Card, Timothy R. and Langan, Sinéad M. and Chu, Thomas P.C. (2016) Extra-gastrointestinal manifestations of inflammatory bowel disease may be less common than previously reported. Digestive Diseases and Sciences, 61 (9). pp. 2619-2626. ISSN 1573-2568

Extra-Gastrointestinal Manifestations of Inflammatory Bowel Disease May Be Less Common Than Previously Reported

Timothy R. Card, Sinead M. Langan, Thomas P. C. Chu

The final publication is available at Springer via

http://dx.doi.org/10.1007/s10620-016-4195-1

Extra-gastrointestinal manifestations of inflammatory bowel disease may be less common than previously reported.

Timothy R Card [1,2], Sinéad M Langan [3], Thomas P C Chu [1]

Timothy R Card, Division of Epidemiology and Public Health, University of Nottingham. and Nottingham Digestive Diseases Centre Biomedical Research Unit, University of Nottingham. tim.card@nottingham.ac.uk

Sinéad M Langan, Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine. Sinead.Langan@lshtm.ac.uk

Thomas P C Chu, Division of Epidemiology and Public Health, University of Nottingham. Thomas.Chu@nottingham.ac.uk

Correspondence:

Dr Timothy R Card

Department of Epidemiology and Public Health, Clinical Sciences Building Phase 2, Nottingham City Hospital, Hucknall Rd, Nottingham, NG5 1PB, United Kingdom

tel: 0115 8231346

This work was funded by a grant from Crohn's and Colitis UK (NACC) (grant number M/10/01).
Dr Langan is funded by an NIHR Clinician Scientist Fellowship (NIHR/CS/010/014). The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the UK Department of Health.

Word count 2779

Abbreviations: IBD Inflammatory bowel disease; PSC Primary Sclerosing Cholangitis; VTE Venous Thrombo-embolism; EIMs extra-intestinal manifestations; CPRD Clinical Practice Research Datalink; BMI body mass index; OR odds ratio; CI confidence interval

Abstract

Background and Aims

Extra-intestinal manifestations are well recognised in IBD. To what extent the commonly recognised extra-intestinal manifestations seen in IBD patients are attributable to IBD is however not clear due to the limited number of controlled studies published.

Methods

We have conducted a study of these manifestations using electronic primary care records. We have identified extra-intestinal manifestations in IBD and non-IBD patients, and derived odds ratios (ORs) using conditional logistic regression.

Results

56,097 IBD patients (32.5% Crohn's disease, 48.3% UC and 19.2% not classified) were matched to 280,382 non-IBD controls. We found records of Pyoderma Gangrenosum (odds ratio = 29.24), Erythema Nodosum (OR = 5.95), PSC (OR = 188.25), Uveitis (OR = 2.81), Ankylosing Spondylitis (OR = 7.07), Sacroiliitis (OR = 2.79) and non-Rheumatoid inflammatory arthritides (OR = 2.66) to be associated with IBD. One or more of these was recorded in 8.1% of IBD patients and 2.3% of controls. Non-specific arthritides were present in many more patients, affecting 30% of IBD patients and 23.8% of controls overall. We also found weaker associations with a number of conditions not generally considered to be extra-intestinal manifestations including Psoriasis, Ischaemic Heart Disease, Multiple Sclerosis and hay fever.

Conclusion

Although “classical” extra-intestinal manifestations are strongly associated with IBD, most IBD patients remain unaffected. Arthropathies, perceived to be the commonest

extra-intestinal manifestation, are not strongly associated with IBD, and the proportion of arthropathies attributable to IBD is likely to be small.

Keywords: Inflammatory Bowel Diseases; Epidemiology; arthritis; iritis; pyoderma

Introduction

It is well recognised that Inflammatory Bowel Disease (IBD) is associated with an increased risk of a number of extraintestinal diseases. Some of these such as Venous Thrombo-embolism (VTE) are regarded as complications of the disease process, whereas others are considered to be extraintestinal features of the underlying disease process. These extraintestinal manifestations (EIMs) usually include skin manifestations (pyoderma gangrenosum and erythema nodosum), joint manifestations (ankylosing spondylitis and seronegative arthritis), eye manifestations (iritis), and apthous ulceration of the mouth. Primary Sclerosing Cholangitis (PSC) is sometimes considered as part of this group. Though there is an extensive literature describing the association of complications with IBD, demonstrating for example that VTE is 3-4 times more common in patients with IBD than in the general population [1,2], the number of controlled studies of extra intestinal manifestations available are remarkably few[3,4]. Most of the literature constitutes case series or cohort studies of IBD patients describing the frequency of these manifestations, which does not allow us to examine variations in the frequency of these problems between patients with and without IBD[5,6]. It is believed from these studies that extra-intestinal manifestations affect about 40% of IBD patients[5,7]. To our knowledge only one other recent high quality epidemiological study has compared extra-intestinal manifestations (EIMs) in IBD to general population controls, but that study did not report on peripheral arthritis which is the most commonly reported EIM in many series[8].

