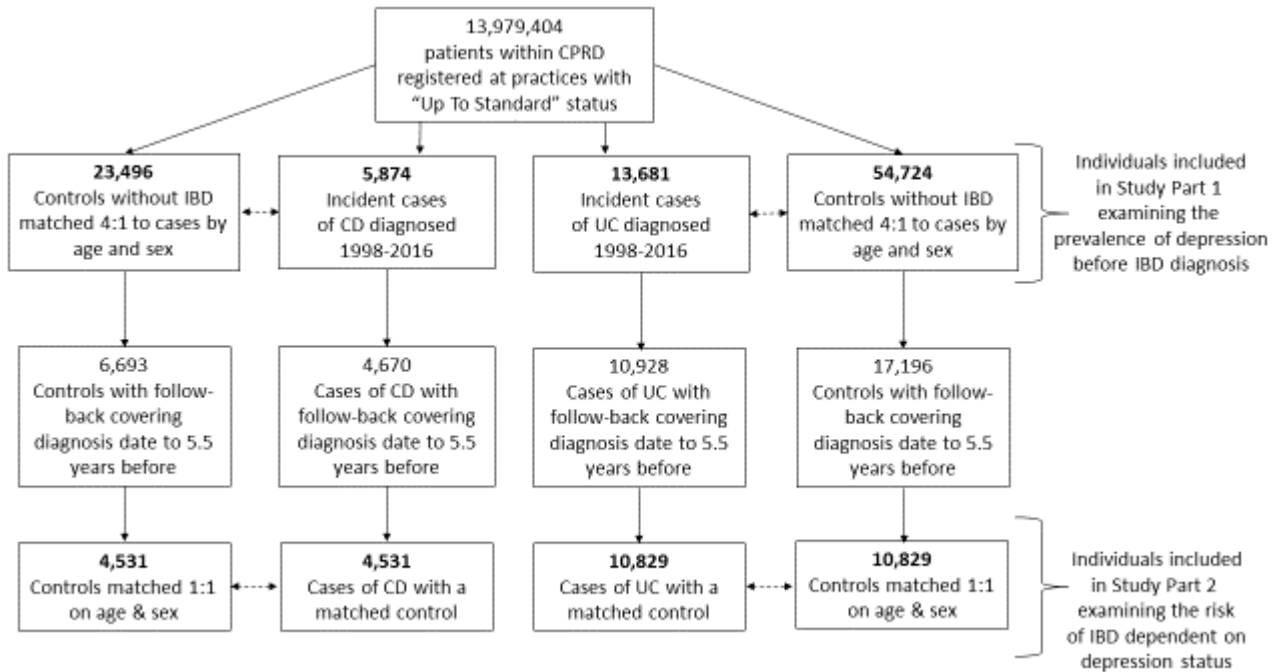


Supplementary Appendices

Appendix A – Selection of cases and controls



IBD – Inflammatory bowel disease

CD – Crohn’s Disease

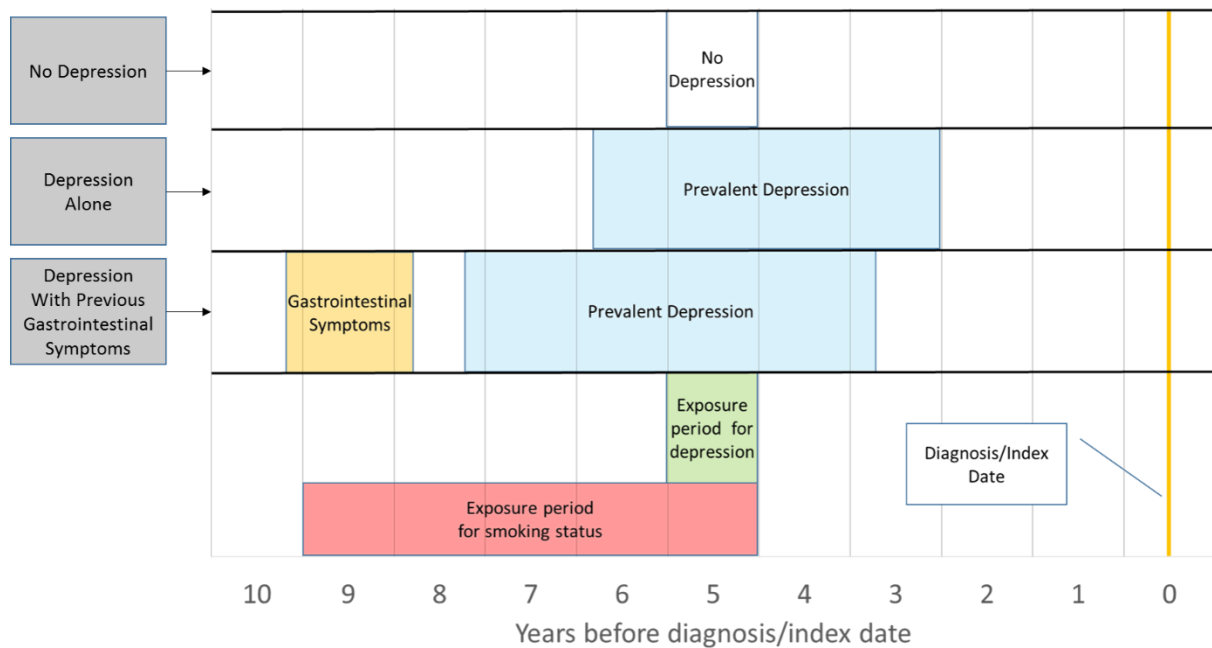
UC – Ulcerative colitis

Incident Case – Individuals with a first ever diagnosis Read code for either CD or UC at least one year after registering with an 'Up To Standard' practice.

Control – An individual with no record of IBD at any time, matched to a case by age and sex

◄-----► – Denotes these cases and controls are matched by age and sex.

Appendix B – Graphical Depiction of the Exposure Periods in relation to the Index Date in Study Part 2



Exposure period for depression: 4.5-5.5 years before the index date

Prevalent depression: Individuals with a code for a diagnosis or symptoms of depression in that year, or a prescription for antidepressant medication in that year *and* a previous code for depression in their clinical record

Depression alone: Individuals with prevalent depression during the exposure period who had no record of gastrointestinal symptoms before their first record of depression or antidepressant medication prescription

Depression with previous gastrointestinal symptoms: Individuals with prevalent depression during the exposure period with a code for gastrointestinal symptoms at any time before their first code for depression or antidepressant medication prescription.

Index Date: Controls were assigned the date of inflammatory bowel disease diagnosis of their matched case as their index date.

Exposure period for smoking status: 4.5-9.5 years before the index date

Appendix C – Antidepressant Medication Code List

Some antidepressant medications, in particular tricyclic antidepressants such as amitriptyline, may be used for indications other than depression, for example abdominal pain and irritable bowel syndrome.¹ We determined that 83% of amitriptyline prescriptions in our dataset were for a dose equal to or less than 30 mg per day, significantly below the dose recommended for the treatment of depression and we therefore excluded tricyclic antidepressants from our analyses.²

