

Citation: Close H, Mason JM, Wilson DW, Hungin APS, Jones R, Rubin G (2015) Risk of Ischaemic Heart Disease in Patients with Inflammatory Bowel Disease: Cohort Study Using the General Practice Research Database. PLoS ONE 10(10): e0139745. doi:10.1371/journal.pone.0139745

Editor: Giorgos Bamias, Laikon Hospital, GREECE

Received: June 10, 2015

Accepted: September 15, 2015

Published: October 13, 2015

Copyright: © 2015 Close et al. This is an open access article distributed under the terms of the <u>Creative Commons Attribution License</u>, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: Due to ethical restrictions under the terms of ethical approval and conditions of use set out by the data provider regarding patient identifying information, data cannot be made available in the manuscript. However, Dr. Helen Close (h.j.close@dur.ac.uk) can be contacted for a copy of the Read codes used to define IBD and IHD.

Funding: This study was funded by the Northern and Yorkshire Research Network (grant no. 108). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. **RESEARCH ARTICLE**

Risk of Ischaemic Heart Disease in Patients with Inflammatory Bowel Disease: Cohort Study Using the General Practice Research Database

Helen Close¹, James M. Mason¹, Douglas W. Wilson¹, A. Pali S. Hungin¹, Roger Jones², Greg Rubin¹*

School of Medicine, Pharmacy and Health, Durham University, Stockton-on-Tees, United Kingdom,
 Department of General Practice and Primary Care, King's College, London, United Kingdom

* g.p.rubin@durham.ac.uk

Abstract

Objective

Patients with inflammatory bowel disease (IBD) demonstrate an inflammatory response which bears some similarities to that seen in ischaemic heart disease (IHD). The nature of the association of IBD with IHD is uncertain. We aimed to define the extent and direction of that association.

Design

This retrospective cohort study examined records from patients aged \geq 15 years with IBD from 1987–2009 (n = 19163) who were age and gender matched with patients without IBD (n = 75735) using the General Practice Research Database. The primary outcome was the hazard ratio for IHD.

Results

A higher proportion of IBD patients had a recorded diagnosis of IHD ever, 2220 (11.6%) compared with 6504 (8.6%) of controls. However, the majority (4494, 51.5%) developed IHD prior to IBD diagnosis (1404 (63.2%) of IBD cases and 3090 (47.5%) of controls). There was increased IHD incidence in the first year after IBD diagnosis. Mean age at IHD diagnosis (UC) who were slightly younger at diagnosis of angina compared to controls (64.5y vs. 67.0y, p = 0.008) and coronary heart disease (65.7y vs.67.9y, p = 0.015). Of those developing IHD following IBD diagnosis, UC patients were at higher risk of IHD (unadjusted HR 1.3 (95% CI 1.1–1.5), p<0.001) or MI (unadjusted HR 1.4 (95% CI 1.1–1.6), p = 0.004).



Competing Interests: APSH was a member of the Independent Advisory Committee of the General Practice Research Database (GPRD) for the duration of the study.

Conclusion

Although IHD prevalence was higher in IBD patients, most IHD diagnoses predated the diagnosis of IBD. This implies a more complex relationship than previously proposed between the inflammatory responses associated with IHD and IBD, and alternative models should be considered.

Introduction

The inflammatory bowel diseases (IBD) ulcerative colitis (UC) and Crohn's Disease (CD) are disorders of uncertain origin. In both UC and CD, an exaggerated immune response to unknown antigens is evident [1] and a number of cytokines with pro-inflammatory effects have been described, notably IFN- γ and IL-17/IL-22 in Crohn's disease, IL-13, TNF- α , IL-1 β , IL-6 and TL1A in ulcerative colitis.[2, 3] The inflammatory response in IBD bears a number of similarities to that seen in rheumatoid arthritis, where TNF- α , IL-1 and IL-6 are prominent factors in synovial inflammation.[4] In both diseases, cytokine and acute phase protein levels are elevated, angiogenesis is up-regulated and endothelial dysfunction can be demonstrated [4, 5, 6] These similarities also exist with other diseases with an underlying inflammatory basis, such as psoriais[7] and diabetic nephropathy.[8]

There is a well-described association between rheumatoid arthritis (RA) and increased cardiovascular mortality, mainly as a result of ischaemic heart disease (IHD).[9, 10] Atherosclerosis is increasingly recognized as a chronic inflammatory disorder, with evidence for endothelial dysfunction, and angiogenesis. More recently a causal relationship between IL-6R related pathways and coronary heart disease has been established.[11]

There are sufficient shared characteristics to the inflammatory responses seen in IBD and RA to hypothesise that the recognized association between RA and IHD might also exist for IBD and IHD. Previous cohort studies have examined the risk of IHD in patients with IBD and have variously found no effect, [12] or a slight increased risk [13]. A large Danish cohort study [13] found a high risk of IHD diagnosis in the first year after IBD diagnosis, followed by a small but statistically significant increased risk in subsequent years, a risk which decreased among users of 5-aminosalicylic acid (5-ASA) preparations. In this study we investigated both the strength and direction of association between IBD and IHD (including its sub-entities myocardial infarction (MI) and angina) in a large British cohort.

Methods

Study Population

The study population for this retrospective cohort study consisted of around 2.1 million male and female patients with an active registration at practices contributing to the General Practice Research Database (GPRD, now accessed via the Clinical Practice Research Datalink, <u>http://</u><u>www.cprd.com/home/</u>) between 1987 and 2009. For each subject with IBD, a further 4 subjects were identified and matched for age and sex but without IBD. All cohort members were followed from the start date (i.e. the date their GPRD record began) until the earliest occurrence of one of the following endpoints: recorded code of IHD, death, date of exit from GPRD registered GP practice, or end of study period (31.12.2009). Patients with less than (1) 2 years upto-standard enrolment with the GP or (2) 1 year of computerized prescription history or (3) no health contacts during their complete period of follow-up were excluded from the cohort. Patients whose date of death or date of transfer out of a GPRD-registered practice preceded date of IBD diagnosis were excluded from the cohort. Patients <15 years of age at entry were excluded.

Disease definitions

We identified all male and female patients with a first diagnosis of IBD who met the following criteria: a first record of ulcerative colitis (UC), or Crohn's Disease (CD), or inflammatory bowel disease (not otherwise specified) (IBD (nos)) recorded on the database since 1987; patients with ICD-10 Read Codes (K50-K51) records of both UC and IBD were coded as UC; CD plus IBD were coded as CD; individual records which included both UC and CD were included only in analyses of IBD (nos). Prevalent IBD cases on 01.01.1987 were excluded. The index date was defined as the date of first recording of IBD. Lifetime IBD severity was determined using an algorithm based on IBD drug-use (5-ASAs, corticosteroids, and immunosuppressants) and surgical intervention (colectomy/stomata) developed by team members with clinical and research expertise in IBD.

Age, sex and practice matched controls were allocated the same index date as their matched case. Because IHD has not been subjected to the same specific validation studies as IBD, our operational definition was developed using advice from clinicians with special interest in cardiovascular disease to include the following: Read Codes for IHD (to include myocarditis; myocardial infarction; acute coronary syndrome; angina; confirmation by exercise treadmill or referral to cardiologist; current prescriptions for glyceryl trinitrate; isosorbide mononitrate; isosorbide dinitrate; nicorandil; ivabradine) Coronary Heart Disease (CHD) was considered for the purpose of this study to be synonymous with IHD and Read Codes for coronary heart disease (including coronary artery disease) were included.

Ethics Statement

Data was accessed within limits set out by the Medical Research Council licence agreement for academic access with Medical Research Ethics Committee ethical approval. The proposal was approved by the Independent Scientific Advisory Committee of the GPRD (protocol number 10_003).

Analysis

Descriptive analysis of baseline characteristics and exploration of the direction of association between IBD and IHD was conducted using the whole cohort of patients aged over 15 years (COHORT A: n = 94,898). Subsequent analysis of the *a priori* hypothesis, that IHD followed IBD, was conducted on a subset which included cases of IHD following IBD and their associated matched controls (COHORT B: n = 77540).

The relative risks of ischaemic heart disease (IHD) and its sub-entities myocardial infarction (MI) and angina), as well as CHD were estimated as hazard ratios (HRs) for patients with IBD compared to non-IBD patients, using Cox proportional hazard models. Models were subsequently adjusted for age, gender, socio-economic status (using general practice postcode as a proxy), comorbidity and concomitant drug use, IBD disease severity, and smoking status. We carried out both forward and backward stepwise covariate selection within the cox proportional hazard model. All covariates were initially included with entry testing based on the significance of the score statistic, and removal testing based on the probability of a likelihood-ratio statistic based on conditional parameter estimates. Models were tested for interactions between fitted variables. Precision of estimates is reported using 95% confidence intervals.

Data management was performed using Stata 10IC. Cox regression proportional hazard computations and Kaplan-Meier survival analysis were conducted using SPSS 21.

Results

Baseline cohort characteristics

Data were examined from electronic primary care records from 221 general practices across the UK from patients with a first diagnosis of IBD recorded from 1st January 1987 to 31st December 2009 (Fig_1). Following exclusions, data from COHORT A (patients with IBD and matched controls aged over 15 years) was analysed to understand baseline characteristics and exploration of the direction of association between IBD and IHD (COHORT A: n = 94898, Tables 1 and 2). A subset of patients with IHD following IBD and their associated matched controls (COHORT B: n = 77540) was analysed to examine baseline characteristics and the strength of association between IBD and IHD (Tables 3–5). The mean follow up period was 6.8 years (SD 5.9). All-cause mortality during follow-up was 6353 (6.7%).

Temporal relationship between IBD and IHD (COHORT A)

Of 19163 IBD cases, a total of 2220 (11.6%) had an IHD diagnosis ever, compared with 6504 (8.6%) of those without IBD. Of these IHD diagnoses, 4494 (51.5%) occurred prior to IBD diagnosis (1404 (63.2%) of IBD cases and 3090 (47.5%) of controls) (Fig 2). According to IBD type, of 12,397 cases of Ulcerative Colitis, 1557 (12.6%) had an IHD diagnosis ever, and of these, 980 (62.9%) occurred prior to IBD diagnosis; while of 4620 cases of Crohn's Disease, 445 (9.6%) had an IHD diagnosis ever, of which 284 (63.8%) occurred prior to IBD diagnosis (S1-S7 Figs). Similar temporal trends were seen in angina, MI and CHD. Sub-group analysis of IHD cases diagnosed during or after the year 2004 also showed similar temporal trends. An increased incidence of IHD, angina, MI, and CHD diagnoses was seen in the first year after IBD diagnosis (<u>S1-S6</u> Figs) but the mean age of IHD diagnosis comparing IBD cases with non IBD cases was not statistically different apart from those with Ulcerative Colitis (UC) who were slightly younger at diagnosis of angina and coronary heart disease (Table 2; S7 Fig). Of those developing IHD following an IBD diagnosis, patients with UC were at higher risk of a diagnosis of IHD (unadjusted HR 1.3, 95% CI 1.1-1.5, p<0.001) or MI (unadjusted HR 1.4, 95% CI 1.1–1.6, p = 0.004). Adjustment for a range of factors including age and gender showed interaction between variables; models did not reach statistical significance and thus are not reported here.

Subset characteristics (COHORT B: IBD preceding IHD)

A total of 17358 patients were excluded from subgroup analysis where IHD preceded IBD or, for controls, the matched IBD date (associated cases/controls were also excluded in order to protect matching of the resulting subset) (Fig 1). Subset characteristics (n = 77540) were comparable to those of the whole cohort (Table 3). Overall, the incidence of IHD following IBD diagnosis (or matched control date) was similar to those without IBD (3.8% vs 3.9% p = 0.001). The incidence of IHD following IBD diagnosis (or matched control was similar to those without IBD (4.4% vs 3.0% vs 3.8%, p = 0.042). This trend was also seen in angina, MI and CHD (Table 4). In unadjusted analysis, Ulcerative Colitis was associated with a small but statistically significant increased risk of IHD, and MI (HR 1.3, 95% CI 1.1–1.5, p<0.001; HR 1.4, 95% CI 1.1–1.6, p = 0.004 respectively) (Table 5). Use of 5ASAs did not alter this risk but users of corticosteroids were at significantly greater risk of IHD and its subtypes.