Since examination of the associations of IBD with EIMs has led to further insights into their aetiology [9,10], a clear understanding of the strengths of these associations is of importance. Equally, knowledge of their prevalence in the population is of value to allow provision of services since affected patients will have greater need of health services and in some instances may be at an increased risk of death[11]. To determine the strength of association between IBD and EIMs including arthritis and how commonly they occur, we have carried out a cross sectional study examining the comparative risks of a series of EIMs in both IBD and non-IBD patients.

Materials and Methods

Data source

The Clinical Practice Research Datalink (CPRD, formerly General Practice Research Database) is a prospectively gathered database of longitudinal records of consultations, diagnoses, investigations and referrals from UK primary care. Clinical data have been submitted by participating primary care practices since 1987. They are coded using the Read code system which is the standard coding system in UK general practice and provides hierarchical coding not only of diagnoses, but also signs, symptoms, interventions and a number of biographical and administrative items. CPRD has been widely used for epidemiological research, and the validity of diagnosis of IBD in these data has been specifically assessed[12], with 92% of diagnoses found highly probable and 95% at least probable.

Study cohort

We used CPRD records between 1987 and January 2011 to identify a cohort of patients with inflammatory bowel disease (IBD), based upon the presence of Read codes within their records indicating the diagnosis. These were matched on sex, date of birth (within 366 days) and GP practice with up to five patients without any records of an IBD diagnosis. Where more than five suitable controls were available, we selected randomly within the available controls.

Covariates

The associations between IBD and extra-intestinal manifestations are estimated with adjustment for body mass index (BMI) and tobacco use status so that these risk

factors for numerous diseases (including ischaemic heart disease, atrial fibrillation and hypertension) should not confound our estimates.

We calculated a trimmed mean of BMI for each patient after removing values that fell outside the 1st- and 99th-centile. For patients without any records of BMI, we calculated BMI from their trimmed mean heights and weights. We categorised BMI as underweight (BMI under 18.5), normal (18.5–25), overweight (25–30), or obese (over 30). We classified tobacco use for each patient as the highest recorded of the following status (from highest to lowest): “current smoker”, “ex-smoker”, or “not current”. We used an “unknown” category for missing values in body mass index or tobacco use, assuming that missingness did not occur at random.

Extra-gastrointestinal manifestations

Outcomes were defined in a similar manner to the diagnosis of IBD, by the presence of diagnostic codes for “red eyes” (divided into uveitis and non-uveitis causes), sclerosing cholangitis, psoriasis, erythema nodosum (both with and without sulphasalazine users to avoid conflating drug side effects with disease effects), pyoderma gangrenosum, arthropathies (divided into osteoarthritis, rheumatoid arthritis, ankylosing spondylitis, sacroiliitis and other specified inflammatory arthritis, arthritis not otherwise specified). Where previously validated code lists were not available we derived them by manually searching the list of Read codes. All lists were compiled by at least two of the authors.

Patients with IBD are likely to consult their general practitioners more often than non-IBD patients, which may lead to bias in the ascertainment of extra-gastrointestinal manifestations since these conditions may also occur in the general population. Hence, we have also examined the following conditions, which are not known to be

strongly associated with inflammatory bowel disease: atrial fibrillation, primary hypertension, ischaemic heart disease, hay fever, sinusitis, migraine and multiple sclerosis to ensure any study findings are not due to ascertainment bias.

Statistical analysis

We examined the association between the risk of developing any extra-gastrointestinal manifestations and inflammatory bowel disease by estimating the odds ratio for each of the outcomes. Odds ratios (ORs) were estimated after adjusting for age, BMI and tobacco use in a multivariate conditional logistic regression model and are presented with 95% confidence intervals (CIs).

Regulatory and ethical approval

As this work utilised existing anonymised data, no separate ethical approval was required. The work was approved by the Independent Scientific Advisory Committee for MHRA database research; protocol number 10_147.

Results

We identified a cohort of 56,097 IBD patients who had valid sex and date of birth recorded, and who contributed prospective data to CPRD. To these cases we matched 280,382 non-IBD patients.

Half of the patients in our IBD cohort were diagnosed with ulcerative colitis and about one-third had Crohn's disease (Table 1) (the remaining IBD patients had either codes for both UC and Crohn's or only codes for indeterminate or non-specific IBD). IBD patients were less likely to be current smokers (28.6% vs. 30.5%) and more likely to be ex-smokers (19.8% vs. 14.5%) than non-IBD patients. Non-IBD patients were more likely to be obese (14.6%) than IBD patients (13.1%). The proportion of non-IBD patients with missing BMI or tobacco use status was higher, presumably due to fewer opportunities for these to be recorded.