Citalopram	Prodcde
Cipralex 10mg tablets (Lundbeck Ltd)	648
Cipralex 10mg/ml oral drops (Lundbeck Ltd)	26056
Cipralex 20mg tablets (Lundbeck Ltd)	6360
Cipralex 20mg/ml oral drops (Lundbeck Ltd)	41062
Cipralex 5mg tablets (Lundbeck Ltd)	785
Cipramil 10mg tablets (Lundbeck Ltd)	3861
Cipramil 20mg tablets (Lundbeck Ltd)	1712
Cipramil 40mg tablets (Lundbeck Ltd)	2408
Citalopram 10mg Tablet (Neo Laboratories Ltd)	34498
Citalopram 10mg tablets	476
Citalopram 10mg tablets (A A H Pharmaceuticals Ltd)	34586
Citalopram 10mg tablets (Actavis UK Ltd)	32848
Citalopram 10mg tablets (Almus Pharmaceuticals Ltd)	42660
Citalopram 10mg tablets (IVAX Pharmaceuticals UK Ltd)	33720
Citalopram 10mg tablets (Mylan Ltd)	34436
Citalopram 10mg tablets (Niche Generics Ltd)	45286
Citalopram 10mg tablets (PLIVA Pharma Ltd)	52824
Citalopram 10mg tablets (Ranbaxy (UK) Ltd)	59193
Citalopram 10mg tablets (Sandoz Ltd)	34499
Citalopram 10mg tablets (Teva UK Ltd)	41528
Citalopram 10mg tablets (Waymade Healthcare Plc)	56355
Citalopram 10mg tablets (Zentiva)	34413
Citalopram 10mg/5ml oral suspension	54827
Citalopram 20mg Tablet (Neo Laboratories Ltd)	34722
Citalopram 20mg tablets	67
Citalopram 20mg tablets (A A H Pharmaceuticals Ltd)	34356
Citalopram 20mg tablets (Actavis UK Ltd)	34871
Citalopram 20mg tablets (Almus Pharmaceuticals Ltd)	48026
Citalopram 20mg tablets (Mylan Ltd)	34415
Citalopram 20mg tablets (Niche Generics Ltd)	34970
Citalopram 20mg tablets (Sandoz Ltd)	26016
Citalopram 20mg tablets (Teva UK Ltd)	34966
Citalopram 20mg tablets (Waymade Healthcare Plc)	60568
Citalopram 20mg tablets (Zentiva)	34822
Citalopram 40mg Tablet (Neo Laboratories Ltd)	43519
Citalopram 40mg tablets	4770
Citalopram 40mg tablets (A A H Pharmaceuticals Ltd)	36746

Citalopram 40mg tablets (Actavis UK Ltd)	46977
Citalopram 40mg tablets (Almus Pharmaceuticals Ltd)	60839
Citalopram 40mg tablets (DE Pharmaceuticals)	55033
Citalopram 40mg tablets (Mylan Ltd)	34603
Citalopram 40mg tablets (Niche Generics Ltd)	45223
Citalopram 40mg tablets (Sandoz Ltd)	34466
Citalopram 40mg tablets (Teva UK Ltd)	45304
Citalopram 40mg tablets (Zentiva)	46926
Paxoran 10mg Tablet (Ranbaxy (UK) Ltd)	32546
Paxoran 20mg Tablet (Ranbaxy (UK) Ltd)	29756

Escitalopram

Escitalopram 10mg tablets	603
Escitalopram 10mg/ml oral drops sugar free	20152
Escitalopram 20mg tablets	6218
Escitalopram 20mg/ml oral drops sugar free	40726
Escitalopram 5mg tablets	6405