Fig 1. Cohort Flowchart. Selection of patients into two cohorts for analysis: COHORT A for descriptive analysis to examine the temporal relationship between IBD and IHD, and COHORT B for sub-group analysis of IHD cases which occurred following IBD diagnosis.

doi:10.1371/journal.pone.0139745.g001



Table 1. COHORT A characteristics comparing non-IBD controls with IBD cases (\geq 15 years).

PLOS ONE

Total number75735 (78 8%)420 (4 9%)1207 (13.1%)214 (6 2.5%)<0.001	Characteristics	Non-IBD (n (%))	Crohn's Disease (n (%))	Ulcerative Colitis(n (%))	IBD (NOS) (n (%))	P ⁶
Mate 96028 (47,6%) 1991 (43,0%) SB68 (47,5%) 913 (42,2%) <0.001 Age 2960 (23,9%) 699 (32,6%) <0.001 35-49y 17058 (26,5%) 1115 (24,1%) 3128 (25,7%) 691 (27,5%) 421 (19,8%) 65-9 17052 (22,1%) 803 (17,4%) 3210 (26,0%) 442 (66,4%) <0.001 Mean age at entry (SD) 48.8 (SD 18.9) 44.2 (SD 18.9) 50.9 (SD 18.5) 46.9 (SD 18.0) <0.001 IBD severity' 7232 (15,7%) 1326 (6,4%) 128 (6,0%) 128 (6,0%) <0.001 IBD severity 2321 (26,0%) 544 (165,7%) 1424 (66,4%) <0.001 IBD severity 723 (15,7%) 1308 (8,4%) 128 (6,0%) 10.001 10.00% 10.001 10.005 <th1< td=""><td>Total number</td><td>75735 (79.8%)</td><td>4620 (4.9%)</td><td>12397 (13.1%)</td><td>2146 (2.2%)</td><td></td></th1<>	Total number	75735 (79.8%)	4620 (4.9%)	12397 (13.1%)	2146 (2.2%)	
Age Issada Dista (20.2%) Bits (30.2%) 2000 (32.6%) Bits (30.2%) Sold (32.5%) Bits (30.2%) Sold (32.5%) Bits (30.2%) Sold (32.5%) Bits (30.2%) Sold (32.5%) Sold (32.5%)	Male	36028 (47.6%)	1991 (43.0%)	5883 (47.5%)	913 (42.5%)	<0.001
15-34y 21759 (28,7%) 1816 (29,3%) 2800 (23,8%) 689 (28,2%) 35-49y 1905 (26,5%) 1116 (24,1%) 3182 (25,7%) 591 (27,5%) 65-4y 17089 (22,6%) 806 (19,2%) 3036 (24,5%) 421 (19,6%) 65-4y 17522 (23,1%) 803 (17,4%) 3219 (26,0%) 435 (20,3%) Marange at entry (SD) 48.6 (SD 18.9) 44.2 (SD 18.9) 50.9 (SD 15.0) 45.0 (SD 19.0) -0.001 IBD severity' - 2225 (60,3%) 5844 (65,7%) 542 (66,7%) 550 (SD 19.0) -0.001 Severe - 723 (56,4%) 540 (60,1%) 1429 (68,1%) 128 (67%) Severe FVer 22120 (45,6%) 540 (60,1%) 1429 (68,1%) 10.0%) -0.001 BM ² - 10.0%) 1 (0.0%) 1 (0.0%) 1 (0.0%) 1 (0.0%) 11-15 197 (0.3%) 29 (0.8%) 170 (44%) 768 (42.%) -0.01 11-15 197 (0.3%) 196 (62,7%) 271 (42.%) 61 (1.4%) 768 (42.%) 11-15 197	Age					
35-64y 19365 (25.6%) 1115 (24.1%) 3182 (25.7%) 504 (27.5%) 50-64y 17089 (22.6%) 806 (19.2%) 3036 (24.5%) 421 (19.6%) 65-y 17522 (23.1%) 803 (17.4%) 212 (86.0%) 435 (20.3%) Mean age at entry (SD) 48.8 (SD 18.9) 44.2 (SD 18.9) 50.9 (SD 18.5) 46.9 (64.4%) Moderate - 2325 (60.3%) 8141 (65.7%) 1424 (66.4%) 50.9 (SD 18.5) Bower - 7232 (15.7%) 1036 (64.4%) 128 (6.0%) 50.9 (SD 18.5) 50.9 (SD 19.5) 50.9 (SD 18.5) 50.9 (SD 19.5) 50.9 (SD 19.5	15-34y	21759 (28.7%)	1816 (39.3%)	2960 (23.9%)	699 (32.6%)	
50-64y 17089 (22.6%) 886 (19.2%) 3036 (24.5%) 421 (19.5%) 65+y 17522 (23.1%) 803 (17.4%) 3219 (26.0%) 435 (20.3%) Mean age at entry (SD) 48.8 (SD 18.8) 42.1 (SD 18.5) 46.9 (SD 19.0) <0.001	35-49y	19365 (25.6%)	1115 (24.1%)	3182 (25.7%)	591 (27.5%)	
65-y 1752 (23.1%) 803 (17.4%) 3219 (26.0%) 435 (20.3%) Maan age at entry (SD) 48.8 (SD 18.9) 44.2 (SD 18.9) 50.9 (SD 18.5) 46.9 (SD 19.0) <0.00 Bid severity	50-64y	17089 (22.6%)	886 (19.2%)	3036 (24.5%)	421 (19.6%)	
Mean age at antry (SD) 48.8 (SD 18.9) 44.2 (SD 18.9) 50.9 (SD 18.5) 46.9 (SD 19.0) <0.001 IBD severity' - 2025 (50.3%) B141 (65.7%) 1424 (66.4%) - Moderate - 1572 (34.0%) 3220 (26.0%) 594 (27.7%) - Severe - 723 (15.7%) 1036 (8.4%) 128 (6.0%) - Smoke ⁷ - 723 (15.7%) 1036 (8.4%) 222 (66.7%) - Ever 2160 (45.6%) 358 (0.95%) 669 (31.9%) 116 (3.3.%) <0.001	65+y	17522 (23.1%)	803 (17.4%)	3219 (26.0%)	435 (20.3%)	
BD severity ¹ Severity ¹ Mild - 222 (50.5%) 1424 (65.7%) 1424 (67.%) Severe - 723 (15.7%) 1005 (8.4%) 128 (6.7%) Smoker ² - 723 (15.7%) 1005 (8.4%) 128 (6.0%) Ever 23120 (45.5%) 358 (0.9%) 669 (31.9%) 16 (3.3%) <0.001	Mean age at entry (SD)	48.8 (SD 18.9)	44.2 (SD 18.9)	50.9 (SD 18.5)	46.9 (SD 19.0)	<0.001
Mid - 2225 (20.3%) 8141 (65.7%) 1428 (66.4%) Moderate - 1572 (34.0%) 3220 (26.0%) 594 (27.7%) Severe - 723 (15.7%) 1036 (8.4%) 128 (6.0%) Smoker ² - 723 (15.7%) 1056 (8.4%) 232 (66.7%) - Never 27635 (54.4%) 540 (60.1%) 1429 (68.1%) 232 (66.7%) <000%)	IBD severity ¹					
Moderate - 1572 (24,0%) 3220 (26,0%) 594 (27,7%) Severe - 727 (15,7%) 1036 (84%) 128 (6,0%) Smoker - - 727 (15,7%) 1036 (84%) 128 (6,0%) Never 27635 (54,4%) 504 (06,1%) 1429 (68,1%) 232 (66,7%) <0.001 Ever 0310 (45,6%) 358 (39,9%) 669 (31,9%) 116 (33,3%) <0.001 BMP ² - - - - - - - - - - - 0.00%) 116 (33,3%) <0.001 - - 0.00%) - - 0.00%) - 0.00%) - 0.00%) - 0.00%) - 0.00% - 0.00% - 0.00% - 0.00% 0.01% - 0.00% 0.01% - 0.00% 0.01% - 0.00% 0.01% - 0.00% 0.01% 0.01% - 0.01% 0.01% - 0.01% 0.01% - 0.01	Mild	-	2325 (50.3%)	8141 (65.7%)	1424 (66.4%)	
Severe - 723 (15.7%) 1036 (8.4%) 128 (6.0%) Smoker ² . . <td>Moderate</td> <td>-</td> <td>1572 (34.0%)</td> <td>3220 (26.0%)</td> <td>594 (27.7%)</td> <td></td>	Moderate	-	1572 (34.0%)	3220 (26.0%)	594 (27.7%)	
Smoker ² Sever 27635 (54.4%) 540 (60.1%) 1429 (68.1%) 232 (66.7%) Ever 23120 (45.6%) 358 (39.9%) 669 (31.9%) 116 (33.3%) <0.001	Severe	-	723 (15.7%)	1036 (8.4%)	128 (6.0%)	
Never 27635 (54.4%) 540 (60.1%) 1429 (68.1%) 232 (66.7%) Ever 23120 (45.6%) 358 (39.9%) 669 (31.9%) 116 (33.3%) <0.001	Smoker ²					
Ever 23120 (45.6%) 358 (39.9%) 669 (31.9%) 116 (33.3%) <0.001 BM ²	Never	27635 (54.4%)	540 (60.1%)	1429 (68.1%)	232 (66.7%)	
BM ³ (10.0%) 1 (0.0%) 1 (0.0%) 0 (0.0%) 11-15 197 (0.3%) 29 (0.8%) 37 (0.4%) 6 (0.3%) 11-15 197 (0.3%) 29 (0.8%) 37 (0.4%) 6 (0.3%) 18-18.49 1415 (2.3%) 195 (5.2%) 255 (2.6%) 51 (2.9%) 18.5-24.9 25499 (40.8%) 1769 (47.0%) 4220 (41.8%) 769 (43.2%) 25-30 22523 (36.0%) 645 (17.1%) 2014 (20.0%) 333 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.4 (SD 5.5) 26.3 (SD 5.3) 26.2 (SD 5.68) 0.198 Practice IMD ⁴ 4758 (20.6%) 371 (14.2%) 811 (16.1%) 108 (13.7%) <0.001	Ever	23120 (45.6%)	358 (39.9%)	669 (31.9%)	116 (33.3%)	<0.001
<10	BMI ³					
11-15 197 (0.3%) 29 (0.8%) 37 (0.4%) 6 (0.3%) 16-18.49 1415 (2.3%) 195 (5.2%) 259 (2.6%) 51 (2.9%) 18.5-24.9 25499 (40.8%) 1769 (47.0%) 4220 (41.8%) 769 (43.2%) 25-30 2252 (36.0%) 1130 (30.0%) 3557 (35.3%) 622 (43.%) >30 12878 (20.6%) 645 (17.1%) 2014 (20.0%) 333 (18.7%) Mean (SD) 2.6.5 (SD 5.4) 2.5.4 (SD 5.5) 2.6.3 (SD 5.3) 2.6.2 (SD 5.68) 0.188 Practice IMD ⁴ 0 4758 (20.6%) 271 (14.2%) 811 (16.1%) 108 (13.7%) <0.001	<10	4 (0.0%)	1 (0.0%)	1 (0.0%)	0 (0.0%)	
16-18.49 1415 (2.3%) 195 (5.2%) 259 (2.6%) 51 (2.9%) 18.5-24.9 25499 (40.8%) 1769 (47.0%) 4220 (41.8%) 769 (43.2%) 25-30 22523 (36.0%) 1130 (30.0%) 3557 (35.3%) 622 (34.9%) >30 12878 (20.6%) 645 (17.1%) 2014 (20.0%) 333 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.4 (SD 5.5) 26.3 (SD 5.3) 26.2 (SD 5.6) 0.198 Practice IMD ⁴ 700 4758 (20.6%) 271 (14.2%) 811 (16.1%) 108 (13.7%) <0.001 1 4759 (20.7%) 391 (20.5%) 1010 (20.1%) 160 (20.3%) <0.001 2 345 (14.9%) 374 (19.6%) 967 (19.2%) 138 (17.5%) <0.001 3 6320 (27.3%) 443 (32.2%) 1193 (23.7%) 205 (26.1%) <0.001 4 3836 (16.6%) 431 (22.6%) 105 (20.9%) 176 (22.4%) <0.001 Comorbidities 769 90.8% 42 (0.9%) 153 (1.2%) 22 (1.0%) <0.001 Diabetes type 2 4869 (6.4%)	11–15	197 (0.3%)	29 (0.8%)	37 (0.4%)	6 (0.3%)	
18.5-24.9 25499 (40.8%) 1769 (47.0%) 4220 (41.8%) 769 (43.2%) 25-30 22523 (36.0%) 1130 (30.0%) 3557 (35.3%) 622 (34.9%) >30 12878 (20.6%) 645 (17.1%) 2014 (20.0%) 333 (18.7%) Mean (SD) 25.5 (SD 5.4) 25.4 (SD 5.5) 26.3 (SD 5.3) 26.2 (SD 5.68) 0.198 Practice IMD ⁴ 0 4758 (20.6%) 271 (14.2%) 811 (16.1%) 108 (13.7%) <0.001 1 4797 (20.7%) 391 (20.5%) 1010 (20.1%) 160 (20.3%) <0.001 2 3451 (14.9%) 374 (19.6%) 967 (19.2%) 138 (17.5%) <0.001 3 6320 (27.3%) 443 (23.2%) 1193 (23.7%) 205 (26.1%) <0.001 4 3836 (16.6%) 431 (22.6%) 1050 (20.9%) 176 (22.4%) <0.001 Comorbidities R 1180 (1.6%) 101 (2.2%) 321 (2.6%) 138 (176.%) <0.001 Diabetes type 1 599 (0.8%) 42 (0.9%) 153 (1.2%) 22 (1.0%) <0.001 Diabetes type 1 </td <td>16–18.49</td> <td>1415 (2.3%)</td> <td>195 (5.2%)</td> <td>259 (2.6%)</td> <td>51 (2.9%)</td> <td></td>	16–18.49	1415 (2.3%)	195 (5.2%)	259 (2.6%)	51 (2.9%)	