With the exception of hypertension, all of the extra-intestinal conditions we examined were more common in patients with IBD. (Table 2). The association of IBD with extraintestinal disease was particularly strong for uveitis (OR = 2.81, 95% CI = 2.65–2.98), sclerosing cholangitis (OR = 188.25, 95% CI = 90.97–389.55), erythema nodosum (OR = 5.95, 95% CI = 5.38–6.59, and after excluding sulfasalazine users OR = 4.84, 95% CI = 4.35–5.39), pyoderma gangrenosum (OR = 29.24, 95% CI = 20.99–40.75), ankylosing spondylitis (OR = 7.07, 95% CI = 6.24–8.01), sacroiliitis (OR = 2.79, 95% CI = 2.45–3.17), and other inflammatory arthritis (OR = 2.66, 95% CI = 2.44–2.91) (Table 3). The association was moderate between IBD and multiple sclerosis (OR = 1.45, 95% CI = 1.26–1.67), all arthropathies combined (OR = 1.47,

95% CI = 1.43–1.50) and psoriasis (OR=1.36, 95% CI=1.30-1.42). Although the associations were substantial, the proportion of IBD patients affected by each of those conditions was small: from 0.5% with pyoderma gangrenosum to 3.4% with uveitis. Overall 8.1% of IBD patients and 2.3 % of controls were affected by at least one of these well recognised associations, i.e. an excess of 5.8% among IBD patients. Many IBD patients had presented to their GP with arthropathy (n = 16,854, 30.0%) or a red eye (n = 12,102, 21.6%), but most of those were attributed to non-specific arthritis (n = 11,585) or non-uveitis causes of red eye (n = 11,073).

Crohn's disease was more strongly associated with uveitis (OR = 3.20, 95% CI = 2.89–3.55), ankylosing spondylitis (OR = 8.98, 95% CI = 7.18–11.23), or cutaneous manifestations such as erythema nodosum (OR = 9.08, 95% CI = 7.70–10.71 and after excluding sulfasalazine users: OR = 7.74, 95% CI = 6.52–9.17) and pyoderma gangrenosum (OR = 47.36, 95% CI = 21.94–102.26) (Table 3). Ulcerative colitis was more strongly associated with sclerosing cholangitis (OR = 313.71, 95% CI = 93.96–1,047.36) than Crohn's disease, although the number of patients affected was small (37 Crohn's disease and 227 ulcerative colitis patients).

Patients with IBD were also more likely to have atrial fibrillation (OR = 1.11, 95% CI = 1.05–1.16), ischaemic heart disease (OR = 1.21, 95% CI = 1.17–1.26), migraine (OR = 1.13, 95% CI = 1.09–1.17), psoriasis (OR = 1.36, 95% CI = 1.3-1.42) or multiple sclerosis (OR = 1.45, 95% CI = 1.26–1.67) (Table 3).

It was notable that with the exceptions of psoriasis and multiple sclerosis all extraintestinal conditions studied were more commonly diagnosed after than before IBD. This was particularly marked for sclerosing cholangitis which was 5 times as commonly diagnosed after IBD (tables 4 and 5).

Discussion

We have shown that the commonly recognised extra-intestinal manifestations of IBD are indeed more commonly diagnosed in IBD patients than in the general population. The degree to which they are associated with IBD varies, with the strongest associations being for sclerosing cholangitis, pyoderma gangrenosum and erythema nodosum, with uveitis and sero-negative arthropathy (except ankylosing spondylitis, which is strongly associated with IBD) being less closely associated. We have also shown that these associations are reasonably specific to the classically recognised extra-intestinal manifestations, and that the proportion of IBD cases affected with sufficient severity to be reported to a general practitioner is in absolute terms only greater than that in controls by about 6%.

Strengths and weaknesses

With 56,097 IBD cases and 280,382 general population controls, ours is the largest study of EIMs yet conducted. This provides us with power to subdivide the manifestations studied and to examine the associations with rare diagnoses such as pyoderma gangrenosum and PSC. We are enabled to have this power by our use of routinely collected clinical data from general practitioners, which also allows us to ensure that our populations of cases and controls have been selected with minimal bias. This ensures that, unlike previous studies from tertiary referral centres, our results should be generalisable to the whole UK population. Using this data source does however have an appreciable scientific cost: we do not have the ability to validate the diagnoses we are describing for individual patients, or to subdivide them into more specific categories. This is not to say that the diagnostic information is

unreliable. A number of the diagnoses we studied have been specifically validated in this data set[11,12] by reference to paper records, and the plethora of validated diagnoses[13,14] suggest that GP recorded diagnoses are generally accurate in about 90% of patients. We cannot however divide arthropathy into large and small joint diseases, determine the extent of skin involvement in PG or psoriasis, or define a detailed phenotype of IBD. Perhaps most importantly when considering the differences between our findings and those of previous studies, we cannot closely examine patients for evidence of subclinical presentations of the diagnoses we are studying. Therefore any such asymptomatic or subclinical presentations may be unrecorded when compared to previous studies. As this will affect both IBD cases and the control population equally it will not however have biased out comparison between them.