Fluoxetine

Fluoxetine 10mg tablets	42499
Fluoxetine 20mg Capsule (Milpharm Ltd)	38890
Fluoxetine 20mg capsules	22
Fluoxetine 20mg capsules (A A H Pharmaceuticals Ltd)	19183
Fluoxetine 20mg capsules (Actavis UK Ltd)	45329
Fluoxetine 20mg capsules (Fannin UK Ltd)	45247
Fluoxetine 20mg capsules (Genus Pharmaceuticals Ltd)	34202
Fluoxetine 20mg capsules (IVAX Pharmaceuticals UK Ltd)	34294
Fluoxetine 20mg capsules (Mylan Ltd)	34288
Fluoxetine 20mg capsules (Niche Generics Ltd)	42107
Fluoxetine 20mg capsules (Ranbaxy (UK) Ltd)	19470
Fluoxetine 20mg capsules (Sandoz Ltd)	45224
Fluoxetine 20mg capsules (Teva UK Ltd)	34456
Fluoxetine 20mg capsules (Tillomed Laboratories Ltd)	34849
Fluoxetine 20mg capsules (Wockhardt UK Ltd)	45316
Fluoxetine 20mg capsules (Zentiva)	33410
Fluoxetine 20mg/5ml oral solution	2548
Fluoxetine 20mg/5ml oral solution (A A H Pharmaceuticals Ltd)	34216
Fluoxetine 20mg/5ml oral solution (IVAX Pharmaceuticals UK Ltd)	42803
Fluoxetine 20mg/5ml oral solution (Teva UK Ltd)	30258
Fluoxetine 20mg/5ml oral solution sugar free	36893
Fluoxetine 60mg capsules	4075
Fluoxetine 60mg capsules (Mylan Ltd)	34856
Prozac 20mg capsules (Eli Lilly and Company Ltd)	418
Prozac 20mg/5ml liquid (Eli Lilly and Company Ltd)	252
Prozac 60mg capsules (Eli Lilly and Company Ltd)	4907

Prozep 20mg/5ml oral solution (Chemidex Pharma Ltd)	37256
Prozit 20mg/5ml oral solution (Pinewood Healthcare)	33779
Ranflutin 20mg capsules (Ranbaxy (UK) Ltd)	29786
Feliciium 20mg capsules (Opus Pharmaceuticals Ltd)	33071
Oxactin 20mg capsules (Discovery Pharmaceuticals Ltd)	14740

Mirtazepine

Mirtazapine 15mg orodispersible tablets	6421
Mirtazapine 15mg orodispersible tablets (A A H Pharmaceuticals Ltd)	43253
Mirtazapine 15mg orodispersible tablets (Aurobindo Pharma Ltd)	43241
Mirtazapine 15mg orodispersible tablets (Focus Pharmaceuticals Ltd)	43248
Mirtazapine 15mg orodispersible tablets (Genus Pharmaceuticals Ltd)	43246
Mirtazapine 15mg orodispersible tablets (Mylan Ltd)	55482
Mirtazapine 15mg orodispersible tablets (Teva UK Ltd)	43237
Mirtazapine 15mg tablets	6795
Mirtazapine 15mg tablets (A A H Pharmaceuticals Ltd)	43239
Mirtazapine 15mg tablets (Actavis UK Ltd)	53699
Mirtazapine 15mg tablets (Arrow Generics Ltd)	46668
Mirtazapine 15mg tablets (Genus Pharmaceuticals Ltd)	43242
Mirtazapine 15mg tablets (Medreich Plc)	54342
Mirtazapine 15mg tablets (Teva UK Ltd)	43257
Mirtazapine 15mg/ml oral solution sugar free	16154
Mirtazapine 15mg/ml oral solution sugar free (A A H Pharmaceuticals Ltd)	53321
Mirtazapine 15mg/ml oral solution sugar free (DE Pharmaceuticals)	61547
Mirtazapine 15mg/ml oral solution sugar free (Rosemont Pharmaceuticals Ltd)	47966
Mirtazapine 30mg orodispersible tablets	6488
Mirtazapine 30mg orodispersible tablets (A A H Pharmaceuticals Ltd)	43250
Mirtazapine 30mg orodispersible tablets (Actavis UK Ltd)	53648
Mirtazapine 30mg orodispersible tablets (Almus Pharmaceuticals Ltd)	48185
Mirtazapine 30mg tablets	742
Mirtazapine 30mg tablets (A A H Pharmaceuticals Ltd)	47945
Mirtazapine 30mg tablets (Actavis UK Ltd)	40160
Mirtazapine 30mg tablets (DE Pharmaceuticals)	60538
Mirtazapine 45mg orodispersible tablets	6481
Mirtazapine 45mg orodispersible tablets (A A H Pharmaceuticals Ltd)	43235
Mirtazapine 45mg orodispersible tablets (Genus Pharmaceuticals Ltd)	43247
Mirtazapine 45mg orodispersible tablets (Teva UK Ltd)	43234
Mirtazapine 45mg tablets	6854
Mirtazapine 45mg tablets (A A H Pharmaceuticals Ltd)	33337
Mirtazapine 45mg tablets (Actavis UK Ltd)	58625
Zispin 30mg tablets (Organon Laboratories Ltd)	4726
Zispin SolTab 15mg orodispersible tablets (Merck Sharp & Dohme Ltd)	6846
Zispin SolTab 30mg orodispersible tablets (Merck Sharp & Dohme Ltd)	10083