25-30 22523 (36.0%) 1130 (30.0%) 3557 (35.3%) 622 (34.9%) >30 12878 (20.6%) 645 (17.1%) 2014 (20.0%) 333 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.4 (SD 5.5) 26.3 (SD 5.3) 26.2 (SD 5.68) 0.198 Practice IMD ⁴ 0 4758 (20.6%) 271 (14.2%) 811 (16.1%) 108 (13.7%) <0.001 1 4797 (20.7%) 391 (20.5%) 1010 (20.1%) 160 (20.3%) <0.001 2 3451 (14.9%) 374 (19.6%) 967 (19.2%) 138 (17.5%) <0.001 3 6320 (27.3%) 443 (23.2%) 1193 (23.7%) 205 (26.1%) <0.001 4 3836 (16.6%) 431 (22.6%) 1050 (20.9%) 176 (22.4%) <0.001 Comorbidities 1180 (1.6%) 011 (2.2%) 321 (2.6%) 43 (2.0%) <0.001 Diabetes type 2 4869 (6.4%) 214 (4.6%) 849 (6.9%) 108 (5.0%) 0.001 Chronic kidney disease 3567 (4.7%) 156 (1.4%) 908 (4.8%) 91 (4.2%) <0.001 Diabet	18.5–24.9	25499 (40.8%)	1769 (47.0%)	4220 (41.8%)	769 (43.2%)	
>30 12878 (20.6%) 645 (17.1%) 2014 (20.0%) 333 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.4 (SD 5.5) 26.3 (SD 5.3) 26.2 (SD 5.68) 0.198 Practice IMD ⁴ 0 4758 (20.6%) 271 (14.2%) 811 (16.1%) 108 (13.7%) <0.001	25–30	22523 (36.0%)	1130 (30.0%)	3557 (35.3%)	622 (34.9%)	
Mean (SD) 26.5 (SD 5.4) 25.4 (SD 5.5) 26.3 (SD 5.3) 26.2 (SD 5.68) 0.198 Practice IMD ⁴	>30	12878 (20.6%)	645 (17.1%)	2014 (20.0%)	333 (18.7%)	
Practice IMD ⁴ Variable Bit (16.1%) 108 (13.7%) <0.001 1 4797 (20.7%) 391 (20.5%) 1010 (20.1%) 160 (20.3%) <0.001	Mean (SD)	26.5 (SD 5.4)	25.4 (SD 5.5)	26.3(SD 5.3)	26.2 (SD 5.68)	0.198
0 4758 (20.6%) 271 (14.2%) 811 (16.1%) 108 (13.7%) <0.001	Practice IMD ⁴	((/ /	
1 4797 (20.7%) 391 (20.5%) 1010 (20.1%) 160 (20.3%) <0.001	0	4758 (20.6%)	271 (14.2%)	811 (16.1%)	108 (13.7%)	<0.001
23451 (14.9%)374 (19.6%)967 (19.2%)138 (17.5%)<0.00136320 (27.3%)443 (23.2%)1193 (23.7%)205 (26.1%)<0.001	1	4797 (20.7%)	391 (20.5%)	1010 (20.1%)	160 (20.3%)	<0.001
3 6320 (27.3%) 443 (23.2%) 1193 (23.7%) 205 (26.1%) <0.001 4 3836 (16.6%) 431 (22.6%) 1050 (20.9%) 176 (22.4%) <0.001 Comorbidities Rheumatoid Arthritis 1180 (1.6%) 101 (2.2%) 321 (2.6%) 43 (2.0%) <0.001 Diabetes type 2 4869 (6.4%) 214 (4.6%) 849 (6.9%) 108 (5.0%) 0.108 Diabetes type 1 599 (0.8%) 42 (0.9%) 153 (1.2%) 22 (1.0%) <0.001 Chronic kidney disease 3567 (4.7%) 156 (3.4%) 590 (4.8%) 91 (4.2%) 0.046 Contraceptive use 7954 (10.5%) 1004 (21.7%) 1757 (14.2%) 459 (21.4%) <0.001 IBD drug use ⁵ 5-Aminosalicylic acid 445 (0.6%) 3264 (70.7%) 9085 (73.3%) 1380 (64.3%) <0.001 Azathioprine/methotrexate 650 (0.9%) 14456 (31.5%) 1983 (16.0%) 326 (15.2%) <0.001 Charlson Score ⁵ 0 43422 (70.2%) 2458 (62.6%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%)	2	3451 (14.9%)	374 (19.6%)	967 (19.2%)	138 (17.5%)	<0.001
43836 (16.6%)431 (22.6%)1050 (20.9%)176 (22.4%)<0.001ComorbiditiesRheumatoid Arthritis1180 (1.6%)101 (2.2%)321 (2.6%)43 (2.0%)<0.001Diabetes type 24869 (6.4%)214 (4.6%)849 (6.9%)108 (5.0%)0.108Diabetes type 1599 (0.8%)42 (0.9%)153 (1.2%)22 (1.0%)<0.001Chronic kidney disease3567 (4.7%)156 (3.4%)590 (4.8%)91 (4.2%)0.046Contraceptive use7954 (10.5%)1004 (21.7%)1757 (14.2%)459 (21.4%)<0.001IBD drug use ⁵ 55-Aminosalicylic acid445 (0.6%)3264 (70.7%)9085 (73.3%)1380 (64.3%)<0.001Oral Corticosteroids10178 (13.4%)3140 (68.0%)8046 (64.9%)1243 (57.9%)<0.001Azathioprine/methotrexate650 (0.9%)1456 (31.5%)1983 (16.0%)326 (15.2%)<0.001Charlson Score ⁵ 043422 (70.2%)2458 (62.6%)5930 (59.7%)1116 (62.1%)110430 (16.9%)908 (23.1%)2204 (22.2%)414 (23.0%)24190 (6.8%)277 (7.1%)877 (8.8%)132 (7.3%)32109 (3.4%)146 (3.7%)468 (4.7%)70 (3.9%)4834 (1.3%)65 (1.7%)210 (2.1%)30 (1.7%)	3	6320 (27.3%)	443 (23.2%)	1193 (23.7%)	205 (26.1%)	<0.001
ComorbiditiesRheumatoid Arthritis1180 (1.6%)101 (2.2%)321 (2.6%)43 (2.0%)<0.001Diabetes type 24869 (6.4%)214 (4.6%)849 (6.9%)108 (5.0%)0.108Diabetes type 1599 (0.8%)42 (0.9%)153 (1.2%)22 (1.0%)<0.001Chronic kidney disease3567 (4.7%)156 (3.4%)590 (4.8%)91 (4.2%)0.046Contraceptive use7954 (10.5%)1004 (21.7%)1757 (14.2%)459 (21.4%)<0.001IBD drug use ⁵ 55-Aminosalicylic acid445 (0.6%)3264 (70.7%)9085 (73.3%)1380 (64.3%)<0.001Oral Corticosteroids10178 (13.4%)3140 (68.0%)8046 (64.9%)1243 (57.9%)<0.001Azathioprine/methotrexate650 (0.9%)1456 (31.5%)1983 (16.0%)326 (15.2%)<0.001Charlson Score ⁵ 043422 (70.2%)2458 (62.6%)5930 (59.7%)1116 (62.1%)110430 (16.9%)908 (23.1%)2204 (22.2%)414 (23.0%)24190 (6.8%)277 (7.1%)877 (8.8%)132 (7.3%)32109 (3.4%)146 (3.7%)468 (4.7%)70 (3.9%)4834 (1.3%)65 (1.7%)210 (2.1%)30 (1.7%)5438 (0.7%)23 (0.6%)23 (0.6%)99 (0.2%)90 (0.5%)	4	3836 (16.6%)	431 (22.6%)	1050 (20.9%)	176 (22.4%)	< 0.001
Rheumatoid Arthritis 1180 (1.6%) 101 (2.2%) 321 (2.6%) 43 (2.0%) <0.001 Diabetes type 2 4869 (6.4%) 214 (4.6%) 849 (6.9%) 108 (5.0%) 0.108 Diabetes type 1 599 (0.8%) 42 (0.9%) 153 (1.2%) 22 (1.0%) <0.001	Comorbidities					
Diabetes type 2 4869 (6.4%) 214 (4.6%) 849 (6.9%) 108 (5.0%) 0.108 Diabetes type 1 599 (0.8%) 42 (0.9%) 153 (1.2%) 22 (1.0%) <0.001	Rheumatoid Arthritis	1180 (1.6%)	101 (2.2%)	321 (2.6%)	43 (2.0%)	<0.001
Diabetes type 1599 (0.8%)42 (0.9%)153 (1.2%)22 (1.0%)<0.001Chronic kidney disease3567 (4.7%)156 (3.4%)590 (4.8%)91 (4.2%)0.046Contraceptive use7954 (10.5%)1004 (21.7%)1757 (14.2%)459 (21.4%)<0.001IBD drug use ⁵	Diabetes type 2	4869 (6.4%)	214 (4.6%)	849 (6.9%)	108 (5.0%)	0.108
Chronic kidney disease $3567 (4.7\%)$ $156 (3.4\%)$ $590 (4.8\%)$ $91 (4.2\%)$ 0.046 Contraceptive use $7954 (10.5\%)$ $1004 (21.7\%)$ $1757 (14.2\%)$ $459 (21.4\%)$ <0.001 IBD drug use ⁵ $$	Diabetes type 1	599 (0.8%)	42 (0.9%)	153 (1.2%)	22 (1.0%)	< 0.001
Contraceptive use 7954 (10.5%) 1004 (21.7%) 1757 (14.2%) 459 (21.4%) <0.001	Chronic kidnev disease	3567 (4.7%)	156 (3.4%)	590 (4.8%)	91 (4.2%)	0.046
IBD drug use ⁵ 5-Aminosalicylic acid 445 (0.6%) 3264 (70.7%) 9085 (73.3%) 1380 (64.3%) <0.001	Contraceptive use	7954 (10.5%)	1004 (21.7%)	1757 (14.2%)	459 (21.4%)	< 0.001
5-Aminosalicylic acid 445 (0.6%) 3264 (70.7%) 9085 (73.3%) 1380 (64.3%) <0.001	IBD drug use ⁵			- ()		
Oral Corticosteroids 10178 (13.4%) 3140 (68.0%) 8046 (64.9%) 1243 (57.9%) <0.001	5-Aminosalicylic acid	445 (0.6%)	3264 (70.7%)	9085 (73.3%)	1380 (64.3%)	<0.001
Azathioprine/methotrexate 650 (0.9%) 1456 (31.5%) 1983 (16.0%) 326 (15.2%) <0.001 Tumour necrosis factor α antagonists 58 (0.8%) 14 (0.3%) 111 (0.9%) 16 (0.8%) <0.001 Charlson Score ⁵ 908 (23.1%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%)	Oral Corticosteroids	10178 (13.4%)	3140 (68.0%)	8046 (64.9%)	1243 (57.9%)	< 0.001
Tumour necrosis factor α antagonists 58 (0.8%) 14 (0.3%) 111 (0.9%) 16 (0.8%) <0.001 Charlson Score ⁵ 9 43422 (70.2%) 2458 (62.6%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%)	Azathioprine/methotrexate	650 (0.9%)	1456 (31.5%)	1983 (16.0%)	326 (15.2%)	< 0.001
Charlson Score ⁵ 43422 (70.2%) 2458 (62.6%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%)	Tumour necrosis factor α antagonists	58 (0.8%)	14 (0.3%)	111 (0.9%)	16 (0.8%)	<0.001
0 43422 (70.2%) 2458 (62.6%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%)	Charlson Score ⁵		11 (0.070)		10 (0.070)	0.001
1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%)	0	43422 (70.2%)	2458 (62.6%)	5930 (59.7%)	1116 (62 1%)	
2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	1	10430 (16.9%)	908 (23.1%)	2204 (22.2%)	414 (23.0%)	
3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	2	4190 (6.8%)	277 (7 1%)	877 (8.8%)	132 (7.3%)	
4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	3	2109 (3.4%)	146 (3.7%)	468 (4 7%)	70 (3.9%)	
5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	4	834 (1.3%)	65 (1.7%)	210 (2.1%)	30 (1.7%)	
	5	438 (0.7%)	23 (0.6%)	89 (0.9%)	9 (0.5%)	