Compared to past literature

Occurrence of EIMs

As for so many features of IBD, the earliest publications about the associations of IBD with its extra-intestinal manifestations were case reports and case series in the first half of the twentieth century[15–17]. The currently recognised associations were described very rapidly. Subsequently many groups have sought out extra-intestinal manifestations in the IBD patients under their care, or IBD in those with arthritis. Few studies however have included control groups and only one to our knowledge included general population controls in whom extra-intestinal manifestations were sought in the same manner as in IBD patients[8].

We find uveitis to be recorded in 3.4% of our IBD cases which is within the range of values (1.8-6%) found in large modern series[5,6,8,18]. For arthropathy overall, we report 30% of our IBD patients as being affected, which is amongst the higher figures reported. For a number of other EIMs, including EN, PG, PSC and AS, we report prevalence lower than in some previous studies. The reasons for this discrepancy may include the fact that we have included all patients with IBD regardless of the length of their history, whilst it is recognised that EIMs may appear more common if one waits many years after diagnosis [6,8]. Equally it may be that as many of the previous studies have been conducted from single centres with an interest in IBD, some cases which will be subclinical, and hence undetected, in the routine practice we describe will have been detected. One observation which might lend weight to this idea is that our figures are rather more similar to more dated British figures from an era before extra-intestinal manifestations might have been expected to be sought out by the clinician[19]. It is of course also possible that these conditions are left undetected in the UK despite causing symptoms, and finally it may be that we are seeing a different spectrum of disease due to the presence in our more recent cohort of milder IBD which would in the past itself have remained undiagnosed, or even because of the success of modern IBD management in suppressing these problems.

With respect to the variation between UC and CD we find, as is commonly reported, that apart from PSC, most EIMs are commoner in CD[5,6,18] and they occur / emerge after the diagnosis of IBD.

Association with IBD

One great advantage of the present study is the presence of general population controls, which allows determination of the degree of association between the

conditions studied and IBD. For each of the classically recognised EIMs we have considered there is a significant association with an odds ratio above 2. It is interesting to note however that a number of other conditions not commonly thought of as EIMs which we included primarily to consider specificity are also statistically significantly associated though with a lower OR. In some of these conditions, such as OA or RA, this may represent evidence of the misdiagnosis of a clinically similar EIM, but in others such as hay fever, sinusitis or migraine it is most reasonable to see this as evidence of ascertainment bias perhaps because increased medical contact increases the opportunity for diagnoses in those followed up with IBD. For ischaemic heart diseases and multiple sclerosis, it might be argued that they are neither related to a known EIM, nor certain not to be related to IBD. Each has previously been proposed to be associated with IBD[20,21], but neither is well recognised to be. Each condition is weakly associated with IBD, but unlike the classical EIMs, they do not appear to occur more commonly in IBD patients before their IBD is diagnosed. We believe therefore that ascertainment bias remains a possible explanation of these associations also.

One other advantage of using controls of course is that we can speculate as to how much of an associated condition in IBD patients might be attributable to the IBD. The attributable risks of the extra-intestinal conditions (calculated making the assumption that the associations are causal) will be the risk in those with IBD minus that in the general population. For example overall arthropathy of one sort or another is reported by 30% of IBD patients, but was also reported by 24% of general population controls. We could argue therefore that in only about 6% at most of IBD patients is this likely to be truly an extra-intestinal manifestation of disease, or that only one fifth of the arthritis in IBD patients is likely to be related to it. If we compare this to PSC which is

very rare in the general population, though PSC occurs in only 0.6% of our IBD cohort, for almost 100% of these it is likely that the two conditions are related.

Clinical implications

For patients with IBD who present with EN, PG and PSC it is quite likely that the aetiology of these conditions may be closely linked to IBD. For patients with arthropathy, this link is far less likely and is in fact likely to be the case in no more than one fifth of cases. Previous reports of EIMs occurring in 40% or more of IBD cases are likely to have overestimated the prevalence of EIMs by including patients with arthropathy which was not truly related to IBD. Though IHD, MS and psoriasis which are not commonly seen as extra intestinal manifestations have been proposed to be associated with IBD, we find their associations to be a good deal weaker than those of the classical EIMs, and with odds ratios little higher than those found for associations with hay fever or migraine it is hard to rule out the possibilities of ascertainment bias or confounding as explanations.

Summary

We have found that commonly recognised skin, joint and eye extraintestinal manifestations of IBD occur in only about 6% more commonly in IBD cases than in the general population. Most arthropathy in IBD patients is unlikely to be a true extraintestinal manifestation.