Paroxetine

Paroxetine 10mg tablets	35021
Paroxetine 10mg tablets (Actavis UK Ltd)	59288
Paroxetine 10mg/5ml oral suspension sugar free	527
Paroxetine 20mg tablets	50
Paroxetine 20mg tablets (A A H Pharmaceuticals Ltd)	34419
Paroxetine 20mg tablets (Actavis UK Ltd)	32899
Paroxetine 20mg tablets (Genus Pharmaceuticals Ltd)	40892
Paroxetine 20mg tablets (IVAX Pharmaceuticals UK Ltd)	34351
Paroxetine 20mg tablets (Medreich Plc)	55023
Paroxetine 20mg tablets (Mylan Ltd)	33978
Paroxetine 30mg tablets	1397
Paroxetine 30mg tablets (A A H Pharmaceuticals Ltd)	34587
Paroxetine 30mg tablets (Actavis UK Ltd)	40165
Seroxat 10mg tablets (GlaxoSmithKline UK Ltd)	35112
Seroxat 20mg tablets (GlaxoSmithKline UK Ltd)	841
Seroxat 20mg/10ml liquid (GlaxoSmithKline UK Ltd)	3601
Seroxat 30mg tablets (GlaxoSmithKline UK Ltd)	1575

Sertraline

Sertraline 100mg tablets	727
Sertraline 100mg tablets (A A H Pharmaceuticals Ltd)	55146
Sertraline 100mg tablets (Actavis UK Ltd)	61503
Sertraline 100mg tablets (Almus Pharmaceuticals Ltd)	59600
Sertraline 100mg tablets (PLIVA Pharma Ltd)	54933
Sertraline 100mg tablets (Teva UK Ltd)	44944
Sertraline 100mg/5ml oral suspension	49519
Sertraline 150mg/5ml oral suspension	54826
Sertraline 50mg tablets	488
Sertraline 50mg tablets (A A H Pharmaceuticals Ltd)	32401
Sertraline 50mg tablets (Accord Healthcare Ltd)	58723
Sertraline 50mg tablets (Actavis UK Ltd)	42387
Sertraline 50mg tablets (Almus Pharmaceuticals Ltd)	45915
Sertraline 50mg tablets (Mylan Ltd)	58664
Sertraline 50mg tablets (Teva UK Ltd)	55488
Sertraline 50mg/5ml oral suspension	7328
Lustral 100mg tablets (Pfizer Ltd)	4352
Lustral 50mg tablets (Pfizer Ltd)	1612

Venlafaxine

Tifaxin XL 150mg capsules (Genus Pharmaceuticals Ltd)	39809
Tifaxin XL 75mg capsules (Genus Pharmaceuticals Ltd)	39770
Tonpular XL 150mg capsules (Wockhardt UK Ltd)	57751
Tonpular XL 75mg capsules (Wockhardt UK Ltd)	52716
Venaxx XL 150mg capsules (AMCo)	40514
Venaxx XL 75mg capsules (AMCo)	40515
Venlafaxine	55424