(Continued)

Table 1. (Continued)

Characteristics	Non-IBD (n (%))	Crohn's Disease (n (%))	Ulcerative Colitis(n (%))	IBD (NOS) (n (%))	P^6
6 or more	459 (0.7%)	51 (1.3%)	154 (1.6%)	27 (1.5%)	<0.001
Major abdominal surgery ⁶	0 (0.0%)	635 (16.2%)	712 (7.2%)	102 (5.7%)	<0.001
Stoma	0 (0.0%)	222 (5.7%)	460 (4.6%)	51 (2.8%)	<0.001

¹Estimated using IBD-drug use and surgical interventions during follow-up as proxies (see text for further detail)

² 43% of patients had missing data

³ 17.4% of patients had missing data

⁴Index of Multiple Deprivation (IMD) based on practice post-code. Quintile 0 is the least deprived, quintile 4 is the most deprived. 67.5% of patients had missing data.

⁵Ever in patient record

⁶ Non-IBD compared to IBD, comparison of binary variables by adjusted χ^2 test; continuous variables by Student's t-test; multiple category variables by χ^2 test adjusted for trend.

doi:10.1371/journal.pone.0139745.t001

	Mean a	ige at diagnosis o	f heart disease (SD, 95	5% Cl ¹ , p)
All heart disease ²				
CD cases	65.2	13.4	-3.8–1.6	0.435
CD controls	66.3	3.5	1-3.8–1.7	
UC	65.8	11.7	-2.60.2	0.021
UC controls	67.4	12.6	-2.8-0.3	
Angina				
CD cases	62.0	11.3	-7.8–0.0	0.052
CD controls	65.9	12.6	-7.50.2	
UC	64.5	11.0	-4.40.7	0.008
UC controls	67.0	12.3	-4.40.8	
Coronary Heart Disease				
CD cases	65.7	12.7	-4.7–2.7	0.589
CD controls	66.7	12.5	-4.8–2.8	
UC	65.7	11.9	-3.90.4	0.015
UC controls	67.9	11.7	-3.90.4	
Ischaemic Heart Disease				
CD cases	68.0	13.6	-2.9–4.8	0.619
CD controls	67.0	12.9	-3.0–5.0	
UC	67.3	11.2	-2.4–1.1	0.460
UC controls	68.0	12.5	-2.3–1.0	
МІ				
CD cases	67.5	13.4	-4.8–5.6	0.877
CD controls	67.1	14.3	-4.7–5.5	
UC	66.3	12.1	-4.2-0.9	0.193
UC controls	67.9	13.3	-4.2-0.7	

Table 2. Mean age at diagnosis of ischaemic heart disease comparing patients with and without IBD (COHORT A)*.

¹ 95% Confidence Interval of the Difference between patients with and without IBD using Student's T-Test ²incorporates IHD, CHD, angina and MI

*Analysis excludes cases of IHD diagnosed prior to IBD diagnosis.

doi:10.1371/journal.pone.0139745.t002



Table 3. COHORT B characteristics comparing non-IBD controls with IBD cases*.