Acknowledgements

This work was funded by a grant from Crohn's and Colitis UK (NACC) (grant number M/10/01).

This study was conceived and designed collaboratively by all authors. Dr Card obtained funding. Dr Chu carried out all analysis. All authors contributed to the interpretation of the results. Drs Card and Chu jointly wrote the first draft after discussions amongst all authors, and all authors edited and amended this and all subsequent drafts. All authors approved the final draft.

References

1 Bernstein CN, Blanchard JF, Houston DS, *et al.* The incidence of deep venous thrombosis and pulmonary embolism among patients with inflammatory bowel disease: a population-based cohort study. *Thromb Haemost* 2001;**85**:430–4.

2 Grainge MJ, West J, Card TR. Venous thromboembolism during active disease and remission in inflammatory bowel disease: a cohort study. *Lancet* 2010;**375**:657–63. doi:10.1016/S0140-6736(09)61963-2

3 Hammer B, Ashurst P, Naish J. Diseases associated with ulcerative colitis and Crohn's disease. *Gut* 1968;**9**:17–21. doi:10.1136/gut.9.1.17

4 Acheson ED. An association between ulcerative colitis, regional enteritis, and ankylosing spondylitis. *Q J Med* 1960;**29**:489–99.http://www.ncbi.nlm.nih.gov/pubmed/13681207

5 Vavricka SR, Brun L, Ballabeni P, *et al.* Frequency and risk factors for extraintestinal manifestations in the Swiss inflammatory bowel disease cohort. *Am J Gastroenterol* 2011;**106**:110–9. doi:10.1038/ajg.2010.343

6 Lakatos L, Pandur T, David G, *et al.* Association of extraintestinal manifestations of inflammatory bowel disease in a province of western Hungary with disease phenotype: results of a 25-year follow-up study. *World J Gastroenterol* 2003;**9**:2300–7.http://www.ncbi.nlm.nih.gov/pubmed/14562397 (accessed 12 Jun2013).

7 Williams H, Walker D, Orchard TR. Extraintestinal manifestations of inflammatory bowel disease. *Curr Gastroenterol Rep* 2008;**10**:597–605.http://www.ncbi.nlm.nih.gov/pubmed/19006617 (accessed 9 Oct2013).

8 Bernstein CN, Blanchard JF, Rawsthorne P, *et al.* The prevalence of extraintestinal diseases in inflammatory bowel disease: a population-based study. *Am J Gastroenterol* 2001;**96**:1116–22. doi:10.1111/j.1572-0241.2001.03756.x

9 Alonso Farto JC, Arias IA, Lopez Longo FJ, *et al.* Clinical significance of abdominal scintigraphy using 99mTc-HMPAO-labelled leucocytes in patients with seronegative spondyloarthropathies. *Eur J Nucl Med* 2000;**27**:1768–73. doi:10.1007/s002590000393

10 Ciccacci C, Biancone L, Di Fusco D, *et al.* TRAF3IP2 gene is associated with cutaneous extraintestinal manifestations in inflammatory bowel disease. *J Crohns Colitis* 2013;**7**:44–52. doi:10.1016/j.crohns.2012.02.020

11 Langan SM, Groves RW, Card TR, *et al.* Incidence, mortality, and disease associations of pyoderma gangrenosum in the United Kingdom: a retrospective cohort study. *J Invest Dermatol* 2012;**132**:2166–70. doi:10.1038/jid.2012.130

12 Lewis JD, Brensinger C, Bilker WB, *et al.* Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. *Pharmacoepidemiol Drug Saf* 2002;**11**:211–8. doi:10.1002/pds.698

13 Herrett E, Thomas SL, Schoonen WM, *et al.* Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2010;**69**:4–14. doi:10.1111/j.1365-2125.2009.03537.x

14 Jick H, Terris BZ, Derby LE, *et al.* Further validation of information recorded on a general practitioner based computerized data resource in the united kingdom. *Pharmacoepidemiol Drug Saf* 1992;**1**:347–9. doi:10.1002/pds.2630010607

15 Cullinan E. Ulcerative colitis: clinical aspects. *Br Med J* 1938;**2**:1351–6.http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2211132/ (accessed 2 Dec2013).

16 STEINBERG VL, STOREY G. Ankylosing spondylitis and chronic inflammatory lesions of the intestines. *Br Med J* 1957;**2**:1157–9.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1963013&tool=pmcentrez&rendertype=abstract (accessed 2 Dec2013).

17 Billson FA, De Dombal FT, Watkinson G, *et al.* Ocular complications of ulcerative colitis. *Gut* 1967;**8**:102–6.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1552509&tool=pmcentrez&rendertype=abstract (accessed 14 Oct2013).