Venlafaxine 150mg Modified-release capsule (Hillcross Pharmaceuticals Ltd)	55501
Venlafaxine 150mg modified-release capsules	2654
Venlafaxine 150mg modified-release capsules (Sandoz Ltd)	43334
Venlafaxine 150mg modified-release tablets	39360
Venlafaxine 150mg/5ml oral solution	50934
Venlafaxine 225mg modified-release tablets	40054
Venlafaxine 37.5mg modified-release tablets	45806
Venlafaxine 37.5mg tablets	301
Venlafaxine 37.5mg tablets (A A H Pharmaceuticals Ltd)	56662
Venlafaxine 37.5mg tablets (Bristol Laboratories Ltd)	59923
Venlafaxine 37.5mg tablets (Teva UK Ltd)	60895
Venlafaxine 37.5mg/5ml oral suspension	13237
Venlafaxine 50mg tablets	2617
Venlafaxine 75mg modified-release capsules	470
Venlafaxine 75mg modified-release capsules (Sandoz Ltd)	43203
Venlafaxine 75mg modified-release tablets	39359
Venlafaxine 75mg tablets	1222
Venlafaxine 75mg tablets (A A H Pharmaceuticals Ltd)	60449
Venlafaxine 75mg tablets (Teva UK Ltd)	56457
Venlafaxine 75mg/5ml oral solution	53326
Venlalic XL 150mg tablets (DB Ashbourne Ltd)	40062
Venlalic XL 225mg tablets (DB Ashbourne Ltd)	40407
Venlalic XL 37.5mg tablets (DB Ashbourne Ltd)	45818
Venlalic XL 75mg tablets (DB Ashbourne Ltd)	40059
Venlaneo XL 150mg capsules (Kent Pharmaceuticals Ltd)	44936
Venlaneo XL 75mg capsules (Kent Pharmaceuticals Ltd)	44937
Vensir XL 150mg capsules (Morningside Healthcare Ltd)	40092
Vensir XL 75mg capsules (Morningside Healthcare Ltd)	40277
Vexarin XL 150mg capsules (Mylan Ltd)	40517
Vexarin XL 75mg capsules (Mylan Ltd)	42600
ViePax 37.5mg tablets (Dexcel-Pharma Ltd)	40764
ViePax 75mg tablets (Dexcel-Pharma Ltd)	40917
ViePax XL 150mg tablets (Dexcel-Pharma Ltd)	40049
ViePax XL 75mg tablets (Dexcel-Pharma Ltd)	40048
Rodome1 XL 150mg capsules (Teva UK Ltd)	41314
Rodome1 XL 75mg capsules (Teva UK Ltd)	41033
Sunveniz XL 150mg tablets (Sun Pharmaceuticals UK Ltd)	59753
Sunveniz XL 75mg tablets (Sun Pharmaceuticals UK Ltd)	60843
Tardcaps XL 150mg capsules (IXL Pharma Ltd)	40817
Tardcaps XL 75mg capsules (IXL Pharma Ltd)	40815
Ranfaxine XL 75mg capsules (Ranbaxy (UK) Ltd)	48199
Politid XL 150mg capsules (Actavis UK Ltd)	43673
Politid XL 75mg capsules (Actavis UK Ltd)	41299
Efexor 37.5mg tablets (Wyeth Pharmaceuticals)	623
Efexor 50mg tablets (Wyeth Pharmaceuticals)	6274
Efexor 75mg tablets (Wyeth Pharmaceuticals)	9182

Efexor XL 150mg capsules (Pfizer Ltd)	5710
Efexor XL 75mg capsules (Pfizer Ltd)	1474
Bonilux XL 150mg capsules (Sandoz Ltd)	61236
Depefex XL 150mg capsules (Chiesi Ltd)	45664
Depefex XL 75mg capsules (Chiesi Ltd)	45959
Foraven XL 75mg capsules (Forum Products Ltd)	43968

