1.63)
Premorbid Depression-anxiety	**0.87 (0.78 - 0.96)**	**1.28 (1.02 - 1.60)**	0.12 (-0.22 - 0.27)	1.17 (0.91 - 1.52)
Premorbid IBS	**0.66 (0.58 - 0.75)**	**1.87 (1.44 - 2.41)**	0.08 (-0.10 - 0.25)	1.18 (0.95 - 1.46)
Era of diagnosis				
Era 1	-	-	-	-
Era 2	1.06 (0.95 - 1.18)	1.04 (0.82 - 1.32)	-0.74 (-0.22 - 0.07)	**1.31 (1.04 - 1.64)**
Era 3	1.01 (0.91 - 1.13)	1.05 (0.83 - 1.32)	-1.13 (-0.28 - 0.27)	**1.57 (1.23 - 1.99)**
Era 4	1.00 (0.89 - 1.12)	0.88 (0.68 - 1.12)	-0.22 (-0.37 - 0.06)	**1.61 (1.26 - 2.03)**

*** See supplementary appendix 5 for unadjusted analyses**

Bold indicates statistical significance in adjusted model Note: Multiple regression includes all variables and covariates of simple regression. Abbreviations: CS, Corticosteroids; IM, Immunomodulator; HR, Hazard Ratio; CI, confidence interval; IMD, index of multiple deprivations

IMD categories 4 and 5 [most deprived] vs IMD categories 1, 2 and 3 [least deprived]

Era 1: 2003 – 2005, Era 2 2006 – 2008, Era 3 2009- 2011 and Era 4 2012 – 2016

First CS use: Time to first CS prescription following diagnosis

CS dependency: Corticosteroid dependency defined as a repeat steroid prescription within 3 months of the end of a previous steroid prescription or patients with steroid prescriptions for greater than 3 consecutive months

Hospitalisation: First IBD-related hospital admission following diagnosis

Time to diagnosis: Time from first primary care consultation for gastrointestinal symptom(s)

Consultation intensity: consultation frequency per person in the year prior to IBD diagnosis

Abbreviation gastrointestinal (GI)