18 Christodoulou DK, Katsanos KH, Kitsanou M, *et al.* Frequency of extraintestinal manifestations in patients with inflammatory bowel disease in Northwest Greece and review of the literature. *Dig Liver Dis* 2002;**34**:781–6.

19 EDWARDS FC, TRUELOVE SC. THE COURSE AND PROGNOSIS OF ULCERATIVE COLITIS. III. COMPLICATIONS. *Gut* 1964;**5**:1–22.http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=1552214&tool=pmcentrez&rendertype=abstract (accessed 30 May2012).

20 Bernstein CN, Wajda A, Blanchard JF. The incidence of arterial thromboembolic diseases in inflammatory bowel disease: a population-based study. *Clin Gastroenterol Hepatol* 2008;**6**:41–5. doi:10.1016/j.cgh.2007.09.016

21 Gupta G, Gelfand JM, Lewis JD. Increased risk for demyelinating diseases in patients with inflammatory bowel disease. *Gastroenterology* 2005;**129**:819–26.

	IBD patients N = 56,097		Non-IBD patients N = 280,382	
	n	%	n	%
Type of IBD				
Crohn's disease	18,204	32.5		
Ulcerative colitis	27,108	48.3		
Not specified	10,785	19.2		
Male	26,283	46.9	131,352	46.8
Mean age (years)	47.2		47.2	
Age group (years)				
0–20	2,658	4.7	13,291	4.7
21–40	19,932	35.5	99,656	35.5
41–60	18,325	32.7	91,625	32.7
61–80	12,395	22.1	61,983	22.1
over 80	2,787	5.0	13,827	4.9
Body mass index				
0–18.5	1,967	3.5	6,751	2.4
18.5–25.0	22,322	39.8	98,790	35.2
25.0–30.0	15,392	27.4	76,443	27.3
30.0–50.0	7,358	13.1	40,967	14.6
Unknown	9,058	16.1	57,431	20.5
Tobacco use				
Current	16,053	28.6	85,533	30.5
Ex-smoker	11,130	19.8	40,732	14.5
Non-current	25,120	44.8	126,969	45.3
Unknown	3,794	6.8	27,148	9.7

Table 1: Characteristics of patients, by inflammatory bowel disease status.

	All IBD patients				Crohn's disease				Ulcerative colitis			
	IBD patients		Non-IBD patients		IBD patients		Non-IBD patients		IBD patients		Non-IBD patients	
	n	%	n	%	n	%	n	%	n	%	n	%
Ophthalmic												
Red eye	12,102	21.6	51,635	18.4	3,704	20.3	16,242	17.8	5,608	20.7	24,894	18.4
Non-uveitis	11,073	19.7	49,880	17.8	3,352	18.4	15,729	17.3	5,149	19.0	23,970	17.7
Uveitis	1,890	3.4	3,392	1.2	636	3.5	1,009	1.1	811	3.0	1,733	1.3
Hepatic												
Sclerosing cholangitis	346	0.6	10	0.0	37	0.2	4	0.0	227	0.8	5	0.0
Dermatological												
Psoriasis	2,856	5.1	10,568	3.8	988	5.4	3,235	3.6	1,256	4.6	5,202	3.8
Erythema nodosum	855	1.5	746	0.3	426	2.3	258	0.3	217	0.8	338	0.2
excluding SSZ users	693	1.2	738	0.3	362	2.0	255	0.3	158	0.6	335	0.2
Pyoderma gangrenosum	275	0.5	52	0.0	95	0.5	15	0.0	112	0.4	25	0.0
Rheumatological												
Osteoarthritis	7,728	13.8	36,265	12.9	1,937	10.6	9,818	10.8	4,284	15.8	19,769	14.6
Rheumatoid arthritis	1,085	1.9	3,084	1.1	312	1.7	899	1.0	558	2.1	1,626	1.2
Arthritis, NOS	11,585	20.7	44,397	15.8	3,472	19.1	12,761	14.0	5,420	20.0	22,949	16.9
Ankylosing spondylitis	617	1.1	436	0.2	231	1.3	131	0.1	235	0.9	221	0.2
Sacroiliitis	375	0.7	692	0.2	129	0.7	228	0.3	158	0.6	340	0.3
Other inflammatory arthritis	795	1.4	1,478	0.5	295	1.6	472	0.5	300	1.1	720	0.5
all arthropathies combined	16,854	30.0	66,786	23.8	4,886	26.8	18,952	20.8	8,346	30.8	35,191	26.0
All IBD associated	**4,548**	**8.1**	**6,536**	**2.3**	**1,614**	**8.9**	**2,032**	**2.2**	**1,867**	**6.9**	**3,247**	**2.4**
Other												
Ischaemic heart disease	5,175	9.2	22,287	7.9	1,350	7.4	5,866	6.4	2,877	10.6	12,470	9.2
Multiple sclerosis	265	0.5	913	0.3	89	0.5	302	0.3	128	0.5	427	0.3
Sinusitis	8,580	15.3	40,254	14.4	2,530	13.9	12,872	14.1	4,037	14.9	19,063	14.1
Migraine	4,380	7.8	19,376	6.9	1,430	7.9	6,545	7.2	1,892	7.0	8,738	6.5
Hay fever	4,819	8.6	22,125	7.9	1,626	8.9	7,550	8.3	2,078	7.7	9,925	7.3
Atrial fibrillation	2,165	3.9	9,903	3.5	554	3.0	2,570	2.8	1,260	4.6	5,680	4.2
Hypertension	12,626	22.5	64,358	23.0	3,304	18.1	17,681	19.4	6,959	25.7	35,159	26.0