Appendix D – Gastrointestinal Symptom Code List

Description	Medcode
Diarrhoea symptoms	5134
Diarrhoea	192
Diarrhoea	4343
Loose stools	1695
Gastrointestinal symptoms	13015
Chronic diarrhoea	6685
Diarrhoea of presumed infectious origin	5090
Diarrhoea symptom NOS	14695
Noninfective diarrhoea	6016
GIT symptoms	10896
Functional diarrhoea	5036
Increased frequency of defaecation	18682
[D] Stools loose	14881
Irritable bowel syndrome with diarrhoea	29835
Infectious diarrhoea	4542
Gastroenteritis	139
Diarrhoea & vomiting, symptom	2182
Diarrhoea and vomiting	7644
Viral gastroenteritis	3107
Diarrhoea & vomiting -? infect	14665
[D]Change in bowel habit	16665
Travellers' diarrhoea	11155
Viral diarrhoea	15289
Abdominal pain	177
[D]Abdominal pain	1763
Abdominal pain type	1976
Abdominal discomfort	2383
Anal pain	3049
Right iliac fossa pain	1181
[D]Abdominal colic	2056
Left iliac fossa pain	2982
Colicky abdominal pain	7812
Infectious gastroenteritis	10294
Rectal pain	2767
[D]Abdominal cramps	716
O/E - abdomen tender	5782
[D]Abdominal pain NOS	3338
Site of abdominal pain	5960
Lower abdominal pain	22608
Central abdominal pain	4617
Gastrointestinal symptoms	13015
Flank pain	7490
[D]Nonspecific abdominal pain	19283
[D]Functional abdominal pain syndrome	103540
Iliac fossa pain	421
[D]Acute abdomen	948
O/E - abdo. pain on palpation	15180
GIT symptoms	10896

Anorectal pain	2866
Generalised abdominal pain	24661
O/E -abd.pain on palpation NOS	14916
O/E - abd. pain - L.ilic	21583
Non-colicky abdominal pain	5691
Abdominal pain in pregnancy	3191
[D]Pain in left iliac fossa	16868
[D]Pain in right iliac fossa	16806
O/E - abd. pain - R.ilic	11647
C/O pelvic pain	2781
Suprapubic pain	7300
Perianal irritation	9837
[D]Colic NOS	1239
Perianal itch	5830
[D]Epigastric pain	542
Perineal irritation	7090
[D] Perineal pain	7248
[D]Pelvic and perineal pain	9920
[D]Recurrent acute abdominal pain	2234
Upper abdominal pain	3978
Right upper quadrant pain	9695
[D]Right upper quadrant pain	7726
O/E - abd. pain - epigastrium	19223
[D]Upper abdominal pain	8436
Left flank pain	701
Gastrointestinal haemorrhage	3097
Epigastric pain	290
[D]Flatulence, eructation and gas pain	14807
Type of GIT pain	14989
Type of GIT pain - symptom	6395
[D]Umbilical pain	4771
Rectal bleeding	621
Bleeding PR	3872
Painless rectal bleeding	11698
Painful rectal bleeding	11718
Blood in stool	2873
Blood in faeces	5462
Blood in faeces symptom	6151
GIB - Gastrointestinal bleeding	1642
Haemorrhoids	195
Piles - haemorrhoids	3833
Haemorrhoids NOS	2096
Bleeding haemorrhoids NOS	2832
PRB - Rectal bleeding	6554

Appendix E – Prevalence of depression in the 10 years before diagnosis of Crohn’s Disease and ulcerative colitis relative to controls.