Total number61882 (9.8 %)6926 (14.9)992 (12.8 %)1798 (2.8 %).Mate2980 (48.3 %)1666 (42.9 %)4667 (47.0 %)754 (42.9 %)40.00Age11516 (62.9 %)1940 (97.8 %)574 (11.9 %)155-4911919 (21.3 %)671 (17.0 %)1310 (21.7 %)1816 (62.9 %)180 (10.8 %)156-4911919 (21.3 %)671 (17.0 %)1528 (15.4 %)181 (10.6 %)1.0 (10.6 %)65-4911919 (21.3 %)671 (17.0 %)1528 (15.4 %)181 (10.6 %)1.0 (10.6 %)65-4911919 (21.3 %)671 (17.0 %)1528 (15.4 %)1192 (63.3 %)1.0 (10.6 %)100 contain-1338 (21.9 %)553 (65.9 %)104 (53.7 %)1.0 (10.6 %)80 contain-1338 (21.9 %)553 (65.9 %)104 (53.7 %)4.0 (10.6 %)80 contain-1338 (21.9 %)142 (91.9 %)1.0 (20.7 %)1.0 (10.7 %)10 contain-132 (10.6 %)553 (65.9 %)10.0 (10.7 %)1.0 (10.7 %)11 contain143 (0.3 %)2.0 (0.5 %)10.0 (0.7 %)1.0 (10.7 %)1.0 (10.7 %)11 contain143 (0.3 %)157 (47.7 %)3811 (40.0 %)688 (43.3 %)1.0 (10.7 %)12 contain143 (0.3 %)157 (47.7 %)3811 (43.0 %)688 (43.8 %)1.0 (10.7 %)13 contain143 (0.5 %)157 (47.7 %)151 (14.3 %)6.0 (11.8 %)1.0 (10.7 %)1.0 (10.7 %)1.0 (10.7 %)1.0 (10.7 %)1.0 (10.7 %)1.0 (10.7 %)1.0 (10.7 %)1	Characteristics	Non-IBD (n(%))	Crohn's Disease (n(%))	Ulcerative Colitis (n(%))	IBD (NOS) (n(%))	P ⁷
Mate 29895 (43.3%) 1686 (42.9%) 496 (47.0%) 758 (42.2%) <0.001 Age 2948 (29.7%) 697 (38.8%) 35-34y 18868 (30.4%) 1007 (46.2%) 3102 (29.7%) 647 (19.9%) 574 (11.9%) 58 65-64y 13192 (21.3%) 67 (17.0%) 3256 (23.7%) 341 (19.9%) 64.69 42.3 (50.16.8) 42.3 (50.16.8) 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.23 64.69 64.	Total number	61882 (79.8%)	3928 (5.1%)	9932 (12.8%)	1798 (2.3%)	
Age 15:34y 21700 (35.1%) 1815 (45.2%) 2946 (25.7%) 697 (38.8%) 35-49y 16866 (30.4%) 1007 (46.2%) 3102 (22.7%) 674 (81.9%) 50-64y 13122 (21.3%) 359 (95.1%) 1528 (15.4%) 161 (10.3%) Mean age at entry (SD) 46.6 (SD 20.6) 29.9 (SD 16.6) 46.2 (SD 16.8) 42.3 (SD 16.6) 0.495 IBD eventry' 1 1333 (34.1%) 2532 (25.5%) 502 (27.9%) 500 (27.9%) Severe - 633 (34.1%) 2532 (25.5%) 502 (67.5%) <0.005	Male	29895 (48.3%)	1686 (42.9%)	4667 (47.0%)	758 (42.2%)	<0.001
15-34y 21700 (33.1%) 1816 (46.2%) 2944 (23.7%) 697 (38.8%) 35-49y 18868 (36.4%) 1637 (46.2%) 3102 (23.7%) 574 (13.9%) 50-64y 13192 (21.3%) 667 (17.0%) 2954 (23.7%) 341 (19.0%) 65-y 8122 (13.1%) 359 (32.1%) 1528 (15.4%) 186 (10.3%) Miderate - 1952 (49.7%) 6547 (65.5%) 1192 (66.3%) Miderate - 638 (16.2%) 853 (6.7%) 1192 (66.3%) Sonoker ² - 638 (16.2%) 5647 (65.5%) 1192 (66.3%) Never 27635 (54.4%) 540 (60.1%) 1429 (69.1%) 228 (66.7%) Ever 23120 (45.6%) 358 (39.%) 669 (31.9%) 116 (33.3%) <0.00	Age					
35-49y 1886 (0.4%) 1087 (6.2%) 3102 (29.7%) 574 (31.9%) 50-64y 13192 (21.3%) 667 (17.0%) 2354 (23.7%) 341 (19.0%) 65-y 8122 (13.1%) 359 (5.1%) 1522 (15.4%) 166 (10.3%) Mean age at entry (SD) 46 (SD 20.6) 33.9 (SD 15.6) 46.2 (SD 16.8) 42.2 (SD 16.8) 42.2 (SD 16.8) 42.3 (SD 16.6) 0.455 BD severity - 1352 (40.7%) 6547 (65.9%) 1192 (66.3%) 502 (27.9%) 502 (27.9%) 502 (27.9%) 502 (27.9%) 503 (16.2%) 659 (31.9%) 104 (5.3%) <0.001	15-34y	21700 (35.1%)	1815 (46.2%)	2948 (29.7%)	697 (38.8%)	
50-64y 13192 (21.31%) 667 (17.0%) 2354 (23.7%) 341 (10.0%) 65-yy 8122 (13.1%) 359 (9.1%) 1528 (15.4%) 186 (10.3%) Mean age at entry (SD) 466 (50.20.6) 39.9 (5D 16.6) 462 (25.0%) 1192 (66.3%) BID severity' - 1338 (34.1%) 2532 (25.5%) 502 (27.9%) Severe - 638 (16.2%) 853 (8.0%) 104 (58.5%) Smoker' - 638 (16.2%) 126 (66.1%) 1429 (68.1%) 222 (65.7%) Ever 23120 (45.6%) 358 (39.9%) 669 (31.9%) 116 (33.3%) <0.001	35-49y	18868 (30.4%)	1087 (46.2%)	3102 (29.7%)	574 (31.9%)	
65-y 8122 (13.1%) 359 (9.1%) 1528 (15.4%) 168 (10.3%) Mean age at entry (SD) 46.6 (SD 2.6.) 39.9 (SD 16.6.) 46.2 (SD 16.8.) 42.3 (SD 16.6.) 0.495 Bild severity	50-64y	13192 (21.3%)	667 (17.0%)	2354 (23.7%)	341 (19.0%)	
Mean age at entry (SD) 46.6 (SD 20.6) 39.9 (SD 16.6) 46.2 (SD 16.9) 42.3 (SD 16.6) 0.495 IBD severity' - 1338 (34.1%) 2532 (25.5%) 502 (27.9%) 503 (15.6%) 1192 (46.3%) 503 (15.6%) 104 (5.8%) 500 (27.9%) 503 (15.6%) 104 (5.8%) 500 (27.9%) 503 (15.6%) 104 (5.8%) 500 (27.9%) 503 (15.6%) 104 (5.8%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (27.9%) 500 (15.3%) 500 (15.3%) 500 (15.3%) 500 (15.3%) 500 (16.3%)	65+y	8122 (13.1%)	359 (9.1%)	1528 (15.4%)	186 (10.3%)	
IBD servity ¹ IBC (49.7%) Server (55.9%) 1192 (66.7%) Moderate - 1338 (34.1%) 2532 (25.5%) 502 (27.9%) Swore C - 638 (16.2%) 853 (6.6%) 104 (5.8%) Smoker ² - - 853 (6.6%) 1429 (68.1%) 232 (66.7%) Ever C 23120 (45.6%) 358 (39.9%) 668 (31.9%) 116 (53.3%) <0.001	Mean age at entry (SD)	46.6 (SD 20.6)	39.9 (SD 16.6)	46.2 (SD 16.8)	42.3 (SD 16.6)	0.495
Mid - 1952 (92,7%) 6547 (65,9%) 1192 (66,3%) Moderate - 1338 (34,1%) 2532 (25,5%) 502 (27,9%) Severe - 638 (15,2%) 853 (66,5%) 104 (5,5%) Smoker ² 27635 (54,4%) 540 (60,1%) 1429 (68,1%) 232 (66,7%) Never 27635 (54,4%) 540 (60,1%) 1429 (68,1%) 232 (66,7%) <000%)	IBD severity ¹					
Mederate - 138 (94,1%) 2532 (25,5%) 502 (27,9%) Server - 638 (16,2%) 853 (8,5%) 104 (5,8%) Smoker ² - 638 (16,2%) 653 (8,5%) 116 (33,3%) <0.001 Ever 23120 (45,6%) 540 (60,1%) 1429 (68,1%) 232 (66,7%) <0.001 Bull - - 0 0.0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 116 (33,3%) <0.001 11-15 143 (0.3%) 27 (0.8%) 23 (0.3%) 3 (0.2%) - 15-18.49 1151 (2.2%) 160 (5.4%) 198 (2.4%) 44 (2.9%) - 25-30 1990 (35.6%) 963 (20.1%) 263 (14.0%) 668 (43.3%) - 25-30 1990 (35.6%) 558 (16.9%) 1671 (19.9%) 288 (18.7%) - Mean (2D) 26.5 (25.4) 25.3 (25.5.4) 26.3 (25.5.3) 26.2 (25.5.4) <0.001 1 3743 (21.0%) 345 (20.6%) 792 (19.9%) 122 (19.4%) <0.001 1 3722 (20.8%)	Mild	-	1952 (49.7%)	6547 (65.9%)	1192 (66.3%)	
Severe · 638 (16.2%) 653 (8.6%) 104 (5.8%) Smoker ² . . <td>Moderate</td> <td>-</td> <td>1338 (34.1%)</td> <td>2532 (25.5%)</td> <td>502 (27.9%)</td> <td></td>	Moderate	-	1338 (34.1%)	2532 (25.5%)	502 (27.9%)	
Smoker ² Never 27635 (54.4%) 540 (60.1%) 1429 (68.1%) 232 (66.7%) Ever 23120 (45.6%) 358 (39.9%) 669 (31.9%) 116 (33.3%) <0.001	Severe	-	638 (16.2%)	853 (8.6%)	104 (5.8%)	
Never 27635 (54.4%) 540 (60.1%) 1429 (68.1%) 232 (66.7%) Ever 23120 (46.5%) 358 (39.9%) 669 (31.9%) 116 (33.3%) <0.001	Smoker ²					
Ever 23120 (45.6%) 358 (39.9%) 669 (31.9%) 116 (33.3%) <0.001 BM ²	Never	27635 (54.4%)	540 (60.1%)	1429 (68.1%)	232 (66.7%)	
BM³ (10 4 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%) 11-15 143 (0.3%) 27 (0.8%) 23 (0.3%) 3 (0.2%) 11-15 143 (0.3%) 27 (0.8%) 23 (0.3%) 3 (0.2%) 18-18.49 1151 (2.2%) 180 (5.4%) 198 (2.4%) 44 (2.9%) 18-5-24.9 21922 (41.3%) 1570 (47.7%) 3611 (43.0%) 668 (43.3%) 25-30 19909 (35.6%) 563 (16.9%) 1671 (19.9%) 288 (13.7%) Mean (SD) 26.5 (SD 5.4) 25.3 (SD 5.4) 26.3 (SD 5.3) 26.2 (SD 5.4) <0.001	Ever	23120 (45.6%)	358 (39.9%)	669 (31.9%)	116 (33.3%)	<0.001
<10	BMI ³					
11-15 143 (0.3%) 27 (0.8%) 23 (0.3%) 3 (0.2%) 16-18.49 1151 (2.2%) 180 (5.4%) 198 (2.4%) 44 (2.9%) 18.5-24.9 21922 (41.3%) 1579 (47.7%) 3611 (43.0%) 668 (43.3%) 25-30 18909 (55.6%) 963 (29.1%) 2901 (34.5%) 538 (34.9%) >30 10948 (20.6%) 558 (16.9%) 1671 (19.9%) 288 (18.7%) Mean (SD) 26.5 (2D 5.4) 25.3 (2D 5.4) 26.3 (2D 5.3) 26.2 (SD 5.4) <0.01	<10	4 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	
16-18.49 1151 (2.2%) 180 (5.4%) 198 (2.4%) 44 (2.9%) 18.5-24.9 21922 (41.3%) 1579 (47.7%) 3611 (43.0%) 668 (43.3%) 25-30 1999 (35.6%) 963 (29.1%) 291 (34.5%) 538 (34.9%) >30 10948 (20.6%) 558 (16.9%) 1671 (19.9%) 288 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.3 (SD 5.4) 26.3 (SD 5.3) 26.2 (SD 5.4) <0.001 Practice IMD ⁴ 7 9 650 (16.3%) 86 (13.4%) <0.001 1 3722 (20.8%) 335 (20.6%) 792 (19.9%) 125 (18.4%) <0.001 2 2574 (14.4%) 310 (19.0%) 774 (19.4%) 112 (17.4%) <0.001 3 4827 (27.0%) 384 (23.6%) 948 (23.8%) 164 (25.5%) <0.001 4 2996 (16.8%) 358 (22.0%) 821 (20.6%) 157 (24.4%) <0.001 Diabetes type 2 3040 (4.9%) 136 (3.5%) 532 (5.4%) 70 (3.9%) 0.309 Diabetes type 1 421 (0.7%) 21 (0.5%) 95 (1.0%) <t< td=""><td>11–15</td><td>143 (0.3%)</td><td>27 (0.8%)</td><td>23 (0.3%)</td><td>3 (0.2%)</td><td></td></t<>	11–15	143 (0.3%)	27 (0.8%)	23 (0.3%)	3 (0.2%)	
18.5-24.9 21922 (41.3%) 1579 (47.7%) 3611 (43.0%) 668 (43.3%) 25-30 18909 (35.6%) 963 (29.1%) 2001 (34.5%) 538 (34.9%) >30 10948 (20.6%) 558 (16.9%) 1671 (19.9%) 288 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.3 (SD 5.4) 26.3 (SD 5.3) 26.2 (SD 5.4) <0.001 Practice IMD ⁴ 0 3743 (21.0%) 242 (14.9%) 650 (16.3%) 86 (13.4%) <0.001 1 3722 (20.8%) 335 (20.6%) 792 (19.9%) 125 (19.4%) <0.001 2 2574 (14.4%) 310 (19.0%) 774 (19.4%) 112 (17.4%) <0.001 3 4827 (27.0%) 384 (23.6%) 948 (23.8%) 164 (25.5%) <0.001 4 2996 (16.8%) 358 (22.0%) 821 (20.6%) 157 (24.4%) <0.001 Comorbidities R Reumabid Arthritis 826 (1.3%) 75 (1.9%) 234 (2.4%) 29 (1.6%) 0.002 Diabetes type 2 3040 (4.9%) 136 (3.5%) 532 (5.4%) 70 (3.9%) 0.003	16–18.49	1151 (2.2%)	180 (5.4%)	198 (2.4%)	44 (2.9%)	
25-30 18909 (35.6%) 963 (29.1%) 2901 (34.5%) 538 (34.9%) >30 10948 (20.6%) 558 (16.9%) 1671 (19.9%) 288 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.3 (SD 5.3) 26.2 (SD 5.4) <0.001	18.5–24.9	21922 (41.3%)	1579 (47.7%)	3611 (43.0%)	668 (43.3%)	