Table 2: Proportion of IBD and non-IBD patients affected by conditions associated or not known to be associated with inflammatory bowel disease.

	All IBD patients			Crohn's disease			Ulcerative colitis		
	OR	95% CI		OR	95% CI		OR	95% CI	
Ophthalmic									
Red eye	1.21	1.18	1.24	1.18	1.13	1.23	1.15	1.11	1.19
Non-uveitis	1.12	1.10	1.15	1.08	1.03	1.13	1.08	1.04	1.11
Uveitis	2.81	2.65	2.98	3.20	2.89	3.55	2.35	2.15	2.56
Hepatic									
Sclerosing cholangitis	188.25	90.97	389.55	60.36	15.89	229.33	313.71	93.96	1,047.36
Dermatological									
Psoriasis	1.36	1.30	1.42	1.53	1.42	1.65	1.23	1.15	1.31
Erythema nodosum	5.95	5.38	6.59	9.08	7.70	10.71	3.26	2.74	3.89
excludes SSZ users	4.84	4.35	5.39	7.74	6.52	9.17	2.39	1.97	2.90
Pyoderma gangrenosum	29.24	20.99	40.75	47.36	21.94	102.26	26.67	16.13	44.12
Rheumatological									
Osteoarthritis	1.10	1.07	1.14	1.04	0.98	1.10	1.11	1.06	1.15
Rheumatoid arthritis	1.76	1.64	1.89	1.70	1.49	1.94	1.74	1.57	1.92
Arthritis, NOS	1.43	1.39	1.46	1.55	1.48	1.62	1.23	1.19	1.28
Ankylosing spondylitis	7.07	6.24	8.01	8.98	7.18	11.23	5.32	4.41	6.42
Sacroiliitis	2.79	2.45	3.17	2.90	2.31	3.63	2.42	1.99	2.94
Other inflammatory arthritis	2.66	2.44	2.91	3.24	2.78	3.77	2.04	1.78	2.34
all arthropathies combined	1.47	1.43	1.50	1.55	1.49	1.62	1.31	1.27	1.35
All IBD associated	**3.70**	**3.55**	**3.85**	**4.34**	**4.04**	**4.65**	**2.99**	**2.82**	**3.18**
Other									
Ischaemic heart disease	1.21	1.17	1.26	1.21	1.13	1.30	1.21	1.15	1.27
Multiple sclerosis	1.45	1.26	1.67	1.49	1.17	1.90	1.54	1.26	1.88
Sinusitis	1.06	1.03	1.09	0.96	0.92	1.01	1.05	1.01	1.09
Migraine	1.13	1.09	1.17	1.09	1.03	1.16	1.08	1.02	1.14
Hay fever	1.06	1.02	1.10	1.08	1.02	1.14	1.00	0.95	1.05
Atrial fibrillation	1.11	1.05	1.16	1.13	1.02	1.24	1.11	1.04	1.19
Hypertension	0.96	0.93	0.98	0.95	0.90	1.00	0.95	0.91	0.98

Table 3: Odds ratios for the studied associations adjusted for age, body mass index and tobacco use.