Years before IBD diagnosis	0	1	2	3	4	5	6	7	8	9	10
Prevalent Depression (%)											
CD	7.0	6.1	4.9	4.6	4.3	3.6	3.3	3.2	2.5	2.1	1.7
Controls (CD)	4.7	4.5	4.3	3.7	3.2	3.0	2.5	2.2	2.1	2.0	1.6
UC	6.8	5.9	5.2	4.8	4.3	3.7	3.4	2.8	2.7	2.1	1.7
Controls (UC)	4.9	4.7	4.1	3.8	3.6	2.9	2.5	2.3	2.1	1.7	1.5

Where the results are significantly different (Chi squared, $p < 0.05$) between the CD and UC case groups to their control groups the results will be highlighted in bold

IBD – Inflammatory Bowel Disease **CD** – Crohn’s Disease **UC** – Ulcerative colitis

Prevalent Depression – Any individual with a code for depression in that year or a prescription for an antidepressant medication, excluding amitriptyline, in that year with a previous code for depression.

Control group (CD) – Individuals without IBD matched by age and sex to the Crohn’s Disease case group.

Control group (UC) – Individuals without IBD matched by age and sex to the ulcerative colitis case group.

Appendix F –Risk of Crohn’s Disease and ulcerative colitis by depression status (Model 1)

Conditional Logistic Regression	Crohn's Disease Model 1 n=9,062		Ulcerative colitis Model 1 n=21,658	
	OR	95% CI	OR	95% CI
Depression Status				
No Depression	1	-	1	-
Depression Alone	1.21	0.90-1.63	1.25	1.03-1.52
Depression with previous GI symptoms	1.36	0.94-1.99	1.58	1.24-2.02
Smoking Status				
Non-Smoker	1	-	1	-
Smoker	1.69	1.47-1.93	1.13	1.04-1.24
Ex-Smoker	1.70	1.46-1.99	1.49	1.37-1.62
Social deprivation (%)				
IMD 1-3	1	-	1	-
IMD 4-5	1.12	1.00-1.26	0.84	0.78-0.91
Unknown	1.00	0.92-1.10	0.92	0.86-0.97

Statistically significant results highlighted in bold.

Model 1 - We calculated the risk of CD or UC dependent on each variable separately conditional on matching for age and sex.

No Depression - No depression in the exposure period

Depression Alone - Prevalent depression in the exposure period but no gastrointestinal symptoms preceding the onset of depression

Depression with previous GI symptoms – Prevalent depression in the exposure period with gastrointestinal symptoms preceding the onset of depression

IMD – Index of Multiple Deprivation, 1 represents the least deprived and 5 represents the most deprived. Index of multiple deprivation data are only available in England.

Appendix G – Baseline characteristics of cases and controls in study part 1

IBD Status	Crohn's Disease	Control Group (CD)	Ulcerative Colitis	Control Group (UC)
n=	5,874	23,496	13,681	54,724
Demographics				
Male (%)	2,721 (46)	10,884 (46)	7,278 (53)	29,112 (53)
Age at diagnosis (%)				
<17	492 (8)	1,968 (8)	380 (3)	1,520 (3)
17-39	2,420 (41)	9,680 (41)	4,194 (31)	16,776 (31)
>39	2,961 (51)	11,844 (51)	9,107 (67)	36,428 (67)
Social deprivation (%)				
IMD 1-3	2,187 (37)	8,484 (36)	5,692 (42)	20,369 (37)
IMD 4-5	1,243 (21)	4,987 (21)	2,437 (18)	11,264 (21)
Unknown	2,444 (42)	10,025 (43)	5,552 (41)	23,091 (42)

IMD – Index of Multiple Deprivation. IMD 1 represents the least deprived and IMD 5 the most deprived.

1. Wong J, Motulsky A, Abrahamowicz M, Egale T, Buckeridge DL, Tamblyn R. Off-label indications for antidepressants in primary care: descriptive study of prescriptions from an indication based electronic prescribing system. *BMJ*. 2017;356:j603-j603. doi:10.1136/bmj.j603
2. Blackwell J, Saxena S, Alexakis C, et al. DOP85 Rising depression and antidepressant use amongst inflammatory bowel disease patients. *J Crohn's Colitis*. 2019;13(Supplement_1):S081-S082. doi:10.1093/ecco-jcc/jjy222.119