>30 10948 (20.6%) 558 (16.9%) 1671 (19.9%) 288 (18.7%) Mean (SD) 26.5 (SD 5.4) 25.3 (SD 5.4) 26.3 (SD 5.3) 26.2 (SD 5.4) <0.001	25–30	18909 (35.6%)	963 (29.1%)	2901 (34.5%)	538 (34.9%)	
Mean (SD) 26.5 (SD 5.4) 25.3 (SD 5.4) 26.3 (SD 5.3) 26.2 (SD 5.4) <0.001 Practice IMD ⁴	>30	10948 (20.6%)	558 (16.9%)	1671 (19.9%)	288 (18.7%)	
Practice IND ⁴ Additional and a stress of the stress of th	Mean (SD)	26.5 (SD 5.4)	25.3 (SD 5.4)	26.3 (SD 5.3)	26.2 (SD 5.4)	<0.001
0 3743 (21.0%) 242 (14.9%) 650 (16.3%) 86 (13.4%) <0.001	Practice IMD ⁴	. ,			. ,	
1 3722 (20.8%) 335 (20.6%) 792 (19.9%) 125 (19.4%) <0.001	0	3743 (21.0%)	242 (14.9%)	650 (16.3%)	86 (13.4%)	<0.001
2 $2574 (14.4\%)$ $310 (19.0\%)$ $774 (19.4\%)$ $112 (17.4\%)$ <0.001 3 $4827 (27.0\%)$ $384 (23.6\%)$ $948 (23.8\%)$ $164 (25.5\%)$ <0.001 4 $2996 (16.8\%)$ $358 (22.0\%)$ $821 (20.6\%)$ $157 (24.4\%)$ <0.001 ComorbiditiesRheumatoid Arthritis $826 (1.3\%)$ $75 (1.9\%)$ $234 (2.4\%)$ $29 (1.6\%)$ <0.001 Diabetes type 2 $300 (4.9\%)$ $136 (3.5\%)$ $532 (5.4\%)$ $70 (3.9\%)$ 0.309 Diabetes type 1 $421 (0.7\%)$ $21 (0.5\%)$ $95 (1.0\%)$ $16 (0.9\%)$ 0.302 Chronic kidney disease $2022 (3.3\%)$ $103 (2.6\%)$ $356 (3.7\%)$ $55 (3.1\%)$ 0.653 Contraceptive use $7894 (12.8\%)$ $999 (25.4\%)$ $1730 (17.4\%)$ $456 (25.4\%)$ <0.001 Diabetes type 1 $421 (0.7\%)$ $2811 (71.6\%)$ $7352 (74.0\%)$ $1160 (64.5\%)$ <0.001 Galar Contraceptive use $7894 (12.8\%)$ $999 (25.4\%)$ $1730 (17.4\%)$ $456 (25.4\%)$ <0.001 Jac Contraceptive use $7894 (12.8\%)$ $999 (25.4\%)$ $1730 (17.4\%)$ $1160 (64.5\%)$ <0.001 Gala Conticosteroids $745 (12.0\%)$ $2811 (71.6\%)$ $7352 (74.0\%)$ $1160 (64.5\%)$ <0.001 Jac Contraceptive use $749 (0.8\%)$ $132 (0.3\%)$ $98 (1.0\%)$ $12 (0.7\%)$ <0.001 Contraceptive and $745 (0.8\%)$ $2810 (23.6\%)$ $7393 (59.7\%)$ <td>1</td> <td>3722 (20.8%)</td> <td>335 (20.6%)</td> <td>792 (19.9%)</td> <td>125 (19.4%)</td> <td><0.001</td>	1	3722 (20.8%)	335 (20.6%)	792 (19.9%)	125 (19.4%)	<0.001
3 4827 (27.0%) 384 (23.6%) 948 (23.8%) 164 (25.5%) <0.001 4 2996 (16.8%) 358 (22.0%) 821 (20.6%) 157 (24.4%) <0.001 Comorbidities Rheumatoid Arthritis 826 (1.3%) 75 (1.9%) 234 (2.4%) 29 (1.6%) <0.001 Diabetes type 2 3040 (4.9%) 136 (3.5%) 532 (5.4%) 70 (3.9%) 0.309 Diabetes type 1 421 (0.7%) 21 (0.5%) 95 (1.0%) 16 (0.9%) 0.032 Chronic kidney disease 2022 (3.3%) 103 (2.6%) 365 (3.7%) 55 (3.1%) 0.653 Contraceptive use 7894 (12.8%) 999 (25.4%) 1730 (17.4%) 456 (25.4%) <0.001 IBD drug use 5- 5-Aminosalicylic acid 327 (0.5%) 2811 (71.6%) 7352 (74.0%) 1160 (64.5%) <0.001 Azathioprine/methotrexate 474 (0.8%) 1320 (33.6%) 1709 (17.2%) 301 (16.7%) <0.001 Location for antagonists 43 (0.1%) 12 (0.3%) 98 (1.0%) 12 (0.7%) <0.001 Azathioprine/methotrexate	2	2574 (14.4%)	310 (19.0%)	774 (19.4%)	112 (17.4%)	<0.001
42996 (16.8%)358 (22.0%)821 (20.6%)157 (24.4%)<0.001ComorbiditiesRheumatoid Arthritis826 (1.3%)75 (1.9%)234 (2.4%)29 (1.6%)<0.001Diabetes type 23040 (4.9%)136 (3.5%)532 (5.4%)70 (3.9%)0.309Diabetes type 1421 (0.7%)21 (0.5%)95 (1.0%)16 (0.9%)0.032Chronic kidney disease2022 (3.3%)103 (2.6%)365 (3.7%)55 (3.1%)0.653Contraceptive use7894 (12.8%)999 (25.4%)1730 (17.4%)456 (25.4%)<0.001IBD drug use55-Aminosalicylic acid327 (0.5%)2811 (71.6%)7352 (74.0%)1160 (64.5%)<0.001Oral Corticosteroids7455 (12.0%)2665 (67.8%)6415 (64.6%)1038 (57.7%)<0.001Azathioprine/methotrexate474 (0.8%)1320 (33.6%)1709 (17.2%)301 (16.7%)<0.001Charlson Score ⁵ 043422 (70.2%)2458 (62.6%)5930 (59.7%)1116 (62.1%)110430 (16.9%)908 (23.1%)2204 (22.2%)414 (23.0%)24190 (6.8%)277 (7.1%)877 (8.8%)132 (7.3%)32109 (3.4%)146 (3.7%)468 (4.7%)70 (3.9%)4834 (1.3%)65 (1.7%)210 (2.1%)30 (1.7%)5438 (0.7%)230 (6%)89 (0.9%)9 (0.5%)	3	4827 (27.0%)	384 (23.6%)	948 (23.8%)	164 (25.5%)	<0.001
ComorbiditiesRheumatoid Arthritis826 (1.3%)75 (1.9%)234 (2.4%)29 (1.6%)<0.001Diabetes type 23040 (4.9%)136 (3.5%)532 (5.4%)70 (3.9%)0.309Diabetes type 1421 (0.7%)21 (0.5%)95 (1.0%)16 (0.9%)0.032Chronic kidney disease2022 (3.3%)103 (2.6%)365 (3.7%)55 (3.1%)0.653Contraceptive use7894 (12.8%)999 (25.4%)1730 (17.4%)456 (25.4%)<0.001IBD drug use55-Aminosalicylic acid327 (0.5%)2811 (71.6%)7352 (74.0%)1160 (64.5%)<0.001Oral Corticosteroids7455 (12.0%)2665 (67.8%)6415 (64.6%)1038 (57.7%)<0.001Azathioprine/methotrexate474 (0.8%)1320 (33.6%)1709 (17.2%)301 (16.7%)<0.001Charlson Score ⁵ 043422 (70.2%)2458 (62.6%)5930 (59.7%)1116 (62.1%)043422 (70.2%)2458 (62.6%)5930 (59.7%)1116 (62.1%)110430 (16.9%)908 (23.1%)2204 (22.2%)414 (23.0%)24190 (6.8%)277 (7.1%)877 (8.8%)132 (7.3%)32109 (3.4%)146 (3.7%)468 (4.7%)70 (3.9%)4834 (1.3%)65 (1.7%)210 (2.1%)30 (1.7%)5438 (0.7%)23 (0.6%)89 (0.9%)9 (0.5%)	4	2996 (16.8%)	358 (22.0%)	821 (20.6%)	157 (24.4%)	< 0.001
Rheumatoid Arthritis 826 (1.3%) 75 (1.9%) 234 (2.4%) 29 (1.6%) <0.01 Diabetes type 2 3040 (4.9%) 136 (3.5%) 532 (5.4%) 70 (3.9%) 0.309 Diabetes type 1 421 (0.7%) 21 (0.5%) 95 (1.0%) 16 (0.9%) 0.032 Chronic kidney disease 2022 (3.3%) 103 (2.6%) 365 (3.7%) 55 (3.1%) 0.653 Contraceptive use 7894 (12.8%) 999 (25.4%) 1730 (17.4%) 456 (25.4%) <0.001	Comorbidities	× /	()	(· · ·	
Diabetes type 2 3040 (4.9%) 136 (3.5%) 532 (5.4%) 70 (3.9%) 0.309 Diabetes type 1 421 (0.7%) 21 (0.5%) 95 (1.0%) 16 (0.9%) 0.032 Chronic kidney disease 2022 (3.3%) 103 (2.6%) 365 (3.7%) 55 (3.1%) 0.653 Contraceptive use 7894 (12.8%) 999 (25.4%) 1730 (17.4%) 456 (25.4%) <0.001	Rheumatoid Arthritis	826 (1.3%)	75 (1.9%)	234 (2.4%)	29 (1.6%)	<0.001
Diabetes type 1 421 (0.7%) 21 (0.5%) 95 (1.0%) 16 (0.9%) 0.032 Chronic kidney disease 2022 (3.3%) 103 (2.6%) 365 (3.7%) 55 (3.1%) 0.653 Contraceptive use 7894 (12.8%) 999 (25.4%) 1730 (17.4%) 456 (25.4%) <0.001	Diabetes type 2	3040 (4.9%)	136 (3.5%)	532 (5.4%)	70 (3.9%)	0.309
Chronic kidney disease 2022 (3.3%) 103 (2.6%) 365 (3.7%) 55 (3.1%) 0.653 Contraceptive use 7894 (12.8%) 999 (25.4%) 1730 (17.4%) 456 (25.4%) <0.001 IBD drug use 5 5 327 (0.5%) 2811 (71.6%) 7352 (74.0%) 1160 (64.5%) <0.001 Oral Corticosteroids 7455 (12.0%) 2665 (67.8%) 6415 (64.6%) 1038 (57.7%) <0.001 Azathioprine/methotrexate 474 (0.8%) 1320 (33.6%) 1709 (17.2%) 301 (16.7%) <0.001 Charlson Score ⁵ 0 43422 (70.2%) 2458 (62.6%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	Diabetes type 1	421 (0.7%)	21 (0.5%)	95 (1.0%)	16 (0.9%)	0.032
Contraceptive use7894 (12.8%)999 (25.4%)1730 (17.4%)456 (25.4%)<0.001IBD drug use5-Aminosalicylic acid327 (0.5%)2811 (71.6%)7352 (74.0%)1160 (64.5%)<0.001Oral Corticosteroids7455 (12.0%)2665 (67.8%)6415 (64.6%)1038 (57.7%)<0.001Azathioprine/methotrexate474 (0.8%)1320 (33.6%)1709 (17.2%)301 (16.7%)<0.001Tumour necrosis factor α antagonists43 (0.1%)12 (0.3%)98 (1.0%)12 (0.7%)<0.001Charlson Score ⁵ 043422 (70.2%)2458 (62.6%)5930 (59.7%)1116 (62.1%)110430 (16.9%)908 (23.1%)2204 (22.2%)414 (23.0%)24190 (6.8%)277 (7.1%)877 (8.8%)132 (7.3%)32109 (3.4%)146 (3.7%)468 (4.7%)70 (3.9%)4834 (1.3%)65 (1.7%)210 (2.1%)30 (1.7%)5438 (0.7%)23 (0.6%)89 (0.9%)9 (0.5%)	Chronic kidnev disease	2022 (3.3%)	103 (2.6%)	365 (3.7%)	55 (3.1%)	0.653
IBD drug use 5-Aminosalicylic acid 327 (0.5%) 2811 (71.6%) 7352 (74.0%) 1160 (64.5%) <0.001	Contraceptive use	7894 (12.8%)	999 (25.4%)	1730 (17.4%)	456 (25.4%)	< 0.001
5-Aminosalicylic acid 327 (0.5%) 2811 (71.6%) 7352 (74.0%) 1160 (64.5%) <0.001	IBD drug use					
Oral Corticosteroids 7455 (12.0%) 2665 (67.8%) 6415 (64.6%) 1038 (57.7%) <0.001	5-Aminosalicylic acid	327 (0.5%)	2811 (71.6%)	7352 (74.0%)	1160 (64.5%)	<0.001
Azathioprine/methotrexate 474 (0.8%) 1320 (33.6%) 1709 (17.2%) 301 (16.7%) <0.001 Tumour necrosis factor α antagonists 43 (0.1%) 12 (0.3%) 98 (1.0%) 12 (0.7%) <0.001 Charlson Score ⁵ 5930 (59.7%) 1116 (62.1%)	Oral Corticosteroids	7455 (12.0%)	2665 (67.8%)	6415 (64.6%)	1038 (57.7%)	< 0.001
Tumour necrosis factor α antagonists 43 (0.1%) 12 (0.3%) 98 (1.0%) 12 (0.7%) <0.001 Charlson Score ⁵ 98 (1.0%) 12 (0.7%) <0.001 0 43422 (70.2%) 2458 (62.6%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	Azathioprine/methotrexate	474 (0.8%)	1320 (33.6%)	1709 (17.2%)	301 (16.7%)	< 0.001
Charlson Score ⁵ Security	Tumour necrosis factor α antagonists	43 (0.1%)	12 (0.3%)	98 (1.0%)	12 (0.7%)	< 0.001
0 43422 (70.2%) 2458 (62.6%) 5930 (59.7%) 1116 (62.1%) 1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	Charlson Score ⁵					
1 10430 (16.9%) 908 (23.1%) 2204 (22.2%) 414 (23.0%) 2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	0	43422 (70.2%)	2458 (62.6%)	5930 (59.7%)	1116 (62.1%)	
2 4190 (6.8%) 277 (7.1%) 877 (8.8%) 132 (7.3%) 3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	1	10430 (16.9%)	908 (23,1%)	2204 (22.2%)	414 (23.0%)	
3 2109 (3.4%) 146 (3.7%) 468 (4.7%) 70 (3.9%) 4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	2	4190 (6.8%)	277 (7.1%)	877 (8.8%)	132 (7.3%)	
4 834 (1.3%) 65 (1.7%) 210 (2.1%) 30 (1.7%) 5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	3	2109 (3.4%)	146 (3.7%)	468 (4.7%)	70 (3.9%)	
5 438 (0.7%) 23 (0.6%) 89 (0.9%) 9 (0.5%)	4	834 (1.3%)	65 (1.7%)	210 (2.1%)	30 (1.7%)	
	5	438 (0.7%)	23 (0.6%)	89 (0.9%)	9 (0.5%)	