	Overall				Before diagnosis date				After diagnosis date			
	IBD patients		Non-IBD patients		IBD patients		Non-IBD patients		IBD patients		Non-IBD patients	
	n	%	n	%	n	%	n	%	n	%	n	%
Ophthalmic												
Red eye	12,102	21.6	51,635	18.4	4,704	8.4	31,702	11.3	7,398	13.2	19,933	7.1
Non-uveitis	11,073	19.7	49,880	17.8	4,253	7.6	30,394	10.8	6,820	12.2	19,486	6.9
Uveitis	1,890	3.4	3,392	1.2	659	1.2	2,102	0.7	1,231	2.2	1,290	0.5
Hepatic												
Sclerosing cholangitis	346	0.6	10	0.0	52	0.1	7	0.0	294	0.5	3	0.0
Dermatological												
Psoriasis	2,856	5.1	10,568	3.8	1,449	2.6	7,231	2.6	1,407	2.5	3,337	1.2
Erythema nodosum	855	1.5	746	0.3	304	0.5	568	0.2	551	1.0	178	0.1
excludes SSZ users	693	1.2	738	0.3	262	0.5	562	0.2	431	0.8	176	0.1
Pyoderma gangrenosum	275	0.5	52	0.0	43	0.1	20	0.0	232	0.4	32	0.0
Rheumatological												
Osteoarthritis	7,728	13.8	36,265	12.9	2,729	4.9	20,280	7.2	4,999	8.9	15,985	5.7
Rheumatoid arthritis	1,085	1.9	3,084	1.1	495	0.9	1,980	0.7	590	1.1	1,104	0.4
Arthritis, NOS	11,585	20.7	44,397	15.8	3,674	6.5	24,271	8.7	7,911	14.1	20,126	7.2
Ankylosing spondylitis	617	1.1	436	0.2	303	0.5	353	0.1	314	0.6	83	0.0
Sacroiliitis	375	0.7	692	0.2	102	0.2	388	0.1	273	0.5	304	0.1
Other inflammatory arthritis	795	1.4	1,478	0.5	217	0.4	880	0.3	578	1.0	598	0.2
all arthropathies combined	16,854	30.0	66,786	23.8	6,109	10.9	39,441	14.1	10,745	19.2	27,345	9.8
All IBD associated	**4,548**	**8.1**	**6,536**	**2.3**	**1,525**	**2.7**	**4,163**	**1.5**	**3,023**	**5.4**	**2,373**	**0.8**
Other												
Ischaemic heart disease	5,175	9.2	22,287	7.9	2,145	3.8	13,347	4.8	3,030	5.4	8,940	3.2
Multiple sclerosis	265	0.5	913	0.3	132	0.2	678	0.2	133	0.2	235	0.1
Sinusitis	8,580	15.3	40,254	14.4	3,284	5.9	24,910	8.9	5,296	9.4	15,344	5.5
Migraine	4,380	7.8	19,376	6.9	2,107	3.8	13,775	4.9	2,273	4.1	5,601	2.0
Hay fever	4,819	8.6	22,125	7.9	2,434	4.3	15,998	5.7	2,385	4.3	6,127	2.2
Atrial fibrillation	2,165	3.9	9,903	3.5	480	0.9	4,124	1.5	1,685	3.0	5,779	2.1
Hypertension	12,626	22.5	64,358	23.0	4,711	8.4	38,106	13.6	7,915	14.1	26,252	9.4

Table 4: Frequency of associations between of extra-gastrointestinal manifestations and IBD, before and after diagnosis.

	Before diagnosis date			After diagnosis date		
	OR	**95% CI**		**OR**	**95% CI**	
Ophthalmic						
Red eye	0.69	0.67	0.72	2.04	1.98	2.10
Non-uveitis	0.65	0.62	0.67	1.89	1.83	1.95
Uveitis	1.57	1.43	1.71	4.76	4.39	5.16
Hepatic						
Sclerosing cholangitis	34.89	13.80	88.23	744.92	148.86	3,727.62
Dermatological						
Psoriasis	0.99	0.94	1.05	2.14	2.01	2.28
Erythema nodosum	2.73	2.37	3.14	16.97	14.12	20.41
excludes SSZ users	2.37	2.04	2.75	13.19	10.92	15.94
Pyoderma gangrenosum	12.87	6.88	24.06	39.30	26.10	59.19
Rheumatological						
Osteoarthritis	0.62	0.59	0.65	1.70	1.64	1.77
Rheumatoid arthritis	1.23	1.12	1.36	2.69	2.43	2.98
Arthritis, NOS	0.72	0.69	0.75	2.24	2.18	2.31
Ankylosing spondylitis	4.26	3.65	4.98	19.42	15.10	24.96
Sacroiliitis	1.30	1.04	1.62	4.87	4.09	5.79
Other inflammatory arthritis	1.21	1.04	1.40	4.95	4.39	5.58
all arthropathies combined	0.71	0.69	0.73	2.39	2.33	2.45
All IBD associated	**1.85**	**1.74**	**1.96**	**6.80**	**6.42**	**7.20**
Other						
Ischaemic heart disease	0.77	0.73	0.81	1.85	1.77	1.94
Multiple sclerosis	0.97	0.80	1.17	2.82	2.27	3.50
Sinusitis	0.61	0.59	0.64	1.82	1.76	1.88
Migraine	0.74	0.71	0.78	2.06	1.96	2.17
Hay fever	0.72	0.69	0.75	1.94	1.84	2.04
Atrial fibrillation	0.56	0.51	0.62	1.51	1.43	1.61
Hypertension	0.51	0.49	0.53	1.69	1.64	1.75

Table 5: Adjusted odds ratios for associations occurring pre and post diagnosis of IBD.