(Continued)

Table 3. (Continued)

PLOS ONE

Characteristics	Non-IBD (n(%))	Crohn's Disease (n(%))	Ulcerative Colitis (n(%))	IBD (NOS) (n(%))	P ⁷
6 or more	459 (0.7%)	51 (1.3%)	154 (1.6%)	27 (1.5%)	<0.001
Major abdominal surgery ⁶	0 (0.0%)	635 (16.2%)	712 (7.2%)	102 (5.7%)	<0.001
Stoma	0 (0.0%)	222 (5.7%)	460 (4.6%)	51 (2.8%)	<0.001

¹Estimated using IBD-drug use as proxies (see text for further detail)

²30.2% of patients had missing data during follow-up (index date to IHD date or end of follow-up).

³14.2% of patients had missing data during follow-up (BMI record nearest to IHD date (+-12 months)).

⁴Index of Multiple Deprivation (IMD) based on practice post-code. Quintile 0 is the least deprived, quintile 4 most deprived.

⁵Charlson index [17] is a validated index of comorbidity taking into account both the number and severity of comorbidities. 0 is no comorbidities. 6 or more is a very high score indicating a high number of cormorbidities and/or severe comorbidities. For example AIDS and metastatic tumour each score 6.

⁶Colectomy during follow-up (index date to IHD date or end of follow-up).

⁷Non-IBD compared to IBD, comparison of binary variables by adjusted χ^2 test; continuous variables by Student's t-test; multiple category variables by χ^2 test adjusted for trend

*Analysis excludes cases of IHD diagnosed prior to IBD diagnosis.

doi:10.1371/journal.pone.0139745.t003

In order to examine the subset in a way that was consistent with previous research,[13] the incidence rate ratios (IRR) for IHD were calculated (<u>Table 6</u>), comparing COHORT B, the partitioned subset, (i.e. IHD>IBD) with COHORT A (i.e. IHD event ever). The IRR for COHORT A was 2.1 in the first year of IBD diagnosis, with an overall IRR of 1.8. In the partitioned subset (COHORT B), the IRR in the first year of IBD diagnosis was lower (1.26) and similarly low overall IRR (1.22).

Discussion

This is the first study to fully examine both the strength and direction of association between development of ischaemic heart disease (IHD) and IBD. An increased incidence of IHD, angina, MI, and CHD diagnoses was seen in the first year after IBD diagnosis but the mean age of diagnosis comparing IBD cases with non IBD cases was not statistically different, apart from those with Ulcerative Colitis (UC) who were slightly younger at diagnosis of angina and coronary heart disease. Of those developing IHD following an IBD diagnosis, patients with UC were at slightly higher risk of a diagnosis of IHD or MI although results were not significant after adjustment for the role of covariates. Most notably, we found that although overall prevalence of IHD was higher in those with IBD, in the majority of cases the diagnosis of IHD actually predated that of IBD.

Table 4.	Incidence of IHD	among cases an	d controls (COHORT B)*.
					,

	Non-IBD	Crohn's Disease	Ulcerative Colitis	IBD (NOS)
All heart disease ¹	2343 (3.8%)	117 (3.0%)	434 (4.4%)	56 (3.1%)
Angina	1172 (1.9%)	48 (1.2%)	196 (2.0%)	33 (1.8%)
CHD	1251 (2.0%)	55 (1.4%)	215 (2.2%)	26 (1.4%)
IHD	1162 (1.9%)	57 (1.5%)	238 (2.4%)	32 (1.8%)
MI	673 (1.1%)	36 (0.9%)	131 (1.3%)	20 (1.1%)

¹incorporates IHD, CHD, angina and MI

*Analysis excludes cases of IHD diagnosed prior to IBD diagnosis.

doi:10.1371/journal.pone.0139745.t004

	ONE
--	-----

	HR (95%Cl), p unadjusted comparing IBD and non-IBD patients	HR (95%Cl), p unadjusted comparing users of Azathioprine/ methotrexate ¹ and non- users	HR (95%Cl), p unadjusted comparing users of Tumour necrosis factor α antagonists ¹ and non- users	HR (95%CI), p unadjusted comparing users of 5ASAs ¹ and non- users	HR (95%Cl), p unadjusted comparing users of Corticosteroids ¹ and non-users
Cardiovascular disease					
IBD	1.2 (1.1–1.3), p<0.001	1.0 (0.8–1.1) p = 0.614	1.5 (0.8–2.8) p = 0.256	1.2 (1.1–1.3) p = <0.001	1.8 (1.6–1.9) p<0.001
CD	1.2 (1.0–1.5), p = 0.059	0.8 (0.6–1.2) p = 0.327	1.4 (0.2–9.8) p = 746	1.1 (0.9–1.4) p = 0.322	1.7 (1.4–2.0) p<0.001
UC	1.2 (1.1–1.4) p<0.001	1.1 (0.9–1.4) p = 0.324	1.0 (0.4–2.4) p = 0.997	1.2 (1.1–1.4) p = 0.001	1.8 (1.6–1.9) p<0.001
Angina					
IBD	1.1 (1.0–1.2) p = 0.235	1.0 (0.7–1.2) p = 0.653	2.0 (0.9–4.4) p = 0.095	1.1 (0.9–1.2) p = 0.449	1.8 (1.6–2.0) p<0.001
CD	1.0 (0.8–1.4) p = 0.836	0.7 (0.4–1.2) p = 0.141	0.1 (0.0–241) p = 0.702	1.1 (0.8–1.5) p = 0.654	2.0 (1.6–2.6) p<0.001
UC	1.1 (0.9–1.2) p = 0.428	1.2 (0.9–1.6) p = 0.287	1.2 (0.4–3.7) p = 0.753	1.0 (0.9–1.2) p = 0.703	1.7 (1.5–2.0) p<0.001
Coronary Heart Disease					
IBD	1.1 (1.0–1.3) p = 0.081	1.2 (0.9–1.4) p = 0.210	1.9 (0.8–4.2) p = 0.128	1.2 (1.0–1.4) p = 0.022	1.7 (1.6–1.9) p<0.001
CD	1.1 (0.8–1.5) p = 0.459	1.0 (0.7–1.6) p = 0.929	2.7 (0.4–19.1) p = 0.326	1.2 (0.9–1.7) p = 0.250	1.9 (1.5–2.5) p<0.001
UC	1.1 (1.0–1.3) p = 0.108	1.3 (1.0–1.7) p = 0.038	1.5 (0.6–4.1) p = 0.404	1.2 (1.0–1.4) p = 0.093	1.7 (1.5–1.9) p<0.001
Ischaemic Heart Disease					
IBD	1.3 (1.2–1.5) p<0.001	1.0 (0.7–1.2) p = 0.688	1.9 (0.9–4.3) p = 0.107	1.3 (1.2–1.5) p<0.001	1.8 (1.6–2.0) p<0.001
CD	1.2 (1.0–1.6) p = 0.180	0.8 (0.5–1.3) p = 0.375	3.0 (0.4–21.6) p = 0.268	1.3 (0.9–1.8) p = 0.145	1.9 (1.5–2.4) p<0.001
UC	1.3 (1.1–1.5) p<0.001	1.1 (0.9–1.5) p = 0.388	1.2 (0.4–3.6) p = 0.789	1.3 (1.1–1.5) p = 0.001	1.8 (1.6–2.0) p<0.001
МІ					
IBD	1.3 (1.1–1.5) p = 0.002	1.1 (0.8–1.5) p = 0.464	1.1 (0.3–4.5) p = 0.878	1.4 (1.2–1.7) p<0.001	1.8 (1.5–2.0) p<0.001
CD	1.2 (0.8–1.7) p = 0.369	0.6 (0.3–1.3) p = 0.215	0.05 (0.0–485) p = 0.749	1.1 (0.7–1.7) p = 0.652	1.5 (1.1–2.0) p = 0.021
UC	1.4 (1.1–1.6) p = 0.004	1.5 (1.0–2.1) p = 0.036	0.7 (0.1–5.1) p = 0.737	1.5 1.2–1.8) p<0.001	1.9 (1.6–2.3) p<0.001

Table 5. Unadjusted hazard ratios for cardiovascular disease comparing IBD drug users* and non-users (COHORT B).

¹Drug users with and without IBD were included in this analysis *Analysis excludes cases of IHD diagnosed prior to IBD diagnosis.

doi:10.1371/journal.pone.0139745.t005

This is the largest British cohort study to examine this issue. It used the General Practice Research Database which is an appropriate and reliable resource for IBD research, having been used for at least 19 studies published in peer-reviewed journals since 2000. The diagnostic reliability of IBD diagnosis and the year of IBD diagnosis in the GPRD has been confirmed in a recent validation study. [14] Other GPRD validation studies have confirmed reliable recording





doi:10.1371/journal.pone.0139745.g002

of cardiovascular disease and other disease groups.[15, 16] The risk of selection bias in this study was low given that GPRD data is collected from a wide cross-section of general practices from across the UK. The prevalence of CD is slightly lower compared to UC than would be expected in a UK population [17]. However, the cohort was a random selection taken from 2 million records and the difference is unlikely to reflect systematic sampling bias. We were careful to exclude from our analysis patients with chronic kidney disease and diabetes mellitus, since both are associated with raised inflammatory markers and could have confounded our results.

As others have highlighted [13], there is a risk of ascertainment bias because IBD patients may have more frequent contact with health care professionals and are therefore monitored more closely, potentially raising the chance of earlier detection of IHD in this group. The fact that patients with UC were at slightly higher risk of IHD and MI could potentially be a selection effect on a conditioned group or simply an artefact of multiple hypotheses in this hypothesis generating study. We sought to overcome this by designing the study to examine the direction of association and clearly delineating prevalent and incident IHD cases. In addition, we allowed adjustment for the effect of comorbidities in both cases and controls by using the Charlson index [18] as a composite measure of comorbidity within multiple analyses, all of which demonstrated no difference between groups.



	Whole dataset (COHORT A)		S	Sub-set (COHORT B)
	Overall IRR (95% CI)	IRR in 1 st year > IBD diagnosis(95% CI)	Overall IRR (95% CI)	IRR in 1 st year > IBD diagnosis (95% Cl)
All IHD	1.8 (1.72–1.89)	2.1 (1.98–2.22)	1.2 (1.12–1.33)	1.3 (1.07–1.48)

Table 6. Incidence Rate Ratios (IRR) comparing whole group analysis with sub-set*.

*Analysis excludes cases of IHD diagnosed prior to IBD diagnosis.

doi:10.1371/journal.pone.0139745.t006

The temporal relationship between IBD and IHD may be weakened by differences with which the diagnosis of each is recorded in the GPRD. IHD is a diagnosis made in the majority of cases fairly soon after the onset of symptoms, because of an event requiring admission to hospital (MI, acute coronary syndrome). Nevertheless, among those with stable angina, nearly half have symptoms for 6 months or more before diagnosis.[19] For IBD the time to reach a diagnosis may be longer. A Swiss cohort study of 1591 patients with IBD estimated the median interval from first presentation to a GP to diagnosis as 4 months (IQR 0–18) for CD and 1 month (0–5) for UC.[20] Independent risk factors for delayed diagnosis included younger age (<40) in Crohn's disease and male sex in ulcerative colitis.[20]

It is possible that IHD cases may have been missed or incorrectly coded within GPRD. Unrecorded diagnoses are increasingly unlikely within UK general practice due to policy and fiscal incentives to assess, monitor and treat cardiovascular disease,[21] although historical records pre-dating these incentives are more likely to have unrecorded IHD diagnoses. Sub-group analysis comparing diagnoses of IHD and its subtypes before and after these incentives (around the year 2004) demonstrate no differences either in temporal trends or in overall risk profiles, thus decreasing the likelihood of reporting bias. Incorrect sub-group coding of types of IHD is another possibility, partly as a result of lack of clinical consensus about definitional boundaries. For this reason, we conducted sub-group analysis on MI, angina and additional group analysis of cases coded as CHD and the fact that trends were entirely consistent with results for IHD goes some way to refuting the potential for this type of recording bias. Although GPRD prescribing and clinical data are robust and reliable, BMI and smoking data were incomplete due to the fact that, in the UK, many general practices do not routinely or systematically collect this data. Data on cholesterol levels were not requested. Thus the effect of these covariates on the association between IHD and IBD remains unknown. We were unable to reliably differentiate between remission and relapse phases, or to capture concomitant extraintestinal manifestations. These data would be recorded in secondary care but not routinely communicated to primary care in a way that would result in the event being routinely coded in the primary care record, and hence the GPRD dataset. The potential association between relapses and incidence of heart disease warrants further investigation.

This is the first known study to examine the temporal relationship between IHD and IBD and we found that the majority of IHD cases predated IBD diagnosis. Previous research has predominantly focused attention on incident cases of IHD occurring at or after diagnosis of IBD. It is notable that the overall risk of prevalent (i.e. whole cohort) IHD was almost identical to a recent Danish study [13] at 2.1 IRR, but that when this was limited to truly incident cases post IBD, the risk reduced to 1.2 IRR. IBD is triggered by a complex interaction between environmental factors, genetic predisposition, and an exaggerated immune response. Our findings suggest that the temporal relationship between IBD and IHD is against the concept of the latter being a long term consequence of IBD-related inflammation, as previously proposed [13]. Instead, the association with IHD is more plausibly explained by common mechanisms in the inflammatory pathway, or even a reverse causality. Our findings suggest that the assessment of

a patient's future risk of IHD should not be modified by the presence of IBD. Among patients who develop IHD, those who have raised cytokine levels, particularly of IL6 and TNF Alpha, may be at increased risk of subsequently developing IBD.

Conclusions

By identifying and quantifying both the strength and direction of association between IBD and IHD, this study provides important insights into the burden of IHD in the IBD population. This is relevant for basic scientists exploring the temporal causal pathway, and clinicians who should be aware of the risks of IHD in patients with IBD and vice versa.

Supporting Information

S1 Fig. Time from IBD diagnosis (T0) to first CVD event by age. Total number of patients showing time from IBD diagnosis (T0) to the first cardiovascular event (incorporating IHD, CHD, angina and MI) according to IBD type and age categories. (TIF)

S2 Fig. Time from IBD diagnosis (T0) to first CVD event by IBD type and gender. Total number of patients showing time from IBD diagnosis (T0) to the first cardiovascular event (incorporating IHD, CHD, angina and MI) according to IBD type and gender categories. (TIF)

S3 Fig. Time from IBD diagnosis (T0) to first coronary heart disease event by IBD type. Total number of patients showing time from IBD diagnosis (T0) to the first Coronary Heart Disease (sub-group of CVD) event according to IBD type. (TIF)

S4 Fig. Time from IBD diagnosis (T0) to first Ischaemic Heart Disease event by IBD type. Total number of patients showing time from IBD diagnosis (T0) to the first Ischaemic Heart Disease (sub-group of CVD) event according to IBD type. (TIF)

S5 Fig. Time from IBD diagnosis (T0) to first angina event according to IBD type. Total number of patients showing time from IBD diagnosis (T0) to the first Angina (sub-group of CVD) event according to IBD type. (TIF)

S6 Fig. Time from IBD diagnosis (T0) to first Myocardial Infarction event according to IBD type Total number of patients showing time from IBD diagnosis (T0) to the first Myocardial Infarction (sub-group of CVD) event according to IBD type. (TIF)

S7 Fig. Age at CVD onset according to IBD type Total number of patients showing age at onset of Cardiovascular Disease (incorporating IHD, CHD, angina and MI) according to IBD type.

(TIF)

Acknowledgments

We thank the Medical Research Council and the General Practice Research Database Research Team for their institutional support and Tarita Murray-Thomas at the GPRD (now CPRD) for her help in obtaining the dataset. We thank Professors Matt Rutter, Ahmet Fuat and Gerry Murphy for their expert advice on clinical issues in relation to IBD and IHD.

Author Contributions

Conceived and designed the experiments: GR JMM APSH RJ. Performed the experiments: HC JMM. Analyzed the data: HC JMM DW. Contributed reagents/materials/analysis tools: DW. Wrote the paper: GR HC JMM DW APSH RJ.

References

- Cassinotti A, Sarzi-Puttini P, Fichera M, Shoenfeld Y, de Franchis R. Immunity, autoimmunity and inflammatory bowel disease. Autoimmunity Reviews 2014; 13: 1–2 doi: <u>10.1016/j.autrev.2013.06.007</u> PMID: <u>23777820</u>
- Maloy KJ, Powrie F. Intestinal homeostasis and its breakdown in inflammatory bowel disease. Nature 2014; 474: 298–306
- Strober W, Fuss IJ. Pro-inflammatory cytokines in the pathogenesis of IBD. Gastroenterology 2011; 140: 1756–1767 doi: <u>10.1053/j.gastro.2011.02.016</u> PMID: <u>21530742</u>
- 4. Choy E. Understanding the dynamics: pathways involved in the pathogenesis of rheumatoid arthritis. Rheumatology 2012; 51 v5–v11
- Konno S, Lizuka M, Yukawa M, Sasaki K, Sato A, Horie Y, et al. Altered expression of angiogenic factors in the VEGF-Ets-1 cascades in inflammatory bowel disease. J Gastroenterol 2004; 39(10): 931–9 PMID: <u>15549445</u>
- Zezos P, Papaioannou G, Nikolaidis N, Vasiliadis T, Giouleme O, Evgenidis N. Elevated plasma von Willebrand factor levels in patients with active ulcerative colitis reflect endothelial perturbation due to systemic inflammation. World J. Gastroenterol 2005; 11:7639–45 PMID: <u>16437691</u>
- Krueger JG, Bowcock A. Psoriasis pathophysiology: current concepts of pathogenesis. Ann Rheum Dis 2005; 64: ii30–ii36 doi: <u>10.1136/ard.2004.031120</u> PMID: <u>15708932</u>
- Navarro-Gonzalez JF, Mora-Fernandez C. The Role of Inflammatory Cytokines in Diabetic Nephropathy. JASN 2008; 19: 433–442 doi: <u>10.1681/ASN.2007091048</u> PMID: <u>18256353</u>
- Maradit-Kremers H, Crowson C.S., Nicola PJ, Ballman KV, Roger VL, Jacobsen SJ, et al. Increased Unrecognized Coronary Heart Disease and Sudden Deaths in Rheumatoid Arthritis. Arthritis and Rheumatism 2005; 52(2): 402–411 PMID: <u>15693010</u>
- Sodergren A, Stwegmayr B, Lundberg V, Öhman M-L, Wållberg-Jonsson S. Increased incidence of and impaired prognosis after acute myocardial infarction among patients with seropositive rheumatoid arthritis. Annals of the Rheumatic Diseases 2007; 66: 263–6 PMID: 16854951
- Sarwar N, Butterworth AS, Freitag DF, Gregson J, Willeit P, Gorman DN et al. Inter4leukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies. Lancet 2012; 379: 1205–13 doi: <u>10.1016/S0140-6736(11)61931-4</u> PMID: <u>22421339</u>
- Osterman MT, Yang UX, Brensinger C, Forde KA, Lichtenstein GR, Lewis JD. No Increased Risk of Myocardial Infarction Among Patients With Ulcerative Colitis or Crohn's Disease 2011; 9(10):875–880 doi: 10.1016/j.cgh.2011.06.032 PMID: 21749853
- Rungoe C, Basit S, Ranthe MF, Wohlfahrt J, Langholz E, Jess T. Risk of ischaemic heart disease in patients with inflammatory bowel disease: a nationwide Danish cohort study. Gut. 2013; 62(5):689–94. doi: <u>10.1136/gutjnl-2012-303285</u> Epub 2012 Sep 8. PMID: <u>22961677</u>
- Lewis JD, Brensinger C, Bilker WB, Strom BL. Validity and completeness of the General Practice Research Database for studies of inflammatory bowel disease. Pharmacoepidemiology and Drug Safety 2002; 11: 211–18 PMID: <u>12051120</u>
- Rodriguez G, Perez-Gutthann S. Use of the UK General Practice Research Database for pharmacoepidemiology. Br J Clin Pharmacol 1998; 45: 419–425 PMID: <u>9643612</u>
- RI Tannen, Weiner MG, Xie D, Barnhart K. A simulation using data from a primary care practice database closely replicated the women's health initiative trial. J Clin Epidemiol. 2007: 60: 686–95 PMID: <u>17573984</u>
- Rubin GP, Hungin AP, Kelly PJ, Ling J. Inflammatory bowel disease: epidemiology and management in an English general practice population. Aliment Pharmacol Ther. 2000 Dec; 14(12):1553–9. PMID: <u>11121902</u>
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987; 40: 373–383. PMID: <u>3558716</u>

- Daly C, Clemens F, Lopez Sendon JL, Tavazzi L, Boersma E, Danchin N, et al on behalf of the Euro Heart Survey Investigators. Gender Differences in the Management and Clinical Outcome of Stable Angina. Circulation. 2006; 113: 490–498 PMID: <u>16449728</u>
- Vavricka S, Spigaglia SM, Rogler G, Pittet V, Michetti P, Felley C. et al. Systematic evaluation of risk factors for diagnostic delay in inflammatory bowel disease. Inflamm Bowel Dis 2011 18, 496–505. 4 doi: <u>10.1002/ibd.21719</u> Epub 2011 Apr 21720. (2012). PMID: <u>21509908</u>
- 21. The NICE QOF indicator programme. Available: <u>http://www.nice.org.uk/aboutnice/qof/qof.</u> jsp#Programme